

On the Synthesis of some Thiophen Compounds, with
Notes on the Metabolism of Thienyl Carboxylic
Acid and of Thienylalanine, and on the
Physiological Action of Thienylethylamine.

Thesis presented to the Faculty of Science of
Edinburgh University, for the Degree of Doctor of
Philosophy.

By

ALEXANDER PETER TAWSE EASSON, B.Sc.

Description of work carried out in the Department
of Medical Chemistry, under the supervision of
Professor George Barger.

March 1930.



Contents.

	<u>Pages.</u>
<u>Introduction</u>	1
Contractions for Literature References, and Nomenclature of thiophen radicles	11
<u>I. Preparation of Thiophen</u>	
Introductory	12
Description of Apparatus	19
Experiments with Original Form of Apparatus	24
Experiments with Modified Form	33
Summary and Conclusion	40
<u>II. Preparation of Thiophen Aldehyde.</u>	42
Introductory	42
Gattermann's Carbon Monoxide Method	43
Rosenmund's Catalytic Reduction Method	45
Gattermann's Method using the Grignard Reaction	50
Preparation of Benzaldehyde	55
Constitution of Thienyl methyl ketone and of Thiophen aldehyde	56
Biedermann's Method	57
Thienyl Methyl ketone	58
Thienyl glyoxylic acid and Thiophen aldehyde	60 66
Ziegler's Process for introduction of -CH ₂ OH group, employing the Grignard reaction	69
Benzyl alcohol	69
Method of Stephen, Short and Gladding for introduction of -CH ₂ Cl group	70
s-Dichloro methyl ether	71
Benzyl Chloride	72

Contents (Contd.)

	<u>Pages</u>
III. <u>Syntheses of Amino methyl α-thienyl ketone</u> ———	74
Amino methyl phenyl ketone —————	75
IV. <u>Synthesis of α-Thienyl-β-ethylamine</u> —————	79
Introductory —————	79
α -Thienyl alcohol —————	80
Phenylethylamine —————	88
Thienyl acrylic acid —————	89
Thienyl propionic acid —————	91
amide of —————	92
Thienyl ethylamine —————	93
Properties of —————	95
Derivatives of —————	95
V. <u>Synthesis of α-Thienyl-β-alanine</u> —————	104
<u>First Method</u> (Erlenmeyer's hippuric acid condensation) —————	104
Azolactone of α -thienyl- α -benzoylamino acrylic acid —————	106
α -Thienyl- α -benzoylamino acrylic acid —————	107
Reduction and hydrolysis of —————	108
α -Thienyl- α -benzoylamino propionic acid —————	112
α -Thienyl- α -alanine —————	115
<u>Second Method</u> (Erlenmeyer's hydantoin condensation) —————	117
Hydantoin —————	120
α -Thienyl Hydantoin —————	121
Hydrolysis of —————	124
α -Thienyl- β -alanine —————	127
Properties of —————	128
VI. <u>Notes on the Physiological Action of Thienyl- Ethylamine, and on the Metabolism of Thienyl Carboxylic Acid and of Thienylalanine</u> —————	129
Thienyl ethylamine —————	129
Thienyl carboxylic acid —————	129
Thienylalanine —————	131
VII. <u>Summary</u> —————	134

INTRODUCTION

Published work on the physiological properties of thiophen and its compounds is very scanty. What has been done tends to show that substitution of the thiophen nucleus for the benzene nucleus, in a physiologically active compound, causes little or no change in the physiological properties of that compound. The type of activity is not altered and any change in the magnitude of the effect is usually almost negligible. The physical properties of thiophen and of benzene are almost identical; their chemical properties are similar, but there are one or two very remarkable dissimilarities which will be indicated shortly.

The main part of this paper is concerned with the syntheses of three compounds of thiophen, these compounds not having been described hitherto. These three compounds are α -thienyl- β -ethylamine, α -thienyl- β -alanine, and α -thienyl aminomethyl ketone. The benzene isologues (i.e. the corresponding compounds having the thienyl radicle replaced by phenyl) of the first two of these are of considerable physiological importance. The first, when injected intravenously, brings about an increase in the blood pressure/

pressure by constricting the blood vessels, the second is important in metabolism as it is an amino acid constituent of many natural proteins. The corresponding thiophen compounds were synthesised in order that they might be compared with these benzene compounds which are of fundamental importance.

The starting material in all the syntheses was thiophen itself, and a special apparatus was erected in order that it could be easily prepared in fairly large quantities, as it is difficult to procure commercially and rather costly. The working of this apparatus is described in Part I. Thiophen aldehyde is the next stage in all of the syntheses, and as some difficulty was met with in its preparation, the results of the various methods investigated are described fully in Part II.

A brief outline will now be given of the chief differences between benzene and thiophen in their physical and chemical properties, and of the work which has been done on the physiological behaviour of thiophen.

Physical/

Physical Properties. There is only one notable difference in the physical properties of thiophen and benzene, and this is in their specific gravities. The specific gravities of benzene and thiophen respectively, at 0°, are 0.899 and 1.088 (Schiff, Ber. 18, 1601). In other physical properties the two substances are almost identical.

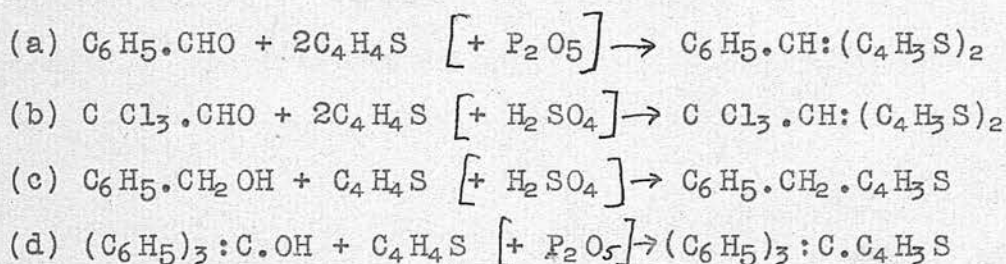
Chemical Properties. Thiophen can take part in most of the reactions which apply to benzene. The reactivity of thiophen and some of its compounds, however, is usually greater than that of benzene and its corresponding compounds, and in some cases is very much greater; this is shown well by comparing the rate of oxidation of thiophenine and of aniline. The nature of the reaction products is generally very similar, but the amino derivatives are remarkable exceptions. A short description of the preparation and properties of the amino compounds is given later.

In the case of benzene all the hydrogen atoms have the same value with regard to the rest of the molecule; this of course is not the case with thiophen, as there are the atoms in the α -position to the sulphur atom and those in the β -position.

The/

The hydrogen atoms in the α -position are more labile than those in the β -position, and more labile than those of benzene, as is shown by the following examples:-

- (1) Formation of mercury derivatives of thiophen.
- (2) Halogenation of thiophen, in the cold, without a catalyst (Gattermann, Ann., 1912; 393, 229)
- (3) Reactions with aldehydes and with alcohols.
(Töhl, Nahki, Ber. 1896, 29, 2205; Peter, Ber., 1884, 17, 1341; Weisse, Ber. 1896, 29, 1402).



In the first two of these reactions incidentally, thiophen resembles phenol which reacts with aldehydes in the presence of dehydrating agents, in the same way. There are other resemblances between thiophen and phenol.

Another difference between thiophen and benzene is seen in the fact that in the case of thiophen it is often difficult to bring about mono substitution only; there is a much greater tendency towards di-substitution (in the two α -positions). (Gattermann, loc./

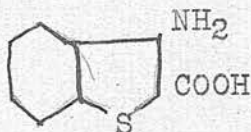
loc. cit., Steinkopf, Ann. 1914, 403, 17).

The most noteworthy differences between benzene and thiophen are found however when the amino derivatives are considered.

Amino thiophenes. cf. Steinkopf, Ann. 1914, 403, 17: Steinkopf and Müller, ibid. 1926, 448, 214.

Only five amino thiophenes are known:-

2-amino thiophen (thiophenine); 4-amino-2-thiophen carboxylic acid; 3-amino-5-thiotolen-4-carboxylic acid; 2-amino thionaphthen; 3-amino-thionaphthen-2-carboxylic acid,



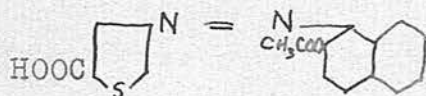
The first two of these are remarkable for their instability, the others are more stable.

From 2-nitrothiophen Steinkopf obtained the stannichloride of 2-amino-thiophen by reduction with Sn and HCl. By making a solution of this stannichloride alkaline in an atmosphere of hydrogen, he obtained the 2-thiophenine as a faintly coloured liquid, b.p. 61°/1 mm. This could be kept for some days, but in presence of a trace of oxygen it rapidly polymerised and subsequently oxidised. The corresponding benzene compound, aniline, /

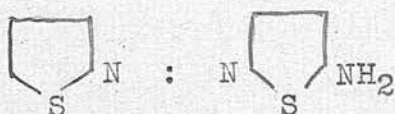
aniline, is of course almost unaffected by oxygen.

Diazotisation. As would be expected from their instability, the aminothiophens are exceedingly difficult to diazotise. Steinkopf and Müller (1926, loc. cit.) were the first to disprove the idea, held until then, that the amino thiophens would not undergo diazotisation at all. Staedler (Ber. 1885, 18, 2319) however, claims that amino thiophen reacted with nitrous acid in a peculiar manner, the reaction consisting of a simultaneous diazotisation, nitration and hydrolysis of the diazo group, giving a nitrothienol, $C_4H_2S.NO_2.OH$. This, however was not obtained by Steinkopf and Müller, and the results of Staedler are probably unproved. Benary and Baravian (Ber. 1915, 48, 603) attempted the diazotisation of 3-amino-5-thiotolen-4-carboxylic acid, but failed to isolate a recognisable product.

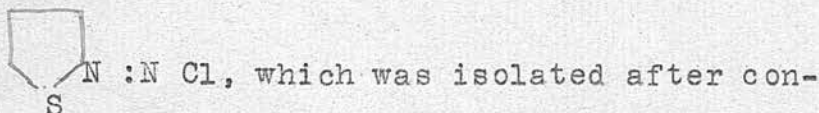
Steinkopf and Müller first diazotised the tin double salt of 4-amino-2-thiophen carboxylic acid, coupled the diazo compound immediately with β -naphthol, and isolated the resulting dye as its acetyl derivative,



Steinkopf and Müller then diazotised the double salt of 2-amino thiophen, and obtained two products. The main product was amino azothiophen,



formed by coupling of the diazo compound with unchanged base. This azo compound was incidentally very unstable; the thiophen ring was ruptured by heating the alcoholic solution, with evolution of H₂S. The other product was the diazonium chloride



siderable trouble.

Physiological/

Physiological Properties.

The comparatively small amount of work which has been done on the physiological properties of thiophen compounds tends to show that thiophen is very like benzene from this point of view. It is necessary to give only a brief outline of what has been done.

The fate of thiophen itself in the animal organism is unknown, it is not poisonous, and is not oxidised (Heffter, Pflüger's Arch. 39, 420).

Like benzoic acid, thiophen carboxylic acid becomes conjugated with glycine, being excreted as thenoyl glycine (Jaffé and Levy, Ber. 1888, 21, 3458) Thiophen aldehyde is oxidised and excreted as thenoyl glycine (Cohn, Hoppe Seyler, 1893, 281).

The substitution of alkyl groups in thiophen brings about an increase in toxicity, as in the case of benzene (Heffter, loc. cit.).

Thiophen has more marked antiseptic action than has benzene. The antiseptic action is increased by introducing two atoms of iodine, and di-iodo thiophen was used by Spiegler (Therap. Monatsheft, 1892, 67) as a substitute for iodoform.

If the p-amino benzoyl group in novocaine be replaced/

replaced by thiophen, the resulting compound, $C_4H_3S.CO.O.(CH_2)_2N(Et)_2$ has a very similar action to novocaine.

The thiophen isologue of cocaine, thenoyl ecgonine, has exactly the same properties as cocaine (Steinkopf and Ohse, Ann., 192⁴7, 437, 14)

Steinkopf and Ohse (Ann., 1926, 448, 205) prepared the 2-thenoyl derivative of quinine, and the thiophen isologues of eucaine and of stovaine and found them similar to the original drugs in anaesthetic action; the thiophen compounds were a little less toxic.

Hartmann and Wybert (Helv. Chim. Acta, 1919, 2, 60) replaced the phenyl group in cinchonic acid by thienyl, and found, as they had expected from the entry of a sulphur containing group, that the antifebrile and analgesic actions were increased.

Most of the work which has been done on the physiological action of thiophen compounds is outlined above. There is, however, a noteworthy case in which thiophen differs from benzene in its physiological behaviour. Toluene is oxidised completely to benzoic acid in the organism, but methyl thiophen or thiotolen gives only a small amount of thienyl carboxylic acid, the chief products/

products have not been isolated (Heffter, loc. cit., Jaffé and Levy, loc. cit.). In view of this difference, the metabolism of thienyl alanine may be expected to be an interesting study.

Contractions/

Contractions for Literature References.

- Abs. _____ Chemical Society Abstracts.
Ann. _____ Liebig's Annalen der Chemie.
Ber. _____ Berichte der deutschen chemischen
Gesellschaft.
Helv. Chim. Acta. Helvetica Chimica Acta.
Hoppe Seyler. _____ Hoppe Seyler's Zeitschrift für
physiologischen Chemie.
Pflüger's Arch. _____ Pflüger's Archiv. für die
gesamte Physiologie des Menschen
und der Tiere.
Therap. Monatsheft. Therapeutisches Monatshefte.

Nomenclature for Radicles containing the
Thiophen Nucleus.

The following names for the various thiophen radicles are fairly general, but are not universally employed. They are used in this paper.

C_4H_3S-	Thienyl, corresponding to Phenyl
$C_4H_3S.CH_2-$	Thenyl " Benzyl
$C_4H_3S.CH=$	Thenal " Benzal
$C_4H_3S.C^O$	Thenoyl " Benzoyl

I. PREPARATION OF THIOPHEN.

In the first place, it is proposed to indicate some of the methods described in the literature for the preparation of thiophen.

Thiophen was discovered by Victor Meyer, in 1883. It had been known for some time that there was some difference between coal tar benzene and benzene prepared synthetically (e.g. by the polymerisation of acetylene). The benzene derived from coal tar gave with isatin a colour reaction which was not shown by the synthetic product. Meyer concluded that this must be due to some impurity in the coal tar benzene, and succeeded in isolating the new compound, thiophen.

Some of the various methods described for the preparation of thiophen are as follows:-

- (1) Extraction from coal tar benzene.
- (2) Reaction of ethylene or acetylene with boiling sulphur (Meyer and Sandmeyer, Ber. 1884, 16, 2176).
- (3) Condensation of 2 molecules of ethyl sulphide at red heat (Kekule, Ber. 1885, 18, 217).
- (4) Reaction of crotonic acid or n-butyric acid with phosphorus sulphide (Nahnsen).
- (5)/

- (5) Reaction of sodium succinate with phosphorus trisulphide (Vohlhard and Erdmann, Ber. 1885, 18, 454).
- (6) Reaction of acetylene and hydrogen sulphide in presence of alumina at 400°. (Tschitschibabin, Journ. Russ. Phys. Chem. Soc. 1915, 407, 703).
- (7) Reaction of acetylene and pyrites at 300° (Steinkopf, Verhandlung der Ges. deutsch. Naturforscher. und Aertzte, 1912, 11, 220-221; Steinkopf and Kirchhoff, Ann. 1913, 403, 1; Steinkopf, Ann. 1921, 428, 123).

Other methods are mainly modifications of the above.

The processes which have been employed for the preparation of thiophen in quantity are Nos. 1, 5, 6 and 7. In our work Method No. 7 was employed on account of the following considerations.

The first method is exceedingly troublesome and tedious, as coal tar benzene contains only about 0.5% of thiophen.

Method No. 5 is the process ordinarily used in the laboratory, but is troublesome and expensive, and the yields are poor.

Method No. 6. The original paper in which this synthesis is described was not available. The Chemical Society abstract of it (Abs. 1915, 1, 638) states that the author finds that the method is more satisfactory than that of Steinkopf, as it gives a purer product and there is no appreciable charring/

charring of the acetylene.

An attempt was made with this method, using ordinary glass apparatus.

A glass tube, about 1 metre long and 2 cm. in diameter, was filled with pumice mixed with aluminium oxide (prepared by precipitation), and fitted with an inlet tube at one end and a tube leading into a Woulff's bottle at the other. An upright condenser was fitted into the other tubulure of the Woulff's bottle. The tube was placed in a trough containing sand. A slow current of a mixture of acetylene with about half its volume of H_2S was passed through the tube, which was then heated to about 400° . The acetylene was prepared from calcium carbide and the H_2S from ferrous sulphide in the usual way. After several hours a small amount of a yellow solid had collected in the receiver. The outlet gases had an extremely disagreeable smell, and the catalyst became covered with carbon. No trace of thiophen could be detected in the product (which, in fact, was completely solid) by means of the indophenin reaction. Experiments were made both with dried and undried gases, with similar results in each case. In the absence of complete details of the process, it was decided not/

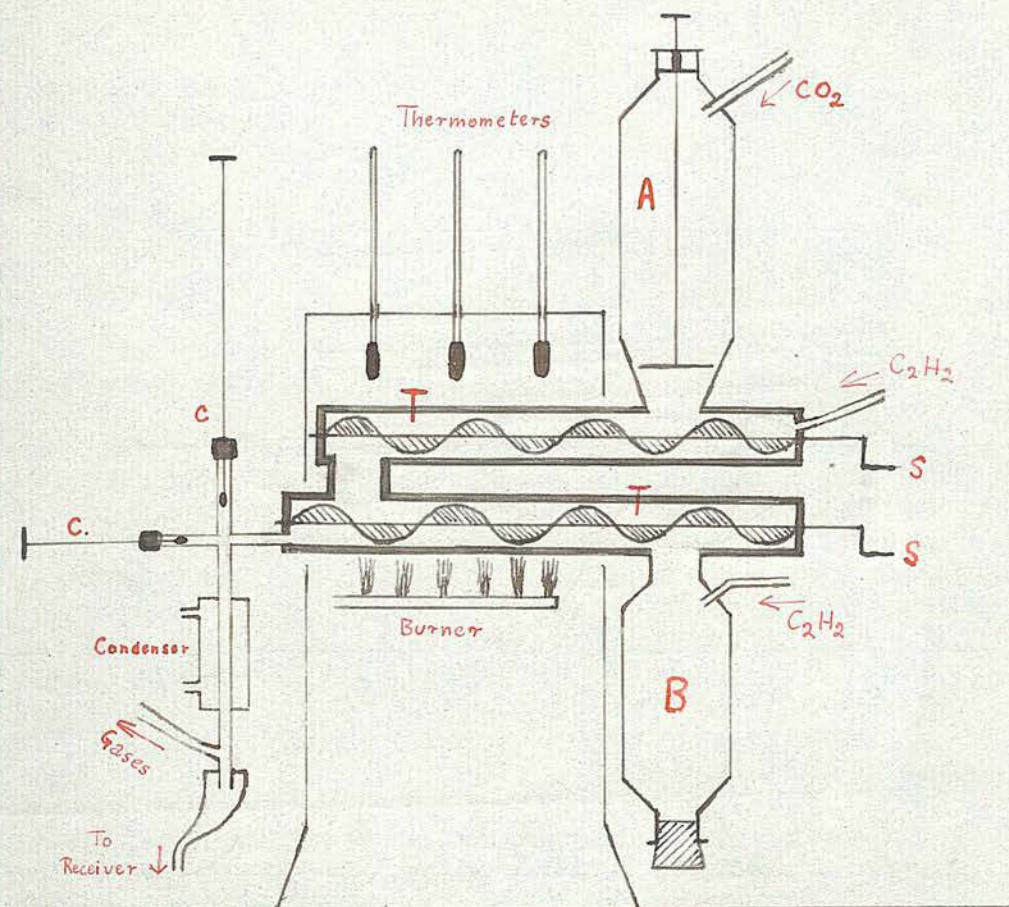
not to proceed any further with it, and to adopt Method No. 7. Also, this is the method chosen by Steinkopf, who has done a large amount of work on thiophen.

Preparation of Thiophen by Passing Acetylene
over Pyrites heated to 300°.

1. Description of the apparatus employed by Steinkopf, with a brief outline of the method.

The periodical in which Steinkopf's first paper appeared could not be obtained, but as the paper extends to two pages only, it may be only a preliminary note. The Chemical Society abstract (Abs. 1912, 1, 292) is to the effect that acetylene is passed through an iron tube containing pyrites at a temperature of 300°, and that 800 gm. of distillate containing 40% of thiophen may be obtained in 7-8 hours. It is stated also that benzene is present in very small amounts only, and that the remainder of the distillate is a complex mixture, from which only a single compound, $C_4H_6S_3$, has been isolated.

In the next communication (Steinkopf and Kirchoff, Annalen, 1913, 403, 1) is described in detail a form of apparatus, together with the method of working. On the next page is a rough diagrammatic sketch of the apparatus.



The heating chamber consists of a horizontal U-shaped iron tube TT. Each limb of the tube is provided with a worm conveyer or transport screw, whose bearings are made gas-tight. The tube is heated in an air oven, whose temperature is observed by means of three thermometers. "A" is a reservoir for fresh pyrites, and "B" a receiver for the spent pyrites. The rods C C are used to clear the outlet tubes of any pyrites dust which may be carried over. The acetylene is prepared from calcium carbide, and stored in a large gasometer. The gas is washed by passing through water, dried with calcium chloride, and is finally led through a meter into the apparatus. The outlet gases pass through a small iron condenser, which partially condenses them, and then through further condensing apparatus not shown the diagram:- first, a glass spiral immersed/

immersed in a freezing mixture, and then a horizontal tube, 1.5 metres long, filled with porcelain chips soaked in paraffin oil and cooled in ice.

The dimensions of the apparatus are not given in this paper.

