

(a.) THE SYNTHESIS OF THIAZOLE DERIVATIVES AND  
OTHER HETEROCYCLIC COMPOUNDS OF POSSIBLE  
PHARMACOLOGICAL VALUE.

(b.) THE DEVELOPMENT OF A RAPID MICRO-METHOD OF  
ESTIMATING SULPHUR.

by

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THE SYNTHESIS OF THIAZOLE DERIVATIVES  
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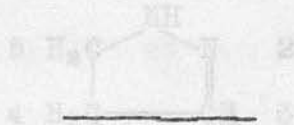
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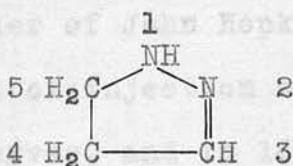
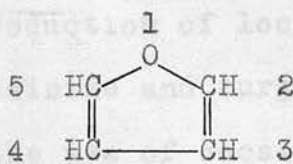
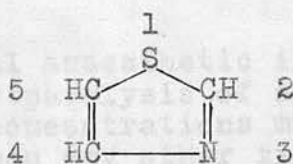
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The thiazole, furane and pyrazoline rings are numbered as follows:-

INTRODUCTION.



Unfortunately, cocaine, whilst still the standard with which other local anesthetics are compared, has two great drawbacks in its clinical use. It is toxic and it tends to be habit-forming. Moreover, it cannot be sterilized without decomposition.

## I N T R O D U C T I O N .

“A true local anaesthetic is a compound which produces temporary paralysis of sensory nerves or nerve endings in concentrations much lower than those required to act upon any other tissues.” A. J. Clark.

The real introduction of local anaesthesia into the practice of medicine and surgery dates from the demonstration of the use of cocaine solutions in ophthalmological surgery by Karl Koller of Vienna in 1884. W. S. Halsted (later of John Hopkins University) investigated the effect of injection of cocaine solution into the vicinity of nerves, and in 1885 was able to report successful local anaesthesia in over one thousand surgical cases.

Unfortunately, cocaine, whilst still the standard with which other local anaesthetics are compared, has two great drawbacks in its clinical use. It is toxic and it tends to be habit-forming. Moreover, it cannot be sterilised without decomposition.

Ever since the introduction of local anaesthesia, attempts have been made to discover substitutes for cocaine, which, whilst equally effective, would lack these disadvantages. The majority of the compounds tried have been synthetic. The perfect local anaesthetic for all purposes has still to be found.

Widely varying types of molecule have been found, in many cases by accident, to be local anaesthetics. Several series of compounds, with groupings of known activity in common, have been prepared, with a view to determining those configurations in which the greatest activity is associated with the minimum toxicity.

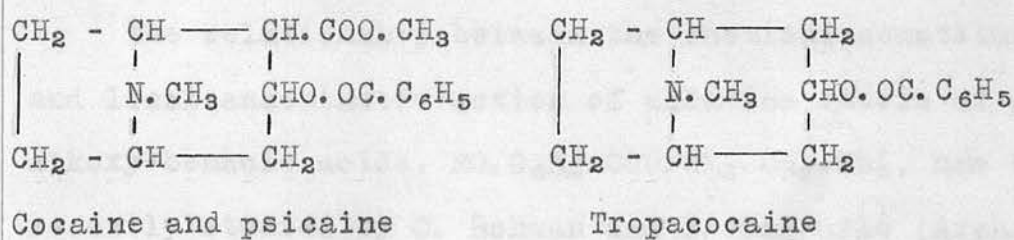
Unfortunately, the biological testing of local anaesthetics has reached no great standard of accuracy. Several procedures are in use, each of which yields a different value for any one drug. Further, the personal factor plays a large part in determining the values found by any one method. From a review of the available data, T. H. Rider (J. Pharm., Balt., 1930, 39, 329) came to the conclusion that no two drugs can be accurately compared unless both compounds have been tested by the same worker and by the same technique.

It is thus impossible to draw general conclusions as to the relationship between chemical structure and local anaesthetic action. At best, the effects of changes in constitution can only be deduced for a group of compounds examined by one worker, and even then it should

be borne in mind that, by the standards of a science such as chemistry, the results are only qualitative. Methods of assaying local anaesthetics are described in Section IV.

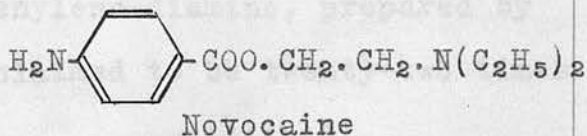
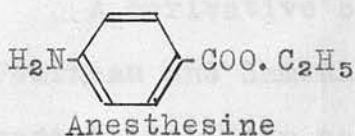
As no useful purpose would be served by giving a full account of all those compounds with local anaesthetic action, a very brief summary only will be attempted here. In one point all local anaesthetics of any importance do resemble each other, and that is in the presence in the molecule of an amino-group. They are generally used as water-soluble hydrochlorides.

Closely related to cocaine itself (methyl ester of benzoyl-tropanol-4-carboxylic acid) are psicaine ( $\psi$  - cocaine) and tropacocaine (benzoyl- $\psi$ -tropanol), in which the different spatial configuration of the tropane nucleus favours desirable properties.



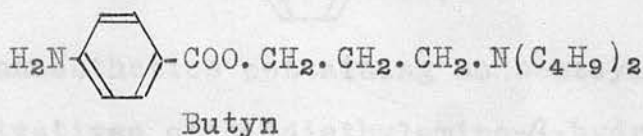
Esters of aminobenzoic acids have been found to possess local anaesthetic action. Those containing amino-groupings in the side-chain, being more soluble, are of greater value as cocaine substitutes. They resemble cocaine in having the benzoyl radical attached

to a basic residue. Many of the cocaine substitutes on the market are of this type. Novocaine (procaine) is the least toxic of all local anaesthetics in general use. In the simpler compounds, increase in size of the N-alkyl-radicals appears to be associated with increased activity, n- being more effective than iso-. The number of carbon atoms between the carbonyl and dialkylamino groups seems to be immaterial, but, if anything, the optimum number is two as in novocaine.



ethyl p-aminobenzoate

$\beta$ -diethylaminoethyl p-amino-  
benzoate

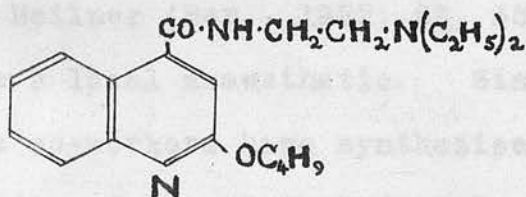


$\gamma$ -di-n-butylaminopropyl p-aminobenzoate

The relationship between the chemical constitution and local anaesthetic action of alkamine esters of p-alkoxy-benzoic acids,  $RO.C_6H_4.COO.CH_2.CH_2.NR'_2$ , has been recently studied by C. Rohman and B. Scheurle (Arch. Pharm., 1936, 274, 110). It was found that increase in size of the alkoxy-group was accompanied by increase in activity, straight chains being more effective than branched. Increase in size of the N-alkyl-radical ( $R'$ ) further increased the activity of the molecule.

One of the most important cocaine substitutes,

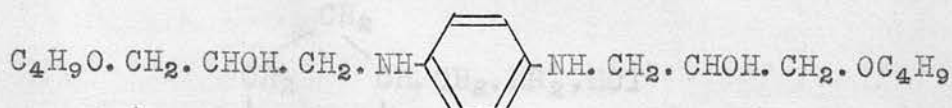
percaine (nupercaine), has quite a different structure from any of those described above. It is fifteen times as strong as cocaine, but five times as toxic.



Percaine

$\alpha$ -butoxycinchonin- $\beta$ -diethylaminoethyl-amide.

A derivative of p-phenylene-diamine, prepared by Fourneau and Sandahl, is claimed to be twenty-two times more potent than cocaine.



Other anaesthetics containing no benzoyl groups are the derivatives of  $\gamma$ -diethylamino- $\beta$ -hydroxypropoxybenzene,  $C_6H_5.O.CH_2.CHOH.CH_2.N(C_2H_5)_2$ , studied by Boedecker and Ludwig (Z., 1934, ii, 3787), who found that introduction of alkyl and alkoxyl residues into the phenyl nucleus increased the anaesthetic action with increasing length of chain. The 2-n-propyl-6-n-butoxy-derivative was twenty times as potent as cocaine.

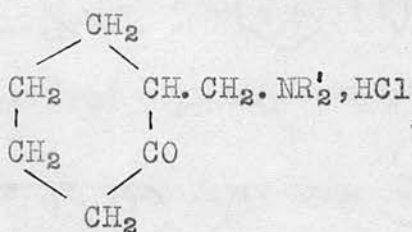
Hartung and Munth (J. A. C. S., 1929, 51, 2570) found p-aminophenyl n-valeryl ketone,  $NH_2.C_6H_4.CO.(CH_2)_4.CH_3$ , to be much stronger and less toxic than cocaine. The benzoyl radical is present in this compound in a differ-

ent state of combination to that in cocaine and novocaine.

$\beta$ -Piperidinoethyl phenyl ketone, prepared by C. Mannich and G. Heilner (Ber., 1922, 55, 356), was found by chance to be a local anaesthetic. Since then, Mannich and his co-workers have synthesised a great many similar compounds, of the general formula



where R = phenyl and alkoxyphenyl and  $NR'_2$  = piperidino, dimethylamino and diethylamino. Dialkylamino-derivatives of cyclohexanone were also prepared.

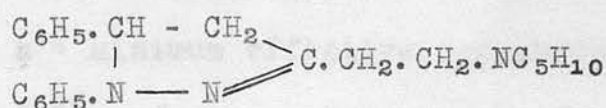


All these compounds are to a greater or less extent local anaesthetics. Unfortunately, they are frequently irritant. Reduction of the ketones to the corresponding secondary alcohols destroyed their activity. The benzoyl derivatives of the alcohols are, however, very potent, but also exceedingly irritant.

Blicke and Blake (J.A.C.S., 1930, 52, 235) observed  $\beta$ -piperidinoethyl pyrrol-2 ketone to be a local anaesthetic. H. K. Sinha (Ph.D. Thesis, University of Edinburgh, 1936) examined  $\beta$ -piperidino- and  $\beta$ -dimethyl-

amino-ethyl thienyl-2 ketones, which proved to be no stronger, but more toxic than cocaine. This is in contrast to the observation that the phenyl group in some of the well-known cocaine substitutes can be replaced with advantage by thienyl (Ann., 1924, 437, 14).

1:5-Diphenyl-3-(β-piperidinoethyl)-pyrazoline was discovered to have a local anaesthetic action about five times as great as that of cocaine, the toxicity being twice that in the latter. It will be noted that this compound is the first described which contains no oxygen.



1:5-diphenyl-3-(β-piperidinoethyl)-pyrazoline

Many pyrazolines of this type have been tested by H. K. Sinha (loc. cit.). From his figures, the following conclusions may be drawn. Alkoxy-substitution (m- and p-) in the phenyl group at position 5 doubles the activity of the pyrazoline, while reducing its toxicity and irritation to those of cocaine. Substitution (m- and p-) in the N-phenyl group has almost as much effect on the activity, but causes no increase in the efficiency of compounds already substituted in the 5-phenyl nucleus, and may render them more toxic. In all cases, replacement of the piperidino residue by dimethylamino reduces the strength and slightly increases the toxicity. Re-

placement of the phenyl group in position 5 by furyl-2 reduces the strength of the anaesthetic by half.

The following table gives the therapeutic values of some of the drugs mentioned above. The figures for the pyrazoline were taken from values given by Sinha (J. Pharm., 1936, 57, 199), and for the other drugs from data collected by Hirschfelder and Bieter (Physiol. Rev., 1932, 12, 190).

$$\text{Therapeutic value} = \frac{b}{a} \cdot \frac{x}{y}$$

where a = minimum effective concentration of drug

b = " " " " cocaine

x = minimum lethal dose of drug

y = " " " " cocaine.

<u>Drug</u>	<u>Therapeutic Value</u>	
	<u>Rabbit's cornea</u>	<u>Human wheal</u>
Cocaine	1	1
Psicaine	2.5	2.5
Tropacocaine	1	3.5
Novocaine	1	5
Butyn	1.5	1.5
Percaine	25	2
1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(3'-ethoxy-4'-methoxyphenyl)-pyrazoline	14	18

It was thought it would be of interest to synthesise  $\beta$ -dialkylaminoethyl ketones containing thiazole and furane nuclei, with a view to examining their activities as local anaesthetics. By preparing as many compounds of each type as possible, it was hoped to gain some insight into the effect of variation of the dialkylamino residue.

The synthesis of 1-phenyl-3-( $\beta$ -dialkylaminoethyl)-5-thiazylpyrazolines was also planned. This proved impossible to accomplish, owing to difficulty in obtaining the starting-material. In its place, the preparation of 1-phenyl-3-( $\beta$ -dialkylaminoethyl)-5-(o-n-alkoxyphenyl)-pyrazolines was undertaken, the results of recent biological work suggesting that these would prove to be very effective local anaesthetics.

## 2. The Synthesis of

pyrazolines

1. The Synthesis of  $\beta$ -Amino-ketones containing Heterocyclic Nuclei.

II.

The Mannich Reaction. It was desired to synthesize  $\beta$ -amino-ketones containing thiazole and furane nuclei by

C H E M I C A L   D I S C U S S I O N .

aldehyde and the hydrochlorides of various secondary bases. This reaction is a general one for carbonyl compounds containing an activated hydrogen atom. It was first studied in 1917 by C. Mannich, who with his co-workers

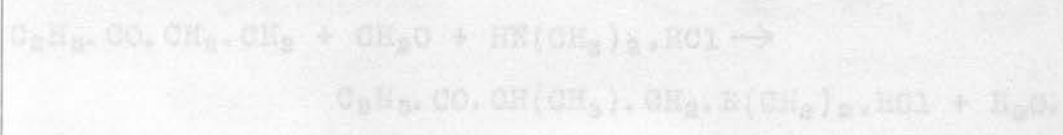
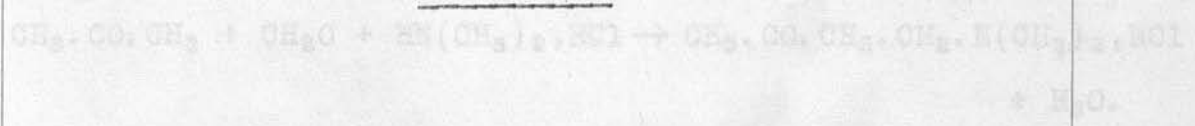
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1. The Synthesis of  $\beta$ -Amino-ketones containing Heterocyclic Nuclei ... .. 10

In his first paper (Arch. Pharm., 1917, 85, 201) Mannich described the condensation of dimethylamine

2. The Synthesis of 1:3:5-Trisubstituted-pyrazolines ... .. 35

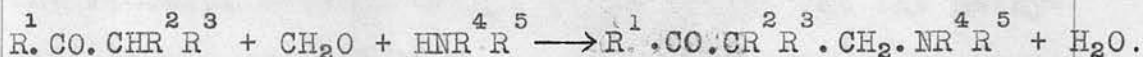
ethyl-ketone and ethyl- $\alpha$ -methyl- $\beta$ -dimethylaminoethyl-ketone hydrochlorides respectively.



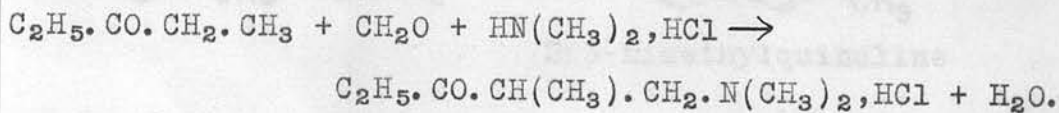
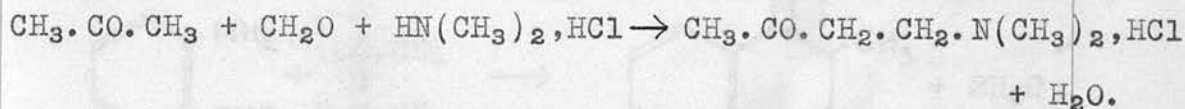
When diethyl ketone was condensed with formaldehyde and methylamine hydrochloride, a mixture was obtained, containing, among other things, a big derivative and a

1. The Synthesis of  $\beta$ -Amino-ketones containing Heterocyclic Nuclei.

The Mannich Reaction. It was desired to synthesise  $\beta$ -amino-ketones containing thiazole and furane nuclei by condensation of appropriate methyl ketones with formaldehyde and the hydrochlorides of various secondary bases. This reaction is a general one for carbonyl compounds containing an activated hydrogen atom. It was first studied in 1917 by C. Mannich, who with his co-workers has since extensively explored its possibilities.



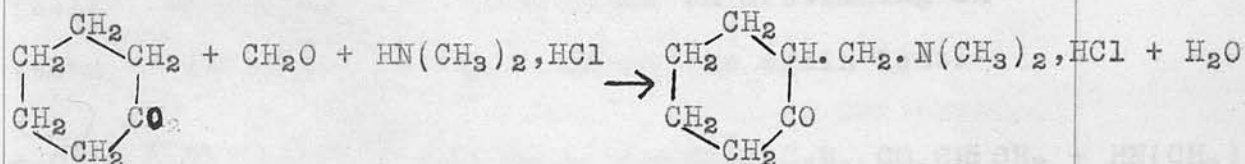
In his first paper (Arch. Pharm., 1917, 255, 261), Mannich described the condensation of dimethylamine hydrochloride and formaldehyde (as formalin) with acetone and with diethyl ketone, to give methyl  $\beta$ -dimethylaminoethyl ketone and ethyl  $\alpha$ -methyl- $\beta$ -dimethylaminoethyl ketone hydrochlorides respectively.



When diethyl ketone was condensed with formaldehyde and methylamine hydrochloride, a mixture was obtained, containing, among other things, a bis derivative and a



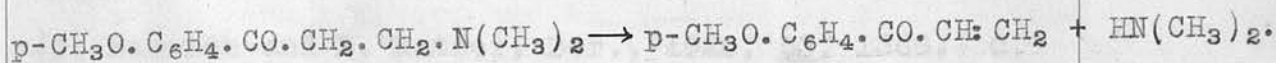
dimethylamine hydrochloride and with methylamine hydrochloride. In the latter case, a complicated product was again obtained.



The anaesthetic properties of these cyclohexanone derivatives has led to the preparation of many others by variation of the amine residue, both from cyclohexanone itself and from its homologues (Abs., 1926, B, 514 from G.P. 422,098; Arch. Pharm., 1927, 265, 598).

Carrying out the reaction in boiling alcohol, with formaldehyde as paraformaldehyde, derivatives of acetophenone, p-methoxyacetophenone, 3:4-dimethoxyacetophenone and  $\beta$ -acetyltetrahydronaphthalene were prepared, one or more of the following amines being used in the case of each ketone: piperidine hydrochloride, dimethylamine hydrochloride, diethylamine hydrochloride, piperazine and isoquinoline (C. Mannich and G. Heilner, Ber., 1922, 55, 356; C. Mannich and D. Lammering, Ber., 1922, 55, 3510). The hydroxy-analogues were obtained from the methoxy-compounds by treatment with hydriodic acid. In all cases it was found that the  $\beta$ -amino-ketones could be reduced to the corresponding secondary alcohols by hydrogenation over palladium. Sodium and alcohol could

not be used as they caused splitting-out of the amine residue. The readiness with which this fission occurred prevented the purification of many of the free bases (oils), decomposition taking place on distilling in vacuo. In steam, the amine group was again lost.

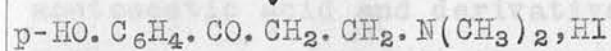


p-methoxyphenyl  $\beta$ -dimethyl-aminoethyl ketone

p-methoxyphenyl vinyl ketone

HI

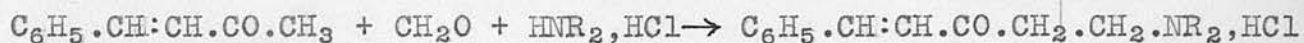
H<sub>2</sub> and Pd



p-hydroxyphenyl  $\beta$ -dimethylaminoethyl ketone hydroiodide

1-p-methoxyphenyl-3-dimethylamino-propyl alcohol.

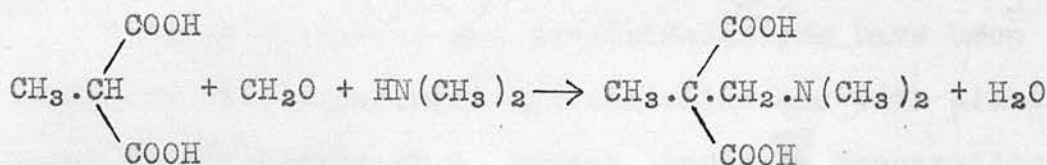
The reaction was extended to unsaturated ketones such as styryl methyl ketone (Abs., 1926, B, 901 from G.P. 430,683; C. Mannich and M. Schütz, Arch. Pharm., 1927, 265, 684). Benzylidene-acetone itself and paraformaldehyde were condensed with piperidine hydrochloride and with dimethylamine hydrochloride. Derivatives of veratrylidene-acetone and piperonylidene-acetone were also prepared. The free bases, obtained by acting on the  $\beta$ -amino-ketone hydrochlorides with alkali, were found to be unstable. Many other compounds of this type have been prepared by H. B. Nisbet (unpublished work - cf. H. K. Sinha, Ph.D. Thesis, University of Edinburgh, 1936) from the condensation products of acetone and substituted benzaldehydes.