The operation of this apparatus may be described briefly as follows:-

The pyrites reservoir is charged with about 10 kg. of very finely powdered ("staubfein") pyrites. The whole apparatus is evacuated and then filled with CO_2 , to expel all air. The burners underneath the tube are lit, and a very slow stream of CO_2 passed until the temperature reaches 260° , when the CO_2 is stopped and replaced by acetylene. The acetylene current is adjusted to about 150 litres per hour (50 litres through the upper inlet tube and 100 through the lower). The temperature is kept between 280° and 310° . When the rate of condensation lessens fresh pyrites is allowed to enter the tube from the reservoir, and is moved along the tubes by careful rotation of the transport screws. The uncondensed outlet gases are burnt.

In this way the authors obtain about 800 gm. of distillate in the course of a day (about 8 hours). Of this a considerable amount is contained in the paraffin oil. The volume of the outlet gases is about one-third of that of the acetylene passed in.

The distillate contains about 40% of thiophen which, by repeated fractionation, may be obtained in a state of purity of about 95%. The specific gravity of this product is 1.040 at 22° , that of pure thiophen at 23° being 1.062. For further purification the authors convert the thiophen to its mercuriacetate derivative, but consider that for ordinary purposes the product of fractionation is sufficiently pure.

In the introduction to this paper Steinkopf and Kirchhoff describe the results of preliminary small scale experiments with glass apparatus, and discuss the possibility of the production of benzene in the process. They find that the reaction commences at a temperature as low as 260° , and that the optimum lies between 280° and 310° . It is pointed out that this temperature is remarkably/

remarkably low when compared with the temperature necessary for the polymerisation of acetylene into benzene. Berthelot found that this begins at the temperature at which glass commences to soften, and that the optimum is between 640° and 650° . Therefore the formation of benzene in this reaction is unlikely. Berthelot also found that only very powerful catalysts like pyrophoric iron can cause any appreciable lowering of this temperature. Steinkopf and Kirchhoff, however, carried out experiments with marcasite (a metastable form of iron disulphide, passing into pyrites when heated to 450°), and with artificial pyrites prepared from ferrous sulphide and sulphur, in order to determine whether any of the impurities present in pyrites were acting catalytically. They found that these varieties of iron disulphide reacted towards the acetylene in exactly the same way as pyrites did; they also found that there was little or no formation of liquid products when the pyrites was replaced by ferrous sulphide.

They were unable to detect benzene in the distillate.

In the third communication (Steinkopf and Schubart, Ann. 428, (1922), is described an improvement in the apparatus, whereby its capacity is increased. The improvement consists of the addition of an electrically driven arrangement to the transport screws, so that these are caused to move through one revolution every 10 minutes. The greater regularity of movement of the pyrites thus achieved enables the acetylene current to be increased to 170 litres per hour (now 100 litres through the upper tube and 70 through the lower), and the rate of distillation is increased to 190 c.c. (previously 100 c.c.) per hour.

The investigation into the nature of the other products of the reaction is described in this paper. The following were identified:-

Carbon, hydrogen, carbon disulphide, methane, 1:3-butadiene, acetone, acetaldehyde, hydrogen sulphide, benzene, 2-thiotolen, 3-thiotolen, 2:3-thioxen, 2-ethyl thiophen, and 3-ethyl thiophen. The authors consider that butane, toluene, xylene, and higher homologues of acetylene are probably present also.

Benzene is now found to be present in very small amount. It was detected in this way: -

29 gm. of the 79-82° fraction (sp.gr. 1.0365 at 16°) were heated with excess of mercuric acetate, which forms a solid compound with the thiophen, and the resulting mixture steam distilled. A small amount of oil came over, most of this being heavier than water. A few drops which floated on the surface were collected. This oil was nitrated and then reduced with tin and HCl. Aniline was shown to be present in the product by means of the test with bleaching solution.

Preparation of Thiophen from Acetylene and Pyrites.

This part of the work was carried out in the Technical Chemistry Department by kind permission of Professor Sir James Walker. I wish also to express my indebtedness to the late Mr Allin Cottrell, Lecturer in Technical Chemistry, in respect of the facilities afforded and of the interest which he took in the progress of the work.

2. Form of apparatus employed.

It was decided to fit up a simpler form of apparatus than that of Steinkopf and Kirchhoff. A diagram of the main part of the apparatus is given on page 20. The apparatus first fitted up was afterwards modified in one or two respects, and in the diagram these modifications are shown by red dotted lines.

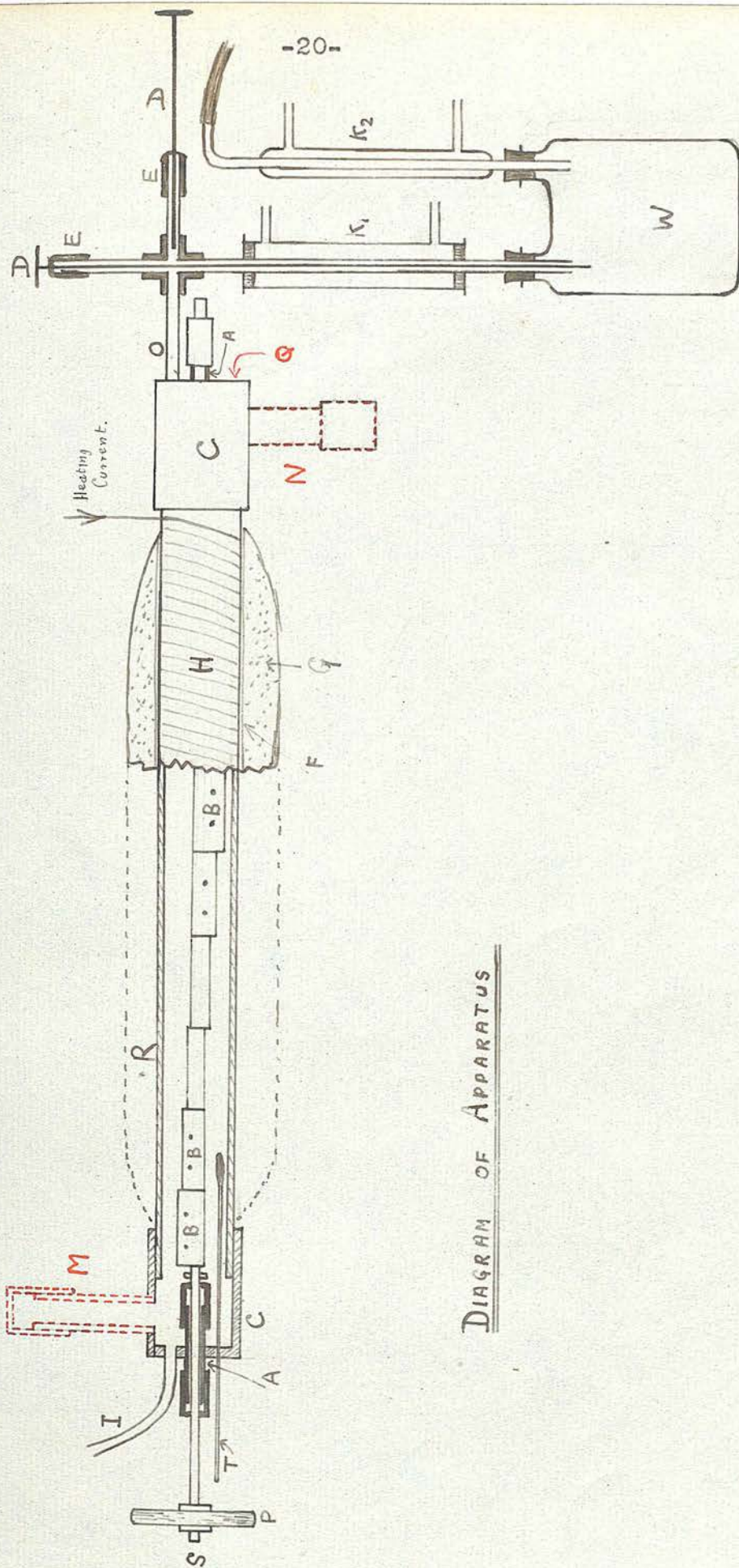


DIAGRAM OF APPARATUS

The apparatus is constructed of iron. In this diagram the left-hand portion of the heating tube "R" is shown in section, and the right-hand portion partly in elevation. The outlet tubes, etc. are in section.

The tube "R" is 2 ft. (76 cm.) long and 3" (7.6 cm.) in internal diameter. It is fitted with a cap "C" at each end, the caps being screwed on externally. In each cap is fitted a gas-tight bearing to carry the stirrer "S". These bearings are made by screwing a piece of $\frac{1}{2}$ " pipe into the centre of the cap; this pipe "A" has a cap screwed on at each end. The rod of the stirrer is $\frac{7}{16}$ " in diameter, and passes through holes in the ends of these caps just big enough to ensure an easy fit. Asbestos thread is wound round the rod so as to fill the space between the end of pipe "A" and the cap; by screwing the caps down the bearing is made gas-tight.

The left-hand cap has also the inlet pipe ($\frac{1}{4}$ " "I" screwed into it, and carries a thermometer "T", fixed by means of asbestos putty. Into the right-hand cap is screwed the outlet pipe "O".

The stirrer consists of a $\frac{7}{16}$ " iron rod, carrying vanes "B". These vanes are of sheet iron about $\frac{3}{64}$ " thick, and are fixed to the rod by bending them round it and clamping them with $\frac{1}{16}$ " bolts. The vanes are parallel to the axis of the rod, but are set at an angle to one another so that they form a spiral. The stirrer carries a pulley "P" so that it can be driven by an electric motor. The arrangements for heating are shown in the right-hand portion of the diagram. Round the tube is wound a layer of asbestos "paper" for electrical insulation. On this is wound a large number of turns of resistance wire ("Nichrome"), spaced about $\frac{3}{8}$ " apart. Leads are taken from the ends of this to the lighting mains, a rheostat being placed in one of the leads so that the current may be varied and the temperature thus controlled. An ammeter is also included in the circuit, and, of course, a switch. "G" is a thick layer of lagging material, consisting of a mixture of magnesium carbonate and asbestos fibre, which is applied in the form of a paste and then allowed to dry.

The/

The outlet pipe "O" leads to a cross-piece carrying 4 pipes at right angles; the object of this arrangement is to allow the outlet to be kept clear of any pyrites dust which may be carried over, as in the apparatus of Steinkopf and Kirchhoff. The rods "D" have asbestos thread wound round them underneath the caps "E"; these bearings are thus made gas-tight.

The condenser "K", is of iron, while "K₂" is an ordinary glass condenser. The Woulff's bottle "W" serves to receive the distillate.

Apparatus not shown in the diagram.

The acetylene was obtained from cylinders (supplied by The British Oxygen Co.). It is first led through a wash-bottle containing water, to remove any acetone, then through a gas-meter and finally through two towers of calcium chloride to the inlet tube "I".

The gases passing out of "K" are led through a spiral of "compo" tubing immersed in ice, then through a horizontal tube 4 feet long, containing porcelain chips soaked in paraffin oil. The gases issuing from this tube are finally burnt by means of a blow pipe, to ensure complete combustion.

The heating tube is supported at each end, by the caps, in a "cradle" of iron strip bolted to two upright posts, which are screwed on to a wooden platform. The tube is held about 3" above this platform, which is placed upon the floor.

The heating current is taken from the 230 volt lighting mains, and at this pressure the current passing through the heating coil is 5 amps. when cold, and about 4.5 amps. when the temperature of the tube is 300°. Thus the resistance of the coil at 300° is 51 ohms. The current necessary to keep the temperature at 300° was found to be about 3 amps., and in order that the current might be taken from the power mains (supplied from a rotary converter in the building giving 100 volts D.C.), the resistance of the coil would require to be reduced to about 30 ohms. In view of the fact/

fact that this alteration would involve considerable trouble, and since the 100 volt supply is available only during a limited part of the day, it was decided not to effect this change. The variable resistance in the circuit had a maximum value of 40 ohms, so that the current could be reduced to 2.5 amps. if necessary. The heating arrangements are not shown in the diagram.

The above is a description of the apparatus in its original form. In using this apparatus, the tube is charged with pyrites by unscrewing one of the caps, removing the stirrer, and pushing in the pyrites by means of a ramrod. This is a very troublesome operation, and for this and other reasons which will appear later, one or two modifications were introduced after a few experiments had been carried out.

Modifications of apparatus.

Provision for renewing the charge without dismantling the tube was made by fitting the caps with 1" pipes "M" "N" as shown in red. The ends of these pipes are closed with caps. A screwing action was imparted to the vanes of the stirrer by giving them a slight twist. To renew the charge, the caps on tubes "M" "N" are removed, and "M" fitted with a funnel. The spent pyrites is ejected via "N" by driving the stirrer with an electric motor, and the fresh pyrites introduced at "M". When fresh pyrites appears at "N" the motor is stopped, cap "N" screwed on, and by careful rotation of the stirrer by hand, any remaining pyrites allowed to enter. The number of turns given by hand is noted, and an equal number then given in the opposite direction, to ensure approximately even distribution of the pyrites along the tube. It was found necessary to drill a small hole at "Q" so that a wire could be introduced to loosen caked pyrites above "N". When the apparatus is in use this hole is closed with a plug of asbestos.

It was found that no condensation occurred in the ice-cooled spiral tube and this was dispensed with.

Pyrites/

Pyrites.

The pyrites used was kindly supplied free of charge, by Messrs J. and J. Cunningham Ltd., sulphuric acid manufacturers, Salamander Street, Leith. From their analysis it contained 2.8% of moisture, and 46.77% of sulphur in a dried sample. Pure iron disulphide contains 53.5% of sulphur. The pyrites contained practically no arsenic.

The pyrites was ground to a fine powder in a ball-mill, and then, in the first two or three experiments, passed through a sieve. As it was soon found that the product, after grinding for an hour or so in the mill, mostly passed a 90-mesh sieve, the process of sieving was discontinued.

Preparation of Thiophen from Pyrites and Acetylene

3. Experiments with the original form of the apparatus.

Five experiments were performed, each occupying one day. For the first three the pyrites charge was not renewed, and one charge also served for the other two. In commencing an experiment, a slow current of CO_2 was passed and the maximum current of 5 amps. sent through the heating coil. During the process of heating up the stirrer was rotated occasionally to make sure that all air had been expelled. When the temperature reached 260° the CO_2 was replaced by acetylene. The time taken for the temperature to/

to reach 300° was found to be about one hour.

The quantities of pyrites and of acetylene used were measured in British units (the pound and the cubic foot respectively), but the corresponding amounts in the metric system are given here.

Experiment No.1.

The tube was charged with 4.1 kg. of pyrites, which passed through a 60-mesh sieve easily. Constant stirring was kept up throughout the experiment.

Duration of experiment	5 hours
Time during which acetylene passed.	4.25 hours
Volume of acetylene used	184 litres
Average rate of acetylene current..	43 litres/hour
Average temperature	300°
Electrical energy used (heating) ..	4.05 kw-hrs.
Volume of distillate (dried).....	30 c.c.;7.05 hr., 16.3/100 Lt.

The amount of electrical energy is an approximate figure, and is obtained from the time and the average reading of the ammeter. The distillate consisted partly of water, which probably came from the moisture in the pyrites. The dried oily portion of the distillate, measuring 30 c.c., was fractionated by means of a column, the following fractions being collected:-

(1)/

- | | | | |
|-------------|----------|---------------|--------|
| (1) To 35°, | 2 c.c. | (5) 85-95°, | 2 c.c. |
| (2) 35-45°, | 2 c.c. | (6) 95-105°, | 5 c.c. |
| (3) 45-82°, | 0.5 c.c. | (7) 105-120°, | 3 c.c. |
| (4) 82-85°, | 8 c.c. | (8) 120-200°, | 3 c.c. |
- Residue, about 5 c.c.

It will be observed that the fourth fraction, which should contain most of the thiophen (b.p. 84°) has the largest volume.

Experiment No. 2.

Pyrites not renewed. Continuous stirring.

Duration of experiment	4 $\frac{1}{4}$ hours
Time during which acetylene was passed..	3 $\frac{1}{2}$ hours
Average temperature.....	325°
Electrical energy used.....	4.31 kw-hrs.
Volume of distillate (dried).....	80 c.c.
	i.e. 22.8 c.c./hr.

The volume of acetylene used was not measured, as the meter was being repaired. In this experiment it was thought that the rate of distillation seemed greater at the higher temperature of 325°, and when the acetylene current was fairly fast, but it is not possible to state the reason for the much increased rate as compared with Experiment 1. The volume of gas passed is not known, and the temperature indicated by the thermometer may not represent the temperature at every portion of the tube.

Fractionation/

Fractionation of distillate:-

- | | |
|----------------------|---------------------|
| (1) To 70°, 4.5 c.c. | (3) 81-86°, 10 c.c. |
| (2) 70-81°, 6.5 c.c. | (4) 86-95°, 7 c.c. |

Experiment No. 3.

Pyrites not renewed. Continuous stirring.

Duration of experiment	6 hours
Time during which acetylene was passed ..	5 hours
Volume of acetylene used	481 litres
Average rate of acetylene current	96 litres per hour.
Average temperature.....	325°
Electrical energy used.....	5.35 kw.hrs.
Volume of distillate (dried)	100 c.c.
Volume of distillate per hour	20 c.c.
Volume of distillate per 100 litres of C ₂ H ₂	20.8 c.c.

In a rough preliminary fractionation, 7 c.c. of liquid boiling between 81 and 86° were obtained.

The process of fractionation at this time was very rough; the column was not a good one and the rate of distillation was too high. In later experiments, the process was much improved, the proportion of the thiophen fraction being greatly increased.

The fractions from 55 - 81° and from 86 - 115° obtained in these three experiments were mixed, and refractionated, under the same conditions as before, with the following results:-

1st Refractionation.

- | | |
|-----------------------|-----------------------|
| (1) To 55° , 3.5 c.c. | (4) 81-86°, 9 c.c. |
| (2) 55-70°, 5.5 c.c. | (5) 86-95°, 11.5 c.c. |
| (3) 70-81°, 10 c.c. | (6) Residue, 11 c.c. |

2nd/

2nd Refractionation. Mixture of above fractions
1, 2, 3, 5 and 6.

(1) To 55°, 3 c.c.	(4) 81-86°, 4 c.c.
(2) 55-70°, 5 c.c.	(5) 86-95°, 10 c.c.
(3) 70-81°, 7 c.c.	(6) Residue, 11 c.c.

3rd Refractionation. Mixture of 1, 2, 3, 5 and 6.

(1) To 55°, 2.5 c.c.	(4) 81-86°, 5 c.c.
(2) 55-70°, 4.0 c.c.	(5) 86-95°, 6 c.c.
(3) 70-81°, 5 c.c.	(6) Residue, 10 c.c.

The total volume of distillate obtained in the first three experiments was thus 210 c.c., from which was obtained 43 c.c. of the thiophen fraction.

Experiment No. 4.

In this experiment more finely divided pyrites was used (passed through a 90 mesh sieve).

The tube was charged with about 4.1 kg. as before.

This experiment was unsatisfactory, as great difficulty was found in keeping the outlet clear. The amount of distillate obtained was extremely small.

Experiment No. 5.

The charge was not renewed. The same difficulty of keeping the outlet clear was encountered, and the amount of distillate obtained was again very small.

The/

The total volume of distillate obtained in experiments 4 and 5 was only 70 c.c., from 438 litres of acetylene, and in 9 hours. Thus we have:-

Volume of distillate per 100
litres of C_2H_2 15.9 c.c.

Volume of distillate per hour. 7.4 c.c.

These figures, and more especially the second, are very much lower than the corresponding figures for the previous experiment. This is probably due entirely to the trouble with the outlet, which trouble was not so evident in the first experiments as coarser pyrites was used.

By modifying the apparatus as described before (page 23) it was considered that this difficulty would be overcome, as the pyrites could be renewed more frequently, so that a smaller charge could be used.

After two fractionations, in the manner described before, a total of 9 c.c. of the 81-86° fraction was obtained from the distillate from Experiments 4 and 5.

From the two fractionations of the paraffin oil extracts from these first five experiments, a total of 11.5 c.c. of this fraction was obtained. The lighter oils were first taken off by placing the porcelain chips together with any oil which had separated from them into a flask, fitting the flask with a condenser and heating it in an air-bath. The results of the fractionation are as follows:-

	1st Fract- ionation.	2nd Fract- ionation.
(1) To 55°	2 c.c.	1.5 c.c.
(2) 55-70°	1.5 c.c.	1 c.c.
(3) 70-81°	2.5 c.c.	2 c.c.
(4) 81-86°	8.5 c.c.	3 c.c.
(5) 86-95°	3 c.c.	3 c.c.
(6) Residue	8 c.c.	6 c.c.

Preparation/

Preparation of Thiophen from Acetylene and Pyrites

4. Experiments with the modified form of the apparatus.

Preliminary notes.

Charging of tube. It was originally intended to renew the charge fairly frequently (every hour or so) but this appeared to be unnecessary.

Using a charge of about 2 kilograms, no trouble was experienced with blocking of the outlet, and very little or no diminution of the rate of distillation occurred towards the end of a "run" of 6-8 hours. As each new charge must be heated up and dried before it can take part in the reaction, it is better to avoid frequent renewal if possible.

Stirring of pyrites. Continuous mechanical stirring in one direction is now, of course, impossible. The screw set on the vanes of the stirrer had been made very slight, in order that it could still be used as a stirrer, with not too frequent reversal of the motor. It was found, however, that occasional hand stirring, to renew the surface of the pyrites, was all that was required.

Eleven/

Eleven experiments were carried out with the apparatus, and on the next page the results of these experiments are tabulated. The results of the fractionation of the distillates are not given in this table, but this process will be described later.

Further notes on the experiments follow the table.

Results of Experiments with Modified Apparatus.

Experiment No.	1	2	3	4	5	6	7	8	9	10	11
Pyrites charge in kg. _____	2.04	1.36	1.81	2.04	2.27	2.27	2.27	2.27	2.27	2.27	2.27
"Mesh" of pyrites (approx.) _____	90	90	90	30	90	90	90	90	90	90	90
Total duration in hours _____	5	4	7.5	6.5	7.75	8.25	8	7.5	9	8	11
Time of passing C_2H_2 in hours _____	4	3	6.5	5.5	6.25	7.25	6.5	6.5	8	7	10
Electrical energy used in kw.hrs. _____	3.84	3.16	5.74	5.07	6.31	6.32	6.50	5.98	6.10	5.52	7.35
Average temperature in $^{\circ}C$. _____	300	300	310	315	325	300	325	325	300	300	300
Volume of distillate in c.c. _____	55	45	136	50	150	175	180	200	235	200	310
Volume of acetylene used in litres _____	226	170	354	326	450	488	510	510	595	495	707
Average rate of C_2H_2 in Lr./hr. _____	56.5	56.6	54.5	59.2	72.0	67.3	78.5	78.5	74.4	70.8	70.7
Volume of distillate /100 L. of C_2H_2 _____	24.4	26.4	38.2	15.4	33.4	35.8	35.3	39.2	39.5	40.5	43.8
Volume of distillate per hour _____	13.7	15.0	20.8	9.1	24.0	24.2	27.7	30.8	29.4	28.6	31.0

Notes on Experiments with Modified Apparatus.

Temperature. It is impossible to draw any definite conclusion, from the above table, as to the effect of varying the temperature between the limits of 300° and 325°, except that it has no very marked effect on the rate of distillation. By occasionally inserting a thermometer into the other end of the heating tube via the outlet pipe, it was found that, at any given moment, the temperature was approximately the same at both ends. Observations made during the course of the experiments seemed to show that the lower temperature of 300° was more efficient. Such observations were made by timing the rate of fall of drops of distillate, and care was taken to have the other conditions as constant as possible during the observations, the other conditions being the rate of the acetylene current and the frequency of stirring. It was found in this way that the efficiency was obviously lowered when the temperature was below 280° or approaching 350°.

Rate of Acetylene Current. A current of about 80 litres per hour seemed to represent the limit of the capacity of the apparatus. In one of the experiments/

experiments (No. 10) the effect of increasing it to 150 litres per hour was tried, for a short time, and this resulted in a very considerable lowering of the rate of distillation. Observations on this were made, as before, by timing the fall of drops.

Condensation of Product. By counting the drops, it was found that about 1/7th of the volume of the liquid collecting in the Woulff's bottle was condensed in the second (glass) condenser. The amount obtained from the paraffin oil scrubber was less than 1/10th of the whole.

Comparison with the results of Steinkopf.

The efficiency of this apparatus improved with experience of its working, but neither its efficiency nor its capacity approaches those of the modified apparatus of Steinkopf. The efficiency attained by Steinkopf (cf. page 18) was 112 c.c. of distillate per 100 litres of acetylene, whereas the maximum efficiency attained with this apparatus, i.e. in Expt. 11, was only 43.8 c.c. per 100 litres. The capacity of Steinkopf's apparatus was such that 170 litres of acetylene could be passed per hour, yielding 190 c.c. of distillate in the same time. The corresponding figures for Expt. 11 are 70.7 litres and 31.0 c.c. per hour, respectively. Various explanations of these differences are possible.

The/

The factors concerned may be (1) quality of pyrites used, (2) quality of acetylene used, (3) regularity of agitation of charge, (4) frequency of renewal of charge, (5) size of the apparatus.

Factors (1) and (2) may almost certainly be discounted. It is possible that more regular stirring might have improved the result to a small extent, as an increase in the rate of distillation could be noticed after stirring.

The question of renewal of the charge was discussed before (page 30). In the second paper in Liebig's Annalen on the subject, Steinkopf and Schubart record the following improvements in the capacity and efficiency of their apparatus accompanying the provision of mechanical means for renewing the charge (cf. page 18):-

Acetylene current increased from 150 to 170 litres per hour, and yield of distillate from 100 to 190 c.c. per hour; yield of distillate per 100 litres of acetylene increased from 66.7 c.c. to 112 c.c.

An alteration in the mode of operation of the apparatus was in the proportions of gas entering via the upper and lower inlet tubes (cf. page 18). The capacity and efficiency of the original apparatus/

apparatus of Steinkopf are more comparable with those of our apparatus.

In one of the above experiments (No. 6) the distillation was very slow during the first three hours. This was found to be due to the fact that the charge had been unevenly distributed in the tube. On effecting a more even distribution, the rate increased at once. From this observation it may be reasonably inferred that a longer heating tube would give better results. As was stated on page 17, Steinkopf and Kirchhoff mentioned no dimensions in their paper. After the conclusion of this part of the work, however, Professor Barger was informed of these dimensions, in a private communication with Herr. Steinkopf. Their tube was 2 metres long in all, and 7 cm. in diameter. The corresponding dimensions of the tube used in the above experiments are 0.76 metre and 7.6 cm. It is probable, therefore, that the main cause of the differences is to be found in the relative lengths of the tubes employed.

The amount of thiophen contained in the product was found to be in the same proportion to the whole as in the experiments of Steinkopf, i.e. about 40%.

Note/

Note on Experiment No. 4. As it is possible that the reaction might not be a surface one (Steinkopf reported no experiments on the degree of division required), it would then be preferable to use coarser pyrites, as less charring of the acetylene would presumably then occur. This experiment was therefore carried out with pyrites of 30 mesh. The results show that a fine state of division is, in fact, required.

Note on Experiments 8-11.

During the last three hours of Expt. 8, the effect of passing dry hydrogen sulphide along with the acetylene was tried. The rate of the H_2S current was about half that of the acetylene. In this experiment the rate of distillation was apparently unaffected, and fractionation of the product showed that the proportion of thiophen was unchanged. In the next three experiments, however, and more especially in the last, it was noticed that the H_2S had an appreciable effect on the rate towards the end of the experiment. This may indicate that in the case of a long experiment like No. 11, a larger charge might be desirable.

Fractionation/

Fractionation of Distillates.

1. Distillate from Experiments 1-4.

The volume fractionated was 250 c.c. The rate of boiling was kept as low as possible.

Below 20°, gas with very penetrating, unpleasant odour.

20-55°, 3 c.c.

55-70°, nil.

70-81°, 15 c.c.

81-87°, 90 c.c. (83-85°, 60 c.c.). This condensate was continuously heavier than water.

The paraffin soaked chips were blown through with steam, and the oil thus obtained (80 c.c.) dried and fractionated; the portion boiling from 81-86° measured only 8 c.c., and was lighter than water.

2. Distillate from Experiments 10 and 11.

Volume, 280 c.c.

To 55°, 5 c.c.

55-70°, 2 c.c.

70-81°, 20 c.c.

81-86°, 108 c.c.

The portion boiling between 86-135° was mixed with the 70-81° fraction and the mixture refractionated, giving a further 33 c.c. of the 81-86° fraction.

3. Refractionation of the total amount of the 81-86° fraction so far obtained.

This and the following fractionations were carried out with a more efficient column, about 30 cm. in length and 1.5 cm. in diameter, filled with glass balls 0.5 cm. in diameter. The liquid was heated in an oil-bath, and the distillation/

distillation kept as slow as possible.
Volume of liquid, 225 c.c. The following fractions were obtained.

To 55°, 0.5 c.c.
55-70°, 3 c.c.
70-82°, 12.5 c.c.
82-84°, 208 gm. Specific gravity of this fraction, 1.030.

The specific gravity of the last portion, of about 50 c.c., was 1.045.

On working up some of the other fractions, a further 35 c.c. of the 82-84° fraction, of specific gravity 1.044, was obtained.

4. Fractionation of distillate from Experiment No.8

This fractionation was done separately in order to determine whether the passage of H₂S had affected the quality of the product.

Volume of distillate, 200 c.c.

To 55°, 2.5 c.c.
55-70°, 1 c.c.
70-81°, 15 c.c.
81-82.5°, 30 c.c.
82.5-84°, 30 c.c. Total, 81-85°, 78 c.c.
84-85°, 18 c.c. Sp. gr. 1.

The proportion of the 81-85° fraction (78/200 = 39%) is almost exactly the same as before (1 and 2 above, 36% and 38.6%). The residue was kept for refractionation.

5. Distillates from Experiments 7,9, 10 and 11.

These were collected together and fractionated in portions of 300 c.c. Their total volume was 925 c.c.

1st portion of 300 c.c.
70-81.5°, 20 c.c.
81.5-85°, 140 c.c.

2nd/

2nd portion of 300 c.c.

70-81°, 17 c.c.

81-85°, 140 c.c.

3rd portion of 325 c.c.

70-81°, 24 c.c.

81-85°, 160 c.c.

The specific gravity of the 81-85° fractions was greater than one.

The portions boiling over 86° from Experiments 7-11 were collected together (measuring approximately 500 c.c.) and the fraction boiling up to 160° (160 c.c.) first taken off in a distilling flask. This portion was mixed with the 70-81° fraction and the mixture refractionated with the column. The following fractions were obtained:-

To 55°, 17 c.c.

55-70°, 5 c.c.

70-81°, 20 c.c.

81-82.8°, 14 c.c.

82.8°-85°, 50 c.c.

The liquid boiling below 82.8° had a specific gravity of less than unity.


The specific gravity of the thiophen obtained in these last five experiments was found to be 1.031. This is not less than the specific gravity of the refractionated product of the preceding experiments (cf. pp. 38 and 39). Hence it was decided not to refractionate the product (whose total volume was 568 c.c.) of these later experiments.

Conclusion.

The total volume of the thiophen fraction obtained from the 16 experiments carried out was 805 c.c. of specific gravity 1.030 at 15°, of which amount 568 c.c. were obtained from the last five experiments.

It/

II. PREPARATION OF THIOPHEN-2-ALDEHYDE.

Thiophenylaldehyde, CHO, is required for the

syntheses of thiophenethylamine and of thienyl-alanine, to be described later. It is therefore proposed to give in the first place an account of the preparation of this aldehyde.

The following methods were tried:-

(1) Method described by Biedermann (Ber. 1886, 19, 636) in the synthesis of thienyl chloride, $C_4H_3S.CH_2Cl$.

(2) Gattermann's method, in which methyl isoformanilide or methoxy methylene aniline, $C_6H_5N:CH(OCH_3)$, is caused to react with the magnesium compound of an aromatic bromo compound.

(3) Gattermann's method, using a mixture of carbon monoxide and hydrogen chloride in the presence of aluminium chloride, and the hydrocarbon. The mixture of gases is supposed to react as formyl chloride, $HCOHCl$, and thus the reaction consists of a modified Friedel Craft synthesis.

(4) Rosenmund's method. Reduction of the acid chloride of thienyl 2-carboxylic acid, $C_4H_3S.COOH$, with hydrogen in the presence of finely divided palladium/

palladium.

Of these methods, Nos. 2-4 have not previously been tried with thiophen.

Gattermann's carbon monoxide method.

(Ann. 1906, 347, 347)

A mixture of carbon monoxide and HCl in the presence of anhydrous aluminium chloride and cuprous chloride, acts on aromatic hydrocarbons (with the exception of benzene) to produce an aldehyde. The mixed gases, in the presence of Cu_2Cl_2 , act as if they had united to give formyl chloride, which has so far not been isolated. The following aldehydes have been prepared by this method:- P-tolyl-, o- and m-xylyl-, mesityl-, pseudocumyl-, diphenyl-, and hydrindene aldehydes, and cuminol. Only one aldehyde group is introduced, and it goes into the p- position to a side-chain. The reaction does not take place in the case of benzene, although benzaldehyde may be prepared by using aluminium bromide in the place of the chloride.

This non-reactivity of benzene is useful when it is desired to prepare the aldehydes of hydrocarbons which are unstable towards AlCl_3 , as benzene can be used as a diluent, other solvents like carbon disulphide being useless as they do not dissolve Cu_2Cl_2 .

Procedure. A wide mouthed vessel with inlet and outlet tubes and a stirrer is used. In it is placed a mixture of the hydrocarbon (diluted with benzene if necessary) and finely powdered AlCl_3 and Cu_2Cl_2 . A mixture of CO and HCl is led in. The temperature varies from 15° to 50° , according to the hydrocarbon used. The mixed gases should contain 33% of HCl by volume. The end of the reaction, which should be reached in 4-8 hours for 50 gm. of hydrocarbon, is generally shown by the thickening of the semi-solid mass, causing the stirrer to stop. The mixture is now carefully decomposed with ice, and both oily and aqueous layers/

layers shaken with saturated sodium bisulphite solution. The aldehyde is recovered from the solid addition product in the usual way.

Gattermann recommends for 50 gm. of xylene, 75 gm. $AlCl_3$ and 8 gm. Cu_2Cl_2 .

The reaction was found not to be applicable to thiophen; in three experiments the following results were obtained.

First Experiment. 12 gm. thiophen were diluted with 10 c.c. of benzene, and 2.5 gm. cuprous chloride added. On adding the aluminium chloride (22 gm.) a violent reaction occurred, and a dark brown solid was produced. This experiment was not carried any further.

Second Experiment. The same quantities of reagents were used, but in this case the dilution was greater, 180 c.c. of benzene being used. This is the dilution employed in the preparation of thienyl methyl ketone by the Friedel Craft reaction (cf. page 57). The aluminium chloride gradually assumed a dark colour, and the mixture became warm before passing any CO and HCl. The stirrer soon became practically completely fixed owing to the formation of a very viscous semi-solid mass, but after the mixed gases had been passed for about 30 minutes this product became more mobile and the stirrer was freed. About 5.5 litres of carbon monoxide, mixed with about half its volume of hydrogen chloride, both gases being dried, were passed; the duration of the experiment was about two hours. The amount of CO theoretically required is about 3.2 litres. The product was a dark brown semi-solid mass, which on treatment with cold water gave a greenish yellow solid. This, together with the benzene layer, was subjected to steam distillation. The benzene and aqueous layers of the distillate were shaken out with sodium bisulphite, this extract made alkaline with Na_2CO_3 , and steam distilled. An ether extract of the distillate left an almost invisible trace of an oil, which possessed a very faint odour of thiophen aldehyde.

Third Experiment. In this case petroleum ether (which is used in the preparation of thienyl methyl ketone) was employed as the diluent, a little benzene/

benzene, however, being added, as the medium for the catalyst Cu_2Cl_2 . 6 gm. thiophen, 80 c.c. petrol, 10 c.c. benzene, and 1.5 gm. Cu_2Cl_2 were mixed, and 11 gm. AlCl_3 added gradually. The CO and HCl were passed for about $1\frac{1}{2}$ hours, and a similar red sticky solid was formed. On adding ice this decomposed to a green cork like solid. No trace of aldehyde came over with steam.

This method is apparently not applicable to thiophen, possibly owing to the action of aluminium chloride on that compound.

Rosenmund's Method.

This method is applicable to many aromatic acyl chlorides, which are reduced by hydrogen in the presence of finely divided palladium to the corresponding aldehyde:-



Procedure. The acyl chloride, mixed with a suitable solvent, is placed along with the catalyst in a round bottomed flask fitted with a reflux condenser. The hydrogen is led in by means of a tube passing down the condenser. A leading off tube, taken from the top of the condenser, passes the outlet gases through water in a flask, into which standard alkali may be measured, so that the HCl produced may be titrated, and the course of the reaction thus followed.

The hydrogen used must be as dry as possible. In the following experiments the hydrogen was obtained from a cylinder, and was purified and dried by passing first through a solution of KMnO_4 , then through KOH, followed by concentrated H_2SO_4 , and finally through phosphorus pentoxide.

The catalyst was prepared by soaking freshly precipitated BaSO_4 in a solution of palladium chloride, drying in an oven at 110° , and placing this product in the reaction vessel with the solvent and the thenoyl chloride, so that the PdCl_2 was reduced to the metal in the first instance. 10 gm. BaSO_4 and 0.2 gm. PdCl_2 were used.

The/

The solvents generally used are benzene, toluene or xylene, or mixtures of these, and the solvent is chosen according to its boiling point. The reaction is carried out at the boiling point of the solvent, so that the mixture is thoroughly agitated, therefore the criterion for choice of the solvent is the optimum temperature for the particular acyl chloride being dealt with. The solvent must be pure (especially must be freed from sulphur compounds, which "poison" the catalyst) and, of course, dry. As a quantity of purified and dried toluene (boiled successively with aluminium chloride and with sodium) was available, this solvent was used in the following experiments.

First Experiment.

Preparation of thenoyl chloride.

This compound has been described before (Jones and Hurd, J. Amer. C.S., 1921, 43, 2444), and boils at 206° , corr. 12.5 gm. thiophenic acid, $C_4H_3S.COOH$, which was obtained as a by-product in the oxidation of acetothienone (cf. page 63), m.p. $121-126^{\circ}$, was boiled with 60 gm. thionyl chloride until evolution of HCl had ceased (about 30 minutes). The product was fractionated, and gave 12 gm. thenoyl chloride, b.p. $200-204^{\circ}$, uncorrected, i.e., 84% theory.

Reduction. 9 gm. acid chloride (b.p. $203-204^{\circ}$ uncorr.), 55 c.c. toluene, and 4 gm. unreduced catalyst were placed in the reaction vessel, and the mixture boiled briskly. A fairly rapid stream of hydrogen was passed, and the outlet gases led into water containing 3 c.c. of 0.734 N. KOH. These first 3 c.c. required about 15 minutes to become neutralised, some of the hydrogen chloride of course being derived from the reduction of the palladium chloride which corresponds to 1.2 c.c. of 0.734 N. KOH. Thus at the beginning the rate of reduction of the acyl chloride corresponded to the neutralisation of 1 c.c. of the KOH in 7 minutes. After a further 5 c.c. had been neutralised, it was found that by adjusting the hydrogen current to the optimum, the rate of neutralisation was about 1 c.c. in 5 minutes. After a total of 15 c.c. had been/

been neutralised, a little water was inadvertently allowed to enter the reaction vessel from the absorption flask. The rate of evolution of HCl then became very rapid, due of course to the hydrolysis of the acid chloride, 1 c.c. of the KOH being neutralised in one minute. In order to determine whether the reduction could be carried on after most of the water had been removed, the hydrogen stream was replaced by nitrogen. After a further 30 c.c. had been neutralised, the evolution of HCl became very slow (10 minutes per c.c. KOH) and the nitrogen was stopped and hydrogen passed again. The rate of evolution became faster again (7 minutes per c.c.) and the experiment was continued until a total of 80 c.c. of the KOH had been neutralised. For complete reduction or hydrolysis of the amount of acyl chloride used 85 c.c. of the KOH would be neutralised. The last 2 c.c. required about 2 hours for neutralisation. The liquid was filtered from the catalyst and the latter washed with ether. The filtrate and washings were first extracted three times by vigorous shaking with sodium carbonate solution, and from this extract 0.9 gm. of the acid were recovered, m.p. 119-124°. The filtrate was then shaken four times with concentrated sodium bisulphite solution, and on acidifying this extract and blowing steam through it 1 gm. of aldehyde was obtained. The toluene had an orange colour, and was dried over Na_2SO_4 and fractionated. 16 c.c. were collected between 90 and 117°; the temperature then rose fairly rapidly to 135°, 6 c.c. collecting over this range, and finally shot up to over 300°, a dark liquid (about 2 c.c.) distilling between 300 and 350°. This was partly soluble in NaOH, and from the solution were obtained about 1.5 gm. of the acid.

Second Experiment.

Preparation of thenoyl chloride.

16.5 gm. thiophen carboxylic acid, 16.5 gm. chloroform, and 50 gm. thionyl chloride, refluxed for 15 minutes, gave 15.5 gm. of the acid chloride, b.p. 203-205°. Yield, 82% theory.

Reduction/

Reduction. 15.5 gm. of the acid chloride, 5 gm. unreduced catalyst, and 50 c.c. toluene were placed in the reaction vessel and the hydrogen passed through the briskly boiling solution as before. The rate of neutralisation of standard alkali in the absorption flask was observed during the course of the experiment. During the first $2\frac{1}{2}$ hours the rate varied between $5\frac{1}{2}$ - 6 minutes per c.c. of 0.734 N. KOH, and during the remaining $7\frac{1}{2}$ hours it gradually decreased to about 11 minutes per c.c. As in the first experiment, water was again allowed to enter the reaction vessel, and the experiment was therefore stopped. A total volume of 82 c.c. of the alkali were neutralised, the volume which would be neutralised if all the acid chloride had been reduced being 145 c.c.

The product was shaken twice, mechanically, with sodium hydroxide solution, the second extract giving no precipitate on acidification. It was then shaken twice with concentrated bisulphite solution, the second extract giving no turbidity on adding excess of concentrated HCl. These last extracts treated with acid and steam distilled gave 1.5 gm. aldehyde. The alkali extracts on acidification gave 5 gm. of thienyl carboxylic acid (confirmed by m.p.). The toluene was noticed to contain a substance with an ester-like smell, and was fractionated, as follows:-

- | | |
|----------------------------------|---------------------------------------|
| (1) To 110° , 22 c.c. | (4) $125-135^{\circ}$, 3 c.c. |
| (2) $110-115^{\circ}$, 19 c.c. | (5) $135-220^{\circ}$, 1 c.c. |
| (3) $115-125^{\circ}$, 2.5 c.c. | (6) Residue, brown
syrup, 0.5 c.c. |

Fractions 1 and 2 on spontaneous evaporation left practically no odour, and probably consisted mostly of toluene. Fraction 3 left the ester-like odour faintly, 4 a strong odour, and 5 contained no or very little toluene. Fraction 6 possessed only very faintly the characteristic smell of thermal decomposition products of thiophen compounds, and had a strong smell of the ester-like compound; on stronger heating it gave a very small quantity of a solid distillate, which was probably the acid. Thiophen carboxylic acid boils at 260° (Stohmann, Kleber. J. pr. [2], 43, 12)

If/

If an ester were present, it is possibly thienyl thienyl carboxylate, formed from thienyl carboxylic acid and thienyl alcohol, which latter might be produced by further reduction of the aldehyde. The formula of this ester would be $C_4H_3S.CO.OCH_2.C_4H_3S$. In order to attempt to discover whether an ester had been formed, and if so, its composition, fractions 5 and 6 were boiled with strong NaOH for a considerable time. The oil went partly into solution, and was separated from the aqueous portion and treated again with NaOH. The two hydrolysates were mixed and washed with ether, and then acidified, giving 0.8 gm. of impure thienyl carboxylic acid. The oil remaining mixed with ether was fractionated, and the main portion boiled under 70° . About 2 c.c. distilled between 70 and 125° , and there was no residue. The first fraction did not give the indophenin reaction, while the second gave a strong colour, and on spontaneous evaporation left a minute amount of the oil with the ester-like odour. There is thus strong evidence for the supposition that an ester was formed, but the nature of the alcohol portion of the ester could not be determined. Thienyl alcohol boils at 207° . It is possible that the alcohol might have been a straight chain one produced by reduction and opening of the thiophen ring, and in this case one would expect the formation of n-butyl alcohol as the most likely; n-butyl alcohol boils at 116.8° . There was insufficient of the oily portion of the hydrolysate for further examination.