+ H<sub>2</sub>O

Benzylidene-acetone  
(styryl methyl ketone)

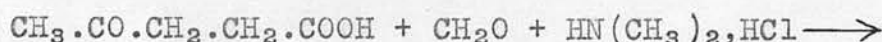
1-Dialkylamino-5-phenyl-  
Δ<sup>4</sup>-penten-3-one hydrochloride

Acids may be used as the ketonic reagent. Secondary amines (free or as the hydrochlorides) and formaldehyde were condensed with malonic acid and derivatives (C. Mannich and B. Kather, Ber., 1920, 53, 1368; C. Mannich and E. Ganz, Ber., 1922, 55, 3486), hydroxymalonic acid (C. Mannich and M. Bauroth, Ber., 1922, 55, 3504), acetoacetic acid and derivatives (Abs., 1925, A, 374 from D.R.-P., 393,633; C. Mannich and K. Curtaz, Arch. Pharm., 1926, 264, 741), nitrophenylacetic acids (C. Mannich and L. Stein, Ber., 1925, 58, 2659), pyruvic and laevulinic acids (C. Mannich and M. Bauroth, Ber., 1924, 57, 1108). In the case of acetoacetic acid, the new linkage is formed at carbon-atom-2, in the case of laevulinic acid at carbon-atom-5.

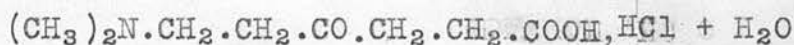


Methylmalonic acid

Dimethylamino-dimethylmalonic acid.



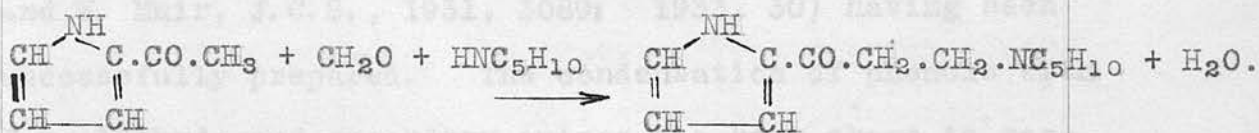
Laevulinic acid



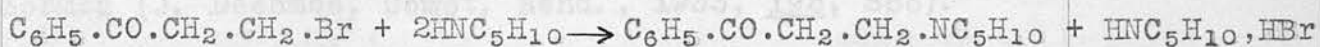
4-Keto-6-dimethylamino-hexoic acid  
hydrochloride.

$\beta$ -Aminoaldehydes have also been prepared by the Mannich reaction (C. Mannich, B. Lesser, F. Silten, Ber., 1932, 65, 378).

The preparation of pyrrol-2  $\beta$ -piperidinoethyl ketone by the Mannich reaction was carried out by F. F. Blicke and E. S. Blake (J.A.C.S., 1930, 52, 235). These authors proved the structure of phenyl  $\beta$ -piperidinoethyl ketone by its synthesis from piperidine and  $\beta$ -bromoethyl phenyl ketone.

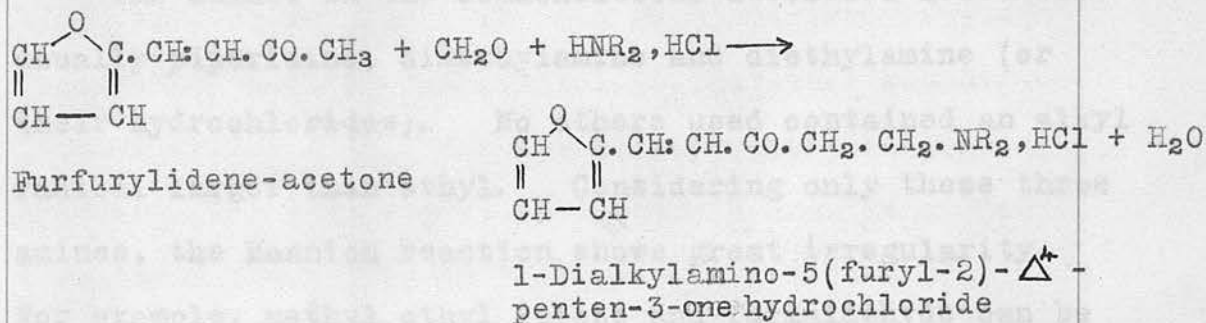


2-Acetylpyrrole

Pyrrol-2  $\beta$ -piperidinoethyl ketone

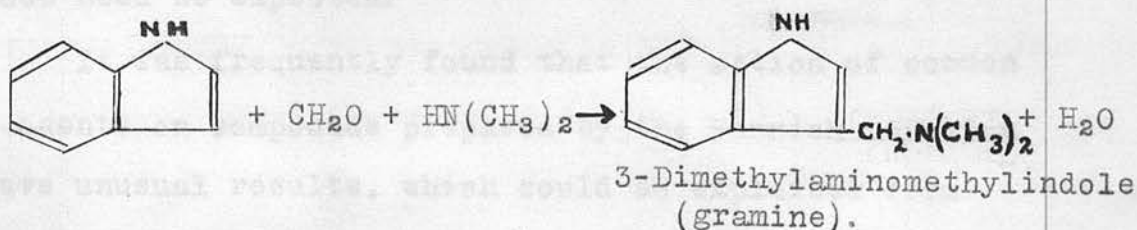
2-Acetylthiophene and paraformaldehyde have been condensed with piperidine hydrochloride and with dimethylamine hydrochloride (H.B. Nisbet, Paper in Preparation).

$\beta$ -Amino-derivatives of furfurylidene-acetone were prepared by H. B. Nisbet and C. G. Gray (J.C.S., 1933, 839).



Formaldehyde and secondary amines may be condensed with compounds containing an activated hydrogen atom, other than carbonyl compounds,  $\omega$ -derivatives of phenylacetylene (C. Mannich and F. T. Chang, Ber., 1933, 66, 418), 2:4-dinitrotoluene and quinaldine (W. O. Kermack and W. Muir, J.C.S., 1931, 3089; 1933, 30) having been successfully prepared. The condensation of phenols with formaldehyde and secondary amines has been shown to resemble the Mannich reaction, o-hydroxybenzylamines being formed (J. Décombe, Compt. Rend., 1933, 196, 866).

A recent synthesis of the alkaloid gramine was carried out by a similar reaction (H. Kühn and O. Stein, Ber., 1937, 70, 567). Analogous compounds were also prepared using diethylamine and piperidine. The use of acetaldehyde instead of formaldehyde and of diethanolamine as the basic residue were suggested.



The amines in the condensations described above were usually piperidine, dimethylamine and diethylamine (or their hydrochlorides). No others used contained an alkyl radical larger than ethyl. Considering only these three amines, the Mannich reaction shows great irregularity. For example, methyl ethyl ketone and formaldehyde can be condensed with piperidine hydrochloride and dimethylamine hydrochloride, but not with diethylamine hydrochloride (Arch. Pharm., 1927, 265, 589; J.C.S., 1931, 3089). In this laboratory it was found that acetophenone could not be condensed with paraformaldehyde and diethylamine hydrochloride, although, when dimethylamine or piperidine hydrochloride was used, the reaction went readily (Ber., 1922, 55, 356 and 3510). This behaviour is characteristic of the reaction. When complete failure to isolate a desired condensation product is met with, as a rule, little can be done in the hope of bringing about smooth reaction. For one thing, the amino-compounds are not usually very stable. The ease with which the amine residue is split out has been noted. In general it would appear, if a ketone and formaldehyde will not react with piperidine hydrochloride, condensation with no other base need be expected.

It was frequently found that the action of common reagents on compounds prepared by the Mannich reaction gave unusual results, which could be explained from lability of the amino-group. While in some cases phenyl-



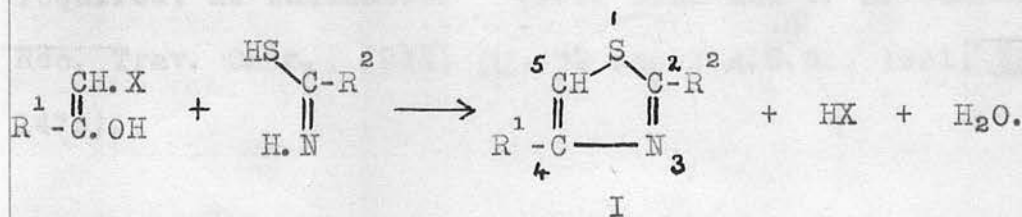
and methyl vinyl ketones. Lability of the amino-group has also been noted in  $\alpha$ -amino-ketones. Gramine reacted with methyl iodide in a neutral medium to give the tertiary base and 3-hydroxymethylindole. Instead of the latter, 3-methoxymethylindole was obtained when the reaction was carried out in presence of alkali (J. Madinaveitia, J.C.S., 1937, 1927). These instances of the lability of the dimethylamino-group may have some bearing on the observation that the oximes of  $\beta$ -dimethyl-amino-ketones cannot be readily prepared (Ber., 1922, 55, 3510).

$\beta$ -Amino-ketones derived from 4-Phenyl-2-acetylthiazole.



As the starting-material for this series (R = 4-phenylthiazyl), 4-phenyl-2-acetylthiazole was prepared.

The general method of synthesis of the thiazole ring is by condensation of  $\alpha$ -halogen-substituted ketones with thioamides (Hantzsch, Ann., 249 and 250).

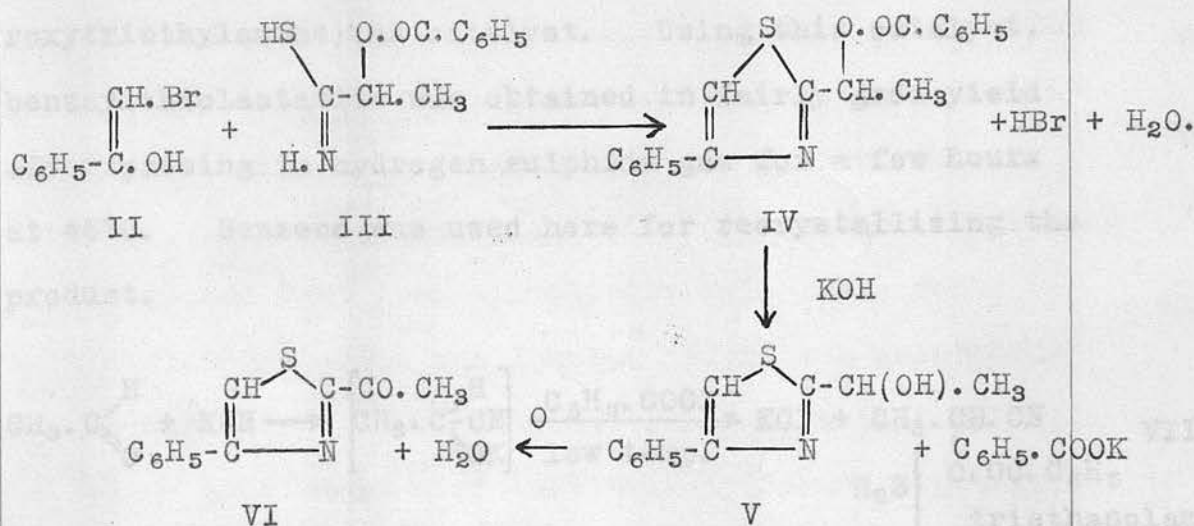


The thiazyl nucleus in the  $\beta$ -amino-ketones obtained

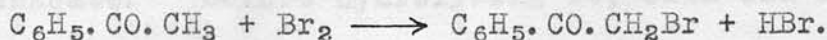
will then be 4-substituted, this substituent group being  $R^1$  in the  $\alpha$ -halogen-substituted ketone used in this condensation.  $R^2$  in the thioamide must be, for present purposes, of such a nature that from it the acetyl group may be readily obtained at position 2 in I.

The preparation of thiazole derivatives unsubstituted at position 4 presents difficulties in the way of starting-materials. The  $\alpha$ -halogen-substituted ketone used here was  $\omega$ -bromoacetophenone (II), selected on grounds of convenience, as it is one of the less unpleasant to work with on the large scale of this type of compound. Moreover,  $R^1$  in I becomes a phenyl group, and there is little likelihood of its being affected in further reactions, or of its having any appreciable effect on the physiological activity of the  $\beta$ -amino-ketone molecule as a whole.

The thioamide with which  $\omega$ -bromoacetophenone was condensed is benzoylthiolactamide (III). The benzoate produced (IV) was hydrolysed to give the secondary alcohol (V), which was oxidised to the 2-acetyl-thiazole (VI) required, as indicated. (J.F. Olin and T. B. Johnson, Rec. Trav. Chim., 1931, 50, 72 and J.A.C.S., 1931, 53, 1473).



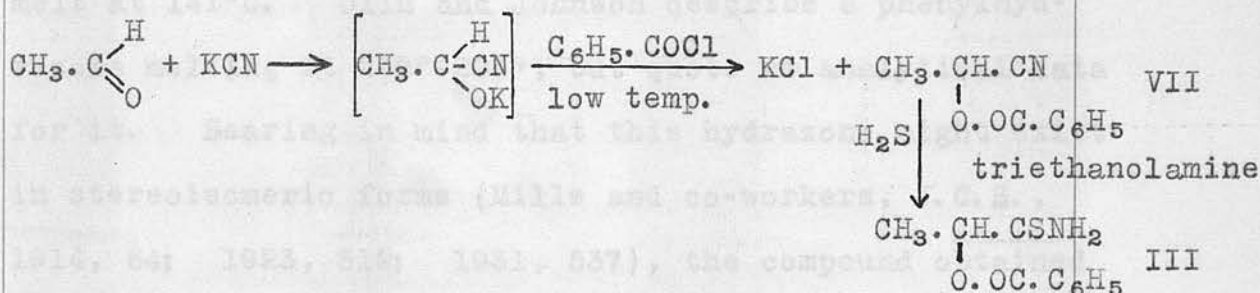
$\omega$ -Bromoacetophenone was obtained by bromination of acetophenone in acetic acid solution at room temperature. (Rather and Reid, J.A.C.S., 41, 77, 1919; Möhlau, Ber., 15, 2, 1882) It is a white solid with pronounced lachrymatory powers. The method of preparation was slightly modified in order to avoid charring.



For the preparation of benzoylthiolactamide, benzoyl-lactonitrile (VII) was required. The latter was synthesised by shaking an equimolecular mixture of acetaldehyde, benzoyl chloride and potassium cyanide at a low temperature. It is essential that the temperature be kept low throughout the reaction (T. B. Johnson, Private Communication). The nitrile was purified by distilling under reduced pressure. It was found here that it solidifies on standing.

The addition of hydrogen sulphide to the nitrile was carried out in the presence of triethanolamine (trihyd-

roxytriethylamine) as catalyst. Using this catalyst, benzoylthiolactamide was obtained in fairly good yield after passing in hydrogen sulphide gas for a few hours at 45°C. Benzene was used here for recrystallizing the product.



In the condensation of  $\omega$ -bromoacetophenone and benzoylthiolactamide to give 4-phenyl-2- $\alpha$ -benzoylhydroxyethylthiazole (IV), they were heated together in alcohol. The addition of dilute alkali then caused the separation of the benzoate. Before hydrolysing it, Olin and Johnson purify the benzoate by distillation under reduced pressure. As extensive decomposition was observed during this, the crude condensation product was used here in the hydrolysis, with satisfactory results.

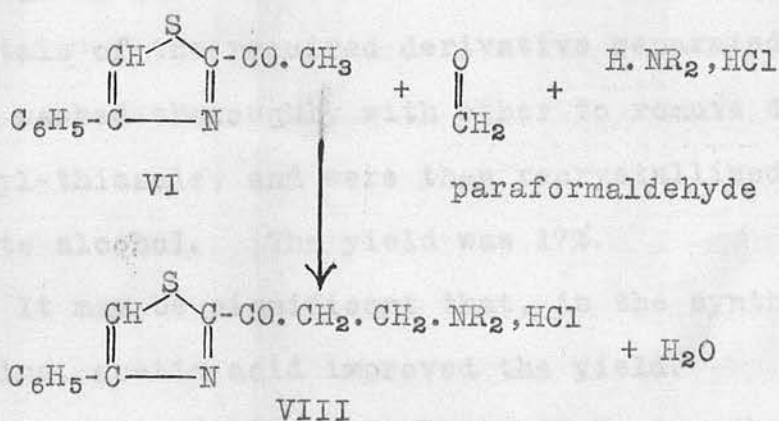
4-Phenyl-2- $\alpha$ -hydroxyethylthiazole (V) was obtained by hydrolysing the benzoate with alcoholic potassium hydroxide. The product was distilled under reduced pressure and recrystallized from chloroform, the yield from II and III being 30% of the theory.

Oxidation to 4-phenyl-2-acetylthiazole (VI) was carried

out with sodium dichromate in acetic acid solution, with good yields. A slightly higher melting-point was obtained for this ketone than that given by Olin and Johnson. The phenylhydrazone (X), prepared by the method of Auwers and Voss (Ber., 1909, 42, 4411), was found to melt at 141°C. Olin and Johnson describe a phenylhydrazone melting at 208°-209°, but quote no analytical data for it. Bearing in mind that this hydrazone might exist in stereoisomeric forms (Mills and co-workers, J.C.S., 1914, 64; 1923, 312; 1931, 537), the compound obtained (m.pt. 141°) was examined for possible conversion into an isomer. It proved stable to the actions of acid, alkali, and heat (Forster and Zimmerli, J.C.S., 1910, 97, 2156; Laws and Sidgwick, J.C.S., 1911, 99, 2085; H. Brederick, Ber., 1932, 65, 1833). Hydrogen sulphide in alcohol caused interconversion of the stable isomeric phenacylaniline hydrazones prepared by Busch, Friedenberg and Tischbein (Ber., 1924, 57, 1783), but had no effect in the present case. Acetylation of the isomer of lower melting-point was found in the case of dinitrophenylhydrazones of furfural and derivatives (H. Brederick, loc. cit., H. Brederick and E. Fritzsche, Ber., 1937, 70, 802) to give the acetyl-derivative of the higher-melting form, the latter being obtained on hydrolysis. On treating the phenylhydrazone of 4-phenyl-2-acetylthiazole in benzene with acetyl chloride, the N-acetyl-derivative was

precipitated. It crystallized from alcohol in pale yellow cubes, m. pt. 209°C. This suggests that, under the conditions of preparation of the phenylhydrazone used by Olin and Johnson, acetylation occurred. The ketone, phenylhydrazone and N-acetylphenylhydrazone were analysed, with satisfactory results.

With a view to gaining some idea of the reactivity of the methyl group in VI, an attempt was made to prepare the anisal derivative, with no great success. There would seem to be a surprising lack of reactivity in this methyl group. The methyl group in 4-phenyl-2-methylthiazole reacts more readily with aromatic aldehydes (Mills, J.C.S., 1922, 121, 2724).



It was expected that, on boiling a solution of 4-phenyl-2-acetylthiazole, piperidine hydrochloride and paraformaldehyde in absolute alcohol, 4-phenyl-(thiazyl-2)

$\beta$ -piperidinoethyl ketone hydrochloride (VIII,  $R_2 = C_5H_{10}$ ) would be obtained after a few minutes, as has been found with other ketones in place of VI. Such was not the case.

In preparing quinaldine derivatives, the reaction was carried on for a considerable time before the compounds formed. In this case, however, even after prolonged boiling, only the starting materials separated on cooling.

It was then thought that a catalyst for dehydrations in general might perhaps be of service. As hydroxyl-ion was ruled out, the effect of hydrogen-ion was tried by adding a few drops of concentrated hydrochloric acid to the reaction mixture. (Using a pure secondary amine hydrochloride, there can be very little if any free hydrogen-ion in the solution.) After 4 hours boiling, crystals of the required derivative separated. These were washed thoroughly with ether to remove 4-phenyl-2-acetyl-thiazole, and were then recrystallized from absolute alcohol. The yield was 17%.

It may be significant that, in the synthesis of gramine, acetic acid improved the yield.

4-Phenyl-(thiazyl-2)  $\beta$ -dimethylaminoethyl ketone hydrochloride (VIII,  $R = CH_3$ ) was prepared in the same manner as the piperidino-compound.

In preparing these two compounds, which were cooled

and sampled at frequent intervals during the refluxing, the impression was arrived at that, even in the presence of the catalyst, the reaction took some time to go to completion.

The reaction mixture was refluxed for 9 hours when 4-phenyl-(thiazyl-2)  $\beta$ -diethylaminoethyl ketone hydrochloride (VIII, R = C<sub>2</sub>H<sub>5</sub>) was prepared, giving a yield of 23% of the theory.

Di-n-propylamine hydrochloride was successfully used as the basic constituent in this condensation, the reaction being carried on for 12 hours to give a 30% yield of the amino-ketone (VIII, R = n-C<sub>3</sub>H<sub>7</sub>).

Judging by the amounts which separated on cooling at intervals in the last two preparations, the slight improvement in yield may be put down to the longer times of boiling. (In preparing derivatives of ketones other than VI, where the reaction went more readily, it has frequently been observed that prolonged heating caused deterioration of the product.)

The attempted preparation of the di-n-butylaminoethyl ketone hydrochloride was unsuccessful, although boiling was continued for 15 hours. Efforts to condense diethanolamine (dihydroxydiethylamine) and para-formaldehyde with 4-phenyl-2-acetylthiazole also met with failure.

From the work performed here, the 4-phenyl-thiazyl nucleus was judged to be a stable one, resisting alkali and dichromate. Its derivatives, in the main, are readily obtained crystalline.