The amounts of aldehyde and of acid recovered correspond together to 8.5 gm. of the acyl chloride, of which 7 gm. thus remain unaccounted for. Calculating from the 82 c.c. of standard alkali neutralised by the HCl evolved, the amount of the acid chloride reduced was 8.75 gm., and the yield of aldehyde, assuming that the experiment might have been carried on until all was reduced, is 22% of the theoretical.

This method is evidently of no practical use for the preparation of thiophen aldehyde.

Gattermann's /

Gattermann's method - reaction of aromatic organo-magnesium compounds with methyl isoformanilide.

(Ann. 1912, 393, 215)

In this paper Gattermann describes two methods for the preparation of aromatic aldehydes from organo-magnesium compounds.

In the first of these methods, an ether solution of the magnesium aryl halide is added slowly, and with cooling, to an ethereal solution of ethyl formate. A vigorous reaction follows, and when this is finished the mixture is acidified with hydrochloric acid, with cooling. The ether and excess ester are now removed on the water bath, and the crude aldehyde driven off with steam.

The second method is similar, but in this case the ethereal solution of methyl iso-formanilide is added drop by drop to the boiling ethereal solution of the magnesium aryl halide. The solid reaction product is decomposed with dilute HCl, with cooling, and the aldehyde thus set free removed with steam.

Examples of the aldehydes which Gattermann has prepared by these methods are:-

p-xylyl aldehyde, with ethyl formate, yield 45%.

1:4-xylyl-5-bromo-2-aldehyde, ethyl formate, 10%.

o-ethoxybenzaldehyde, ethyl formate, 30%.

Thianisaldehyde, methyl iso formanilide, 60%.

This aldehyde could not be prepared successfully with formic ester.

p-thiophenetol aldehyde, emthyl iso formanilide, 32%.

Naphthaldehydes, emthyl iso formanilide, 40-50%.

Thiophen aldehyde, ethyl formate, 15%.

Monobromothiophen aldehyde, ethyl formate, 10%.

These yields are mostly fairly good, but are very poor in the cases of the two thiophen compounds. It was not stated in the paper whether the preparation of thiophen aldehyde had been tried with methyl iso formanilide. It was therefore decided to attempt the preparation of this aldehyde by means of this modification of the method.

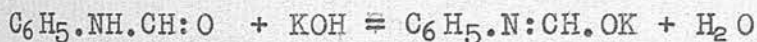
Preparation/

Preparation of the Reagent.

Comstock and Kleeberg (J. Amer. Chem. Soc. 1890, 12, 497) describe the preparation of methyl iso formanilide, or methoxy methylene aniline, $C_6H_5.N:CH.OCH_3$, by the action of methyl iodide on the silver salt of isoformanilide. Their directions were carried out as follows.

Formanilide was prepared by refluxing aniline with 1.25 mols. of 100% formic acid, the yield being 90% of theory (if 50% acid were used, the yield was only 75%), after distilling off the product under diminished pressure; at 15 mm. it boiled between 171-173°.

Formanilide, when dissolved in potassium hydroxide solution, undergoes an isomeric change, with the formation of the salt of the isomeric compound, thus:



The formanilide is dissolved in 50% alcohol, and treated with slightly less than the equivalent amount of KOH dissolved in 50% alcohol. A 50% alcoholic solution of the equivalent quantity of silver nitrate was now added slowly, with stirring, and a white precipitate of the silver salt, $C_6H_5.N:CH.OAg$, was produced. Excess of alkali must be avoided as this causes the silver salt to blacken rapidly.

The silver salt was treated with the equivalent of methyl iodide, and sufficient dry ether added to form a thick paste, and the mixture left overnight. The mixture became more fluid, and the white silver formanilide gave place to the pale yellow silver iodide. The liquid was filtered off, the silver iodide washed with dry ether, and the filtrate and washings fractionated. The yield of methyl iso formanilide, b.p. 195-198°, was 65% of the theoretical. Unless the silver salt were thoroughly washed and dried, it was found that the product of the reaction with methyl iodide was not methyl iso formanilide, but an unknown liquid which boiled over 230° and smelt strongly of isonitriles.

Preparation/



Preparation of thienyl magnesium bromide.

In the bromination of thiophen, which reaction takes place readily in the cold and in the absence of any catalyst, it is impossible to introduce one bromine atom quantitatively into the molecule. It is found that there is a great tendency for two atoms to be introduced.

To overcome this difficulty, Gattermann recommends that the di-bromo compound be first prepared, and one of the bromine atoms then be removed by means of the Grignard reaction; one atom of magnesium is added to the di-bromo compound dissolved in dry ether and the bromothiophen magnesium bromide thus obtained decomposed to the mono-bromo thiophen by means of dilute HCl. In this way Gattermann obtains a yield of about 70% of theory, calculated on the amount of thiophen taken. Steinkopf (Ann. 1921, 424, 62) was unable to obtain this yield.

Töhl and Schütz (Ber. 1894, 27, 2835) report "satisfactory" yields of monobromothiophen by adding slightly less than the theoretical amount of bromine for substitution of one atom to thiophen diluted with five times its volume of glacial acetic acid. These authors thus obtain a yield of 28.5% theory.

One experiment in which the theoretical amount of bromine (2 atoms) to give the mono-substitution product was taken was tried. 19 gm. of thiophen were treated in the cold, slowly, and in the presence of aluminium-mercury couple (this was found later to be unnecessary) with 38 gm. bromine, under reflux. The reaction was very vigorous. The product was shaken with dilute NaOH to remove HBr, the oil washed with water, separated, dried, and distilled. There were two main fractions, one boiling between 145-160°, and the other between 190-220°, the amounts of these fractions being 5 gm. and 10 gm. respectively. The lower fraction probably consisted mostly of monobromo thiophen, which boils at 150°, and the other of the dibromo compound which boils at 210°. The second fraction was dissolved in dry ether and treated with 0.75 gm. (1 atom) of magnesium, which dissolved slowly, giving a green solution. This was treated with dilute HCl, the oil separated, dried/

dried, and distilled, and 2.5 gm., boiling between 150-160°, were obtained. The total yield of bromo thiophen obtained, 7.5 gm., is 20% of the theoretical.

Second Preparation. 20 gm. of thiophen were treated slowly with 80 gm. of bromine, in the absence of any catalyst. The reaction took place readily with the evolution of HBr. The resulting red liquid, was shaken with NaOH, washed, and dried. On attempting to distil a small portion, it became very dark in colour, and HBr was evolved. The main portion was treated with boiling alcoholic potash for some time, water added, the alcohol removed and the oil extracted with ether, and dried. On attempting to distil, it again became dark in colour, and HBr was evolved. It was shaken with NaOH again, and this time completely distilled, but still contained HBr. The distillate weighed 40 gm. and was left overnight in contact with potassium carbonate. On redistilling, no HBr came off, and the final yield was 31 gm., i.e. 54% of theory. It boiled between 200-215°. Converting it to the monobromo compound as before, 12 gm. of the latter, b.p. 150-160°, were obtained, i.e. 31% theory on the 20 gm. of thiophen used. Steinkopf and Otto (Ann. 1921, 424, 62) were also unable to obtain yields of bromothiophen approaching those of Gattermann.

In three other experiments the HBr, which would seem to be combined in some way with the dibromo compound, was removed by steam-distilling from a concentrated aqueous solution of NaOH, in one case this operation having to be repeated. The average yield of dibromo thiophen was 60%; the yield of monobromothiophen was 31%, calculating from the amount of thiophen used. The thiophen employed in these preparations was obtained commercially, and was supposed to be pure.

The thienyl magnesium bromide was prepared as required by dissolving the equivalent amount of magnesium in the ethereal solution of the monobromo compound, and was, of course, immediately treated with the methoxy methylene aniline.

Preparation /

Preparation of Aldehyde.

1st Experiment. 6.5 gm. of monobromo thiophen were dissolved in 22 c.c. dry ether and warmed with 1 gm. of magnesium. When all the metal had disappeared, giving a green solution which later became red, the latter was treated slowly with 5.8 gm. methyl isoformanilide dissolved in ether. After all had been added, the mixture was kept boiling for an hour, and then treated with water and dilute HCl. The mixture, which was very dark in colour, was extracted with ether, the extract evaporated, and the residue shaken with concentrated bisulphite solution. After thorough shaking, the dark coloured mixture was washed with ether, giving a clear yellow solution. This was made strongly acid and extracted with ether, the extract dried and distilled, giving 1.25 gm. of the aldehyde, b.p. 180-190°. The yield is 28% of theory, on the amount of bromo thiophen taken. It may, of course, contain bromo thiophen.

2nd Experiment. 15 gm. monobromo thiophen were dissolved in dry ether and boiled with 2.2 gm. of magnesium. The metal did not dissolve completely. On addition of a little fresh magnesium, some of this dissolved. Addition of magnesium was therefore continued until there was no further action. The Grignard solution was decanted from excess metal, which was washed by decantation with ether. To the decantates were added slowly 13 gm. methyl isoformanilide dissolved in ether. A reaction sufficiently vigorous to cause the ether to boil ensued, and the colour of the solution changed from dark green to light red, and a yellowish solid was precipitated. The mixture was kept boiling for 2 hours. It was then decomposed with water and HCl and steam distilled. The oil was shaken with concentrated bisulphite solution, the resulting solution washed with ether, which left about 1 gm. of an oil. Excess of NaOH was added to the solution, and the aldehyde steam distilled off, yield 2 gm., b.p. 190-200°, i.e. 19.5% theory on the amount of bromo thiophen taken.

3rd/

3rd Experiment. The yields obtained in the first two experiments are very poor. As it was possible that the reaction with methoxymethylene aniline might proceed better with bromo thiophen magnesium bromide, the following experiment was tried, using dibromo thiophen. It was intended that the remaining bromine atom would then be removed by means of the Grignard reaction, or at a later stage of a synthesis in which the aldehyde was to be employed, by reduction.

17 gm. of dibromo thiophen were dissolved in dry ether and treated with 1.7 gm. of magnesium, which did not dissolve completely. The Grignard solution was treated with the methyl isoformanilide as before, and the temperature rose slightly. The mixture was boiled for $\frac{1}{2}$ hours, decomposed with dilute HCl, and steam distilled. The ether extract of the distillate was treated with concentrated bisulphite solution, which dissolved most of the oil, and the solution washed with ether. Thus was obtained a mixture of aldehydes boiling between 190-225°, and weighing 3.5 gm.

Thus the yields are similar to those obtained by Gattermann with the formic ester method, in the case of the methyl isoformanilide reaction itself, although the yield of monobrom-thiophen prepared via the dibromo compound was less than half that recorded by Gattermann.

Benzaldehyde.

The preparation of benzaldehyde from bromobenzene had been undertaken before the experiments with thiophen, in order to become familiar with the reaction. The yield of benzaldehyde obtained was quite satisfactory. From 15.7 gm. of bromobenzene were obtained 6 gm. of benzaldehyde, b.p. 176-182°, i.e. 56.5% of theory.

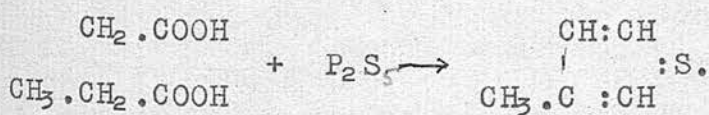
This method was not proceeded with any further, being evidently of no practical use for the preparation of thiophen aldehyde in quantity. For this purpose the first of the four methods enumerated on page was employed.

Constitution/

Constitution.

Acetothienone is the starting point of all the syntheses which follow, and it might therefore be desirable to give in the first place a short note on the constitution of this compound, as regards the position of the side-chain relative to the sulphur atom.

This is determined by a consideration of the two carboxylic acids, one of which is obtained by a complete oxidation of the side-chain in acetothienone, prepared by means of the Friedel Craft reaction (cf. Hollemann and Voermann, Proc. K. Akad. Wetensch. Amsterdam, 1907, 9, 514; Abs. 1907, 1, 334). The other acid is prepared (Muhlert, Ber. 1885, 18, 3003) by oxidation of the methyl thiophen obtained by the action of phosphorus pentasulphide on methyl succinic acid. This methyl thiophen must have the CH₃ group in the β-position to the sulphur, thus:-



The side-chain in acetothienone must therefore be in the α-position to the sulphur atom. The two acids are distinguished by their melting points, the α-acid melting at 126.5° (Nahnsen, Ber. 1884, 17, 2646) and/

and the other at 136° (Muhlert), and also by their solubilities. The saturated solution of the α -acid is 0.00445 N. at 21° , the β -acid being about ten times as soluble, its saturated solution at $15-18^{\circ}$ is 0.0346 N. (Meyer, Ann. 236, 208).

Biedermann's synthesis of thienyl chloride (cf. page 42) includes the preparation of thienyl aldehyde, thus:-

1. Thiophen with acetyl chloride and AlCl_3 , gives
 $\text{C}_4\text{H}_3\text{S.CO.CH}_3$.
2. Acetothienone with alkaline KMnO_4 gives
 $\text{C}_4\text{H}_3\text{S.CO.COOH}$.
3. Thienyl glyoxylic acid, heated alone, CO_2 evolved gives
 $\text{C}_4\text{H}_3\text{S.CH:O}$
4. Thienyl aldehyde, Cannizzaro reaction, gives
 $\text{C}_4\text{H}_3\text{S.CH}_2.\text{OH}$.
5. Thienyl methyl alcohol, with dry HCl , gives
 $\text{C}_4\text{H}_3\text{S.CH}_2.\text{Cl}$.

Biedermann describes the first three of these stages as follows:-

Stage 1. 50 gm. thiophen and 55 gm. acetyl chloride are dissolved in 500 gm. petroleum ether. With vigorous shaking, 160 gm. of AlCl_3 are added during 30 minutes to 1 hour. Brisk evolution of HCl takes place, and the double compound of acetothienone and AlCl_3 is thrown to the bottom of the vessel. The flask is now warmed until evolution of HCl has almost ceased, and the ether removed by decantation. The ether is treated with 5 gm. acetyl chloride and 50 gm. AlCl_3 . The solid reaction product is decomposed with cold water or better, with ice, and the ketone driven off with steam. The aqueous layer of the distillate, which contains a fair amount of the ketone in solution, is/

is extracted with ether and dried with CaCl_2 and distilled. The methyl thienyl ketone boils at 213° , and the yield is 90% of theory.

Stage 2. 12 gm. of the ketone are shaken with a solution of 50 gm. KMnO_4 and 12 gm. NaOH in 4 litres of water, until the colour, at first purple and then green, has completely disappeared. The alkaline solution is filtered from MnO_2 , and the filtrate acidified and extracted with ether. The thienyl glyoxylic acid is thus obtained, contaminated with unchanged ketone. To purify, the acid is dissolved in NaOH and the solution washed with ether. The acid is obtained on adding HCl as an oil which slowly solidifies.

Stage 3. The acid is subjected in portions of 5 gm. to dry distillation. To prevent possible oxidation of the aldehyde, this operation is carried out in an atmosphere of CO_2 . Partial carbonisation occurs, and a half crystalline, half oily distillate comes over. To remove any thienyl carboxylic acid and unchanged thienyl glyoxylic acid, the product is treated with aqueous NaOH . The brown mobile oil which is left is dissolved in ether, dried with CaCl_2 , and fractionated. A clear yellow liquid distils at 198° , this being the aldehyde, and the yield is less than 50% of theory. The aldehyde resembles benzaldehyde in its odour and in that it slowly oxidises to thienyl carboxylic acid on exposure to air.

It is possible to eliminate the second of these stages in the manner described by Steinkopf and Wolfram, Ann. 1924, 437, 27. To do this the Friedel Craft reaction is carried out with thiophen, AlCl_3 and ethyl oxalyl chloride, Cl.OC.CO.OEt . Thus is obtained thienyl glyoxylic ester, b.p. 263° , from which the acid may be obtained. Crystallised from benzene, the acid melts at 92° . The ethyl oxalyl chloride is, however, exceedingly troublesome to prepare, and this method was therefore not attempted.

α -Thienyl methyl ketone. Twelve preparations of this compound were carried out. The results of these preparations are tabulated on next page.
Prep./

Prep. No.	Weight of thiophen used in gm.	B.P. of product in °C. (un-corrected)	Percentage yield.
1	10	-	60
2	20	206-209	68
3	-	-	68
4	50	208-216	77
5	-	-	70
6	15	210-220	62
7	50	206-214	65
8	50	206-214	59
9	50	209-220	69
10	50	205-215	67
11	50	206-216	78
12	100	206-218	82

Preparations 1-5 were made with thiophen obtained commercially, and the others with the product of the synthesis which has been described. Preparations 1-9 were carried out in the manner described by Biedermann (cf. page 57): in the remaining three the procedure was modified as follows:-

Instead of adding the aluminium chloride to the petroleum ether solution of thiophen and acetyl chloride, the $AlCl_3$ was placed in a flask along with some of the ether, and the thiophen and acetyl chloride, dissolved in the remainder of the ether, added. It was found that the yield was improved by adding this solution fairly rapidly. The mixture was stirred vigorously by mechanical means. Taking the last preparation as an example, 320 gm. of $AlCl_3$ and 1200 c.c. of petrol were placed in a flask and stirred well. 100 gm. of thiophen and 110 gm. acetyl chloride dissolved in 400 c.c. petrol were added during 1 hour. A semi-liquid brown mass was formed at the bottom of the flask. The operation was, of course, carried out under reflux. The product was left overnight, and boiled gently until most of the HCl had been driven off. The ether was removed by decantation, and the semi-liquid mass decomposed with cold water, the ketone removed with steam, and the distillate extracted with ether. The extract was then dried and fractionated.

Preparation/

4

Preparation of α -thienyl glyoxalic acid, and of
 α -thienyl aldehyde.

The thienyl glyoxylic acid prepared by the method described on page 58 is impure, containing small amounts of thienyl carboxylic acid, and varying amounts of water, depending on the length of time for which it is dried; thienyl glyoxylic acid forms a monohydrate, which slowly loses its water of crystallisation on keeping over concentrated sulphuric acid, giving the anhydrous acid (m.p. 92° after crystallisation from benzene). For conversion to the aldehyde by destructive distillation careful purification is unnecessary, therefore in order to examine the efficacy of any particular modification of the oxidation, the yield of the acid was not used, but that of the aldehyde, calculated on the amount of ketone from which the acid had been prepared, was employed to make this comparison. A sample of pure acid was, however, prepared by recrystallisation of the crude acid from benzene, and was found to melt between $89-91^{\circ}$. On conversion of this to the aldehyde by the most efficient method of decarboxylation, the yield of the aldehyde was found to be 80% of theory calculated/

calculated on the amount of pure acid used. Thus, by comparing the yield of aldehyde obtained from any particular sample of the crude acid with this 80% yield from the pure acid, the percentage of acid in the sample, and thus the efficacy of the particular modification of the oxidation employed in its preparation, may be estimated.

The decarboxylation of the acid was also carried out in different ways; in comparing the results of these the yields from a particular sample of the acid were compared.

Thienyl glyoxylic acid. The preparation of this compound according to the method of Biedermann is troublesome, in view of the large amount of water employed (4 litres in the oxidation of 12 gm. ketone). The acid is fairly soluble, and the extraction with ether is therefore tedious. Several experiments were carried out, using higher concentrations, the permanganate, however, being added in portions, so that its concentration did not rise above that recommended by Biedermann. The results of these experiments are now given.

1st Experiment. 12 gm. ketone were added to 500 c.c. water and the mixture stirred vigorously to form a suspension. An almost saturated solution of/

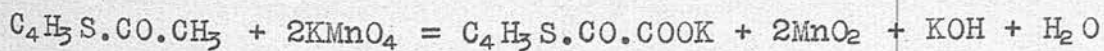
of KMnO_4 (50 gm. in 800 c.c. water), containing 12 gm. NaOH , was added slowly to the stirred suspension, the addition occupying $1\frac{1}{2}$ hours. At first the temperature rose to about 35° , but the mixture was immediately cooled. The solution was allowed to stand for 24 hours, and filtered from MnO_2 . The filtrate was dark green, and was decolorised with SO_2 and refiltered. The filtrate was acidified, there being copious evolution of CO_2 , and extracted with ether. The weight of crude acid obtained, after drying in vacuo over H_2SO_4 for 24 hours was 10.5 gm.

2nd Experiment. The concentration was further increased. 20 gm. ketone were suspended in 800 c.c. water, and 75 gm. KMnO_4 were added in portions, each portion being allowed to become decolorised before addition of the next. A solution of 20 gm. NaOH in a little water was added gradually at the same time. The temperature rose to 40° during the early stages. The weight of crude acid obtained was 14 gm.

13 gm. of a mixture of these preparations were heated in a sealed tube as described below (in this case, however, the alkalified product from the tube was not steam distilled, the aldehyde being merely extracted from it and fractionated) and gave 5 gm. of the aldehyde, b.p. $82-86^\circ$ at 19 mm.

13 gm. of pure acid would give 7.5 gm. of the aldehyde (yield 80%); the percentage of pure acid in the above sample is therefore $5/7.5$ of 100, i.e. 67%. This figure, however, may tend to be high as the aldehyde had not been steam distilled.

3rd Experiment. For the oxidation of 12 gm. of the ketone, according to the equation:-



The amount of KMnO_4 required is 31 gm. Thus the amount recommended by Biedermann (50 gm.) is in large/

large excess of the theoretical quantity. In this experiment the theoretical amount was used. The concentration was again increased, but the temperature was not allowed to rise above 20°. 60 gm. ketone were suspended in a solution of 60 gm. NaOH in 1500 c.c. of water. 150 gm. KMnO_4 (Biedermann would take 250 gm.) was added slowly. On acidifying the filtrate, there was copious evolution of CO_2 , and a small white precipitate was formed. This was filtered off and dried, and was found to have the appearance of benzoic acid. It melted between 121-125°, and is probably thiophen α -carboxylic acid, which melts at 126°, and which is much less soluble than thienyl glyoxylic acid. It weighed 8 gm. The yield of crude thienyl glyoxylic acid after 36 hours drying over H_2SO_4 was 52 gm.

30 gm. of this product by the sealed tube method gave 12 gm. of the aldehyde, b.p. 195-198°. Allowing for the 8 gm. of thiophen carboxylic acid isolated, the product of this oxidation contains 48% of pure thienyl glyoxylic acid.

4th Experiment. 45 gm. ketone and 45 gm. NaOH dissolved in a little water, were placed in burettes. Into a heavy glass beaker were put 100 c.c. water and 100 gm. of ice. The contents of the beaker were stirred and 115 gm. KMnO_4 (theoretical amount), 800 gm. ice, the ketone and the NaOH solution were all slowly added in approximately equivalent proportions. Thus the concentration of ketone and of permanganate, were not allowed to become too high. Until all the ice had been added, there was very little precipitation of MnO_2 , but the colour of the permanganate disappeared and gave place to the green colour of the manganate (tested by allowing a drop to run into filter paper). After all the ice had been added, the temperature rose gradually to 26°, the addition of KMnO_4 , of ketone, and of NaOH having been completed as well. The stirring was continued for another hour, when the green colour had almost disappeared. Solution left overnight, and filtered. The filtrate was extracted with ether, giving 0.5 gm. of ketone. The solution was acidified and extracted with ether. After drying for 24 hours over H_2SO_4 in vacuo, the crude product weighed 45 gm.

Before/

Before converting this preparation to the aldehyde, it was partially purified. 40 gm. were dissolved in NaOH, and the solution, which was dark brown, was boiled with animal charcoal and filtered. The filtrate was washed with ether, the dissolved ether removed, and the solution acidified. There was a precipitate, which was filtered off and dried. It was apparently thiophen carboxylic acid, for it distilled unchanged and melted between 118-125°, and it weighed 14 gm. The filtrate was extracted with ether. After 48 hours drying over H₂SO₄ in vacuo the partly purified product weighed 25 gm.

12.5 gm. of this product gave 5 gm. aldehyde, b.p. 195-198°. This partially purified acid therefore contains 70% of thienyl glyoxylic acid. Before the above purification the acid obtained in this oxidation therefore contained 44% of thienyl glyoxylic acid.

5th Experiment.

25 gm. ketone, 500 c.c. water, 500 gm. ice, and 25 gm. NaOH were placed in a vessel surrounded by a mixture of ice and salt. The theoretical amount of KMnO₄, 64 gm. was added during two hours, and the temperature was not allowed to rise above -5°. The mixture was kept in the freezing mixture for about 2 hours after all the permanganate had been added, and then left overnight. The MnO₂ was filtered off and washed, and the filtrate and washings washed with ether, which left about 1 gm. of the ketone. The dissolved ether was driven off, and the solution acidified after cooling. There was no precipitate, but a small amount of CO₂ was evolved. The solution was extracted with ether. The weight of crude partially dried acid was 25 gm.

12.5 gm. of this product gave 3.0 gm. of aldehyde, and hence contains 42% of pure thienyl glyoxylic acid.

This it is evident that the process is not improved by prevention of rise of the temperature. The experiments reported below were carried out at dilutions approximating to those of Biedermann, and the results are much improved over the above. The reason for this may be that the concentration of thienyl glyoxylic acid becomes so high that it is oxidised preferentially to the ketone.

6th/

6th Experiment. 9 gm. ketone, 9 gm. NaOH, and 24 gm. KMnO_4 (theoretical) were shaken up with 3 litres of water, and left overnight. The solution was filtered off, and neutralised, evaporated to a small volume and acidified and extracted with ether. After drying for several days in vacuo the acid weighed 11.5 gm. This particular preparation was recrystallised from benzene, and 5.5 gm. of the pure thienyl glyoxylic acid, m.p. $88-90^\circ$, were thus obtained. The mother liquors gave, on evaporation of the solvent and heating the residue in a sealed tube with glacial acetic acid, 1.5 gm. aldehyde, b.p. $196-200^\circ$, corresponding to 2.6 gm. of thienyl glyoxylic acid. Thus the original product of this oxidation contained 70% of thienyl glyoxylic acid.

7th Experiment. This was carried out in the same way as the last, with 36 gm. ketone and the theoretical amount of permanganate, the volume of water being 12 litres. The product was again purified by crystallisation from benzene, and the yield was 28 gm. The mother liquors yielded 5 gm. of aldehyde, and the total amount of pure acid obtained in this oxidation is therefore 36.5 gm. The weight of crude acid is not recorded.

8th Experiment. From 36 gm. ketone, as in the last experiment, were obtained 41 gm. of crude acid. 14.25 gm. of this gave 7.0 gm. of aldehyde, and thus the product contains 85% of thienyl glyoxylic acid.

9th Experiment. In this case the concentration used was about double that recommended by Biedermann. From 66 gm. ketone were obtained 67 gm. of crude acid, 30 gm. of which gave 12.5 gm. of aldehyde. Thus the product of this oxidation contained 73% of thienyl glyoxylic acid.

10th Experiment. Concentration $1\frac{1}{2}$ times that given by Biedermann. 40 gm. ketone gave 42 gm. crude acid, 27 gm. of which gave 10.8 gm. aldehyde. The crude product hence contains 70% of thienyl glyoxylic acid.

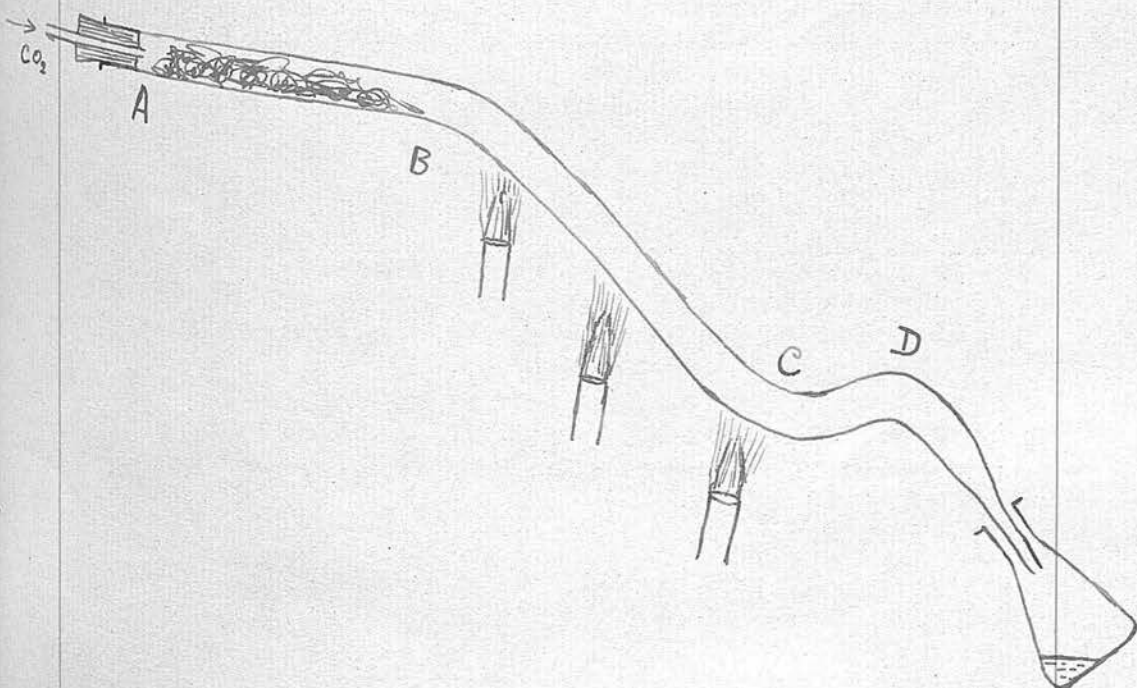
From/

From these results it may be taken that the concentrations used by Biedermann may be approximately doubled without detriment to the quality of the product, but that concentrations of approximately the order of tenfold lead to serious degree of oxidation of the thienyl glyoxylic acid, the yield of this being decreased by nearly one half.

Other oxidations were conducted at the lower concentrations.

Preparation of α -thienyl aldehyde.

The first method used, that described by Biedermann, consisted in heating the thienyl glyoxylic acid in a small distilling flask, in portions of 5 gm. This was obviously unsatisfactory, as a large amount of charring always occurred. The method was modified slightly, by using a form of apparatus represented in this sketch:



The tube is of hard glass, and is about 700 cm. long and 1.5 cm. in diameter. The slightly inclined portion A-B forms a reservoir for the acid, small amounts of which can be melted and run down to be heated and decomposed in the portion B-C. The portion C-D is inclined in the opposite direction to B-C to prevent undecomposed acid from entering the receiver R. A slow current of CO₂ is passed during the experiment.

The method finally used, however, consisted in the heating of the acid with glacial acetic acid in a sealed tube to about 200° for about 2 hours. It was found in the first method, in which the flask was heated in an oil bath, that the temperature necessary was about 200°, which incidentally approximates to the boiling point of the aldehyde. The effect of heating in the sealed tube to a higher temperature than 200° (225°) was found to consist of a decreased yield of the aldehyde. The time necessary was found by cooling and opening the tube after a certain time, driving off all the dissolved CO₂ by warming, and then resealing and reheating. If the original time of heating were 2 hours or longer, no further amount of CO₂ was liberated on opening the tube after the second heating.

The aldehyde was isolated from the product by neutralising the contents of the tube with alkali, and driving off the aldehyde with steam, extracting the distillate with ether, drying, and fractionating.

The average yields of aldehyde obtained by the first modification of the first method, the second modification, and by the second method, calculated on 50 gm. of crude glyoxylic acid (prepared by oxidation of the ketone in dilute solution) are as follows:-

- (1) 9 gm. (2) 12 gm. (3) 18.5 gm.

The first of these figures is an estimate, as the product of the decarboxylation by the first modification was not steam distilled in every case.

Modifications of the second method were tried, by heating the acid (1) with naphthalene, (2) with diphenyl methane, at ordinary pressure, under reflux/

reflux, to the boiling point of the solvent. Naphthalene boils at 218° and diphenyl methane at 262° . In both cases the temperature employed was about 200° . The aldehyde was isolated from the hydrocarbon solution by shaking mechanically three times with concentrated bisulphite solution. The yields obtained were poor, being of the same order as those in the case of the first modification of the dry distillation method.

Thienyl Chloride and Thienyl Alcohol.

The first synthesis of thienyl ethylamine attempted involved the preparation of thienyl methyl chloride. The preparation of this from thiophen aldehyde has been described by Biedermann (cf. page 42), the aldehyde being first converted to the corresponding alcohol by means of the Cannizzaro reaction. Two other methods for the preparation of thienyl methyl chloride were investigated, one of these being a direct synthesis in one step of this substance from thiophen, and the other a preliminary synthesis of the alcohol, from the magnesium compound of thiophen bromide.

The second of these methods consists in the action of formaldehyde on Grignard reagents, and is described by Ziegler, Ber. ¹⁹²¹ 54B, 737, as follows:

By/

"By passing the vapours of dry-distilled, i.e. depolymerised, trioxymethylene into vigorously stirred Grignard solutions, the action of the formaldehyde is greatly simplified. The trioxymethylene was dried for 1-2 days in vacuo over P_2O_5 . 1.5 to 2 times the calculated amount was distilled into the well stirred Grignard solution, which was cooled in ice. From 80 gm. of bromobenzene, 12 gm. of Mg, and 25 gm. of trioxymethylene were obtained 38 gm. of benzyl alcohol. Similarly, from 64 gm. of α -naphthol bromide were obtained 28 gm. of α -naphthyl methyl alcohol."

Benzyl Alcohol.

A modification of this method was first tried with bromobenzene. 1.7 gm. (1 mol.) of Mg was dissolved in 11.5 gm. of bromobenzene in dry ether. This Grignard solution was not treated with the vapours of trioxymethylene, but was boiled with the dry powder (dried for 6 days in vacuo over H_2SO_4), 3.3 gm. or 1 mols. being used, for 30 hours. The reaction product was a thick syrup of a greenish colour. On treatment of this with dilute HCl it was partially decomposed. The resulting solution was extracted with ether. From the extract was obtained 2 gm. of benzyl alcohol, b.p. 200-210°. The corresponding yield obtained by Ziegler was 5.5 gm.

This procedure was now carried out with bromothiophen. 12 gm. of this were dissolved in ether and treated with 1.8 gm. of Mg, which dissolved completely to give a brown solution. This was boiled for 9 hours with 2.2 gm. of trioxymethylene (corresponding to 1 mol. of formaldehyde). After this time the ethereal solution had no smell of formaldehyde, and a dark brown, sticky deposit had formed. This was decomposed with HCl, the solution extracted with ether and the extract dried with sodium sulphate. The extract had a very dark brown colour. The ether was removed and the residue distilled at 5 mm. and gave a brownish/

brownish yellow distillate with an unpleasant smell, and which had no definite boiling point; it distilled between 30-100°. At ordinary pressure this liquid boiled between 130-150°, and decomposed with evolution of HBr.

The method is apparently not applicable to thiophen, and was not investigated further.

The method for the preparation of thienyl methyl chloride which was attempted was that of Stephen, Short and Gladding, who describe in J.C.S., 1920, ¹¹⁷1, 510, this general method for the introduction of the chloromethyl group into the aromatic nucleus, as follows:-

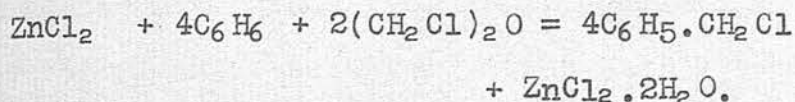
"The method consists in the treatment of an aromatic compound, in presence of a dehydrating agent, with the product obtained by the action of hydrogen chloride on paraformaldehyde or on aqueous solutions of formaldehyde, which product has been shown to consist of symmetrical dichloro methyl ether.

The formation of a chloromethyl aromatic compound is usually accompanied by the formation of a diphenylmethane derivative, produced by the condensation of the chloromethyl compound with the original aromatic substance. This side reaction depends on the kind of dehydrating agent employed. The temperature is also an important factor, and should not exceed 35° in most cases.

To prepare the s-dichloromethyl ether, 40% formaldehyde solution is allowed to percolate down a tower against a rapid upward stream of HCl. The ether, which is an oil boiling at 105°, may be dried with potassium carbonate, which also removes HCl, the oil being slightly decomposed; more decomposition occurs if sodium sulphate is used.

In calculating the quantities to be used in the preparation of benzyl chloride, so much ZnCl₂ is used that it would be completely converted to the dihydrate if the reaction were to/

to proceed completely according to the equation:



"A mixture of 108 gm. benzene and 68 gm. powdered anhydrous ZnCl_2 was shaken mechanically and 79.5 gm. crude oil added gradually, the temperature being kept below 25° . An immediate red coloration was observed which became darker. After all the oil had been added, the shaking was continued for an hour. Ice water was then added, when the red colour disappeared, and the mixture steam distilled. Unchanged benzene came over rapidly, accompanied by the odour of formaldehyde. When the oil passing over was observed to be heavier than water, the receiver was changed, and the distillation continued until a white solid began to collect in the condenser. The distillation was stopped, a pale brown oil remaining, which partially solidified on cooling. The aqueous suspension of the oil was treated with dilute KMnO_4 solution until there was no odour of formaldehyde, the oil separated, dried, and distilled, giving 44 gm. of benzyl chloride, b.p. 174° .

Other yields obtained were (1) 35 gm. p-methyl benzyl chloride from 55 gm. toluene, (2) 3 gm. of m-nitrobenzyl chloride from 63 gm. nitrobenzene, this yield being very poor."

Preparation of s-dichloro methyl ether.

A 40% solution of formaldehyde was passed down a tower containing glass beads, and 30 cm. long, against an upward current of HCl . A very small amount of oil was formed, and the solution was again passed down the tower, when the quantity was considerably increased. Exactly similar results were obtained by using a much longer absorption tower (180 cm.).

It/

It was found that this preparation could be much more conveniently and as efficiently carried out by means of the following modification.

The formaldehyde solution, mixed with concentrated HCl and salt, was placed in a flask fitted with a dropping funnel and outlet tube, and concentrated sulphuric acid slowly added through the funnel. The oil gradually collected on the surface of the aqueous portion.

Benzyl Chloride.

For the purpose of investigating this reaction, the preparation of benzyl chloride was first carried out.

27 gm. of benzene and about 20 gm. anhydrous zinc chloride were placed in a beaker, and 20 gm. of the crude oil, containing HCl, added slowly, with stirring. The mixture assumed a dark red colour. After all had been added, the stirring was continued for about an hour. The product was treated with cold water and steam distilled. The yield of benzyl chloride was only 2 gm., whereas Stephen, Short and Gladding obtained 11 gm.

This experiment was repeated with the same quantities, this time, however, vigorous mechanical shaking being employed instead of stirring. The yield of benzyl chloride was 9 gm. in this case.

Reaction of s-dichloro methyl ether with thiophen.

20 gm. of thiophen and 15 gm. of $ZnCl_2$ were mixed and 15 gm. of the crude oil added gradually, with cooling. On addition of the first few drops of the oil, there was a violent reaction, with rise of temperature, and copious evolution of HCl. A large amount of a dark red solid was formed. The mixture/

mixture was shaken for about 15 minutes, and water added. No action was evident. Steam was blown through the mixture. There was no oil in the distillate. The solid, which in its texture resembled cork, was washed with dilute HCl to remove zinc and filtered off. It was apparently unaffected by organic solvents, concentrated HCl, or NaOH. It was partially dissolved by concentrated sulphuric acid, giving a red solution, which after dilution was shaken with ether, but nothing was separated from it thereby; on making the diluted solution alkaline and shaking with ether, a similar result was observed. The solid was treated with boiling alcohol for an extended period. The solvent assumed a slight brownish tinge. The solution was filtered off, a little water added, and the alcohol removed. The aqueous residue was extracted with ether, which left an almost invisible amount of a brown oil. The cork like solid was dried and subjected to a gradually increasing temperature up to 300°, under a pressure of 5 mm. A small trace of a colourless liquid, with an unpleasant smell, distilled off. The residue retained the cork like texture of the original product, and was very little altered in colour.

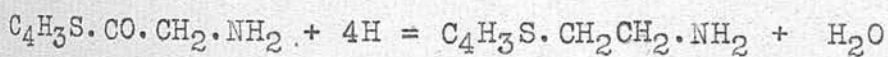
This method apparently cannot be used for the preparation of thienyl methyl chloride.

III./

III. SYNTHESIS OF AMINO-METHYL α -THIENYL KETONE

The preparation of this compound was undertaken with the following objects in view:-

(1) It was considered possible that the substance might be used as an intermediate for the synthesis of thienylethylamine, the preparation of which is described later. The ketone group might be reducible, thus:-

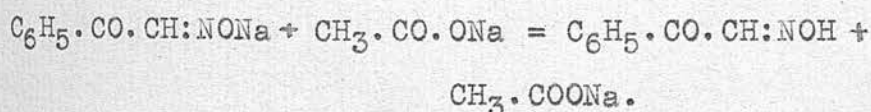
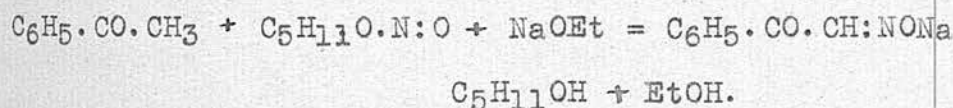


(2) The structure of this amino ketone, which has an oxygen atom attached to the carbon atom adjacent to the thiophen ring, is more similar to that of adrenaline. It might also be possible to methylate the amino group and to reduce the carbonyl group to give a secondary alcohol, whose structure would approach that of adrenaline more closely.

The method used is that described in the literature for the preparation of the corresponding benzene compound. In this synthesis isonitroso acetophenone is first prepared from acetophenone, and the isonitroso compound then reduced to the amino ketone. The first stage is described by Claisen and Manaase, Ber. 1887, 20, 2194, as follows/

follows:-

"Sodium (1 atom) is dissolved in 20 times its weight of alcohol, and to the solution is added one molecule of amyl nitrite, the mixture being kept cool during the addition. The acetophenone (1 mol.) is then added in portions. The mixture is left in a well stoppered bottle for 1-2 days. The sodium salt is deposited as a copious reddish brown precipitate, and is filtered off and washed with ether. The salt is dried in air, and dissolved in ice water. The theoretical amount of glacial acetic acid is added, and the yellowish precipitate filtered off and recrystallised from a little hot chloroform or ethyl acetate, to remove any benzoic acid.



"The yield of the sodium salt is 70% of the theoretical, that of the nitroso ketone being about 50%. The latter melts at 126-128°, and decomposes at 155°. It is a strong acid, and the sodium salt is unstable."

The reduction to the amino ketone is described by Rupe (Ber. 1895, 28, 254) thus:-

"A concentrated alcoholic solution of 40 gm. iso-nitroso acetophenone is added, with cooling, to a solution of 130 gm. stannous chloride in 196 c.c. of concentrated hydrochloric acid, in the presence also of a small amount of tin. The hydrochloride thus prepared is stable, but the free base is very unstable. The hydrochloride melts at 183-184°."

The benzene compound was first prepared in order to become familiar with the reaction.

Following/

Following the method described above, 10 gm. of crude isonitroso acetophenone, m.p. 105-115°, were obtained from 12 gm. acetophenone. The product was recrystallised from a little chloroform, giving 4.5 gm. of the pure product, m.p. 121-124°.