J. F. Olin and T. B. Johnson (loc. cit.) suggest 4-phenyl-2-acetylthiazole to be similar in properties to acetophenone, for example giving an  $\omega$ -bromo-derivative with ease. In the reactions carried out here, however, a great difference in the reactivity of the methyl group in the thiazyl-ketone from that in acetophenone is found. The fragrant odour associated with the latter is also lacking (cf. 2-acetylfurane).

Of the four new  $\beta$ -amino-ketones prepared, we find an increasing solubility in hot absolute alcohol as we go from the piperidino- through the dimethyl- and diethyl- to the dipropyl-compound, the piperidino- being the only one to separate from the reaction mixture whilst still boiling. Apart from the last mentioned ( $R_2 = C_5H_{10}$ ), which gives an emulsion, all are more or less soluble in hot water. Alkali throws out the bases from the aqueous solutions. As expected, none of the hydrochlorides is soluble in ether. They are not hygroscopic.

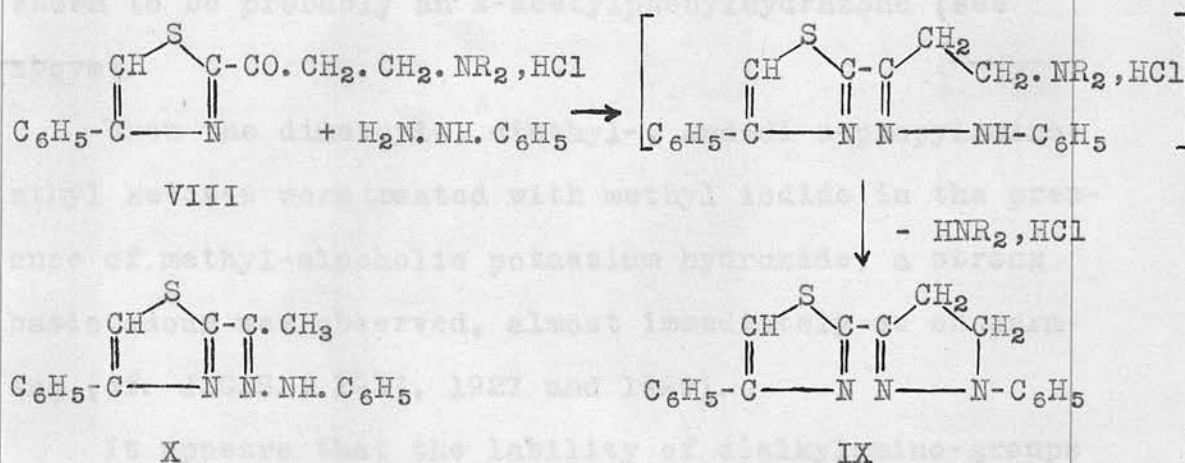
Loss of sensation is experienced on placing a little of any one of the hydrochlorides on the tip of the tongue.

All the pure compounds were found to give a blue coloration in a test with sodium nitroprusside described

by Feigl ("Tüpfelreaktionen", p. 375) as specific for methyl ketones.  $\beta$ -Aminoethyl-ketones derived from 2-acetylthiophene and from 2-acetylfurane also answered this test. Thiazole-derivatives, other than 4-phenyl-2-acetylthiazole (answering to  $4\gamma$ ) and the new amino-ketones, gave negative results. In two cases in which the test was carried out quantitatively, responses to  $10\gamma$  of amino-ketone were observed. Although the cause of this unexpected property is not clear, it may be due to reversal of the Mannich reaction (as distinct from splitting-out of the amine residue - cf. J.C.S., 1931, 3089), a view not incompatible with the behaviour of the condensation in the case under immediate discussion.

Preparation of the phenylhydrazones of the  $\beta$ -dialkyl-aminoethyl 4-phenyl-(thiazyl-2) ketone hydrochlorides (VIII) was attempted in alcoholic solution in presence of acetic acid. On standing at room temperature, instead of the desired derivatives, there separated crystals which were found to have the same melting-point ( $198^\circ$ ) from all four sources. Samples of mixed origin showed no depression in melting-point. Analysis of preparations from different amino-ketones confirmed this derivative to be identical in all cases. Negative results were met with in testing for the presence of halogen. From the percentages obtained for carbon, hydrogen and nitrogen (micro-Dumas), the compound appears to be 1-

phenyl-3-(4-phenylthiazyl-2)-pyrazoline (IX), formed by the loss of the amine residues from unstable phenylhydrazones of VIII (see also Section II, Part 2). This conclusion is in agreement with observations on the action of phenylhydrazine on  $\beta$ -dimethylaminoethyl-ketones quoted above.



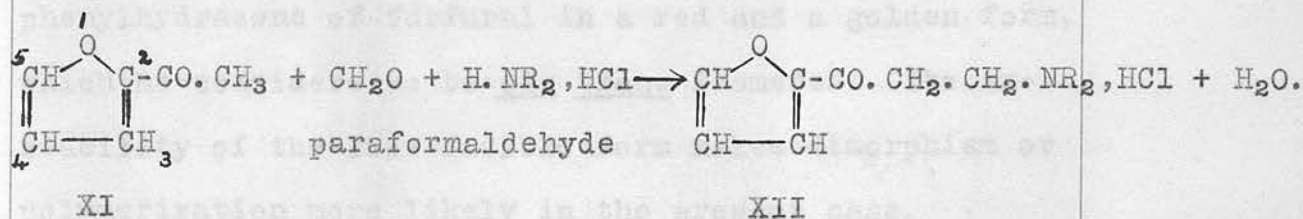
The compound is not very soluble in the usual solvents, but when in solution it exhibits a strong green fluorescence, destroyed on addition of mineral acid, but returning on neutralization. (Many similar pyrazolines have been observed to fluoresce - Ber., 1932, 65, 832.). It crystallized from a large quantity of alcohol in pointed yellow needles, a structure frequently found in aryl-substituted pyrazolines (Raiford and Peterson, J. Org. Chem., 1937, 1, 544). A dark blue colour was obtained in Knorr's test for pyrazolines (Ann., 1887, 238, 200), in which a sulphuric acid digest of the substance is treated with an oxidising agent.

The analytical figures for the pyrazoline differ little from those for the phenylhydrazone of 4-phenyl-2-acetylthiazole (X), which might conceivably be formed by reversal of the Mannich reaction. The latter, however, has been prepared and found to melt at 141°, and a form melting at 208°-209° described by Olin and Johnson shown to be probably an N-acetylphenylhydrazone (see above).

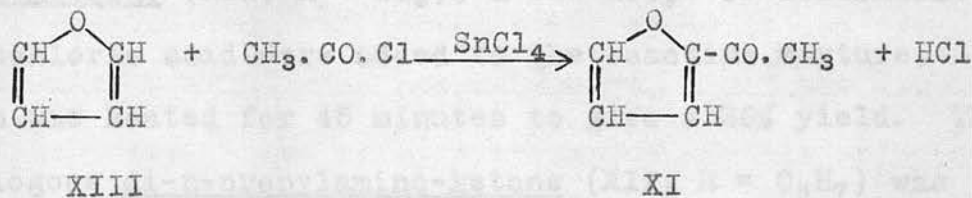
When the dimethyl-, diethyl-, and di-n-propylaminoethyl ketones were treated with methyl iodide in the presence of methyl-alcoholic potassium hydroxide, a strong basic odour was observed, almost immediately or on warming (cf. J.C.S., 1937, 1927 and 1929).

It appears that the lability of dialkylamino-groups in this connection is independent of the type of ketone. In the case of <sup>the</sup>thiazyl-derivatives, it is shown to be also independent of the size of the N-alkyl-radical (R). Although not quantitatively studied, increase in the size of R seems to favour formation of the pyrazoline. 1:3-Diphenylpyrazoline could not be obtained from  $\beta$ -dimethylaminoethyl phenyl ketone under the conditions used in the preparation of IX (which are much less vigorous than those by which the former pyrazoline was prepared by Miss A. Jacob and J. Madinaveitia, loc. cit.).

It may be that general use could be made of the reaction with phenylhydrazine in the preparation of pyrazoline derivatives.

$\beta$ -Amino-ketones derived from 2-Acetylfurane.

2-Acetylfurane (XI) was prepared by acetylation of furane (XIII) (from 2-furoic acid) at 0°, in presence of anhydrous stannic chloride catalyst (T. Reichstein, Helv. Chim. Acta, 1930, 13, 356). The product was distilled off from the reaction-mixture in steam, and distilled under reduced pressure to give a 30% yield of a white solid with a fragrant odour resembling that of acetophenone. The methyl ketone gives a blue coloration with sodium nitroprusside.



The golden-coloured phenylhydrazone (Sandelin, Ber., 1900, 33, 493) was prepared. It decomposed on standing. There also separated a less soluble red solid of higher melting-point. This remained unchanged over a considerable period, but could not be purified as almost quantitative transformation to the more fusible form occurred on attempted recrystallization. Bredereck (Ber., 1932,

65, 1833) has described the isolation of the dinitro-phenylhydrazone of furfural in a red and a golden form, which he considers to be cis trans isomers. The instability of the less fusible form makes dimorphism or polymerization more likely in the present case.

On heating 2-acetylfurane in alcohol with piperidine hydrochloride and paraformaldehyde, a homogeneous solution was obtained in a few minutes, and on cooling (furyl-2)  $\beta$ -piperidinoethyl ketone hydrochloride (XII,  $R_2 = C_5H_{10}$ ) separated. After washing free from excess of XI with ether, it was crystallized from water. The yield was 10%.

In preparing (furyl-2)  $\beta$ -dimethylaminoethyl ketone hydrochloride (XII,  $R = CH_3$ ), a few drops of concentrated hydrochloric acid were added to the reaction mixture, which was heated for 45 minutes to give a 26% yield. The homologous di-n-propylamino-ketone (XII,  $R = C_3H_7$ ) was prepared in a similar fashion, but evaporation of the mother liquor was necessary for its separation, and the yield was only 12%.

Di-n-butylamine hydrochloride was also condensed with 2-acetylfurane and paraformaldehyde. As in the case of the dipropyl-compound, the reaction mixture had to be evaporated to a smaller volume before the amino-ketone (XII,  $R = n-C_4H_9$ ) separated, the yield again be-

ing poor.

Use of diethanolamine as the basic constituent in the condensation was successfully attempted. The syrup obtained by evaporation of a weighed quantity of diethanolamine with an equivalent volume of dilute hydrochloric acid was refluxed in alcohol with 2-acetylfurane and paraformaldehyde for 75 minutes. As there were no signs of separation occurring, the reaction mixture was evaporated to dryness on the steam-bath, and the residual viscous mass left for a week in a vacuum-desiccator. Prolonged stirring then caused crystallization to set in. (Furyl-2)- $\beta$ -di-( $\beta$ -hydroxyethyl)-aminoethyl ketone hydrochloride (XII, R= HO.CH<sub>2</sub>.CH<sub>2</sub>-) is light brown in colour, whereas the other members of the series are white. It is further distinguished by its aromatic odour.

2-Acetylfurane and formaldehyde could not be condensed with diethylamine hydrochloride, which was recovered unchanged. The erratic behaviour of this amine in the Mannich reaction has already been noted.

The solubilities at room temperature given below show decrease in the influence of the electrovalent linkage in these hydrochlorides as the size of the N-alkyl-group is increased. The small solubility of (5.) in alcohol was unexpected. Compounds (1.) and (2.) were slightly hygroscopic.

	-NR <sub>2</sub>	Alcohol	Water	Acetone	Ether
(1.)	-NC <sub>5</sub> H <sub>10</sub>	Soluble	Very Soluble	Insoluble	Insoluble
(2.)	-N(CH <sub>3</sub> ) <sub>2</sub>	"	" "	"	"
(3.)	-N(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub>	"	Soluble	Soluble	"
(4.)	-N(C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub>	"	"	"	Slightly soluble
(5.)	-N(C <sub>2</sub> H <sub>4</sub> OH) <sub>2</sub>	Slightly soluble	"	—	Insoluble

These compounds did not separate readily on recrystallization, which partly accounts for the poor yields obtained. On addition of dilute alkali to any of the aqueous solutions, separation was first observed, and on warming the odour of the amine used in preparation became perceptible.

The pure hydrochlorides resembled the corresponding phenylthiazyl-derivatives in answering Feigl's test for methyl ketones with sodium nitroprusside.

No marked loss of sensation was caused by any of the furyl-ketones on the tongue.

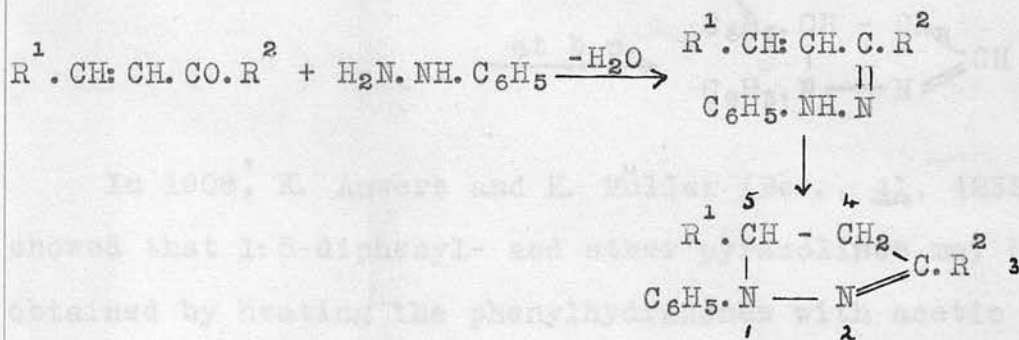
The halogen present could not be determined by titration with alkali, but satisfactory results were obtained in carbon, hydrogen and nitrogen (micro-Dumas) estimations.

No crystalline products could be isolated from attempts to prepare the phenylhydrazones in alcoholic and in aqueous solution. The appearance of the reaction mixtures was suggestive of decomposition. This is hardly surprising when, in addition to the behaviour of phenyl-

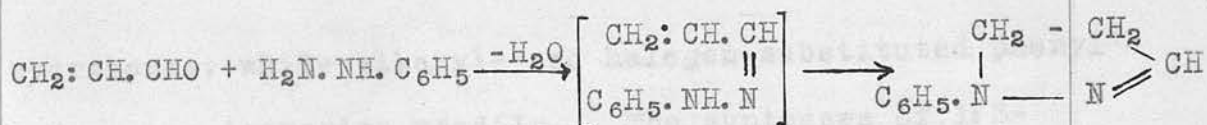
hydrazine with more stable  $\beta$ -amino-ketones, the instability of the phenylhydrazone of 2-acetylfurane itself is considered. Analogous  $\beta$ -amino-derivatives of 2-acetylthiophene were observed to act similarly - the phenylhydrazone of this methyl ketone is very unstable (Peter, Ber., 1884, 17, 2645).

## 2. The Synthesis of 1:3:5-Trisubstituted Pyrazolines.

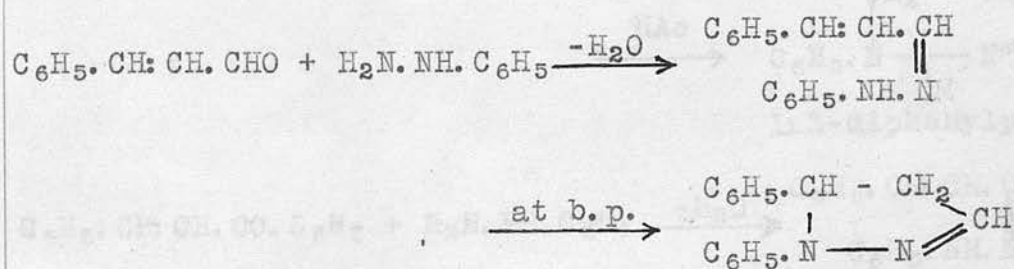
Pyrazoline-derivatives may be prepared by a general reaction from  $\alpha$ -unsaturated aldehydes or ketones.



By the action of phenylhydrazine, the pyrazoline is in some cases obtained directly from the aldehyde or ketone, the isomeric phenylhydrazone never being isolated. Thus E. Fischer and O. Knoevenagel (Ann., 1887, 239, 194) observed that acrolein when treated with phenylhydrazine gave 1-phenylpyrazoline, it being impossible at that time to isolate the phenylhydrazone.



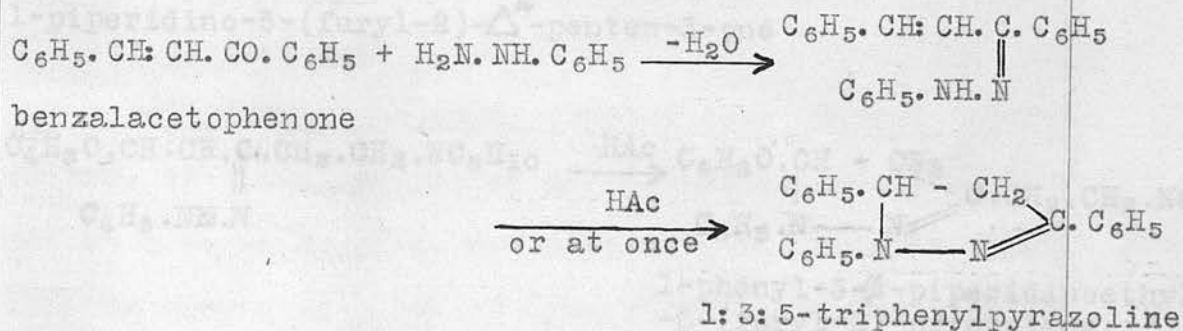
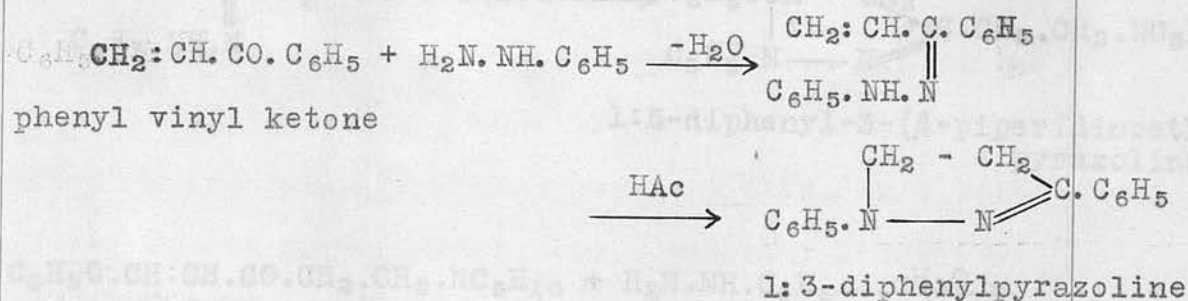
In other cases, the hydrazone is formed, and this must then be made to isomerise to the pyrazoline. At one time, the only method known for converting a phenylhydrazone to the isomeric pyrazoline was to distil it. The phenylhydrazone of cinnamic aldehyde was in this way isomerised to 1:5-diphenylpyrazoline (Laubmann, Ber., 1888, 21, 1213).



In 1908, K. Auwers and K. Müller (Ber., 41, 4232) showed that 1:5-diphenyl- and other pyrazolines may be obtained by heating the phenylhydrazones with acetic acid. Many pyrazoline-derivatives have since been prepared from the corresponding hydrazones by the use of this agent.

If the phenylhydrazone is derived from a ketone, the pyrazoline will be substituted at position 3. Should the vinyl group in the aldehyde or ketone started with be substituted, the same substituent will appear at position 5 in the pyrazoline. The radical at position 1 may be varied by use of substituted phenylhydrazines. A nitro-group in the phenyl nucleus tends to stabilize the phenyl-

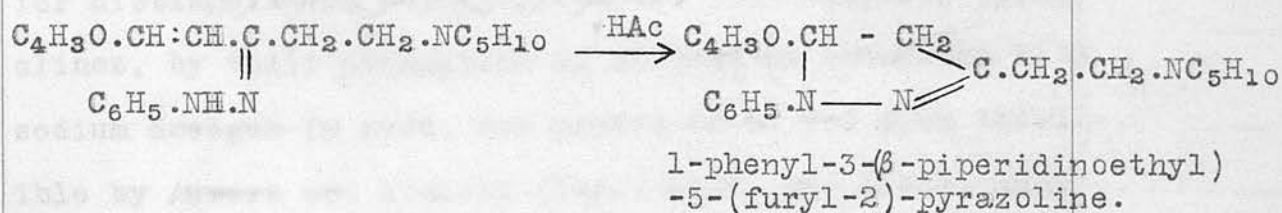
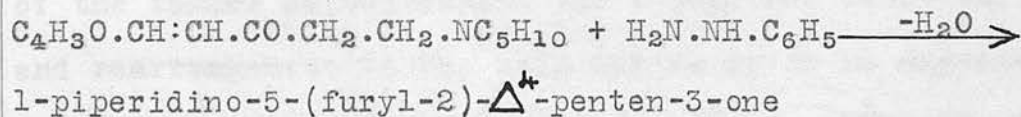
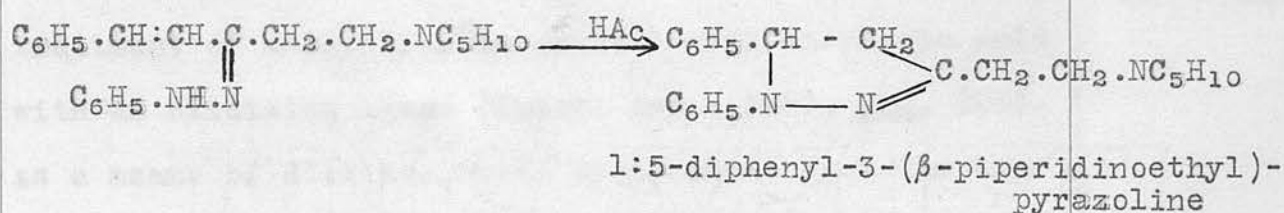
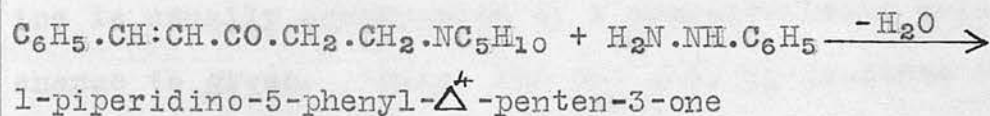
hydrazones, while alkoxy- and halogen-substituted phenylhydrazones isomerise readily. The syntheses of 1:3-diphenyl- and 1:3:5-triphenyl-pyrazoline further illustrate the former points. (Auwers and co-workers, Ber., 1932, 65, 833; *ibid.*, 1909, 42, 4412. Raiford and co-workers, J.A.C.S., 1934, 56, 174; *ibid.*, 1933, 55, 1125; *ibid.*, 1928, 50, 159.)