13 gm. of stannous chloride were dissolved in 20 c.c. of concentrated HCl in the presence of a little tin. A solution of 4 gm. of the nitroso ketone in the minimum amount of cold alcohol was added slowly, with cooling. The solution was kept for several hours, and then diluted to about three times its volume, and the tin removed with H₂S. The stannous sulphide was filtered off, and the filtrate evaporated almost to dryness. The crystalline hydrochloride, which was quite colourless, was filtered off, washed with alcohol, and dried. The yield was 2.5 gm., melting point 183-185°.

On dissolving a little of the salt in water and making alkaline with NaOH, a yellowish brown solid was precipitated. It was amorphous, and rapidly became darker in colour. The solution of the hydrochloride was acid, and on carefully neutralising it (to litmus) a reddish brown colour was developed which became darker on keeping. A solution of the salt in water was quite stable and did/

did not become coloured.

Isonitroso acetothienone. From 12.6 gm. of acetothienone, by following the same method, 6 gm. of a buff coloured substance were obtained; it was crystalline and melted between 107-110°. A little was recrystallised from chloroform, and the melting point was then 110-111°. The substance was found to contain both nitrogen and sulphur.

Amino-methyl α -thienyl ketone. The reduction was carried out as in the preparation of the corresponding benzene compound, with tin and HCl. From 4.1 gm. of the isonitroso acetothienone were obtained 1.8 gm. of the crystalline hydrochloride, melting point 215-218°.

The melting of this substance was interesting. In the first place, it will be observed that the melting point differs from that of the benzene analogue by about 30 degrees. This difference is greater than that observed for any other of the pairs of analogues prepared in this work. The substance melted to give a blood-red liquid, which almost immediately re-solidified, giving a brown solid. On heating this to 235°, blackening commenced, and the substance did not melt again, on raising the temperature further, but became converted/

converted into a completely black solid. It might be interesting to investigate the constitution of the brown solid; the production of this from the blood-red liquid was not attended by the usual phenomena which attend the liquefaction of a high melting substance (decomposition with evolution of gas or vapour), and it is possible that some condensation had occurred.

The yield of the reduction product could be improved on repetition of the process; 1.8 gm. is only 48% of the theoretical.

The percentage of chlorine in the hydrochloride was determined by precipitation with silver nitrate; after drying to constant weight:-

0.2574 gm. subs. gave 0.2094 gm. of AgCl; Cl, 20.12%

$C_4H_3S.CO.CH_2.NH_2$: (HCl) requires 19.96%.

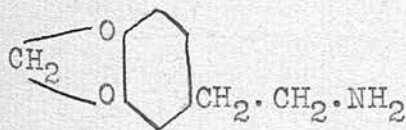
The behaviour in alkaline and in neutral solutions was found to be similar to that of the benzene compound; the free base is very unstable.

IV. /

IV. SYNTHESIS OF α -THIENYL ETHYLAMINE.

Four possible methods were considered for the synthesis of α -thienyl ethylamine:

- (1) Preparation of thienyl methyl cyanide by the action of potassium cyanide on thienyl methyl chloride, whose preparation has been described by Biedermann (cf. p. 57). Reduction of the cyanide with sodium and alcohol might then possibly yield the base.
- (2) By the reduction of the nitro styrol obtained by the condensation of thiophen aldehyde with nitromethane.
- (3) As mentioned on p. 74 , it might be possible to reduce amino methyl thienyl ketone to thienyl ethylamine.
- (4) Method described by Haworth, Perkin and Rankine (J.C.S., 1924, 1693) for the synthesis of 3:4-methylene dioxy-phenylethylamine,



Method/

Method No. 1. Biedermann's synthesis of thienyl methyl chloride has been outlined on p.57 . The two further stages in its preparation as described by this author are as follows:-

"Stage 4. 3 gm. of thiophen aldehyde are shaken with a concentrated solution of KOH in water (2.7 gm. KOH and 1.8 gm. water) until a permanent emulsion forms. After 12 hours the reaction mass, which is solid, due to the formation of the potassium salt of thienyl carboxylic acid, is dissolved in water and extracted with ether. The extract, dried with fused KOH, leaves a clear oil, which boils at 207°."

Stage 5. "Hydrochloric acid gas is passed through thienyl methyl alcohol, until it is saturated. The solution is left standing for some time. Thienyl methyl chloride is produced, and boils at 175° with some decomposition. It is a colourless liquid, resembling benzyl chloride."

Three preparations of the alcohol were carried out:

- (1) On the addition of the concentrated KOH solution to 3 gm. of impure aldehyde, there was immediate separation of a solid, no emulsion being formed in the first instance. The yield of the alcohol was 0.8 gm. distilled.
- (2) This experiment was also carried out with impure aldehyde, and gave similar results.
- (3) On mixing 5 gm. of pure aldehyde with the concentrated alkali, an emulsion formed, which, however, separated/

separated almost immediately into a solid and a liquid. The yield of the alcohol, distilled, was 1.6 gm., i.e. 63% of the theoretical.

Only one preparation of the thienyl methyl chloride was attempted. 2.3 gm. of the alcohol were saturated with dry hydrogen chloride. The liquid became green in colour, and small droplets of water appeared. After standing for about three hours no further change had apparently occurred, except that the colour was darker. The mixture was left overnight, and it was then found that it had changed almost completely into a rubber-like mass, probably due to polymerisation. Water was added, and the whole extracted with ether. The ether left behind about 0.1 gm. of a brown oil, which smelt like benzyl chloride. The rubber-like mass was insoluble in alcohol or in acetone, but was partly soluble in chloroform, with which solvent it was extracted. The residue, on heating to about 350°, decomposed and gave a liquid distillate, which did not smell like benzyl chloride, and whose amount was too small to be examined further. The chloroform extract on evaporation left practically no residue.

The production of the rubber-like mass is presumably due to polymerisation and might not occur if the solution of HCl in the alcohol were left for
a/

a shorter time. Biedermann does not give details as to the time necessary.

No attempts were made to repeat this preparation as the fourth of the other methods enumerated above was found to be satisfactory.

Method No. 2. This method was not investigated beyond the first stage, i.e. the condensation of thiophen aldehyde with nitromethane, to give the nitro styrol compound, which condensation was found to be unsatisfactory.

The condensation of aromatic aldehydes with nitromethane is discussed by J. Thiele, (Ber. 1888, 1293) as follows:-

"The condensation of nitromethane with aliphatic aldehydes by means of potassium carbonate is not applicable to aromatic aldehydes. Condensation in the presence of zinc chloride is certainly possible, but not in all cases. Nitromethane reacts very easily, however, with aromatic aldehydes or with cinnamic aldehyde in the presence of alcoholic potassium hydroxide. In this way the potassium salt of addition products seems generally to be precipitated in the first place, and these on acidification are transformed into styrol derivatives.

"The reaction with benzaldehyde is carried out as follows:- One molecule of benzaldehyde is mixed with a little alcohol and one mol. of nitromethane. To this mixture is added, drop by drop and with cooling, 1 mol. of KOH in concentrated alcoholic solution. The solution is now treated with water until it becomes clear, and acidified. The nitrostyrol compound falls out as an oil which rapidly/

rapidly crystallises. The yield is good. Re-crystallised from alcohol the compound melts at 58°."

This process was first carried out with benzaldehyde; from 9 gm. of this, 5.2 gm. of nitromethane, and 4.8 gm. of KOH were obtained 6 gm. of the nitrostyrol, i.e. 47% of the theoretical amount.

Action of nitromethane on thiophen aldehyde.

2 gm. of thiophen aldehyde and 1.1 gm. (1 mol.) nitromethane were mixed with a little alcohol and treated with 1.0 gm. (1 mol.) of KOH dissolved in alcohol, the solution being added slowly and with cooling. Dry ether was added to the solution, and the potassium salt which was precipitated was filtered off. A small quantity was dissolved in water and warmed, a dark colour being produced. On acidifying with acetic acid, a dark coloured oil, which partially solidified, separated.

The main bulk of the potassium salt was dissolved in water and acidified with acetic acid without previous warming. A dark coloured oil separated and did not crystallise. This oil was partly soluble in cold water, and on boiling the solution and then cooling, a crystalline solid was precipitated. This solid was volatile in steam, and/

and it was purified in this way, giving a bright yellow crystalline distillate, which was extracted with ether. After removing the ether and drying the crystals which were left on filter paper, these were found to weigh 0.5 gm., to contain both sulphur and nitrogen, and to melt between 79 and 83°. The oil which remained was treated with boiling water, which on cooling became milky, and bright yellow. It was separated while hot as far as possible from the oil remaining, cooled and extracted with ether, giving a very small quantity of an oil which partially crystallised.

The explanation of the above may be as follows: The potassium salt may be that of an enol form of the ω -nitro secondary alcohol, $C_4H_3S.CH_2.CHOH.NO_2$, and the oil obtained on acidifying is this secondary alcohol. On heating this water is split off, giving the ω -nitro styrol, $C_4H_3S.CH:CH.NO_2$, this being the bright yellow substance.

The yield is poor and no further attempts were made with this method; as mentioned before Method No. 4 was found to be the most satisfactory.

Method No. 3. After the preparation of the amino methyl thienyl ketone had been carried out, it was noticed that an attempt had previously been made to reduce/

reduce the benzene analogue. Gabriel (Ber., 30, 1126) states that on reduction of this with sodium amalgam, acetophenone and ammonia are produced. This reduction was therefore not attempted.

Method No. 4. This method is described by Haworth, Perkin and Rankine (J.C.S. 1924, 1693); Perkin and Robinson (J.C.S. 1907, 1079); and Buck and Perkin, (J.C.S. 1924, 1679), in connection with the syntheses of 3:4-methylene-dioxy-phenylethylamine, $C_2H_2:O_2C_6H_3 \cdot CH_2CH_2 \cdot NH_2$ and of homoveratrylamine, $(CH_3O)_2:C_6H_3 \cdot CH_2 \cdot CH_2 \cdot NH_2$.

Commencing with an aromatic aldehyde, there are four stages in this synthesis. The first and third of these stages are described in the first of the above communications, the initial material being piperonal.

"Piperonal (100 gm.) and malonic acid (150 gm.) are dissolved in pyridine (300 c.c.) and piperidine (5.c.c.) and the mixture heated for 1 hour on the steam bath. There is rapid elimination of CO_2 , and the reaction is completed by boiling the solution for about 5 minutes. The product is cooled, and poured into water, and an almost quantitative yield of the pure acid, 3:4-methylene dioxy-phenyl acrylic acid, is obtained. This is reduced to the substituted propionic acid as described by Perkin and Robinson". (Second stage, second of the above communications) "and then converted to the amide by the following means." (Third stage).

"100 gm. of the acid, dissolved in 340 c.c. of chloroform, are allowed to react for 12 hours with 74 c.c. of thionyl chloride, at room temperature. The product is then poured into a solution containing sodium hydroxide (50 gm.) and concentrated ammonia (1200 c.c.). The chloroform is removed by distillation, and after filtering from traces of tar, the solution is cooled when the amide (100 gm.) separates in a state sufficiently pure for the next operation. The conversion to the amine" (Fourth stage, third of the above papers) "is brought about by means of sodium hypochlorite."

The second state is described by Perkin and Robinson, in the preparation of veratryl propionic acid, as follows:-

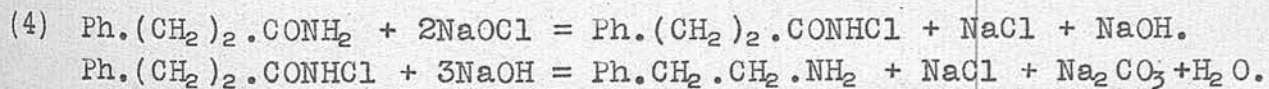
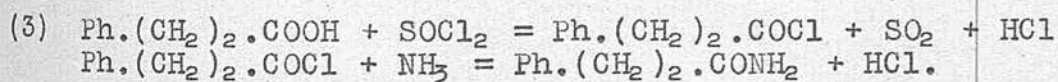
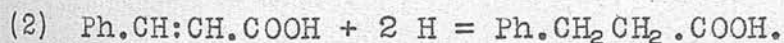
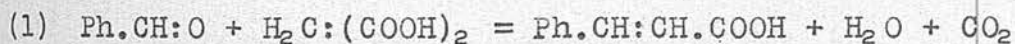
"Reduction of dimethoxy cinnamic acid. The acid, prepared from 100 gm. of veratraldehyde, is dissolved in excess of NaOH and treated with 2 kilograms of 3% sodium amalgam, provision being made for mechanical stirring. Small amounts of hydrochloric acid are frequently added to neutralise most of the alkali as it is formed. The product is rendered just acid with HCl, when tar and a little of the dihydro acid separate; the latter dissolves on adding sodium carbonate, and the former is then filtered off. The solution is digested with charcoal, filtered, cooled and acidified, when the acid separates."

The fourth and last stage, described by Buck and Perkin, in the synthesis of homoveratrylamine, is as follows:-

"The use of sodium hypochlorite is recommended by Decker (Annalen, 1913, 395, 291)" (to replace the older practice of employing the hypobromite). "A solution of sodium hypochlorite is prepared by passing the chlorine from 6 gm. of potassium permanganate, and HCl into cold NaOH (230 c.c. of a 10% solution. 20 gm. of the amide (veratryl propionamide, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\cdot\text{CH}_2\cdot\text{CH}_2\text{CO}\cdot\text{NH}_2$) are added and dissolve on warming gently. The temperature is/

is then gradually raised to 70-75° and kept there for one hour, during which time an oil separates. Solid KOH (60 gm.) is now added and the whole heated at 80° for a few minutes, cooled for 2 hours and extracted three times with benzene. After drying over KOH and evaporation of the solvent, homoveratrylamine remains as a pale yellow oil. Yield, 70%. "

The series of reactions is represented by the following equations, for the preparation of phenylethylamine. The radical phenyl- is represented by "Ph".



In order to become familiar with the reactions, the preparation of phenylethylamine was first carried out.

Cinnamic acid. From 6.5 gm. of benzaldehyde were obtained 10 gm. of cinnamic acid, m.p. 131-132.5°.

Yield theoretical. Another preparation gave a similar result.

Dihydrocinnamic/

Dihydrocinnamic acid. From 15 gm. of cinnamic acid were obtained 14.5 gm. of the dihydrocinnamic acid, m.p. 46-48°. A little was recrystallised from alcohol, and then melted also between 46-48°. Yield 95% of theory.

Dihydrocinnamide. 12 gm. of dihydrocinnamic acid were dissolved in chloroform, and allowed to react with 12 c.c. of thionyl chloride. The product was poured into a solution of 8.6 gm. of NaOH (first dissolved in a small amount of water) and 208 c.c. of concentrated ammonia. The yield of the amide was 7.0 gm., i.e. 60% of theory; m.p. 98-100°. Recrystallised from alcohol, it melted between 98.5-100°. It is stated by Hoffmann (Ber, 18, 2740) that the melting point of this amide is 105°; by Hughes (Ber. 25, 2, 747) it is given as 82°.

Phenylethylamine. The chlorine evolved by the action of 2.5 gm. of KMnO_4 on HCl was passed into 93 c.c. of 10% NaOH. 6 gm. of dihydrocinnamide dissolved in this solution readily on warming. The solution was heated at 70-75° for one hour, and then for a few minutes at 80° after adding 25 gm. of solid KOH. The oil which separated was extracted with/

with benzene and dried with KOH. The solution was filtered, some dry ether added, and the base precipitated as the hydrochloride by means of alcoholic HCl. The yield of the salt was 2.55 gm., m.p. 217°; this yield being 40% of theory.

Synthesis of thienylethylamine.

Thienyl acrylic acid. This compound has already been described (Biedermann, Ber. 19, 1855).

Biedermann prepared it in 30% yield by heating thiophen aldehyde with acetic anhydride and fused sodium acetate, and found its melting point to be 138°.

First preparation. From 6.8 gm. of thiophen aldehyde were obtained 8.5 gm. of a fine, white powder, which melted between 141-143°. Recrystallised from alcohol, it melted between 143-145°. The equivalent weight of the recrystallised product was found by titration in dilute alcoholic solution with 0.0734 N. KOH, to be 154; $C_4H_3S.CH:CH.COOH$ requires 154.

Second Preparation. 21 gm. of the aldehyde, 47 gm. of malonic acid, 90 c.c. pyridine, and 1.5 c.c. piperidine were heated on the steam bath for/

for two hours. The solution was then boiled for five minutes, cooled, poured into water, and made acid by addition of HCl. No smell of the aldehyde remained. The heat generated by the neutralisation of the bases was absorbed by cooling in water, and the precipitated acid filtered off. The yield of this precipitate was 24 gm., m.p. 138-144°. The filtrate was extracted with ether, which left a dark coloured residue. This was dissolved in NaOH, and the solution washed with ether, and then boiled with animal charcoal, filtered, and acidified, giving a small amount of an acid which retained a yellow colour, and which melted between 140-170°. It is evidently an impurity.

The 24 gm. of the precipitated acid was slightly coloured, and was dissolved in NaOH and the solution washed with ether and boiled with animal charcoal. The acid thus purified was colourless, and after drying for 30 hours in vacuo over concentrated sulphuric acid, again weighed 24 gm., but melted between 143-145°.

Yield, 85% of theory.

Thienyl/

Thienyl propionic acid.

First prep. From 5 gm. of thienyl acrylic acid were obtained 4.7 gm. of a yellowish white powder, m.p. 42-46°. Recrystallised from alcohol, it melted between 45.5-47.5°.

0.2003 gm. of the recrystallised acid gave 0.2992 gm. of BaSO_4 , after oxidation with fuming nitric acid in a sealed tube at 300°.

Hence S = 20.54%; $\text{C}_4\text{H}_3\text{S}(\text{CH}_2)_2\text{COOH}$ requires S = 20.55%.

Second prep. 24 gm. of thienyl acrylic acid were dissolved in NaOH and treated with 510 gm. of 3% sodium amalgam. The amalgam was added slowly, the solution was well stirred, the temperature was kept below 15°, and the NaOH was neutralised as it was formed by means of HCl. The solution was filtered from a very small amount of a black solid, and the filtrate was pale yellow. It was acidified, and an oil separated, which soon became solid, and the solid was filtered off. The filtrate was extracted with ether. The yield was 23.8 gm., m.p. 43-45°; this yield is 98% of theory.

The reason for keeping the temperature below 15°/

15° was that in another reduction of a thiophen compound with sodium amalgam (reduction of aceto-thienone oxime) it was noticed that the ring was reduced, with evolution of H₂S, at higher temperatures.

Thienyl propionamide.

First prep. 4 gm. of thienyl propionic acid were dissolved in chloroform and 4 c.c. of thionyl chloride added. After standing for 12 hours, the product was poured into a solution containing 3 gm. of NaOH and 70 c.c. of concentrated ammonia. The chloroform was removed and the amide filtered off. A further quantity was obtained by extraction of the filtrate with ether. The yield was 2.4 gm., m.p. 99-100°.

By the method of Carius, 0.1566 gm. gave 0.2313 gm. BaSO₄.

Hence S = 20.31%; C₄H₃S.(CH₂)₂.CONH₂ requires
S = 20.68%.

Second prep. 22 gm. of thienyl propionic acid were dissolved in chloroform and 25 c.c. of thienyl chloride added. After standing for 12 hours, the product was poured into a solution containing 385 c.c. conc. ammonia and 17 gm. NaOH. The chloroform was removed and the amide filtered off after cooling. The filtrate was extracted with chloroform three times/

times. The total yield was 20 gm., the chloroform extractions giving 4 gm. The melting point was 97-99°, and the yield is 91% of theory.

Thienylethylamine.

First prep. 19.5 gm. of the amide dissolved easily, on warming, in the solution of sodium hypochlorite prepared by passing the chlorine from 7.7 gm. KMnO_4 into 300 c.c. of 10% NaOH. The solution was heated at 70-75° for one hour. 77 gm. of solid KOH were then added, and the whole heated to 80° for a few minutes. The oil was removed from the aqueous portion, which was then extracted three times with benzene. The benzene extract, mixed with the base which had separated, was dried overnight with KOH. On attempting to distil, water and a solid separated. The solution was dried further by refluxing for one hour over solid KOH, and then was distilled at ordinary pressure. The first fraction, which was collected up to 120°, was treated with an alcoholic solution of HCl, and gave 2.3 gm. of a white crystalline hydrochloride, m.p. 200-202°.

The/

The remaining liquid was fractionated. The base boiled between 200-201°, and the weight of this fraction was 5.5 gm. The 120-200° and the 201-215° fractions were dissolved in dry ether and treated with alcoholic hydrogen chloride, giving a further 3.2 gm. of the white crystalline hydrochloride, m.p. 194-198°. This 3.2 gm. was recrystallised from dilute alcohol, giving 2.9 gm. of colourless prisms, m.p. 200-202°.

The total yield of hydrochloride obtained is thus 5.2 gm. corresponding to 4.05 gm. of the free base, the total yield of which is therefore 9.55 gm. i.e. 63% of theory.

Second prep. From 2.2 gm. of thienyl propionamide were obtained 1.1 gm. of thienylethylamine hydrochloride, m.p. 198-200°. Yield, 50% of theory.

Analysis. The percentage of sulphur in the hydrochloride was determined by means of Carius' method, and the percentage of chlorine by dissolving in water and precipitating with silver nitrate.

0.2030 gm. subs. gave 0.2909 gm. BaSO₄

Hence S = 19.67%; $C_4H_3S(CH_2)_2.NH_2.HCl$ requires S = 19.49%.

0.3010 gm. subs. gave 0.2640 gm. AgCl.

Hence Cl = 21.69%; $C_4H_3S.(CH_2)_2NH_2:HCl$ requires Cl = 21.67%

Properties/

Properties of α -thienyl β -ethylamine.

The free base is a pale yellow oil, which boils at 200-201° at about 750 mm.

Its specific gravity, determined by means of a small pyknometer, was found to be 1.087 at 15°.

When exposed to air, it rapidly absorbs carbon dioxide, with the formation of a solid carbonate. It is stable when kept out of contact with air in a sealed tube.

The hydrochloride, crystallised from dilute alcohol, forms colourless prisms, which melt between 200-202°. This salt is stable.

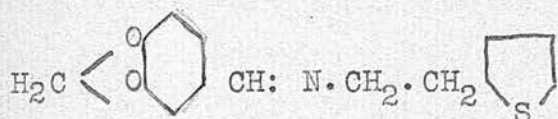
The picrate of the base is oily.