(The formation of 1:3-disubstituted pyrazolines from  $\beta$ -aminoethyl-ketones discussed on previous pages may take place through primary loss of the amine residues, followed by immediate isomerisation of the phenylhydrazones of the resultant vinyl ketones.)

$\alpha$ -Unsaturated methyl ketones such as benzylideneacetone may be condensed with formaldehyde and secondary amines by the Mannich reaction. The phenylhydrazones of the  $\beta$ -piperidinoethyl-derivatives of benzylidene- and

furfurylidene-acetone were shown by H. B. Nisbet and C. G. Gray (J.C.S., 1933, 839) to isomerise to the corresponding 3- $\beta$ -piperidinoethyl-pyrazolines on treatment with acetic acid.



The analogous  $\beta$ -dimethylaminoethyl-pyrazolines could not be obtained from the isomeric phenylhydrazones by treating with acetic acid. At a later date, however, Dr. H. B. Nisbet succeeded in carrying out these isomerisations in presence of hydrochloric acid.

In this way, pyrazolines capable of forming water-

soluble salts may be prepared.

The conversion of a phenylhydrazone into a pyrazoline is usually accompanied by a characteristic colour change to green. Many, but not all, pyrazolines fluoresce in solution. A blue-violet colour is produced on treatment of a solution in concentrated sulphuric acid with an oxidising agent (Knorr, Ann., 1887, 238, 200). As a means of distinguishing pyrazolines from the isomeric hydrazones, this test is unreliable, as a trace of the former is sufficient for a positive reaction, and rearrangement in the acid medium is to be expected.

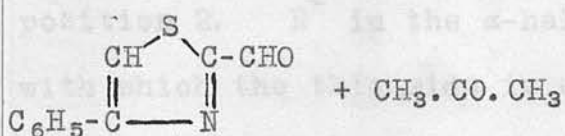
The method described by Tafel (Ber., 1889, 22, 1854) for distinguishing phenylhydrazones from isomeric pyrazolines, by their production of aniline on reduction with sodium amalgam in acid, was proved to be far from infallible by Auwers and Kreuder (Ber., 1925, 58, 1976), many phenylhydrazones yielding no aniline at all. In any case, the test requires excessive quantities of the hydrazone. Reduction to the phenylhydrazone of the corresponding saturated ketone in an alkaline medium has been used in cases where the latter is known (Raiford and Peterson, J. Org. Chem., 1937, 1, 544).

To distinguish between certain pairs of isomers, Raiford and Peterson (loc. cit.) have also made use of a colour reaction with bromine, the vapour of which causes

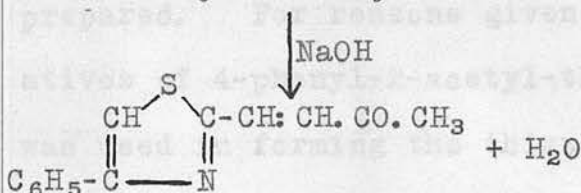
the hydrazones to turn red-orange and the pyrazolines green. Different typical crystalline structures for the isomers were noted.

4-Phenyl-2-formylthiazole.

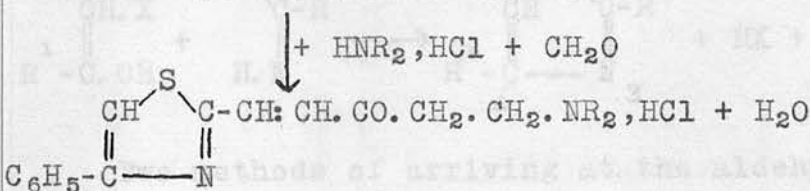
The synthesis of 1-phenyl-3-( $\beta$ -dialkylaminoethyl)-5-(4-phenylthiazyl-2)-pyrazolines was planned as follows:-



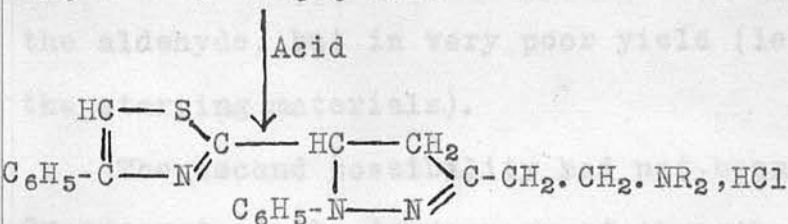
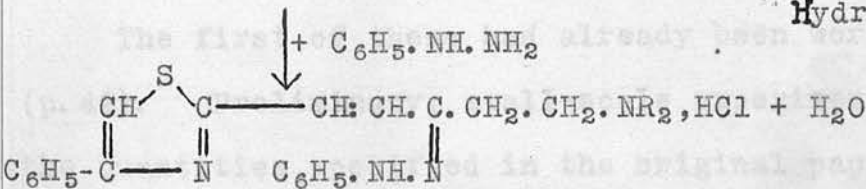
4-Phenyl-2-formylthiazole



4-Phenylthiazylidene-acetone



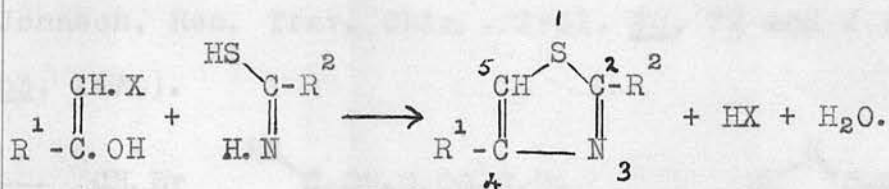
1-Dialkylamino-5-(4-phenylthiazyl-2)- $\Delta^4$ -penten-3-one Hydrochloride



1-Phenyl-3-( $\beta$ -dialkylaminoethyl)-5-(4-phenylthiazyl-2)-pyrazoline Hydrochloride.

$\alpha$ -Unsaturated ketones such as 4-phenylthiazylideneacetone are, as a rule, readily prepared by condensation of appropriate aldehydes with acetone in presence of alkali (cf. benzal-acetone, "Chem. Synth.", III).

To obtain the thiazyl aldehyde,  $R^2$  in the thioamide used in synthesising the thiazole ring must be of such a nature that the formyl group may be readily formed at position 2.  $R^1$  in the  $\alpha$ -halogen-substituted ketone, with which the thioamide is condensed, determines the nature of the substituent at position 4 in all compounds prepared. For reasons given in the discussion of derivatives of 4-phenyl-2-acetyl-thiazole,  $\omega$ -bromoacetophenone was used in forming the thiazole ring ( $R^1 = C_6H_5$ ).



Two methods of arriving at the aldehyde suggested themselves.

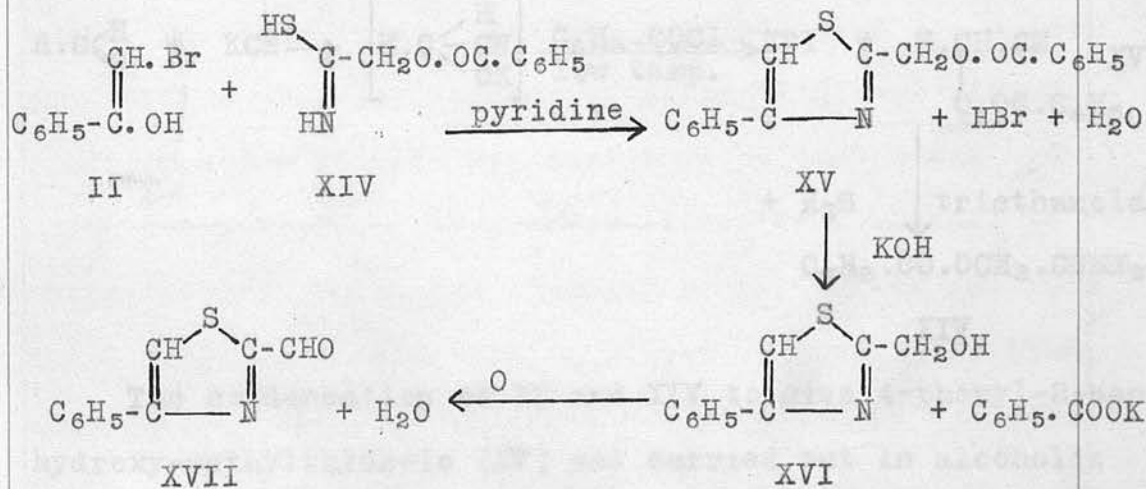
The first of these had already been worked out (p. 42). Preliminary, small-scale experiments, using the quantities specified in the original paper, gave the aldehyde, but in very poor yield (less than 2.5% of the starting materials).

The second possibility had not been explored (p. 45). On account of the inadequacy of the other, however, it was tried out. The attempts were unsuccessful.

Returning to the first method, it was gone through on a larger scale, only to find that extensive decomposition occurred in the final stage.

On account of the difficulty of obtaining a sufficient quantity of the aldehyde, and the waste of materials involved even when the method worked without a hitch, this line of research was abandoned as impracticable.

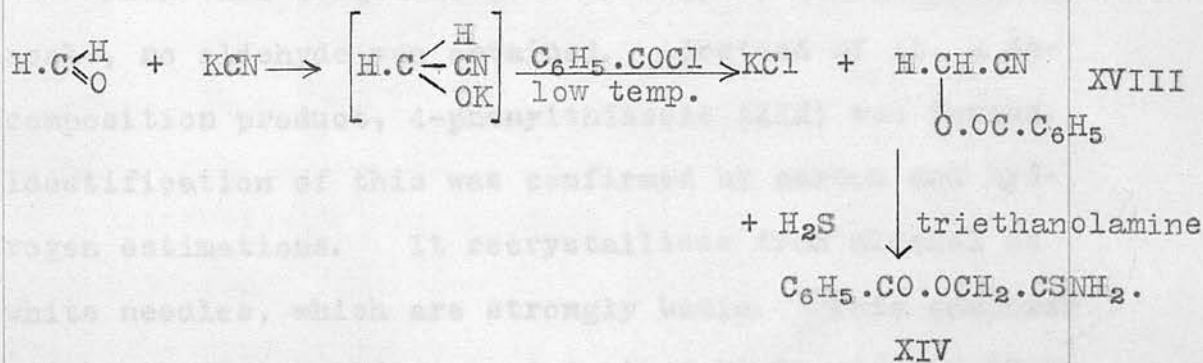
4-Phenyl-2-formylthiazole: First Method.  $\omega$ -Bromo-acetophenone (II) was condensed with benzoylhydroxythioacetamide (XIV). The benzoate produced (XV) was hydrolysed to the primary alcohol (XVI), which was in turn oxidised to the aldehyde required (XVII). (J. F. Olin and T. B. Johnson, Rec. Trav. Chim., 1931, 50, 72 and J. A. C. S., 1931, 53, 1470).



The preparation of  $\omega$ -bromoacetophenone has already been discussed.

To prepare benzoylhydroxythioacetamide, the corresponding nitrile (XVIII) was required. An equimolecular mixture of formaldehyde (as 40% solution), benzoyl chloride and potassium cyanide was shaken at a low temperature. The mixture must be kept cold throughout the reaction. The product was distilled under reduced pressure to give the nitrile, which was found to solidify at room temperature.

Hydrogen sulphide was made to react with the nitrile in the presence of triethanolamine as catalyst. Benzoylhydroxythioacetamide was obtained after passing in hydrogen sulphide gas for a few hours at 45°C. Benzene was found suitable for recrystallising the product, for which a melting-point 4°-5° higher than that given in the paper quoted was found.



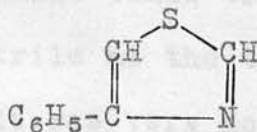
The condensation of II and XIV to give 4-phenyl-2-benzoylhydroxy-methylthiazole (XV) was carried out in alcoholic solution in presence of pyridine. The product was washed with dilute acid to remove the pyridine, and recrystallised from alcohol to give a 60% yield of white solid.

This was hydrolysed by alcoholic potassium hydroxide

to the free alcohol, 4-phenyl-2-hydroxymethylthiazole (XVI). As the alcohol was obtained as a solid instead of as an oil at the end of the hydrolysis, the ether-extraction and distillation under reduced pressure described in the original paper were unnecessary. From dilute alcohol, brown cubes, melting  $1^{\circ}$  higher than the m. pt. given by Olin and Johnson, were obtained in 75% yield.

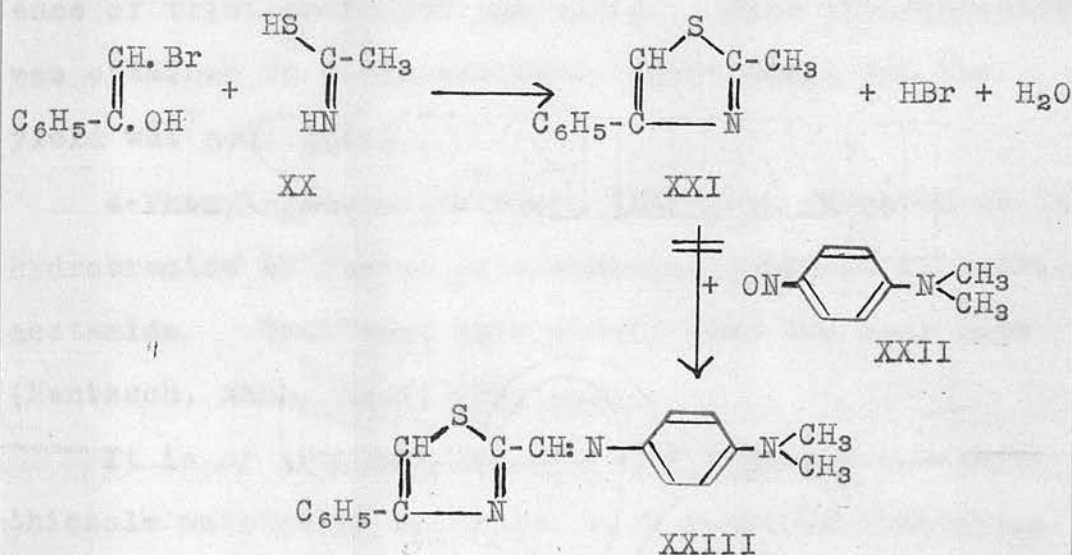
Oxidation of a small quantity of (XVI) with sodium dichromate in acetic acid solution gave 4-phenyl-2-formylthiazole (XVII). The aldehyde was purified by distillation under reduced pressure, and was found to solidify at room temperature. The yield was very poor. The phenylhydrazone was prepared.

When this stage was gone through on a slightly larger scale, no aldehyde was obtained. Instead of it, a decomposition product, 4-phenylthiazole (XIX) was formed. Identification of this was confirmed by carbon and hydrogen estimations. It recrystallises from alcohol as white needles, which are strongly basic. This compound and its hydrochloride were described by Popp (Ann., 1889, 250, 279). The hydrochloride was prepared as further evidence of identity. The base gives a loose addition compound with benzoyl chloride.

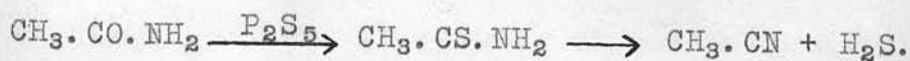


XIX

4-Phenyl-2-formylthiazole: Second Method.  $\omega$ -Bromoacetophenone was made to react with thioacetamide (XX). Attempts to condense the compound formed (XXI) with p-nitrosodimethylaniline (XXII) met with failure. If the condensation had been successful, hydrolysis of the product (XXIII) by acid would have been expected to give the aldehyde required (Cf. Kaufmann and Vallette, Ber., 1912, 45, 1740).



Thioacetamide was prepared by fusing phosphorus pentasulphide with acetamide in presence of benzene, in which the product is soluble (Hantzsch, Ann., 1889, 250, 264). Care must be taken not to heat any longer than is absolutely necessary, as thioacetamide tends to give off hydrogen sulphide to form acetonitrile at the temperature of fusion. The yield of thioamide was very poor.

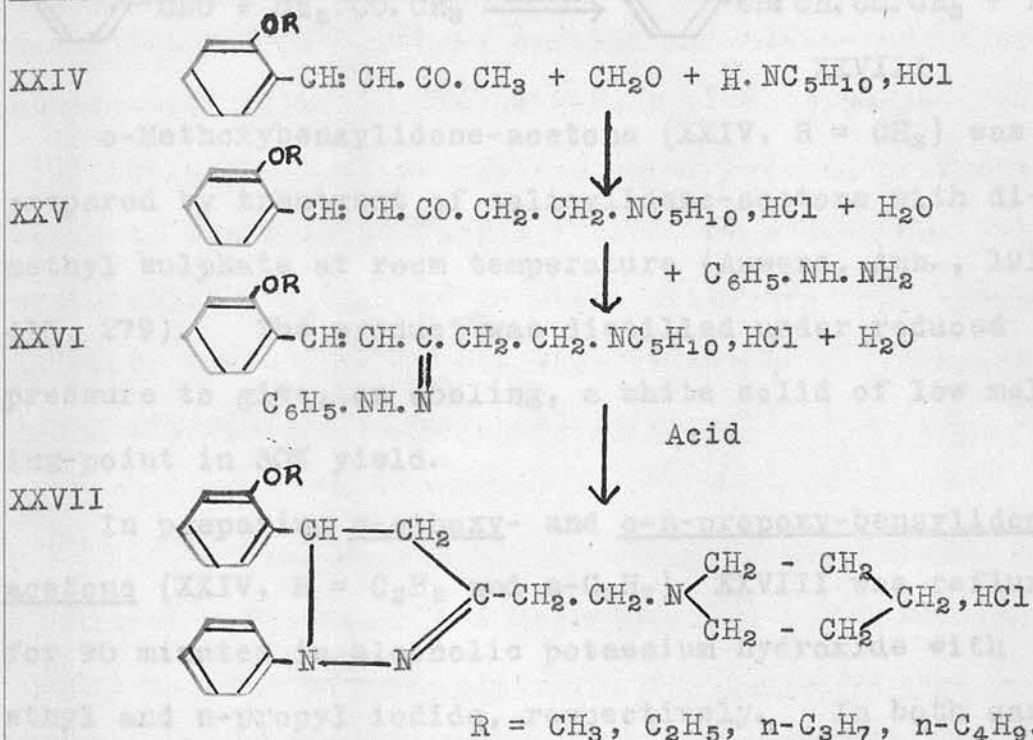


Thioacetamide has been prepared from acetonitrile by addition of hydrogen sulphide in the presence of ammonia (Bernthsen, Ann., 1878, 192, 46). The preparation took weeks and the product could not be purified. Olin and Johnson (Rec. Trav. Chim., 1931, 50, 72) have shown triethanolamine to be preferable to ammonia as a catalyst in forming thioamides from nitriles. The addition of hydrogen sulphide to acetonitrile in the presence of triethanolamine was tried. Pure thioacetamide was obtained in a comparatively short time, but the yield was negligible.

4-Phenyl-2-methylthiazole (XXI) was prepared as the hydrobromide by fusion of  $\omega$ -bromoacetophenone with thioacetamide. Treatment with alkali gave the free base (Hantzsch, Ann., 1889, 250, 269).

It is of interest to note that 4-phenyl-2-methylthiazole methiodide condenses with p-nitrosodimethylaniline (W. H. Mills, J.C.S., 1922, 121, 2724). In view of the difficulty encountered in the isolation of 4-phenyl-2-formylthiazole in large quantity, it was deemed unlikely that use could be made of this reaction for present purposes.

$\beta$ -Amino-ketones and Related Pyrazolines derived from  
o-Alkoxy-benzylidene-acetones.

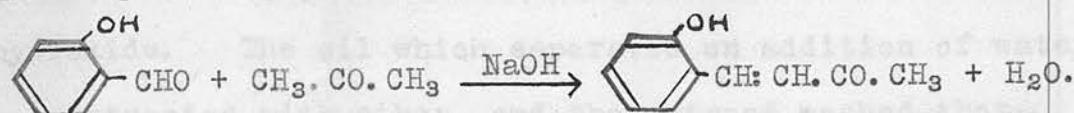


o-Alkoxy-benzylidene-acetones (XXIV) were prepared by alkylation of salicylidene-acetone (XXVIII).



The latter was obtained in good yield by condensation of salicylic aldehyde in alkaline solution with acetone (Harries, Ber., 1891, 24, 3180), the product separating on addition of acid. Recrystallization was found to be in itself sufficient for purification, the steam-distillation described by Harries for removal of excess aldehyde being omitted as it caused extensive

charring.