Derivatives of α -thienyl β -ethylamine.

1. Quaternary methiodide. This was prepared by boiling 0.2 gm. of the free base repeatedly with small amounts of methyl iodide. Recrystallised from dilute alcohol, it melted between 236-238°, and formed colourless plates.

2./

2. 3:4-methylenedioxy-benzal thienylethylamine.



This Schiff's base was prepared by heating equivalent amounts of thienylethylamine (0.25 gm.) and piperonal (0.3 gm.) on the water bath for 15 minutes. A very viscous syrup was obtained, and this crystallised on scratching to a hard, pale yellow mass, which on being powdered appeared to be colourless, and melted between 54.5-57°. Recrystallised from alcohol, it melted between 57-58°; colourless prisms.

3. Formyl thienylethylamine, $\text{C}_4\text{H}_3\text{S} \cdot (\text{CH}_2)_2 \cdot \text{NH} \cdot \text{CH:O}$

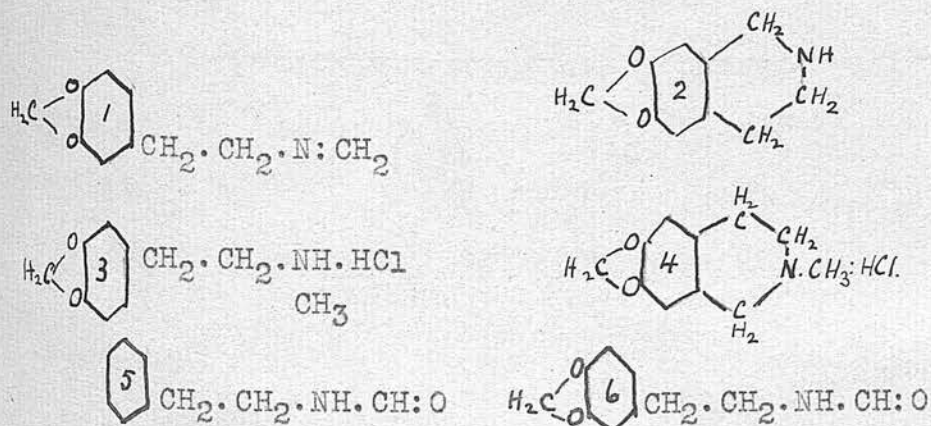
3.1 gm. of the free base were treated slowly with 1.3 gm. of dry formic acid, in a distilling flask, and with cooling (to prevent loss of formic acid). The flask was heated in a metal bath gradually from 80 to 170°. Evolution of steam became vigorous at 150°, but soon slackened. The temperature was raised to 180° and kept there for about one hour. Evolution of water had then almost ceased. The temperature was raised to 195-200° and/

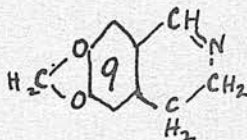
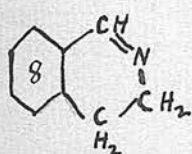
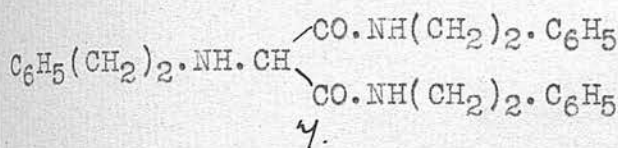
and maintained at this for $1\frac{1}{2}$ hours. At the end of this time the colour, which had been pale yellow; became darker. The liquid was cooled and remained completely fluid. It was distilled at a low pressure, and the formyl thienylethylamine boiled between 187 and 189° at 20 mm., and was a pale yellow oil. The yield was 3.5 gm., i.e. 93% of theory.

This preparation was carried out according to the method of Becker and Decker, an extract of their paper being given below.

Unsuccessful attempts were made to prepare certain isoquinoline analogues from thienylethylamine following the methods of Becker and Decker, who, in a paper appearing in Vol. 395 of Liebig's Annalen, p. 342, describe syntheses of hydrastinine compounds from derivatives of homopiperonylamine. Extracts from this paper are now given.

1913 395 342





"N-methylene h-piperonylamine (1), which is a Schiff's base, is prepared by adding 5 gm. of a 20% solution of formaldehyde, drop by drop, to 5 gm. of h-piperonylamine, with continuous shaking.

"The hydrochloride of norhydrodrastinine (2) may be prepared by treating (1) with an equal quantity of water, and, with stirring, adding a slight excess of 20% HCl over the exact amount which is required for re-solution of the condensation product. The solution is heated on the water bath in an open vessel, and after 30-40 minutes crystals begin to form. On cooling the whole sets to a crystalline mass of the hydrochloride of norhydrodrastinine. The yield, from the h-piperonyl amine, is 85% of theory.

"Norhydrodrastinine hydrochloride may be prepared directly from homopiperonylamine hydrochloride by heating 5 gm. of the latter with 10 c.c. of 40% formaldehyde in a sealed tube for 3 hours at 130°. The partly crystalline residue, weighing about 5 gm. is recrystallised from alcohol and ether several times.

"From N-methyl h-piperonylamine hydrochloride, (3), hydrodrastinine hydrochloride, (4), was obtained."

The other methods are concerned with the preparation of compounds in which the new ring is unsaturated.

"Preparation of formyl phenylethylamine (5).

"10 gm. of the amine are treated slowly and with cooling (to prevent loss of acid) with 4 gm. (5% excess) of dry formic acid in a distilling flask. On cooling the formate crystallises. The flask is heated on an oil bath, and water begins to be evolved at 100°, and the substance melts/

melts between 140 and 150°. Between 170 and 180° the evolution of water becomes brisk; to complete the reaction, the flask is heated at this temperature for 4 hours. The product is distilled in vacuo. The yield of the pure distilled formyl derivative is 95% of theory. If the temperature be raised above 220° before all the water is split off, the distillate may contain some undecomposed formate."

"On treatment of formyl phenylethylamine with condensing agents, one obtains chiefly phenylethylaminomalonyldiphenylethylamide (7). The phosphate of this is insoluble in water. Besides this phosphate there are formed also small amounts of phosphates which are soluble in hot water (Phosphorus oxychloride having been used as the condensing agent). These turn out to be the phosphates of phenylethylamine and of dihydro isoquinoline (8). These experiments have not been carried any further.

"Better yields of the isoquinoline derivatives are obtained in the case of formyl piperonylamine (6), possibly because the oxygen atom which is in the p-position to the hydrogen atom makes the latter more labile.

"Narcotarnine (9) is obtained from (6) by the action of phosphorus oxychloride in toluene. The condensation takes place comparatively smoothly. The precipitated phosphate is dissolved in water, NaOH added and the base extracted."

Attempts were made to bring about ring formation in the case of thienylethylamine, using the three methods described above, without success.

(1) 0.5 gm. of thienylethylamine were treated, drop by drop, with a 20% solution of formaldehyde. A viscous oil separated, and the smell of the aldehyde, during the addition of the first $\frac{1}{2}$ c.c. disappeared. After $\frac{1}{2}$ c.c. had been added, the addition of a further 3-4 drops produced a permanent odour, which was/

was however very faint, of the aldehyde. Addition of formaldehyde was now stopped. A slight excess of the amount of 20% HCl necessary to bring about complete solution of the oil was now added. A strong odour of formaldehyde was immediately developed. The solution was heated on the water bath for about 50 minutes. No crystallisation occurred during this time, and a deep red, sticky solid was left. This was soluble in water. On making the solution alkaline, the red colour disappeared, and a sticky yellow semi-solid mass was precipitated. The clear aqueous portion was decanted from the solid, which was redissolved in dilute HCl, and again heated on the water bath. The hot solution now had no smell of the formaldehyde, but again no crystallisation occurred on evaporation and the same red semi-solid mass was left.

(2) 0.5 gm. of thienylethylamine hydrochloride and 2.5 c.c. of 40% formaldehyde were heated in a sealed tube for 3 hours at 130°. The contents of the tube became slightly yellow. A small portion made alkaline gave a liquid base. Another small portion was evaporated, leaving a sticky residue which gave the smell of formaldehyde on heating. The main portion/

portion was made alkaline, extracted with ether, the latter quickly evaporated, and the residue taken up with dry ether. Alcoholic HCl was added to this solution, and gave a sticky precipitate. This was redissolved in water, the base precipitated with NaOH, extracted with ether, and the extract dried over K_2CO_3 . On adding alcoholic HCl to the extract, a sticky precipitate was again formed. Picric acid gave a mainly solid precipitate, which however was sticky, and could not be purified by recrystallisation. As thienylethylamine has a liquid precipitate, it may be that the new base, if it had been formed, was contaminated with the unchanged starting material, and longer heating in the sealed tube might give better results.

A second experiment was therefore performed, in which 0.2 gm. of the hydrochloride was heated with 1 c.c. of formaldehyde for 6 hours at 130° . The contents of the tube had not crystallised, and the solution was pale yellow. It was made strongly alkaline with KOH, extracted with ether, and the extract dried with solid KOH. The extract was treated with alcoholic HCl and gave a yellow precipitate which would not crystallise from alcohol. Picric acid added to a solution of the HCl/

HCl precipitate gave a brown solid, which was amorphous, was not very soluble in alcohol and could not be crystallised from this solvent or from acetone.

(3) Formyl thienylethylamine (1 gm.) was dissolved in 40 c.c. of toluene and a solution of just over 1 gm. of phosphorus in 20 c.c. toluene was added. The mixture was boiled for 30 minutes with occasional shaking. The solution rapidly deposited a dark brown resinous mass, and HCl was evolved. The toluene was poured off and the resinous mass extracted twice with boiling water, in which it partly dissolved. The solution was filtered and made alkaline, extracted with benzene and the extract dried. A small portion diluted with dry ether and treated with alcoholic HCl gave a brown precipitate, which partly dissolved in water and then gave a brown precipitate with picric acid. The main portion of the extract was distilled under diminished pressure. There was no fraction boiling over 90° at 25 mm. The distillate was treated with alcoholic HCl and gave a liquid precipitate; on making this alkaline a very small amount of a white solid base was formed. The quantity of this was too small to allow of further investigation.

This/

This experiment was repeated; in this case, however, the toluene solution was not boiled, but was heated on a water bath. The dark coloured resinous mass was treated with boiling aqueous NaOH, and the oil which remained extracted with benzene and dried. The extract was distilled, after removal of the solvent, under diminished pressure. After the last traces of benzene had been removed, the residue distilled at temperatures gradually rising from 80 to about 250°, when decomposition commenced; the pressure was 20 mm. This experiment was not carried any further.

A third experiment, in which phosphorus pentoxide replaced the oxychloride as the condensing agent, gave similar results.

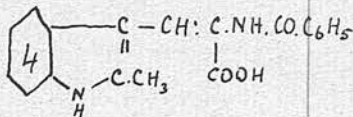
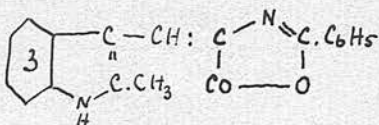
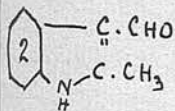
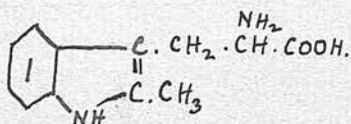
The reactions which occur in these three cases would appear to be of a complex nature, and the desired condensations apparently do not preponderate to any marked extent. It is possible that by using larger quantities the isoquinoline derivatives might be isolable, but large quantities of the base were not at the time available, and these experiments were discontinued.

V. SYNTHESIS OF α -THIENYL β -ALANINE.

The two methods which were investigated in the course of this synthesis were two of the general methods of Erlenmeyer for the synthesis of α -amino acids, of the substituted alanine type. In the first of these, an aldehyde is in the first place condensed with hippuric acid, and in the second, with hydantoin.

First Method. Condensation of an aldehyde with hippuric acid.

The instructions followed were those of Barger and Ewins, Biochem. Journal, 1917, 60, for the synthesis of Pr-2-methyl tryptophan,



First Stage.

17.3 gm. of the aldehyde (2), 22.3 gm. of hippuric acid, 8.84 gm. of anhydrous sodium acetate, and 39.3 gm. of acetic anhydride are heated for 15 minutes on the water bath. The azo-lactone (3) began to separate while the solution was still hot. After cooling, the azo-lactone is/

is filtered off and crystallised at once from glacial acetic acid, and was thus obtained in 30.5 gm. yield, m.p. 204-207°, as brownish red plates."

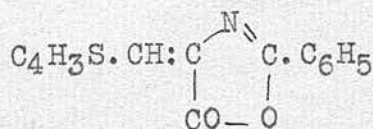
Stage 2. "By repeated boiling with 100 times its weight of 1% NaOH, the lactone was hydrolysed to the sodium salt of the acid (4), and on acidifying the acid was precipitated. After recrystallisation from 70% alcohol, it was obtained in 75% yield."

Stage 3. "4 gm. of the acid were dissolved in 120 c.c. of absolute alcohol, the solution heated on the water bath, and 12.5 gm. of sodium added during half an hour. 20 c.c. of absolute alcohol were then added and the solution boiled for 20 minutes. After adding 15 c.c. of water the removal of the benzoyl group was completed by boiling for a further 45 minutes. The solution was poured into five times its volume of cold water, and this solution washed with ether, acidified to Congo red and left in a cold room overnight. It was then filtered, washed with ether and with ethyl acetate, made up to 5% with sulphuric acid, and precipitated with Hopkins' reagent. After decomposing the mercury precipitate with H₂S and treatment with lead carbonate in the usual way, a yield of 60% of theory of an amorphous product was obtained, which gave sphaerocrystals from 50% alcohol, but could not be purified by crystallisation. By re-precipitation with Hopkins' reagent, it could be obtained pure by crystallisation in a yield of 40% of theory."

Synthesis/

Synthesis of thienyl alanine from the
condensation product of thiophen aldehyde and
hippuric acid.

First Stage. The initial condensation with hippuric acid was found to take place very readily, so that it will suffice if one of the three preparations which were carried out be described as an example. The average yield of the condensation product, the azo-lactone of α -thienyl - α - benzoyl amino acrylic acid,



after recrystallisation from glacial acetic acid, was 65-70% of theory.

Thiophen aldehyde (7.1 gm.), 16 gm. of hippuric acid, 5.1 gm. of anhydrous sodium acetate, and 23 c.c. of acetic anhydride were heated together on the water bath. The solids soon dissolved, and thereafter there was an almost immediate yellow crystalline precipitate. This did not dissolve on boiling. A further 10 c.c. of acetic anhydride were added, and complete solution resulted on boiling, which was continued for 15 minutes. The thick/

thick crystalline mass which separated on cooling was filtered off, and recrystallised from glacial acetic acid, filtered, and washed with alcohol.

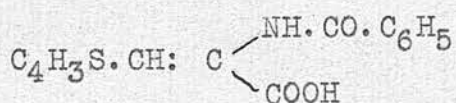
The crystals thus obtained were in the form of yellow needles, melting point 175°.

Recrystallised again from a mixture of alcohol and chloroform, it formed long, fine, yellow needles, m.p. 175°.

0.1826 gm. subs. gave 0.1670 gm. BaSO₄

Hence S = 12.57%; C₁₄H₉O₂NS requires S = 12.58%

Second Stage. The hydrolysis of the azolactone, with the production of α -thienyl- α -benzoylamino acrylic acid,



also took place very readily. One of the three preparations which were carried out is described as follows:-

10.5 gm. of the azolactone were boiled with 1000 c.c. of 1% NaOH. After about 45 minutes all had dissolved, and after a further 15 minutes the slight yellow colour remained constant in intensity. A small portion was withdrawn and acidified, giving an almost colourless precipitate. The whole was therefore cooled and acidified, and filtered, and the/

the precipitate dried. The yield of the acid was 11.1 gm., m.p. 230-238°.

Recrystallised from alcohol, it melted between 238-240° in a bath preheated to 235°, with decomposition. The yield is almost theoretical.

0.1571 gm. subs. gave 0.1342 gm. BaSO₄.

Hence S = 11.74%; C₁₄H₁₁O₃NS requires S = 11.75%

By titration in dilute alcoholic solution, the equivalent weight was determined as (1) 269.4, (2) 270.7.

C₁₄H₁₁O₃NS requires 273.

Third Stage. Only one attempt was made with the simultaneous reduction and hydrolysis of the benzoyl amino thienylacrylic acid, according to the method of Barger and Ewins. This method was apparently unsuitable in this case.

1.2 gm. of the acid were dissolved in 40 c.c. of absolute alcohol, and 4.2 gm. of sodium added during one hour. After the first small portion of sodium had been added, the solution set to a semi-solid mass. Another 20 c.c. of alcohol were added, and after another small piece of sodium had been added, /

added, the precipitate redissolved, the solution becoming yellow. Ammonia was evolved during the addition of sodium.

The resulting solution was treated with 8 c.c. of water, and boiled for 45 minutes, and then heated in a porcelain basin to drive off alcohol. A little more water was added, and a brown oil separated. This was insoluble in ether and in benzene, which did not extract any basic substance from the oil. The alkaline solution was acidified and washed with ether, which removed a small quantity of a yellow oil with a peculiar smell, and which did not solidify.

The solution, which gave the ninhydrin reaction, was evaporated in vacuo to dryness, a little absolute alcohol added and the mixture re-evaporated. To convert any amino acid to the ester hydrochloride, the residue was treated with a saturated absolute alcoholic solution of HCl, and the alcohol evaporated. This process was repeated, and the residue then extracted with alcohol, which on evaporation left a very small quantity of a brown sticky residue, which set to a glassy solid on keeping in a desiccator. This solid was very hygroscopic. It gave the ninhydrin reaction, but contained sodium and its quantity/

quantity was too small for further purification.

The evolution of ammonia in the above process may indicate that hydrolysis took place before reduction.

It is evident, in any case, that the method is not suitable for this particular preparation, as the evolution of ammonia means the loss of a certain amount of the amino acid. It might be interesting, however, to investigate the nature of the oils which form by-products. The amount of the first of these was large enough to account for a considerable proportion of the starting material.

The process was now modified, in that the reduction was first carried out with sodium amalgam, in neutral solution. This reduction was carried out three times, with the results which are now to be described.

First Reduction with Sodium Amalgam.

5 gm. of the acid (benzoylamino thienyl-acrylic acid) were dissolved in dilute NaOH and 65 gm. of 3% sodium amalgam added gradually, with stirring. Hydrochloric acid was added frequently to neutralise most of the alkali as it was formed.

The alkaline solution of the unsaturated acid was of a fairly deep reddish brown colour. When most/

most of the amalgam had been added, the colour suddenly became less intense, and the solution was almost colourless at the end. The temperature rose to about 40° during the reduction. The solution was filtered from a small amount of a black solid, and then it was observed to possess a faint yellow colour. On acidification a yellow, sticky oil was precipitated, which re-dissolved completely in dilute NaOH. No attempt was made to isolate the pure reduction product in this case; the whole was hydrolysed as described later.

Second Reduction with Sodium Amalgam.

This experiment was carried out in exactly the same way as was the first, with 5.5 gm. of the benzoylamino thienylacrylic acid, with the exception, however, that the temperature was not allowed to rise above 10°. The original brown colour of the alkaline solution disappeared in the same way. After filtration and acidification a similar sticky solid was precipitated; this again was treated directly with a hydrolytic agent without first attempting to isolate the pure reduction product. The solid was separated from the solution and the latter extracted with ether, which left an oil which did not crystallise.

Third/

Third Reduction.

10 gm. of benzoylamino thienylacrylic acid were dissolved in dilute NaOH and treated with 130 gm. of 3% sodium amalgam, the alkali in this case being neutralised with CO₂. The reduction occupied about one hour. After filtering the solution it was noticed that it became turbid. This turbidity was removed by extraction with ether. On evaporation, this extract left about 1 gm. of a pleasant smelling oil, which boiled at 195°. The solution was acidified, and there was no immediate precipitate, but after standing overnight, an almost completely crystalline substance had separated. This was filtered off, and recrystallised from alcohol, giving 2.4 gm. of a product which melted between 170-176°. The mother liquors were treated with a hydrolytic agent as described later.

Benzoylamino thienyl propionic Acid.

The crystalline product was found to be an acid. It was crystallised again from alcohol, when it melted between 176-180°. Unfortunately it was omitted to carry out an estimation of sulphur, but a determination of its equivalent weight was made, and this was found to be 279. The composition of the reduction product expected, C₁₄H₁₃O₃NS, corresponds/

corresponds to an equivalent weight of 275.

Hydrolysis of the Reduction Products.

Product of first reduction. The crude product, which dissolved completely in alkali, was boiled with about 100 c.c. of water and 10 gm. of NaOH. As soon as the solution began to boil, ammonia was evolved. The boiling was continued for about 3 hours, when evolution of ammonia had ceased. The solution was evaporated almost to dryness. During the evaporation an oil separated, but on treating the thick paste which was left with a little water, a clear solution was obtained; the oil had disappeared. The solution was neutralised and evaporated again (having been found to give a positive reaction with ninhydrin), treated with absolute alcohol and re-evaporated in vacuo, and then evaporated once more with a saturated alcoholic solution of HCl. The residue was extracted with boiling alcohol, and the extract evaporated. The residue was boiled with water and animal charcoal, filtered, evaporated to a small volume, and left in a desiccator. The residue was almost colourless, and gave the ninhydrin reaction strongly, but contained a large amount of sodium chloride. It was/

was discarded.

Product of second reduction. In order to avoid the difficulty of separating the product of hydrolysis from sodium salts, this hydrolysis was conducted with dilute HCl. The sticky precipitate and the oily ether extract were boiled with 10% HCl for five hours. The aqueous portion acquired a brown colour, and the sticky solid had not dissolved completely. The aqueous portion was washed with ether several times. The solution was boiled with animal charcoal, filtered, and the filtrate evaporated. The residue was found to contain sodium and calcium, which came from the charcoal, an impure sample. It could not be recrystallised from a mixture of alcohol and water.

The residue was evaporated twice with concentrated alcoholic HCl, and the residue then dissolved almost completely in absolute alcohol. The small residue was partly inorganic. It was evaporated with aqueous HCl to hydrolyse the ester, and then repeatedly treated with methyl alcohol and evaporated, to remove HCl.