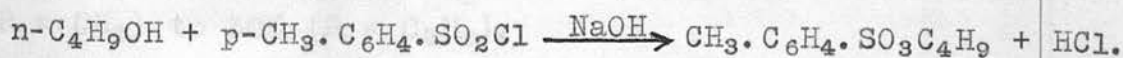


XXVIII

*o*-Methoxybenzylidene-acetone (XXIV, R = CH<sub>3</sub>) was prepared by treatment of salicylidene-acetone with dimethyl sulphate at room temperature (Auwers, Ann., 1917, 413, 279). The product was distilled under reduced pressure to give, on cooling, a white solid of low melting-point in 30% yield.

In preparing *o*-ethoxy- and *o*-*n*-propoxy-benzylidene-acetone (XXIV, R = C<sub>2</sub>H<sub>5</sub> and *n*-C<sub>3</sub>H<sub>7</sub>), XXVIII was refluxed for 90 minutes in alcoholic potassium hydroxide with ethyl and *n*-propyl iodide, respectively. In both cases, the oil thrown out by addition of water to the reaction mixture was extracted with ether and distilled under 1 mm. pressure. The ethoxy-compound was obtained as a low-melting white solid, and the propoxy- as an almost colourless liquid which crystallized only after a considerable time. Both proved perfectly stable. The yields were 50% and 35%, respectively.

For butylation of salicylidene-acetone, *n*-butyl-*p*-toluene-sulphonate was manufactured from *n*-butyl alcohol and *p*-toluene-sulphonyl chloride ("Chem. Synth.", IX, 28).



The preparation of *o*-*n*-butoxybenzylidene-acetone

(XXIV, R = n-C<sub>4</sub>H<sub>9</sub>) was carried out in alcoholic potassium hydroxide. The oil which separated on addition of water was extracted with ether, and the extract washed thoroughly with alkali. Great care was found necessary in distilling the butoxy-compound under reduced pressure, owing to its extreme instability. Even at 3 mm., it could only be distilled in small portions. The yield, however, was 50%. On standing, the mobile, amber-colored oil rapidly darkens and thickens.

Each of the four o-alkoxy-benzylidene-acetones was condensed with piperidine hydrochloride and paraformaldehyde to give the corresponding  $\beta$ -piperidinoethyl ketone hydrochloride (XXV). Condensation was brought about by heating the reagents in alcohol for a short time, after which, on cooling and scratching, the white amino-ketone separated. It was found inadvisable to carry out the reaction in too little solvent, or to heat any longer than absolutely necessary (cf. derivatives of 4-phenyl-2-acetylthiazole), a resinous product being obtained under such conditions. The condensation-products were, in each case, washed free from methyl ketone with ether, and recrystallized from alcohol. Yields varied from 13% (R = CH<sub>3</sub>) to 30% (R = C<sub>2</sub>H<sub>5</sub>).

The hydrochlorides were all more or less readily soluble in water and slightly soluble in alcohol at room

temperature. All were quite insoluble in ether. Hydrolysis, with separation of the free bases, was caused by warming, or adding dilute alkali to, the aqueous solutions.  $R = CH_3$ . Emmer's test was inconclusive.

None of these ketones gave a colour reaction with sodium nitroprusside.

The phenylhydrazones (XXVI) of the 1-piperidino-5-(2'-alkoxyphenyl)- $\Delta^4$ -penten-3-one hydrochlorides were prepared after the method of Auwers and Voss (Ber., 1909, 42, 4411), the ketone in absolute alcohol being treated at room temperature with an equivalent quantity of phenylhydrazine, and a weight of acetic acid equal to that of the latter.

In some cases, the phenylhydrazones did not separate readily from the reaction mixtures. All four, however, proved to be isomorphous, crystallizing out at once on seeding the solutions with any member of the homologous series. The average yield was greater than 80%.

Repeated recrystallization of the o-ethoxystyryl ketone phenylhydrazone was found to lower the melting-point and to make it less sharp, suggesting that some isomerisation to the corresponding pyrazoline (XXVII,  $R = C_2H_5$ ) occurred in hot alcohol. (The readiness with which rearrangement of the phenylhydrazones of  $\alpha$ -unsaturated ketones may take place has been pointed out above. That this is enhanced by alkoxy-substitution in styryl

groups has been shown by Raiford and Hill, J. A. C. S., 1934, 56, 174.) As expected, this hydrazone answered Knorr's test for pyrazolines. With the lower homologue (XXVI, R = CH<sub>3</sub>), Knorr's test was inconclusive. The phenylhydrazones of the o-n-propoxystyryl and o-n-butoxystyryl ketones, however, did not answer the test. These latter two hydrazones had, in contrast to the former two, well-defined crystalline structures. No colour-change was observed on exposing any one of the four phenylhydrazones, spread on filter-paper, to bromine vapour (cf. Raiford and Peterson, loc. cit.).

On heating for a short time on the steam-bath with dilute hydrochloric acid, the phenylhydrazones (XXVI) were converted into the isomeric pyrazolines (XXVII).

In the preparation of 1-phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-methoxyphenyl)-pyrazoline hydrochloride, the phenylhydrazone dissolved in the hot acid, from which, on cooling, the pyrazoline separated as a green oil. This, on scratching, gave a white solid. The homologous 5-(2'-ethoxyphenyl)-pyrazoline separated from the hot acid solution in the solid state. In the case of the propoxy-compound (XXVII, R = n-C<sub>3</sub>H<sub>7</sub>), a homogeneous solution was never obtained. As the yellow phenylhydrazone disappeared, it was replaced by the white pyrazoline. 1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-n-butoxyphenyl)-pyrazoline hydrochloride separated as a green oil as the isomeric



phenylhydrazonē was rearranged by hot acid. On cooling and scratching, the oil solidified.

The pyrazoline hydrochlorides differed from the phenylhydrazones in being slightly soluble in hot water, from which they were recrystallized. They were also much more soluble in cold alcohol than the hydrazones, but, as expected, resembled the latter in their insolubility in ether.

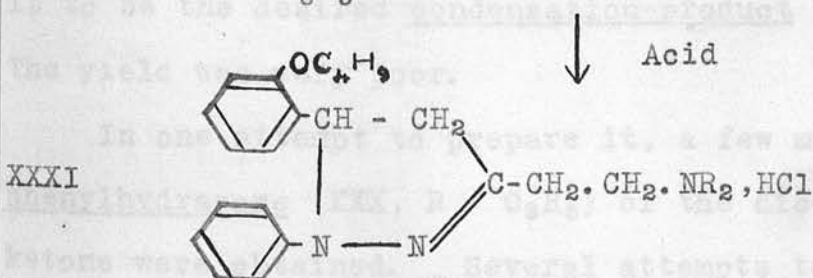
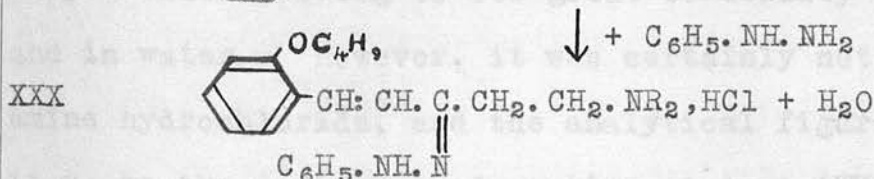
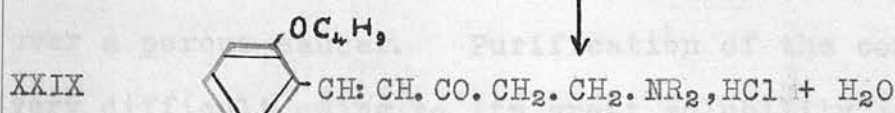
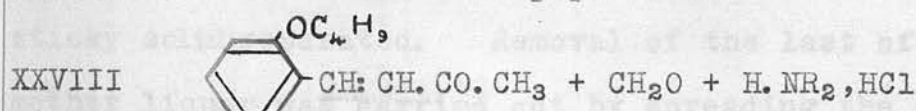
The ethoxyphenylpyrazoline had the same m. pt. as the isomeric phenylhydrazone. A mixed m. pt., however, showed a depression of 20°.

Knorr's test was answered by all four pyrazolines. Exposure of the solids to bromine vapour was found to cause an immediate colour-change to blue-violet. This marked reaction contrasted strongly with the behaviour of the isomeric hydrazones. The test thus proved to be much more reliable than Knorr's for distinguishing between the isomers. None of the pyrazoline-hydrochlorides fluoresced in solution.

All four caused marked loss of sensation when placed on the tip of the tongue. Although the hydrochlorides were not very soluble in cold water, aqueous solutions, concentrated enough for comparisons of their local anaesthetic activities with that of cocaine, could be obtained (see Section IV).

As 1-phenyl-3- $\beta$ -piperidinoethyl)-5-(2'-n-butoxy-phenyl)-pyrazoline hydrochloride (XXXI,  $R_2 = C_5H_{10}$ ), proved on testing to be the most powerful in local anaesthetic activity of the four compounds, it was planned to prepare a series of dialkylaminoethyl-pyrazolines from o-n-butoxybenzylidene-acetone, with a view to studying the effect of variation of the dialkylamino-residue on the physiological activity of the molecule.

This called for, in the first place, condensation of o-n-butoxybenzylidene-acetone and formaldehyde with secondary bases other than piperidine.



Several efforts were made in each case to replace piperidine hydrochloride in this reaction by dimethylamine, di-n-propylamine, di-n-butylamine and diethanolamine hydrochlorides. All were unsuccessful. Vari-

ations in the conditions suggested by previous experience of the Mannich reaction did not bring about condensation. Frequently, large amounts of the amine hydrochlorides started with were recovered.

After removal by extraction with ether of unchanged butoxy-benzylidene-acetone from the reaction mixtures, attempts were made to isolate condensation-products as phenylhydrazones; but this also failed.

On thoroughly cooling the solution obtained by heating *o*-*n*-butoxybenzylidene-acetone and paraformaldehyde with diethylamine hydrochloride in alcohol, a very sticky solid separated. Removal of the last of the mother liquor was carried out by spreading the solid over a porous saucer. Purification of the compound was very difficult owing to its great solubility in alcohol and in water. However, it was certainly not diethylamine hydrochloride, and the analytical figures suggest it to be the desired condensation-product (XXIX,  $R = C_2H_5$ ). The yield was very poor.

In one attempt to prepare it, a few mgm. of the phenylhydrazone (XXX,  $R = C_2H_5$ ) of the diethylaminoethylketone were obtained. Several attempts to repeat this preparation under exactly similar conditions resulted in a white solid, which has not been identified. It was not the  $\beta$ -diethylaminoethyl-pyrazoline (XXXI,  $R = C_2H_5$ ). The readiness with which phenylhydrazones of  $\beta$ -amino-

ketones decompose has been already pointed out. It was first observed in the case of styryl derivatives by C. Mannich and M. Schütz (Arch. Pharm., 1927, 265, 684).

Conversion of the isomeric phenylhydrazones into pyrazolines with amino-side-chains is seen to occur readily on heating with dilute hydrochloric acid. Reaction is smoother and quicker than in the presence of glacial acetic acid, and the product is readily obtained as the hydrochloride, a form suitable for carrying out physiological tests. But for losses incurred in purification, yields would be almost quantitative.

It is unfortunate that variants of a compound found to be a strong local anaesthetic, could not be prepared, as an even more active molecule might have been discovered. The anomalous behaviour of the Mannich reaction has been fully discussed elsewhere. In the present instance, the bulky ortho-grouping may have caused steric hindrance.

11. 3-amino-ketone derived from 4-Phenyl-2-acetyl-

Yields are quoted as percentages of the maximum possible from theory.

Melting-points are corrected, the thermometer used having been calibrated against short stem "Standard Thermometers." In dealing with hygroscopic substances, the procedure was to dry thoroughly in a vacuum desiccator before filling the melting-point tube, which was then immediately sealed, the tip being later broken off when the temperature of the bath exceeded 100°C.

Quantitative analyses were carried out on the micro-scale by the author (Pregl, "Quantitative Organic Micro-Analysis"). The method for weighing-out hygroscopic compounds described by Friedrich and Mandl (Mikro-Chemie, 1937, 16, 14) was found satisfactory in micro-Dumas estimations.

The qualitative tests used were, as a rule, those given in Feigl's "Qualitative Analyse mit Hilfe von Tüpfelreaktionen."

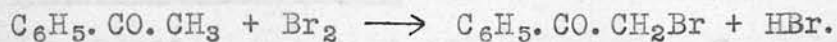
New compounds are denoted by an asterisk.

(about 3 litres in all) containing a little sodium carbonate. Leave overnight, and filter off the crystals which separate.

Recrystallisation from 90% alcohol gives pure white

1.  $\beta$ -Amino-ketones derived from 4-Phenyl-2-acetyl-thiazole.

$\omega$ -Bromoacetophenone.



At first, the method described by Rather and Reid (J. A. C. S., 1919, 41, 77) was used. As uncontrollable charring occurred, recourse was made to Möhlau's method (Ber., 1882, 15, 2), in which bromination is carried out in more dilute solution. The product was again unsatisfactory; the following modification, in which smaller quantities are treated and heating is done without, however, is reliable and yields an excellent product.

20 gm. acetophenone are dissolved in 100 c. c. glacial acetic acid. 9 c. c. bromine are run in slowly from a burette, the solution being constantly shaken. Ten quantities of acetophenone are treated thus, one after the other.

Hydrogen bromide is evolved, and, after about 20 minutes, the solution suddenly changes in colour to a light yellow. As the contents of each flask change in colour, they are immediately poured into ice-water (about 8 litres in all) containing a little sodium carbonate. Leave overnight, and filter off the crystals which separate.

Recrystallisation from 95% alcohol gives pure white

prisms, melting at 50°C.

Yield 70% - 80%.

Benzoylthiolactamide.

(a.) Benzoyllactonitrile.

(J. F. Olin and T. B. Johnson, Rec. Trav. Chim.,  
1931, 50, 72)



In a private communication from the authors, the necessity of continued addition of ice during the reaction was learned of - a point not stressed in the paper above.

The oil obtained differed from that of these authors in that it changed to a white crystalline solid at room temperature.

48.4 gm. (1.1 mol.) acetaldehyde.

71.5 gm. (1.1 mol.) pulverised potassium cyanide.

140 gm. (1.0 mol.) benzoyl chloride.

500 gm. crushed ice.

The acetaldehyde is added to the ice in a wide-necked bottle (capacity 1.5 litres). Add a little water, and then the benzoyl chloride and potassium cyanide. Stopper and shake till the smell of benzoyl chloride is no longer detectable (about 1½ hours), adding more ice as that present melts. Extract the white solid or oil, which separates, in chloroform, and dry over calcium

chloride.

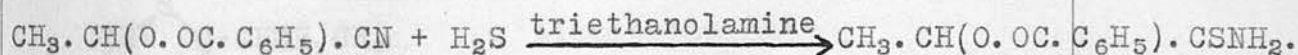
The chloroform is distilled off and the oil distilled in vacuo. B.pt. 158°-165° at 35 mm.

Yield 70% (calculated on benzoyl chloride).

The almost colourless oil has the same refractive index as glass. On boiling with alkali, ammonia is evolved. The oil solidifies at room temperature.

(b.) Benzoylthiolactamide.

(J. F. Olin and T. B. Johnson, loc. cit.)



250 gm. benzoyllactonitrile.

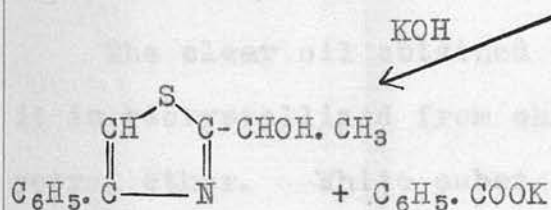
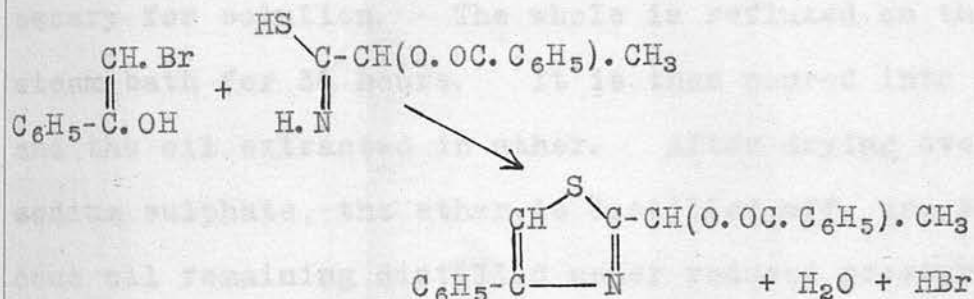
13 gm. triethanolamine.

250 cc. 95% alcohol.

The triethanolamine is dissolved in alcohol and the solution saturated with hydrogen sulphide. Benzoyllactonitrile is now added, and hydrogen sulphide passed in for 6 hours at 45°. The temperature is raised to 60°, and the solution poured into an equal volume of cold water. The solid which separates is filtered off and dried.

Benzene was found to be more suitable for recrystallization than alcohol which was used by Olin and Johnson. The cream-white needles obtained from benzene are washed with petrol ether.

M.pt. 104°C. Yield 45%.

4-Phenyl-2-acetylthiazole.(a.) 4-Phenyl-2- $\alpha$ -hydroxyethylthiazole.(J. F. Olin and T. B. Johnson, J. A. C. S., 1931, 53, 1473)

As extensive decomposition, with separation of benzoic acid, occurred in distilling the benzoate at 14 mm., hydrolysis was carried out on the crude condensation product.

Condensation: 160 gm. benzoylthiolactamide.

150 gm.  $\omega$ -bromoacetophenone.

450 c. c. alcohol.

The solution of  $\omega$ -bromoacetophenone and thioamide in alcohol is refluxed on the steam-bath for 4 hours. Part of the alcohol is then allowed to evaporate. Dilute sodium hydroxide solution is added till alkaline. The oil which separates is extracted in ether, and the ether distilled off to leave 200-300 gm. viscous oil.

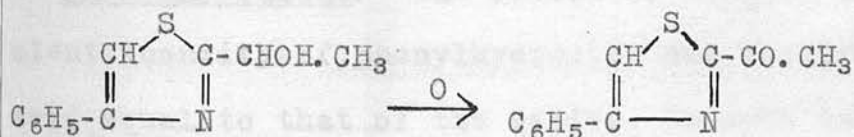
Hydrolysis: To the crude benzoate, dissolved in alcohol, is added about two-thirds of its weight of potassium hydroxide in the minimum quantity of water necessary for solution. The whole is refluxed on the steam-bath for  $3\frac{1}{2}$  hours. It is then poured into water, and the oil extracted in ether. After drying over fused sodium sulphate, the ether is distilled off, and the viscous oil remaining distilled under reduced pressure. B.pt.  $191^{\circ}$ - $194^{\circ}$  at 16 mm.

The clear oil obtained solidifies in the receiver. It is recrystallized from chloroform, being washed with petrol ether. White cubes are obtained.

M.pt.  $76^{\circ}$ . Yield 30%.

(b.) 4-Phenyl-2-acetylthiazole.

(J. F. Olin and T. B. Johnson, loc. cit.)



50 gm. 4-phenyl-2- $\alpha$ -hydroxyethylthiazole.

40 gm. sodium dichromate.

500 cc. glacial acetic acid.

50 cc. water.

To the thiazole derivative dissolved in acetic acid is added dichromate in water. The mixture is heated for  $2\frac{1}{2}$  hours on the steam-bath, and then poured

on to crushed ice. Red crystals separate which, when recrystallized from 75% alcohol, have a m.pt. of 79°-80°. On further recrystallization, white needles of the same m.pt. are obtained.

Yield 65%.

As Olin and Johnson describe the ketone as yellow needles melting at 78°, and as the phenylhydrazone they describe for it is quite different from that obtained, this compound was studied further.

Mixed m.pt. with 4-phenyl-2- $\alpha$ -hydroxyethylthiazole 56°-58°.

Test for methyl ketones with sodium nitroprusside is positive to 4  $\gamma$  (acetophenone answers to 2  $\gamma$ ).

Found: C, 64.98%; H, 4.30%.

Calculated for  $C_{11}H_9ONS$ : C, 65.38%; H, 3.96%.

\* Phenylhydrazone: The ketone is treated with an equivalent quantity of phenylhydrazine and a weight of acetic acid equal to that of the latter, in cold absolute alcohol. The phenylhydrazone separates almost immediately. It crystallizes from absolute alcohol in yellow prisms, m.pt. 141°C.

Found: C, 69.35%, 69.45%; H, 4.92%, 5.02%.

Calculated for  $C_{17}H_{15}N_3S$ : C, 69.61%; H, 5.12%.

On dropping acetyl chloride into a cold benzene solution of the phenylhydrazone, the N-acetyl-derivative

separates as a brick-red solid. Recrystallization from absolute alcohol gives pale yellow cubes, m.pt. 209°C.

Olin and Johnson (loc. cit.) give 208°-209° as the melting-point of the phenylhydrazone, but quote no analysis. It appears as if, under their conditions for the preparation of the phenylhydrazone, acetylation had occurred.

Found: N, 13.92%, 13.78%.

Calculated for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>S: N, 13.68%.

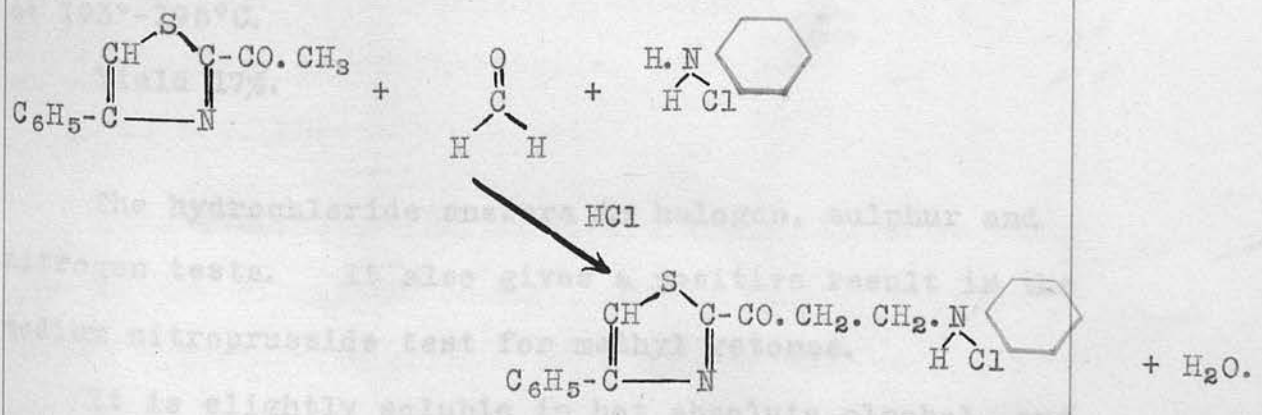
\* Anisylidene derivative: 10% NaOH is dropped into equimolecular proportions of the ketone and anisaldehyde in absolute alcohol. A very poor yield of a compound sintering at 127° and melting at 139°-141°C. was obtained. Lack of material prevented further purification.

Found: C, 68.40%; H, 4.73%.

Calculated for C<sub>19</sub>H<sub>15</sub>O<sub>2</sub>NS: C, 71.03%; H, 4.67%.

\* 4-Phenyl-(thiazyl-2) β-Piperidinoethyl Ketone Hydrochloride.

(Cf. H. B. Nisbet and C. G. Gray, J. C. S., 1933, 839)



10 gm. 4-phenyl-2-acetylthiazole.

6.1 gm. piperidine hydrochloride.

1.5 gm. paraformaldehyde.

20 c.c. absolute alcohol.

To the alcohol in a 100 c.c. conical flask, fitted with reflux condenser, is added 1 c.c. concentrated hydrochloric acid. The ketone and piperidine hydrochloride are dissolved by boiling for a few moments, and then 1.5 gm. paraformaldehyde and a little porous chips are added. After boiling for 15 minutes, the paraformaldehyde goes into solution. Another 0.75 gm. paraformaldehyde is put into the flask, and the boiling is continued for 3 hours. Crystals will then be observed separating from the hot liquid, and the flask is thoroughly cooled.

The solid is filtered off and washed thoroughly on the filter with ether to remove unchanged ketone. From absolute alcohol (filtering off the porous chips when hot) are obtained cream-white crystals, which decompose at 193°-195°C.

Yield 17%.

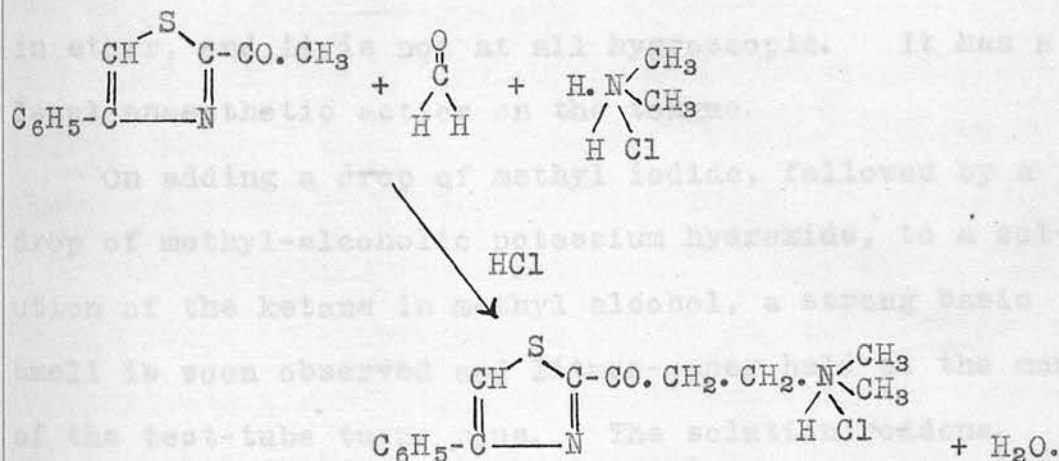
The hydrochloride answers to halogen, sulphur and nitrogen tests. It also gives a positive result in the sodium nitroprusside test for methyl ketones.

It is slightly soluble in hot absolute alcohol, and

forms a suspension on boiling with water, but is insoluble in ether and in cold water. It is not hygroscopic. Decided local anaesthesia is produced by placing a little on the tip of the tongue.

The hydrochloride Found : C, 60.72%, 60.32%; H, 6.19%, 6.08%.  
Calculated for  $C_{17}H_{21}ON_2ClS$ : C, 60.53%; H, 6.23%.

\* 4-Phenyl-(thiazyl-2)- $\beta$ -Dimethylaminoethyl Ketone Hydrochloride.



10 gm. 4-phenyl-2-acetylthiazole.

4.1 gm. dimethylamine hydrochloride.

1.5 gm. paraformaldehyde.

20 c.c. absolute alcohol.

This preparation is carried out exactly as in the case of the piperidino-ketone, in presence of concentrated hydrochloric acid. When it has been refluxed

for 4 hours, the homogeneous liquid is cooled, and the solid which separates washed with ether and recrystallized from absolute alcohol to give almost white platelets.

M.pt. 174°C. Yield about 20%.

The hydrochloride answers to halogen, sulphur and nitrogen tests, and gives a positive in the sodium nitroprusside test for methyl ketones.

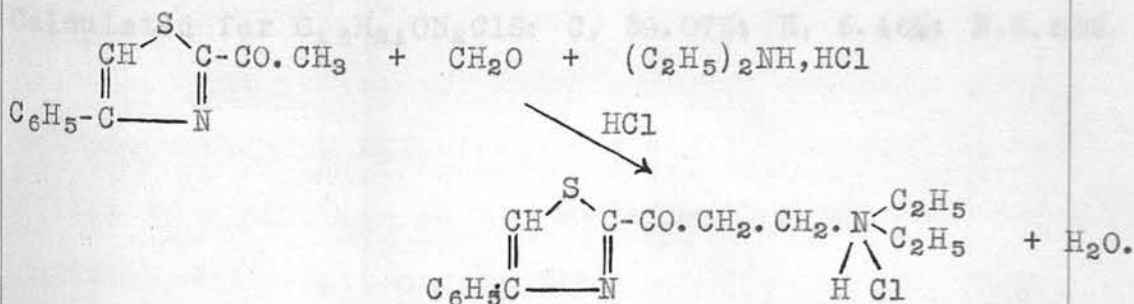
It is slightly soluble in hot absolute alcohol and in hot water; from the latter alkali throws out the base as an oil. The hydrochloride will not dissolve in ether, and it is not at all hygroscopic. It has a local anaesthetic action on the tongue.

On adding a drop of methyl iodide, followed by a drop of methyl-alcoholic potassium hydroxide, to a solution of the ketone in methyl alcohol, a strong basic smell is soon observed and litmus-paper held at the mouth of the test-tube turns blue. The solution reddens.

Found: C, 56.35% ; H, 5.45%.

Calculated for  $C_{14}H_{17}ON_2ClS$ : C, 56.56% ; H, 5.72%.

\* 4-Phenyl-(thiazyl-2)- $\beta$ -Diethylaminoethyl Ketone Hydrochloride.



10 gm. 4-phenyl-2-acetylthiazole.

5.4 gm. diethylamine hydrochloride.

1.5 gm. paraformaldehyde.

20 c.c. absolute alcohol.

This preparation is carried out in exactly the same manner as those of the two preceding ketones.

The reaction mixture is, however, refluxed for 9 hours before cooling in the ice-chest.

A pure white amorphous solid is obtained.

M.pt. 142°C. Yield 23%.

Positive results are obtained in the sulphur, nitrogen, halogen, and "methyl ketone" tests. (In the last, transient blue observed with 10γ.)

The hydrochloride is not at all hygroscopic. It is insoluble in ether, but is fairly readily soluble in hot absolute alcohol, and in hot water, from the latter the base being thrown out by alkali.

Addition of methyl iodide and alkali to the ketone in methyl alcohol causes, on warming, evolution of a vapour with a basic odour and darkening of the solution.

Found: C, 58.99%; H, 6.49%; N, 8.41%.

Calculated for  $C_{16}H_{21}ON_2ClS$ : C, 59.07%; H, 6.46%; N, 8.63%.

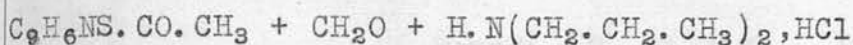
It is readily soluble in hot absolute alcohol,

and very slightly soluble in hot water. The addition of

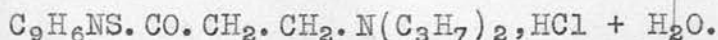
alkali to a solution in the latter giving an opalescence.

The compound is not hygroscopic.

\* 4-Phenyl-(thiazyl-2)  $\beta$ -Di-n-propylaminoethyl Ketone Hydrochloride.



HCl  
↓



6.7 gm. 4-phenyl-2-acetylthiazole.

4.6 gm. di-n-propylamine hydrochloride.

1 gm. paraformaldehyde.

13.5 c.c. absolute alcohol.

To the alcohol is added 1 c.c. concentrated hydrochloric acid and the preparation is proceeded with as in the case of the other similar ketones. The reaction mixture is refluxed for 12 hours before cooling in the ice-chest.

Recrystallization from absolute alcohol gives a pale yellow amorphous solid, which decomposes on heating over a large range, starting about 142°C.

Yield 31%.

Positive results are obtained in the sulphur, nitrogen, halogen and "methyl ketone" tests.

The hydrochloride is insoluble in ether and in acetone. It is readily soluble in hot absolute alcohol, and very slightly soluble in hot water, the addition of alkali to a solution in the latter giving an opalescence.

The compound is not hygroscopic.

Methyl iodide and alkali added to the ketone in methyl alcohol cause evolution of a vapour which turns litmus-paper blue.

Found: C, 61.41% ; H, 7.14%.

Calculated for  $C_{18}H_{25}ON_2ClS$ : C, 61.19% ; H, 7.08%.

Attempts to Prepare 4-Phenyl-(thiazyl-2)  $\beta$ -Di-n-butyl-aminoethyl Ketone Hydrochloride.

Di-n-butylamine hydrochloride was prepared in quantitative yield by neutralizing an alcoholic solution of the free base with dilute hydrochloric acid, followed by evaporation to dryness on the steam-bath.

An alcoholic solution of this compound and 4-phenyl-2-acetyl-thiazole was treated with paraformaldehyde as in the preparation of 4-phenylthiazyl  $\beta$ -di-n-propyl-aminoethyl ketone hydrochloride. Although the mixture was eventually refluxed for 15 hours, there was no evidence of the formation of the desired hydrochloride.

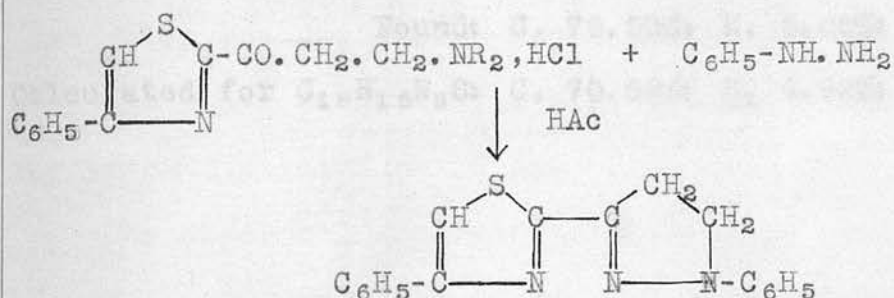
The reaction mixture was then made alkaline with sodium hydroxide solution, but nothing resembling the base could be separated.

Attempting to prepare the hydrochloride in acetic acid, using formalin in place of paraformaldehyde, proved of no assistance.

Attempts to Prepare 4-Phenyl-(thiazyl-2)  $\beta$ -Di-( $\beta$ -hydroxyethyl)-aminoethyl Ketone Hydrochloride.

In one attempt to prepare this compound, diethanolamine was used, and concentrated hydrochloric acid was added, slightly in excess of molecular proportions, to the alcoholic solution. The reaction mixture with 4-phenyl-2-acetylthiazole and paraformaldehyde was refluxed for 22 hours, but neither the desired hydrochloride nor base could be isolated.

In another attempt, hydrochloric acid gas was passed into the alcoholic solution of diethanolamine for a few minutes, before addition of the other reagents. This attempt was also unsuccessful.

\* 1-Phenyl-3-(4-phenylthiazyl-2)-pyrazoline.

To any one of the four 4-phenyl-(thiazyl-2)  $\beta$ -di-alkylaminoethyl ketone hydrochlorides described above, in the minimum quantity of cold absolute alcohol necessary for solution, is added an equivalent weight of phenylhydrazine and the same amount of glacial acetic acid. The yellow needles, which separate overnight, are recrystallized from absolute alcohol. Sintering occurs at  $190^\circ$ , followed by melting at  $198^\circ\text{C}$ .

The compound is not very soluble in organic solvents. It gives a dark blue colour in Knorr's test for pyrazolines (Ann., 1887, 238, 200), in which concentrated nitric acid is added to a digest of the substance in concentrated sulphuric acid. It was shown to be free from halogen. In solution, the pyrazoline exhibits a strong green fluorescence, which is destroyed on addition of mineral acid, but which returns on neutralization.

The identity of samples from all sources was shown by mixed melting-points, no depression being found.

Increase in the size of the alkyl group (R) in the amino-

ketone seems to promote formation of the pyrazoline.

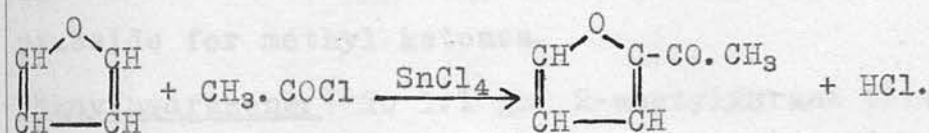
Found: C, 70.50%; H, 5.00%; N, 13.98%.

Calculated for  $C_{18}H_{15}N_3S$ : C, 70.82%; H, 4.92%; N, 13.77%.

## 2. $\beta$ -Amino-ketones derived from 2-Acetylfurane.

### 2-Acetylfurane.

(Tadeus Reichstein, Helv. Chim. Acta, 13, 1930, 356.)



20 gm. furane.

20 c.c. acetyl chloride (freshly distilled).

80 gm. anhydrous stannic chloride.

130 c.c. benzene (dried over sodium).

After drying over fused sodium sulphate, the furane is dissolved in 40 c.c. benzene and cooled to  $0^\circ\text{C}$ . Acetyl chloride is added, and stannic chloride in 90 c.c. benzene dropped in with cooling and shaking. A brown-black solid separates.

The reaction mixture is allowed to stand for 3 hours, and is then shaken with water and steam-distilled. Solid potassium carbonate is added to the distillate, which is extracted with several small quantities of ether. The

ethereal solution is shaken with a little solid potassium carbonate, and dried over fused sodium sulphate.

The ether is distilled off, and the fragrant oil remaining distilled at 12 mm.

The clear oil obtained solidifies on cooling.

M.pt.  $30^{\circ}$  -  $32^{\circ}\text{C}$ . B.pt.  $60^{\circ}$  at 12 mm.

Yield 30% (twice that obtained by Reichstein, who used quarter-quantities).

2-Acetylfurane has an odour similar to that of acetophenone. It answers the test with sodium nitroprusside for methyl ketones.

Phenylhydrazone: To 1.1 gm. 2-acetylfurane dissolved in a few drops of absolute alcohol is added 1.1 gm. phenylhydrazine in 11 c.c. alcohol, followed by 1.1 c.c. glacial acetic acid. After it has stood overnight, water is dropped into the solution till separation begins. A red solid is filtered off. On further addition of water to the filtrate, more solid is precipitated. This is golden in colour, and, on recrystallization from dilute alcohol, melts at  $86^{\circ}$  -  $87^{\circ}\text{C}$ ., in agreement with the m.pt. given for 2-acetylfurane phenylhydrazone by Sandelin (Ber., 1900, 33, 493).

The red solid, which is originally obtained in greater amount, cannot be purified as recrystallization yields the golden-coloured phenylhydrazone. However, the red solid remains unchanged on standing for a con-

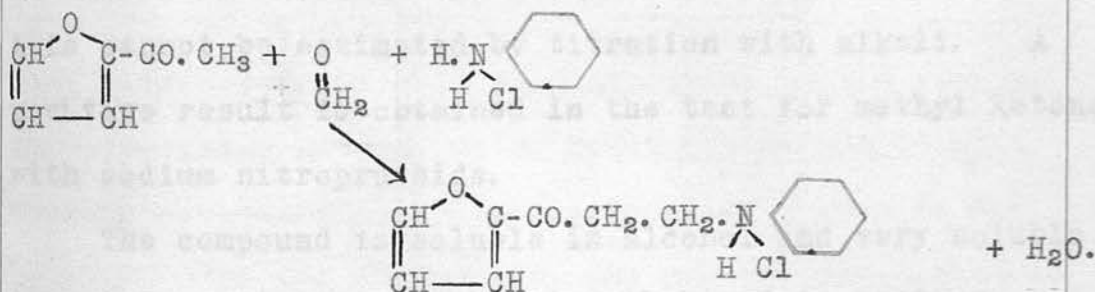
siderable period, while the golden-coloured compound undergoes extensive decomposition in a few weeks. The following data were obtained for the former in the crude state:

M. pt. 187-188°C.

Found: C, 69.33% ; H, 6.23%.

Calculated for  $C_{12}H_{12}ON_2$ : C, 72.00% ; H, 6.00%.

\* (Furyl-2)  $\beta$ -Piperidinoethyl Ketone Hydrochloride.



5.5 gm. 2-acetylfurane.

6.1 gm. piperidine hydrochloride.

1.5 gm. paraformaldehyde.

20 c. c. absolute alcohol.

The ketone and the hydrochloride are dissolved in boiling alcohol in a 100 c. c. conical flask, fitted with reflux condenser and containing porous chips. After addition of 1.5 gm. paraformaldehyde, the reaction mixture is refluxed for 15 minutes, by which time it is homogeneous. Another 0.75 gm. paraformaldehyde is added,

followed by boiling for 15 minutes more. The contents of the flask are then thoroughly cooled.

The solid, which separates, is filtered off, and washed on the filter with ether to remove unchanged ketone. It is recrystallised from water (filtering off the porous chips when hot), acetone being used for washing. The white powder obtained melts at 185°-186°C.

Yield 10%.

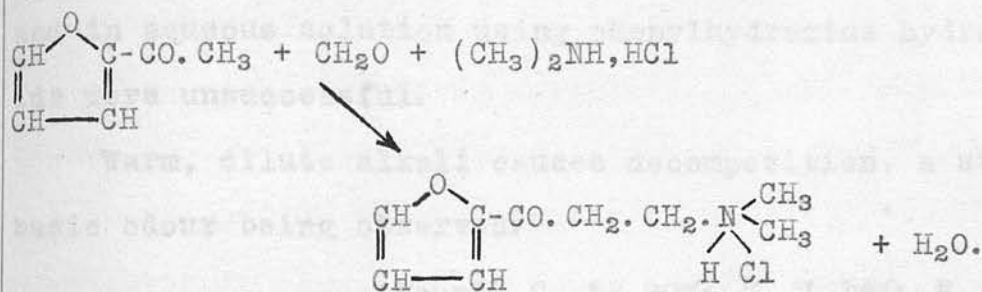
The hydrochloride crystallizes from absolute alcohol as long needles. It answers to tests for halogen, but this cannot be estimated by titration with alkali. A positive result is obtained in the test for methyl ketones with sodium nitroprusside.

The compound is soluble in alcohol and very soluble in water. It is insoluble in ether and in acetone. No phenylhydrazone could be obtained.

Addition of dilute alkali to the aqueous solution causes separation of the base. On warming the alkaline solution, decomposition occurs, with formation of piperidine.

Found: C, 58.87%; H, 7.48%; N, 6.21%.

Calculated for  $C_{12}H_{18}O_2NCl$ : C, 59.02%; H, 7.38%; N, 5.75%.

\* (Furyl-2)  $\beta$ -Dimethylaminoethyl Ketone Hydrochloride.

5.5 gm. 2-acetylfurane.

4.1 gm. dimethylamine hydrochloride.

1.5 gm. paraformaldehyde.

15 c.c. absolute alcohol.

This preparation is carried out as in the case of the piperidino-ketone, with, however, the addition of 4 drops concentrated hydrochloric acid. When it has been refluxed for 45 minutes, the homogeneous liquid is cooled in the ice-chest, and the solid which separates filtered off and washed with ether.

Recrystallization from water, washing with acetone, gives white leaflets, m. pt. 178°C.

Yield 26%.

The compound answers to tests for halogen, and gives a positive in the sodium nitroprusside test for methyl ketones. It is soluble in alcohol, and very soluble in water, tending to absorb moisture from the atmosphere. Neither ether nor acetone will dissolve the hydrochloride.