It was dissolved in water and boiled for ten minutes with excess of freshly precipitated copper hydroxide, and filtered hot. The filtrate was blue. It was evaporated to a small volume and cooled/

cooled, when a semi-crystalline blue precipitate was formed. This was filtered off, washed with cold water, and dissolved in dilute HCl. The copper was removed with H_2S , and the filtrate evaporated. The residue was almost pure white. It was digested with hot absolute alcohol, in which it was partly soluble. The insoluble portion still contained a metal, and gave the ninhydrin reaction strongly. It was then found that the amino acid could be separated from the inorganic matter by sublimation at a low pressure. At a pressure of 5 mm. most of the residue from the alcohol extraction was sublimed at a temperature of about 210° . The very small non-volatile portion was inorganic.

The sublimate melted at about 240° . It was washed with boiling toluene and with ether, to remove decomposition products, and then melted between $250-255^\circ$, and weighed 0.9 gm. Recrystallised from slightly diluted alcohol, it melted between $274-275^\circ$ (bath preheated to 270°), and formed thin plates. The yield was about 40 mg. (0.04 gm.).

0.028 gm. of the substance were dried in vacuo for two hours at 100° , and sent to Fein Chemie, Tübingen, for micro analysis. Their report was as follows:-

5.2 mg. gave 9.3 mg. CO₂, 2.45 mg. H₂O, and 0.025 mg. residue.

4.796 mg. gave 0.336 c.c. N₂ at 18°, and 716 mm.

A determination of sulphur miscarried, and there was insufficient of the substance for a repetition.

From these results the composition is as follows, allowing for the small residue:-

C = 49.0%; H = 5.26%; N = 7.77%.

C = 49.1%; H = 5.26%; N = 8.19% are required by the formula C₇H₉O₂NS.

A determination of sulphur was carried out later, when a larger amount of the substance was available, and the result will be subsequently reported.

Hydrolysis of product of third reduction.

0.5 gm. of the recrystallised benzoylamino thienyl propionic acid was boiled with 10% HCl for six hours, and it gradually went almost completely into solution. On cooling, crystals with the appearance of benzoic acid separated. The solution was extracted with ether, and evaporated to dryness in vacuo. The residue was dissolved in water, and the solution was very slightly coloured. The water was removed, and the residue washed/

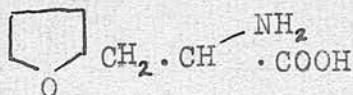
washed with benzene and with ether, and then sublimed yielding 0.1 gm. of a pale yellow powder. This was recrystallised from dilute alcohol, and the yield was 50 mg., m.p. 274-275°.

The mother liquors from the crystalline product of the third reduction were also boiled with 10% HCl, and yielded 30 mg. of the pure amino acid.

Synthesis of Thienylalanine - Second Method.

Condensation of thiophen aldehyde with hydantoin.

Sasaki (Ber. 1921, 54, 2056) in describing the preparation of furylalanine,



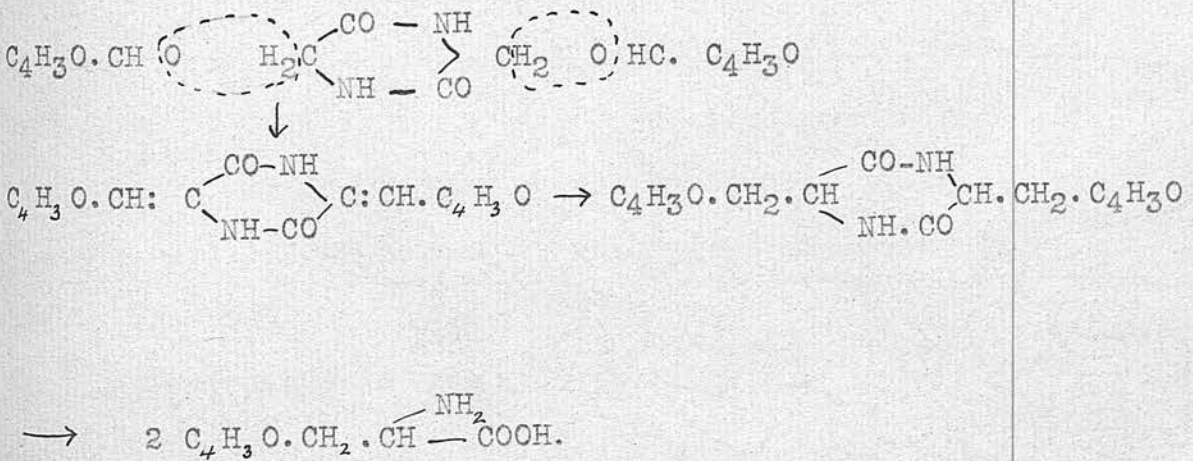
refers to a communication by Flatow (Hoppe Seyler, 1910, 64, 387) concerning the synthesis of this compound from furyl aldehyde and hippuric acid.

Sasaki points out that Flatow was successful in the preparation of the furyl benzoyl amino acrylic acid lactimide, but that he apparently encountered difficulty in splitting off the benzoyl group.

Sasaki observes further that it is doubtful whether Flatow's preparation was pure, as neither melting nor decomposition point is given, and since his single/

single nitrogen estimation was incorrect.

Sasaki describes a synthesis in which the aldehyde is first condensed with glycine anhydride. The condensation product is then reduced with sodium amalgam, and finally the benzoyl group is hydrolysed off by means of baryta. In view of the instability of the furane ring towards mineral acids, the above reduction is not carried out with hydriodic acid.

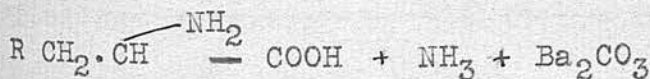
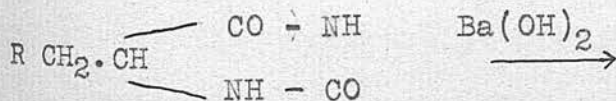
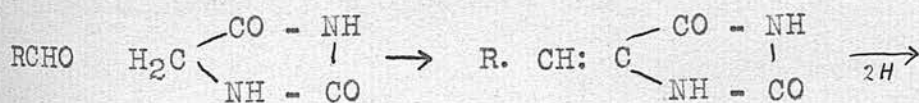


As/

As furane is very similar to thiophen in structure and properties, it is possible that the difficulties encountered by Flatow might also be met with in the case of thiophen. The hydrolysis of the benzoyl group was, as has been described, found to be troublesome.

The synthesis of amino acids by means of hydantoin is very similar to the procedure when using glycine anhydride. One advantage of using hydantoin is that in the final hydrolysis ammonia is evolved, and by leading this into standard acid, the progress of the reaction, which is a slow one, may be observed.

The synthesis is sketched as follows:-



The method was found to be satisfactory for the synthesis of thienylalanine.

The/

The first and second stages were carried out in a manner exactly similar to the processes described by Sasaki, with the difference that glycine anhydride was replaced by hydantoin. The hydrolysis is described by ^{I.H.L.}Wheeler and ^{C.}Hoffmann (Am. Chem. J. 1911, 45, 368) in connection with the preparation of phenylalanine from benzaldehyde and hydantoin.

Preparation of Hydantoin (Harries and Weiss, Ber. 1900, 33, 3418).

70 gm. glycine ester hydrochloride were dissolved in the minimum amount of cold water, and 40 gm. potassium cyanate treated likewise. The solutions were mixed and the mixture kept in ice for one hour, and allowed to stand overnight. The crystals of hydantoin ester hydrochloride were filtered off and washed with water. The ester hydrochloride was hydrolysed without drying by evaporation on the water bath with 25% HCl. The residue was washed with a little boiling alcohol, the mixture cooled and filtered, and the crystals dried. Yield 38 gm., m.p. 210-216°, i.e. 76% of the theoretical.

Condensation

Condensation of thiophen aldehyde with hydantoin.

Three condensations were carried out, and as the reaction was found to take place very readily and to give a good yield, one only of these will be described.

In his description of the condensation of furyl aldehyde with glycine anhydride, Sasaki takes excess of the aldehyde, presumably because this was more easily obtained than the anhydride. The yield is calculated on the amount of the latter.

As hydantoin is more easily prepared than thiophen aldehyde, slight excess of the former was taken.

A mixture of 38.5 gm. of the aldehyde, 36.8 gm. hydantoin, 25 gm. anhydrous sodium acetate, and 145 c.c. acetic anhydride was heated to 110°. The solids first dissolved completely, and after about thirty minutes at this temperature crystals began to form. The mixture was left overnight, and filtered. The pale yellow crystals were washed with a little alcohol, then with ether, and finally several times with water. After drying, the yield was 37 gm. The filtrate, on keeping, gave a further 2.2 gm. Melting point, 214-216°, with decomposition.

Sulphur/

Sulphur in Condensation Product.

It was found that the substance changed in melting point and in composition by dissolving in NaOH and reprecipitating with acid.

On recrystallisation of the substance from alcohol, it melted between 217-219° and formed pale yellow needles.

- (1) 0.1981 gm. subs. gave 0.1900 gm. BaSO₄; S = 13.14%
(2) 0.1805 gm. " " 0.1734 gm. " ; S = 13.17%

This result corresponds to an empirical formula weight of 243.8.

If the condensation product were first dissolved in NaOH (solution occurred easily in the cold) and then reprecipitated with HCl, it changed in melting point, in solubility in alcohol and in crystalline form. After reprecipitation and crystallisation from alcohol, it melted between 253-255°, and formed thin plates.

- (1) 0.0870 gm. subs. gave 0.1026 gm. BaSO₄: S = 15.97%
(2) 0.1125 gm. " " 0.1322 gm. " : S = 16.12%

This corresponds to a formula weight of 199.5.

A possible explanation of this is that the condensation product is acetylated. Acetylation has been observed before in the case of hydantoin condensation/

condensations carried out in presence of acetic anhydride. The acetyl group would be removed on dissolving in NaOH.

The molecular weight of thenal hydantoin, $C_8H_6O_2N_2S$ is 194. This agrees fairly well with the result of the analysis of the reprecipitated product. Assuming monoacetylation, the composition of the condensation product would be $C_{10}H_8O_3N_2S$, and the molecular weight 241.5, which also agrees fairly well with the above analysis. Assuming monoacetylation, the above yield of 39.5 gm. of the condensation product corresponds to 49% of the theoretical.

? 236

Reduction of Thenal Hydantoin.

This reaction occurred very readily, and only one experiment will be described.

13.8 gm. of thenal hydantoin were suspended in 2000 c.c. rectified spirit and shaken mechanically with 400 gm. of 3% sodium amalgam, the alkali being neutralised with H_2SO_4 as it was formed. The shaking was continued until reduction appeared to be complete (about one hour after complete solution of the light yellow powder). The sodium sulphate was/

was removed by filtration, the alcohol distilled off in vacuo, and the residue treated with water. The crystalline product thus obtained weighed 10 gm., m.p. 175-180°. Yield, 75% theory.

Recrystallised from a mixture of alcohol and chloroform, it melted between 188-190°, and two Carius determinations resulted as follows:-

Subs. dried 1 hour in vacuo at 100°.

- (1) 0.1715 gm. subs. gave 0.2011 gm. BaSO₄: S = 16.18%
(2) 0.1625 gm. " " 0.1886 gm. " : S = 15.90%

(Thenyl hydantoin, C₈H₈O₂N₂S, requires S = 16.32%)

Hydrolysis of thenyl hydantoin.

This operation, the last stage in the synthesis, at first caused some trouble. It is therefore proposed to describe in detail all the experiments performed.

First Experiment.

0.5 gm. thienyl methyl hydantoin was boiled with 50 c.c. water and 8 gm. Ba(OH)₂. The ammonia was swept out by means of a slow air current and led into 0.0966 N. HCl. The theoretical amount of this which should be neutralised is 26.7 c.c. The first 15 c.c. of acid were neutralised at the rate of 2 c.c./

c.c. per hour. After 18 c.c. had been neutralised the rate had fallen to 2 c.c. in 1 hours. Owing to the fact that some of the absorption liquid was inadvertently allowed to enter the reaction vessel, the total amount of NH_3 liberated could not be estimated. After 29 c.c. of the HCl had been neutralised, the mixture was evaporated to dryness, the residue digested with water, the solution filtered, shaken with silver oxide, filtered, colloidal silver precipitated with H_2S , filtered, filtrate evaporated to dryness, and the residue dissolved in a small amount of water. On adding absolute alcohol to this solution, a white precipitate was obtained. This was washed with alcohol and with ether, and dried, when it weighed 0.17 gm. It contained sodium, and to separate the amino acid from the metal the mixture was heated at $200-220^\circ$ in vacuo. A very small sublimate was obtained, the amount being too small for further investigation.

Second Experiment.

In this experiment the concentration of barium hydroxide used was much greater.

6 gm. of the crude reduction product were boiled with 100 c.c. water and 50 gm. of recrystallised barium/

barium hydroxide. The ammonia was passed into 0.966 N. HCl, the theoretical volume of this which should be neutralised being 32 c.c. At the beginning the rate of neutralisation was 1 c.c. in 3 minutes. The reaction was exceedingly slow after 31 c.c. had been neutralised, and was stopped. The barium was precipitated with CO_2 , and filtered off. The filtrate still contained Ba, which was removed with slight excess of H_2SO_4 . The filtrate was evaporated to dryness, and the residue contained sodium. The amino acid present was converted to its ester hydrochloride by heating with alcoholic HCl and evaporating, this process being carried out twice. The residue was digested with alcohol, and the solution filtered from the small insoluble portion. The filtrate was evaporated to dryness and the residue dissolved in water, the solution treated with Ag_2O followed by H_2S as before, to remove HCl. The filtrate from the H_2S precipitation was evaporated to dryness and the residue dissolved in the minimum amount of water, and the solution treated with alcohol and ether, and allowed to cool in the ice chest. The crystalline precipitate was filtered off, washed with alcohol and ether, and dried.

It/

It weighed 1.4 gm., and melted between 274-275°. A melting point of a mixture of this preparation with a sample of that sent to Germany for micro analysis, was taken, and found to be 274-275°.

Sulphur in Product of Hydrolysis.

Dried one hour in vacuo at 100°. M.P. 274-275°.

- (1) 0.1164 gm. subs. gave 0.1558 gm. BaSO₄; S = 18.33%
(2) 0.1768 gm. " " 0.2358 gm. " ; S = 18.28%

(C₇H₉O₂NS requires S = 18.72%)

The product of this experiment contained a trace of sodium.

Third Experiment.

It was noticed in the preceding experiment that the glass flask used for the reaction vessel was affected by the alkali, becoming rough inside. It is possible that the trace of sodium in the product is derived from this source. In order to overcome this difficulty, a copper flask was used in this and the following experiments.

4.85 gm. of thienyl methyl hydantoin, 42 gm. recrystallised barium hydroxide, and 85 c.c. water were placed in the copper flask and the mixture boiled./

boiled. After 22.5 c.c. of 0.966 N. HCl had been neutralised by the ammonia (the possible volume being 26 c.c.) the reaction became very slow and was stopped. The contents were washed out of the flask with hot water, and the solution and washings boiled and the barium removed with slight excess of H_2SO_4 . After filtering from $BaSO_4$, the filtrate was seen to have a blue colour. This was due to some copper having been dissolved from the flask. The copper was removed with H_2S , and the filtrate evaporated to a small volume, alcohol and ether added, and the amino acid filtered off and washed as before. The yield was 2.0 gm., 44% theory, m.p. 274° .

Other experiments gave similar results. The total amount of the amino acid obtained was 9.2 gm.

Properties of α -thienyl- β -alanine.

Thin plates, m.p. $274-275^\circ$ with decomposition.

A saturated solution, in water at 15° , contained about 2.5% by weight of the amino acid.

The solubility was much increased by adding a little ammonia.

The amino acid gave negative results with the indophenin test.

VI. NOTES ON THE PHYSIOLOGICAL ACTION OF THIENYLALANINE, AND ON THE METABOLISM OF THIENYL CARBOXYLIC ACID AND OF THIENYLALANINE.

Thienyl ethyl amine.

Dr J.H. Burn of the Research Laboratory of the Pharmaceutical Society, reports on this compound as follows:-

The substance raises the blood pressure, on intravenous injection, in a manner qualitatively and quantitatively indistinguishable from phenyl-ethyl amine. This would indicate that the activity of the amines depends primarily on physical rather than on chemical properties.

Thienyl carboxylic acid.

In order to become familiar with the processes of extraction of products of metabolism from urines, and especially in order to find whether substances containing the thiophen nucleus were easily extracted, the following experiment was performed.

A rabbit was given orally 2.125 gm. thienyl carboxylic acid in 10% aqueous solution, and the following 24 hours' sample of urine collected. The urine/

urine measured 230 c.c.

The urine was boiled with excess of milk of lime for about ten minutes, and the solution filtered and evaporated to dryness. The residue gave the indophenin reaction. A small portion of the residue was acidified with HCl. A precipitate easily soluble in ether was formed, and the ether extract gave a crystalline residue with an unpleasant smell.

The main portion of the residue was therefore acidified. There was no effervescence. The precipitate was filtered off, washed and dried in vacuo. It was of a brown colour, and weighed 0.72 gm. The filtrate was extracted three times with ether, the third extract leaving very little residue. The extracts on evaporation left a residue weighing 0.22 gm.

The ether extract was recrystallised from a mixture of alcohol and water, when it melted from 119-122°. This gave the indophenin reaction, and is probably unchanged thienyl carboxylic acid.

The acid precipitate was very soluble in alcohol, and was recrystallised from dilute alcohol, when it melted between 168-170°.

0.1005 gm. acid were neutralised (to phenolphthalein) by 6.35 c.c. 0.0844 N. HCl.

Therefore equivalent weight of acid = 187.5.

Thus/

Thus the acid precipitate is thenoyl glycine, equivalent weight 189, m.p. 171-172°. (Jaffe and Levy, Ber. 1888, 21, 3458).

The rabbit used in this experiment died shortly afterwards.

Thienylalanine.

0.5 gm. thienylalanine, dissolved in 27 c.c. water containing a little NH_4Cl and a trace of NH_3 , were injected into the ear vein of a rabbit which had during the previous 29 hours passed 380 c.c. of faintly alkaline urine. After the injection the urine was collected in batches for various successive periods, and these batches measured and tested for amino acids by means of the ninhydrin reaction.

A second rabbit was used as a control, no injection being made and the urine collected at the same times as in the case of the experimental animal.

First sample, after 2 hours, measured 13 c.c., ninhydrin reaction very decided, faintly alkaline to litmus.

Second sample, after a further 18 hours, volume 105 c.c. decided ninhydrin reaction, faintly alkaline.

Third sample. After a further 6 hours, volume only about 3 c.c., which was collected along with the next 18 hours sample, this 24 hours sample measuring 75 c.c.; it gave the ninhydrin reaction.

Fourth sample. 24 hours, 170 c.c., ninhydrin positive

Fifth/

Fifth Sample. 24 hours, 175 c.c., ninhydrin positive

Sixth Sample. 24 hours, 115 c.c., ninhydrin positive
(not very definite)

Seventh Sample. 24 hours, 135 c.c., ninhydrin positive

The collection of samples was now stopped.

The urines of the control rabbit, and the urine of the experimental animal before injection, were negative to the ninhydrin reaction. All of the urines were negative to the indophenin reaction.

The collection of urines from the experimental animal was discontinued, although the ninhydrin reaction remained positive six days after the injection, because it was noticed that the urine of the control gave the reaction after keeping, this being due presumably to the decomposition of proteins, although the samples were kept under a layer of toluene. The continuance of positive ninhydrin results from the urines of the experimental animal might be due to such decomposition during the time of collection, especially as the introduction of the thienylalanine might conceivably lead to a greater excretion of proteins, by interference with the metabolic processes.

Discussion/

Discussion of Results.

Owing to lack of time, an analysis of the urines was not possible, neither was it possible to repeat the above experiment, nor to carry out intended experiments on perfusion of a solution of thienylalanine through the surviving liver.

Very little can be deduced from the above experiment. There is evidence that some of the thienylalanine is excreted unchanged, and that none of it is excreted in the form of simple thiophen compounds which would give the indophenin reaction (not given by thienylalanine itself). If it is the case that all of the thienylalanine is excreted unchanged, then this amino acid differs from the benzene isologue, which of course is entirely oxidised. More work is necessary, however, before any definite conclusions can be drawn.

VII. /

VII. SUMMARY.

(1) In a brief introduction, the physical and chemical properties of benzene and of thiophen are compared and contrasted. A review of what is known of the physiological behaviour of thiophen and its compounds is given.

(2) The preparation of thiophen by a method similar to that of Steinkopf is described. The efficiency attained was comparable with that reported by Steinkopf in his earlier experiments. The method was found to be satisfactory for the preparation of large quantities of thiophen.

(3) The results are described of a number of experiments in which different methods for the preparation of -thiophen aldehyde were investigated. A full description of the most satisfactory method is given.

(4) The syntheses of the following hitherto undescribed derivatives of thiophen are described:-

1. Amino methyl α -thienyl ketone hydrochloride.
2. Thienyl propionic acid.
- 3./

3. Thienyl propionamide.
- 4-6. α -Thienyl- β -ethylamine; hydrochloride, quaternary methiodide.
7. 3:4-methylene dioxy-benzal thienyl ethylamine.
8. Formyl thienylethylamine.
9. Azolactone of α -thienyl- α -benzoyl amino acrylic acid.
10. α -Thienyl- α -benzoylamino acrylic acid.
11. α -Thienyl- α -benzoylamino propionic acid.
12. α -Thenal hydantoin; 13. Acetyl derivative.
14. α -Thenyl hydantoin.
15. α -Thienyl- β -alanine.

Most of these have been analysed and characterised.

(5) A note on the results of pharmacological tests of thienyl-ethylamine is given. The physiological action is exactly similar to that of phenylethylamine.

Results of a preliminary experiment on the metabolism of thienylalanine are reported. There are indications from this experiment that thienylalanine does not behave in the same way as phenylalanine. No definite conclusions, however, can be drawn.