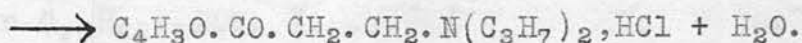
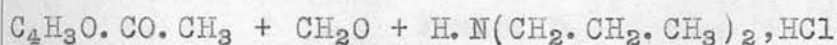
Efforts to obtain the phenylhydrazone in alcohol, and in aqueous solution using phenylhydrazine hydrochloride were unsuccessful.

Warm, dilute alkali causes decomposition, a strong basic odour being observed.

Found: C, 52.90%; H, 7.16%; N, 6.97%.

Calculated for  $C_9H_{14}O_2NCl$ : C, 52.94%; H, 6.86%; N, 6.88%.

\* (Furyl-2)  $\beta$ -Di-n-propylaminoethyl Ketone Hydrochloride.



3.7 gm. 2-acetylfurane.

4.6 gm. di-n-propylamine hydrochloride.

1 gm. paraformaldehyde.

7.5 c.c. absolute alcohol.

To the alcohol, 3 drops concentrated hydrochloric acid are added, and the preparation is proceeded with as in the case of the dimethylamino-compound. The reaction mixture is refluxed for one hour. Crystals of the condensation product separate on cooling in the ice-chest. A further crop is obtained on evaporating the mother liquor.

Recrystallization from absolute alcohol gives white cubes which decompose sharply at  $129^\circ$ - $130^\circ$ C.

Yield 12%.

Positive results are obtained in the halogen and "methyl ketone" tests.

The hydrochloride is soluble in water, alcohol, and acetone. It is insoluble in ether. Dilute alkali causes separation of the base from aqueous solution. Decomposition occurs on warming the alkaline solution, a basic odour becoming perceptible.

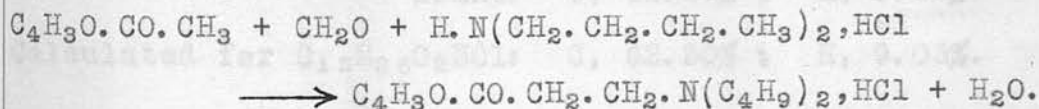
The compound has a transitory local anaesthetic action on the tongue.

No phenylhydrazone could be obtained.

Found: C, 60.03%; H, 8.57%; N, 5.32%.

Calculated for  $C_{13}H_{22}O_2NCl$ : C, 60.00%; H, 8.46%; N, 5.39%.

\* (Furyl-2)  $\beta$ -Di-n-butylaminoethyl Ketone Hydrochloride.



5.5 gm. 2-acetylfurane.

8.3 gm. di-n-butylamine hydrochloride.

1.5 gm. paraformaldehyde.

15 c.c. absolute alcohol.

The preparation is carried out in exactly the same manner as that of the corresponding dimethyl compound. As nothing separates on cooling the reaction mixture after it has refluxed for  $1\frac{1}{4}$  hours, it is allowed to

evaporate to half the original volume on the steam-bath. White crystals of the amino-ketone then separate on cooling. They are washed with ether and recrystallized from absolute alcohol.

M.pt. 111°C. Yield 10%.

The hydrochloride answers to tests for halogen, and to the test for methyl ketones with sodium nitroprusside. It is soluble in water, alcohol, and acetone, and slightly soluble in ether. In aqueous solution, addition of alkali causes separation of the base as a solid, and, on warming, decomposition.

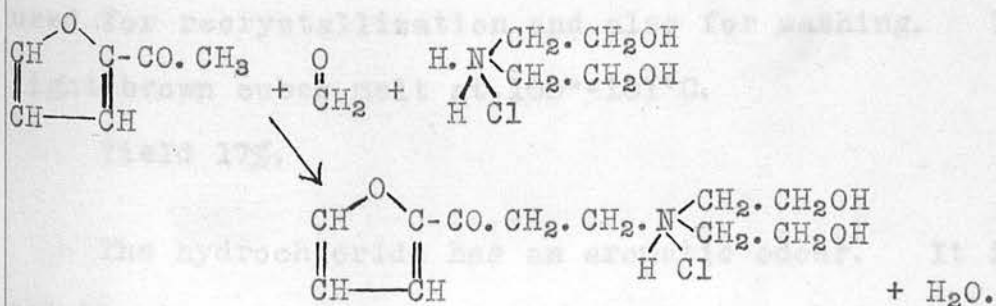
The compound has a slight local anaesthetic action on the tongue.

No phenylhydrazone could be isolated.

Found: C, 62.27% ; H, 9.32%.

Calculated for  $C_{15}H_{26}O_2NCl$ : C, 62.50% ; H, 9.03%.

\* (Furyl-2)  $\beta$ -Di-( $\beta$ -hydroxyethyl)-aminoethyl Ketone Hydrochloride.



- 5.5 gm. 2-acetylfurane.
- 5.3 gm. diethanolamine.
- 1.5 gm. paraformaldehyde.
- 20 c.c. absolute alcohol.

Dilute hydrochloric acid is mixed with the diethanolamine until the solution is neutral. It is then evaporated to dryness on the steam-bath. The viscous oil obtained is dissolved in absolute alcohol, and 2-acetylfurane and 0.5 c.c. concentrated hydrochloric acid added. On warming, the mixture becomes homogeneous. After addition of the paraformaldehyde, it is refluxed for 15 minutes, by which time it is again uniform throughout. Another 0.75 gm. paraformaldehyde is put in, and boiling continued for one hour.

The reaction mixture is taken to dryness on the steam-bath. The viscous mass remaining is allowed to stand in a vacuum desiccator for a week. Prolonged, vigorous stirring then causes separation of brown crystals of the condensation product. Absolute alcohol is used for recrystallization and also for washing. The light brown cubes melt at  $100^{\circ}$ - $101^{\circ}$ C.

Yield 17%.

The hydrochloride has an aromatic odour. It is soluble in cold water and in hot alcohol, but is only slightly soluble in cold alcohol. Neither ether nor

benzene will dissolve it.

The compound is not hygroscopic. Tests for halogen and the nitroprusside test for methyl ketones are answered.

Addition of dilute alkali to an aqueous solution causes separation of the base, and, on warming, decomposition.

No phenylhydrazone could be obtained.

Found: C, 50.08%; H, 7.00%; N, 5.51%.

Calculated for  $C_{11}H_{18}O_4NCl$ : C, 50.00%; H, 6.82%; N, 5.31%.

Attempt to Prepare (Furyl-2)  $\beta$ -Diethylaminoethyl Ketone Hydrochloride.

Attempts to condense diethylamine hydrochloride with 2-acetylfurane and paraformaldehyde met with no success, although the reagents were eventually heated together in alcohol for 2 hours. Extremely hygroscopic crystals, melting at  $221^{\circ}$ - $223^{\circ}C.$ , were recovered on evaporation. A micro-Dumas estimation confirmed this compound as diethylamine hydrochloride.

The benzoyl chloride and potassium cyanide, the bottle is stoppered and shaken till the smell of the former is no longer detectable. More ice is added during the shaking as that present melts.

Extract the white solid or oil, which separates, in chloroform, and dry over calcium chloride.

The chloroform is taken off, and the brown oil remaining distilled at 18 mm., the fraction coming over at  $150^{\circ}$ - $153^{\circ}$  being collected.

3. 4-Phenyl-2-formylthiazole.Benzoylhydroxythioacetamide.(a.) Benzoylhydroxyacetonitrile.(J.F. Olin, and T.B. Johnson, Rec. Trav. Chim., 1931, 50, 72)

Ice must be added during the reaction as that originally present melts. The oil obtained differed from that of the above authors in that it changed to a white crystalline solid at room temperature.

82.5 gm. (1.1 mol. HCHO) formalin.

71.5 gm. (1.1 mol.) pulverised potassium cyanide.

140 gm. (1.0 mol.) benzoyl chloride.

500 gm. crushed ice.

The formalin is added to the ice in a wide-necked bottle (capacity 1.5 litres). After the addition of the benzoyl chloride and potassium cyanide, the bottle is stoppered and shaken till the smell of the former is no longer detectable. More ice is added during the shaking as that present melts.

Extract the white solid or oil, which separates, in chloroform, and dry over calcium chloride.

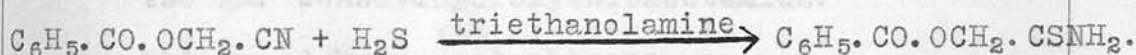
The chloroform is taken off, and the brown oil remaining distilled at 18 mm., the fraction coming over at 158°-163° being collected.

B.pt. of pure nitrile 158°C. Yield 50% (calculated on benzoyl chloride).

On boiling the nitrile with alkali, ammonia is evolved. The oil solidifies at room temperature.

(b.) Benzoylhydroxythioacetamide.

(J.F. Olin and T.B. Johnson, loc. cit.)



The pure thioamide was found to melt at 107°-108° - above authors give m.pt. 103°C.

250 gm. benzoylhydroxyacetonitrile.

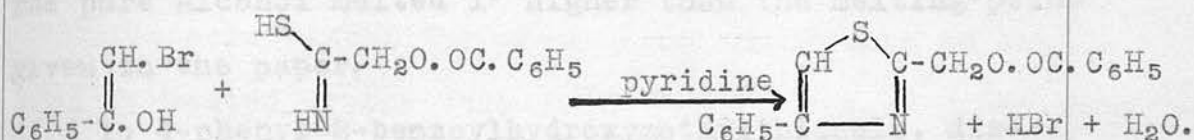
13 gm. triethanolamine.

250 c.c. 95% alcohol.

The triethanolamine is dissolved in alcohol and the solution saturated with hydrogen sulphide. The nitrile is added and hydrogen sulphide gas passed in for 3 hours at 45°. The temperature is raised to 60°, and the solution poured into an equal volume of cold water, and rapidly stirred.

Benzene was found suitable for recrystallizing the solid which separates. The cream-white needles are washed with petrol ether.

Yield 35%-40%.

4-Phenyl-2-formylthiazole.(a.) 4-Phenyl-2-benzoylhydroxymethylthiazole.(J.F. Olin and T.B. Johnson, J.A.C.S., 1931, 53, 1470)

150 gm. benzoylhydroxythioacetamide.

114 gm.  $\omega$ -bromoacetophenone.

60 c.c. pyridine.

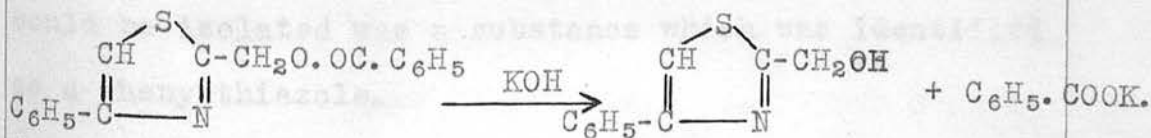
300 c.c. alcohol.

The solution of thioamide,  $\omega$ -bromoacetophenone and pyridine in alcohol is refluxed on the steam-bath for 4 hours. It is then poured into about 3 litres of ice-water. The smeary solid which separates is washed thoroughly in a beaker with dilute hydrochloric acid. When most of the pyridine has been removed, the benzoate is recrystallized from 95% alcohol to give white rosetts.

M.pt. 73°-74°C. Yield 60% (calculated on  $\omega$ -bromoacetophenone).

(b.) 4-Phenyl-2-hydroxymethylthiazole.

(J.F. Olin and T.B. Johnson, loc. cit.)



As the product obtained solidified at an earlier stage, the extraction and distillation under reduced pressure described in the paper quoted were unnecessary. The pure alcohol melted 1° higher than the melting-point given in the paper.

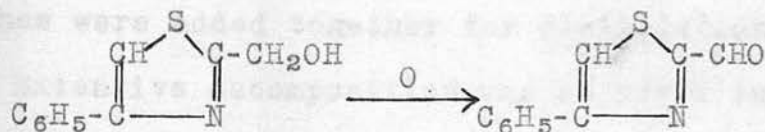
To 4-phenyl-2-benzoylhydroxymethylthiazole, dissolved in the minimum quantity of absolute alcohol necessary, is added half its weight of potassium hydroxide in the minimum of water. The whole is refluxed on the water-bath for 2 hours, and is then poured into ice-water. The oil which first separates soon solidifies, and is filtered off.

From 60% alcohol, brown crystals are obtained.

M.pt. 89°-90°C. Yield 75%.

(c.) 4-Phenyl-2-formylthiazole.

(J.F. Olin and T.B. Johnson, loc. cit.)



When 19 gm. of the alcohol was oxidised with dichromate, a small yield of the aldehyde was obtained. With larger quantities of starting material, all that could be isolated was a substance which was identified as 4-phenylthiazole.

19 gm. 4-phenyl-2-hydroxymethylthiazole.

20 gm. sodium dichromate.

135 c.c. glacial acetic acid.

The solution of the alcohol and dichromate in acetic acid is heated on the steam-bath for 2 hours. It is then poured into water and the aldehyde extracted with ether. After drying over calcium chloride, the ether is removed and the remaining oil distilled under reduced pressure.

B.pt.  $160^{\circ}$ - $165^{\circ}$  at 14 mm. Yield 23%.

The oil obtained solidifies in the receiver.

Phenylhydrazone: Identical with that described by Olin and Johnson. Yellow prisms, m.pt.  $131^{\circ}$ - $132^{\circ}$ C.

4-Phenylthiazole: 50 gm. 4-phenyl-2-hydroxymethylthiazole were treated with an equal weight of sodium dichromate as described above. The products of two or three such batches were added together for distillations in vacuo.

Extensive decomposition was observed in distilling at 14 mm., the product coming over through a wide range of temperature. Reducing the pressure to 10 mm. made no improvement. The oil first obtained solidified. The solid was recrystallized from absolute alcohol till a constant m.pt., viz.  $52^{\circ}$ , was attained (white needles).

The compound gave no phenylhydrazone, nor did it answer to tests for aldehydes. It was easily soluble

in mineral acids, being precipitated, without change in melting-point, by alkali. Tests for sulphur and nitrogen were positive.

Addition of benzoyl chloride to a solution in benzene gave a white precipitate, melting ca. 95°. This decomposed in solution, unless excess benzoyl chloride were present.

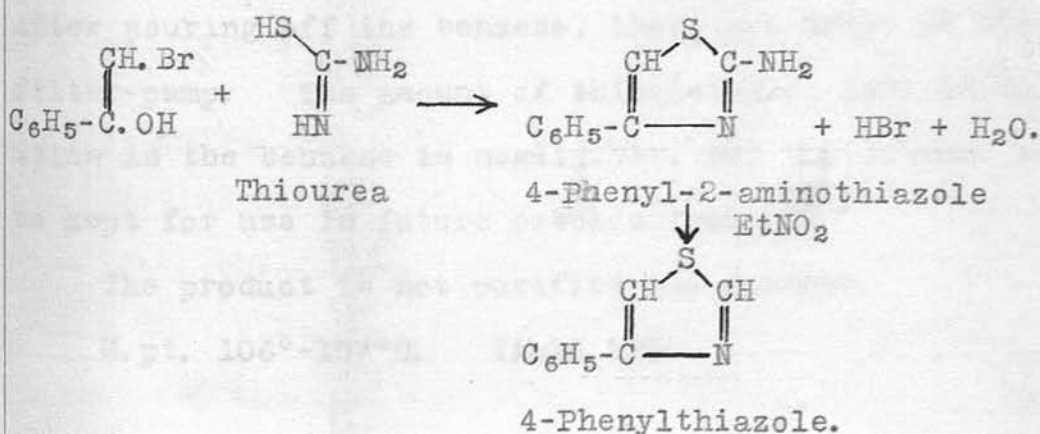
The identification of the decomposition product as 4-phenylthiazole was completed by carbon and hydrogen estimations.

Yield 25%.

Found: C, 67.03, 67.08%; H, 4.29, 4.24%.

Calculated for  $C_9H_7NS$ : C, 67.08%; H, 4.35%.

4-Phenylthiazole (m.pt. 52°) was prepared by Popp (Ann., 250, 1889, 279) by treating the condensation product of  $\omega$ -bromoacetophenone and thiourea with ethyl nitrite.



4-Phenylthiazole Hydrochloride: A solution of the base in warm, dilute hydrochloric acid was evaporated to dryness.

The oil obtained solidified on cooling. From absolute alcohol white, slightly hygroscopic, crystals, melting at 80°-82°, separated. Popp (loc. cit.) gives m.pt. as 80°.

Yield 95%.

#### 4-Phenyl-2-formylthiazole.

##### (a.) Thioacetamide.

(Hantzsch, Ann., 1889, 250, 264.)



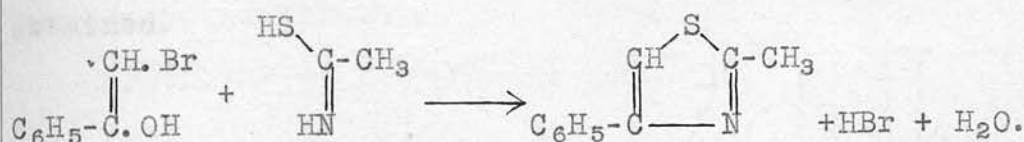
30 gm. (0.5 mol.) acetamide.

22 gm. (0.1 mol.) phosphorus pentasulphide.

The reagents are ground together in a mortar and the mixture is heated with 1,500 c.c. benzene on the water-bath for 8 minutes. The liquid is filtered while hot, and is then left overnight. White laminae separate. After pouring off the benzene, these are dried at the filter-pump. The amount of thioacetamide left in solution in the benzene is negligible, but the solvent should be kept for use in future preparations.

The product is not purified any further.

M.pt. 106°-107°C. Yield 18%.

(b.) 4-Phenyl-2-methylthiazole.(Hantzsch, Ann., 1889, 250, 269)20 gm.  $\omega$ -bromoacetophenone.

8 gm. thioacetamide.

To the  $\omega$ -bromoacetophenone at 100°, the thioamide is slowly added. Heating is continued for 30 minutes. The product is made alkaline with sodium hydroxide solution, and the solid which separates is filtered off and washed with water.

M.pt. 58°C.

(c.) 4-Phenyl-2-formylthiazole.(Cf. Kaufmann and Vallette, Ber., 1912, 45, 1740.)

Attempts to condense 4-phenyl-2-methylthiazole and p-nitroso-dimethylaniline met with no success.

Thioacetamide.

(Cf. Bernthsen, Ann., 1878, 192, 46. Olin and Johnson, Rec. Trav. Chim., 1931, 50, 72.)

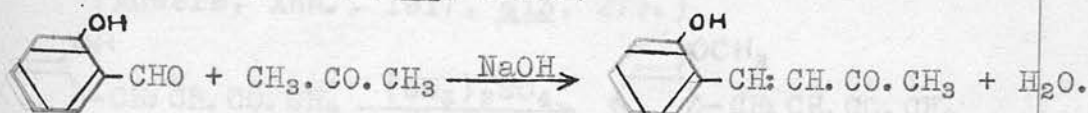
4 gm. triethanolamine were dissolved in 20 c.c. alcohol and the solution saturated with hydrogen sulphide. 20 gm. acetonitrile were added and hydrogen sulphide passed in for 6 hours at 45°. A very small quantity of thioacetamide separated.

In another attempt, hydrogen sulphide was passed in for 20 hours at 0°. A very small yield was again obtained.

4.  $\beta$ -Amino-ketones and Related Pyrazolines derived from o-Alkoxy-benzylidene-acetones.

Salicylidene-acetone.

(Harries, Ber., 1891, 24, 3180.)



It was found advisable to omit the steam-distillation described by Harries for removal of excess salicylaldehyde, as it caused extensive charring of the condensation-product. Recrystallization from benzene or from acetone proved sufficient for purification.

43 c.c. salicylaldehyde

70 c.c. acetone

240 c.c. 10% sodium hydroxide solution.

The aldehyde is dissolved in 140 c.c. sodium hydroxide solution, and mixed with shaking with acetone. After addition of the remainder of the alkali, which dissolves any precipitate, the solution is diluted to 2 litres and allowed to stand for 3 days. Salicylideneacetone is thrown out of solution by hydrochloric acid

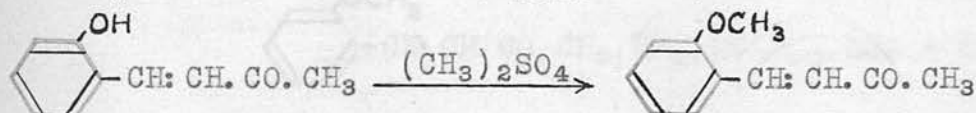
(1 part concentrated to 1 part water). The yellow solid is washed with water, dried, and recrystallized from benzene or acetone.

M. pt. 139°C. Yield 80%-90%.

1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-methoxyphenyl)-pyrazoline Hydrochloride.

(a.) o-Methoxy-benzylidene-acetone.

(Auwers, Ann., 1917, 413, 279.)



30 gm. salicylidene-acetone.

20 c. c. dimethyl sulphate.

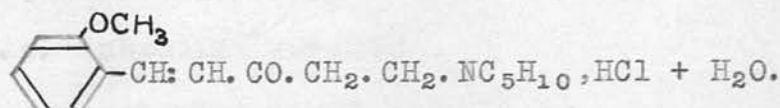
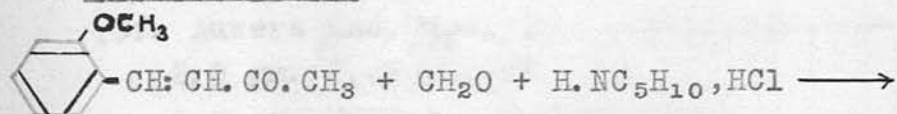
To salicylidene-acetone, dissolved in 150 c. c. 2N sodium hydroxide solution, dimethyl sulphate is added in small portions, <sup>with</sup> shaking after each addition. The mixture is allowed to stand for a short time, shaken with a further 100 c. c. of alkali, poured into 300 c. c. of water, and extracted with ether. The ether layer is washed thoroughly with very dilute sodium hydroxide solution and then with water. After drying over anhydrous potassium carbonate, the ether is removed, and the residue (which solidifies on cooling) is distilled under reduced pressure. The almost colourless liquid gives a white solid on cooling.

M.pt. 48°-50°C. B.pt. 152°-153° at 1 mm.

Yield 30%.

The compound may be recrystallized from benzene, but is more effectively purified by distillation.

\* (b.) 1-Piperidino-5-(2'-methoxyphenyl)- $\Delta^4$ -penten-3-one  
Hydrochloride.



10 gm. o-methoxybenzylidene-acetone.

7 gm. piperidine hydrochloride.

2 gm. paraformaldehyde.

15 c.c. absolute alcohol.

The above mixture is refluxed in a 100 c.c. conical flask for 15 minutes. A further 1 gm. of paraformaldehyde is added, and heating continued 15 minutes longer.

On cooling thoroughly and scratching, a white solid separates. This is filtered off, washed thoroughly with alcohol and then with ether, and recrystallized from absolute alcohol with hot filtration. The white cubes melt at 177°-178°C.

Yield 13%.

The hydrochloride is slightly soluble in cold alcohol and readily soluble in water, but insoluble in ether.

On adding alkali to the aqueous solution, the free base is precipitated. Warming the aqueous solution also causes hydrolysis.

Found: C, 65.86% ; H, 7.40%.

Calculated for  $C_{17}H_{24}O_2NCl$ : C, 65.81% ; H, 7.74%.

\* (c.) Phenylhydrazone:

(Cf. Auwers and Voss, Ber., 1909, 42, 4411.)

2.0 gm.  $C_{17}H_{24}O_2NCl$ .

0.7 gm. phenylhydrazine.

12 c.c. absolute alcohol.

0.7 c.c. glacial acetic acid.

On scratching or on seeding with any one of the homologous phenylhydrazones, a yellow solid is deposited from the reaction mixture. It separates from absolute alcohol as <sup>a</sup>yellow powder, m.pt.  $160^{\circ}$ - $162^{\circ}C$ .

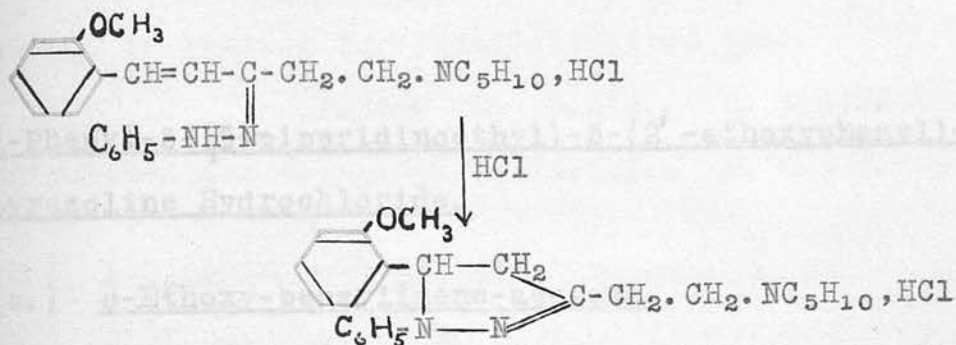
Yield 80%.

In Knorr's reaction, a dark-red colour is observed. The phenylhydrazone is slightly soluble in cold alcohol, but insoluble in water and in ether.

Found: N, 10.59%.

Calculated for  $C_{23}H_{30}ON_3Cl$ : N, 10.50%.

\* (d.) 1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-methoxyphenyl)-pyrazoline Hydrochloride.



The phenylhydrazone (1.5 gm.) is heated under reflux with normal hydrochloric acid (15 c.c.) on the steam-bath for 20 minutes. Almost immediately heating is started, a clear solution is obtained. On cooling, a green oil separates, and this on scratching gives a white solid, which is filtered off and washed with water. The pyrazoline is recrystallized from water (15 c.c.), filtering when hot. It separates as very fine particles, forming a suspension that takes a very long time to filter.

M.pt.  $74^{\circ}-75^{\circ}\text{C}$ . Yield 55%.

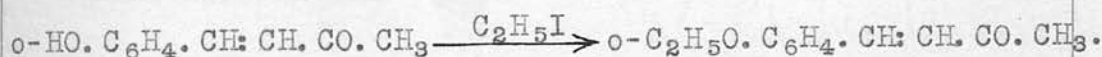
A positive is obtained in Knorr's test. Exposure to bromine vapour causes an immediate colour change to violet. The hydrochloride is slightly soluble in cold water, from which alkali precipitates the base. It has a powerful local anaesthetic action on the tongue. Halogen may be estimated by titration with 0.02 N alkali, using phenolphthalein as indicator.

Found: N, 10.21% ; Cl, 9.2%.

Calculated for  $C_{23}H_{30}ON_3Cl$ : N, 10.50% ; Cl, 8.9%.

1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-ethoxyphenyl)-  
pyrazoline Hydrochloride.

\* (a.) o-Ethoxy-benzylidene-acetone.



30 gm. salicylidene-acetone.

32 gm. ethyl iodide.

14 gm. potassium hydroxide.

100 c. c. absolute alcohol.

Potassium hydroxide, in the minimum of water necessary for solution, is added to salicylidene-acetone and ethyl iodide in absolute alcohol. The mixture is heated under reflux on the water-bath for  $1\frac{1}{2}$  hours, and is then poured into 1 litre of water. The oil which separates is extracted with ether, the ethereal solution being washed with very dilute sodium hydroxide solution and with water. After drying over anhydrous potassium carbonate, the ether is removed, and the red oil remaining (which gives a yellow solid on cooling) is distilled under reduced pressure. The almost colourless product solidifies on cooling.

M.pt.  $46^\circ\text{-}47^\circ\text{C}$ . B.pt.  $143^\circ\text{-}145^\circ$  at 1 mm.

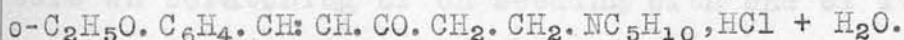
Yield 50%.

The compound is soluble in the usual solvents, but cannot be readily recrystallized from them.

Found: C, 75.47% ; H, 7.34%.

Calculated for  $C_{12}H_{14}O_2$ : C, 75.79% ; H, 7.37%.

\* (b.) 1-Piperidino-5-(2'-ethoxyphenyl)- $\Delta^4$ -penten-3-one Hydrochloride.



6.3 gm. o-ethoxybenzylidene-acetone.

4.1 gm. piperidine hydrochloride.

1 gm. paraformaldehyde.

7 c.c. absolute alcohol.

The reaction mixture is refluxed for 20 minutes, a further 0.5 gm. paraformaldehyde added, and heating continued 15 minutes longer. The solid which separates on cooling and scratching is filtered off and washed with alcohol and with ether. From absolute alcohol, white prisms, melting at  $190^\circ C.$ , are obtained.

Yield 30%.

The hydrochloride is slightly soluble in cold alcohol, soluble in water, and insoluble in ether. Warming, or adding alkali to, the aqueous solution causes hydrolysis with separation of the base.

Found: C, 66.46% ; H, 7.64%.

Calculated for  $C_{18}H_{26}O_2NCl$ : C, 66.67% ; H, 8.02%.

\* (c.) Phenylhydrazone:

2.0 gm.  $C_{18}H_{26}O_2NCl$ .

0.7 gm. phenylhydrazine.

17 c.c. absolute alcohol.

0.7 c.c. glacial acetic acid.

The phenylhydrazone separates from the above mixture on scratching or on seeding with one of its homologues. It is recrystallized from absolute alcohol. The yellow powder melts at  $165^{\circ}$ - $167^{\circ}C$ .

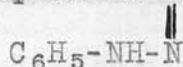
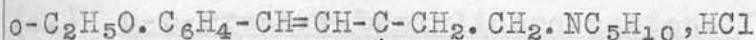
Yield 90%.

As repeated recrystallization lowers the m.pt., it is probable that isomerisation to the pyrazoline occurs in the boiling solvent. The phenylhydrazone gives a positive result in Knorr's test for pyrazolines, but shows no colour change with bromine vapour. It is not very soluble in cold alcohol and insoluble in cold water and in ether.

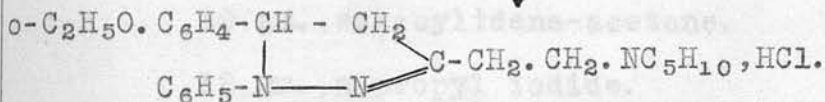
Found: N, 9.87%.

Calculated for  $C_{24}H_{32}ON_3Cl$ : N, 10.14%.

\* (d.) 1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-ethoxyphenyl)-pyrazoline Hydrochloride.



HCl



On heating the phenylhydrazone (1.5 gm.) on the steam-bath with normal hydrochloric acid (15 c.c.), a clear solution is first obtained, from which in a short time a white solid is seen to separate. After refluxing for 20 minutes, followed by thorough cooling, the solid is filtered off and washed with water. It is recrystallized from water with a hot filtration. The white needles obtained melt at 166°C.

Yield 60%.

Knorr's test for pyrazolines is answered, and the crystals turn blue immediately on exposure to bromine vapour. The hydrochloride is only slightly soluble in cold water, but very soluble in alcohol.

It has a local anaesthetic action on the tongue.

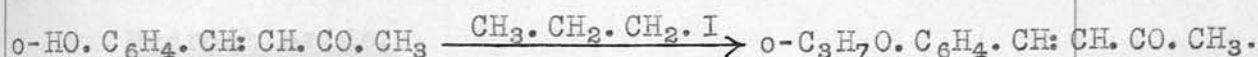
Mixed m.pt. with isomeric phenylhydrazone ca. 145°C.

Found: N, 10.40% ; Cl, 8.6%.

Calculated for  $\text{C}_{24}\text{H}_{32}\text{ON}_3\text{Cl}$ : N, 10.14% ; Cl, 8.6%.

1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-n-propoxyphenyl)-pyrazoline Hydrochloride.

\* (a.) o-n-Propoxy-benzylidene-acetone.



30 gm. salicylidene-acetone.

32 gm. n-propyl iodide.

14 gm. potassium hydroxide.

100 c.c. absolute alcohol.

Salicylidene-acetone and propyl iodide are dissolved in absolute alcohol. Potassium hydroxide, in the minimum quantity of water necessary for solution, is added, and the solution is refluxed on the water-bath for  $1\frac{1}{2}$  hours. It is then poured into 1 litre of water, and the oil which separates is extracted with ether. The ether layer is washed with very dilute sodium hydroxide solution and with water, and dried over anhydrous potassium carbonate. The oil remaining after distilling off the ether is distilled under reduced pressure to give a mobile, almost colourless, liquid which may crystallize on standing. This distils over a wide temperature range, approximately  $155^\circ\text{-}165^\circ$  at 1 mm.

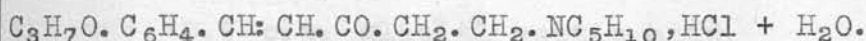
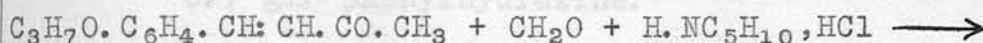
Yield 35%.

The compound showed no signs of decomposition on standing for several weeks.

Found: C, 76.62% ; H, 7.45%.

Calculated for  $C_{13}H_{16}O_2$ : C, 76.47% ; H, 7.84%.

\* (b.) 1-Piperidino-5-(2'-n-propoxyphenyl)- $\Delta^4$ -penten-3-one  
Hydrochloride.



6.8 gm. o-n-propoxybenzylidene-acetone.

4.1 gm. piperidine hydrochloride.

1 gm. paraformaldehyde.

7 c.c. absolute alcohol.

The above mixture forms a homogeneous solution after it has been heated under reflux for 15 minutes. A further 0.5 gm. paraformaldehyde is added and heating continued 15 minutes longer. On cooling and scratching, a white solid separates. This is filtered off, washed with alcohol and with ether, and recrystallized from absolute alcohol.

M.pt.  $182^\circ C$ . Yield 26%.

The hydrochloride is slightly soluble in cold alcohol, readily soluble in water, and insoluble in ether. Addition of alkali to the aqueous solution causes separation of the free base. Hydrolysis is also brought about by warming the aqueous solution.

Found: C, 67.35% ; H, 7.85%.

Calculated for  $C_{19}H_{28}O_2NCl$ : C, 67.46% ; H, 8.28%.

\* (c.) Phenylhydrazone:

2.0 gm.  $C_{19}H_{28}O_2NCl$ .

0.7 gm. phenylhydrazine.

14 c.c. absolute alcohol.

0.7 c.c. glacial acetic acid.

Scratching or seeding with any one of the homologous phenylhydrazones causes separation of a yellow solid from the reaction mixture. From absolute alcohol clusters of yellow needles, m.pt.  $161^{\circ}$ - $162^{\circ}C.$ , are obtained.

Yield 70%.

The compound does not answer to Knorr's test for pyrazolines. It is slightly soluble in cold alcohol, insoluble in water and in ether.

Found: N, 9.47%.

Calculated for  $C_{25}H_{34}ON_3Cl$ : N, 9.81%.

\* (d.) 1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-n-propoxyphenyl)-pyrazoline Hydrochloride.

$C_3H_7O.C_6H_4-CH=CH-C-CH_2.CH_2.NC_5H_{10},HCl$

$C_6H_5-NH.N$

$C_3H_7O.C_6H_4-CH-CH_2$   
 $C_6H_5-N-N=C-CH_2.CH_2.NC_5H_{10},HCl$

The phenylhydrazone (1.5 gm.) is heated under reflux on the steam-bath with normal hydrochloric acid (15 c.c.). In a short time, the yellow crystals darken in colour, and are then seen to be replaced by a white solid. After 20 minutes heating, followed by thorough cooling, the solid is filtered off and washed with water. Recrystallization from water, filtering when hot, gives creamy-white needles melting at 193.5°C.

Yield 75%.

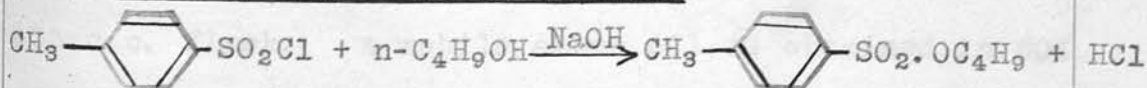
A positive result is obtained in Knorr's test. The crystals change in colour to blue on exposure to bromine vapour. The hydrochloride is not very soluble in cold water, but is readily soluble in alcohol. It has a local anaesthetic action on the tongue.

Found: N, 10.08% ; Cl, 8.3%.

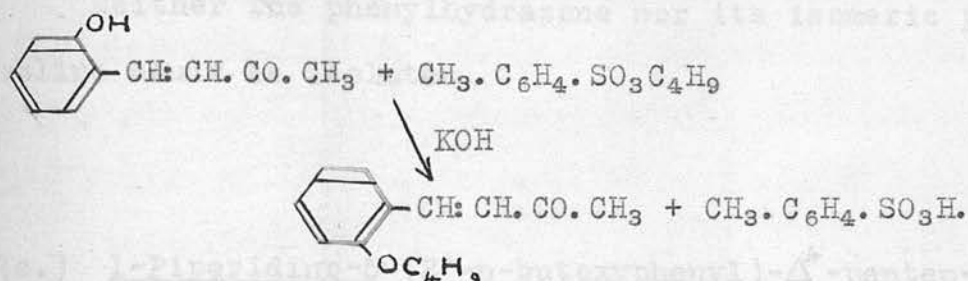
Calculated for  $C_{25}H_{34}ON_3Cl$ : N, 9.81% ; Cl, 8.3%.

1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-n-butoxyphenyl)-pyrazoline Hydrochloride.

(a.) n-Butyl-p-toluene-sulphonate.



"Chemical Syntheses", Vol. IX, p. 28.

\* (b.) o-n-Butoxy-benzylidene-acetone.

178 gm. (1.1 mol.) salicylidene-acetone.

228 gm. (1.0 mol.) n-butyl-p-toluene-sulphonate.

70 gm. potassium hydroxide.

500 c.c. 95% alcohol.

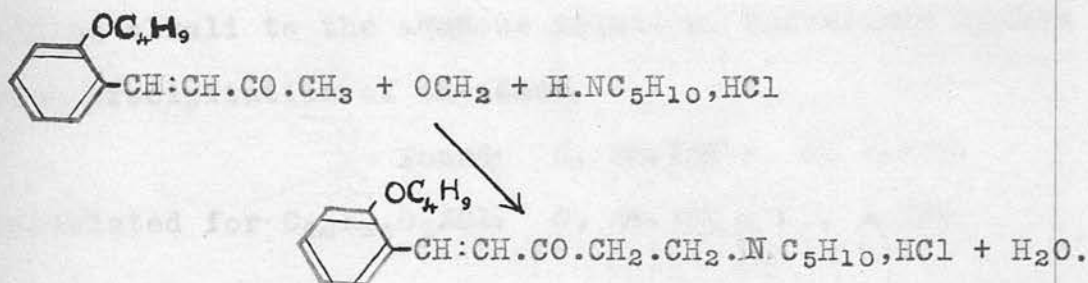
Salicylidene-acetone and butyl-toluene-sulphonate are dissolved in warm alcohol. Potassium hydroxide, in the minimum quantity of water necessary for solution, is now added, and the mixture is heated under reflux on the water-bath for  $1\frac{1}{2}$  hours. It is then poured into 5 litres of water, and the oil which separates is extracted with ether. The ethereal solution is washed with 2% sodium hydroxide solution and with water, and is thoroughly dried over anhydrous potassium carbonate. After distilling off the ether, the remaining oil is distilled under reduced pressure in portions of 25 c.c. from a 100 c.c. flask. A mobile amber oil is obtained in 50% yield.

B.pt. of pure ether  $177.5^\circ$  at 3 mm.

The compound decomposes on standing. In the distillation, allow to cool before letting in air.

Neither the phenylhydrazone nor its isomeric pyrazoline could be isolated.

\* (c.) 1-Piperidino-5-(2'-n-butoxyphenyl)- $\Delta^4$ -penten-3-one  
Hydrochloride.



7.3 gm. o-n-butoxybenzylidene-acetone.

4.1 gm. piperidine hydrochloride.

1 gm. paraformaldehyde.

7 c.c. absolute alcohol.

The ketone and piperidine hydrochloride are added to 7 c.c. alcohol in a 50 c.c. conical flask, containing porous chips. On warming, partial solution is effected. This mixture is heated with paraformaldehyde under reflux for 15 minutes, by which time a homogeneous solution is obtained. After the addition of a further 0.5 gm. paraformaldehyde, boiling is continued 10 minutes longer. The contents of the flask are then thoroughly cooled.

The solid which separates on scratching is filtered off, and washed with a little alcohol and with ether.

Recrystallization from absolute alcohol (filtering when hot) yields white needles, melting at  $164^{\circ}$ - $165^{\circ}$ C.

Yield 26%.

It is readily soluble in alcohol and fairly soluble in cold water, but insoluble in ether. On warming or adding alkali to the aqueous solution, hydrolysis occurs with precipitation of the base.

Found: C, 68.13% ; H, 8.75%.

Calculated for  $C_{20}H_{30}O_2NCl$ : C, 68.18% ; H, 8.52%.

\* (d.) Phenylhydrazone:

2.0 gm.  $C_{20}H_{30}O_2NCl$ .

0.7 gm. phenylhydrazine.

7.0 c.c. absolute alcohol.

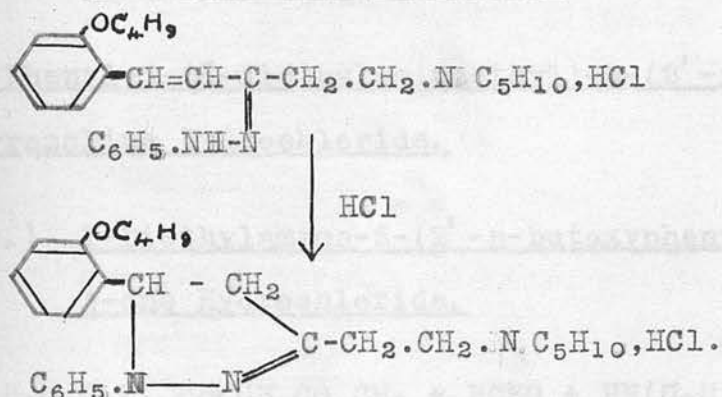
0.7 c.c. glacial acetic acid.

On cooling and scratching the reaction mixture, the phenylhydrazone separates. Recrystallization from absolute alcohol, washing with a little alcohol, gives yellow needles m.pt.  $154^{\circ}$ - $155^{\circ}$ C.

Yield 90%.

Knorr's test for pyrazolines is not answered. The compound is slightly soluble in cold alcohol, insoluble in water and in ether.

Found: N, 9.76%.

Calculated for  $C_{26}H_{36}ON_3Cl$ : N, 9.50%.\* (e.) 1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-n-butoxyphenyl)-pyrazoline Hydrochloride.

The phenylhydrazone (2 gm.) is heated under reflux with normal hydrochloric acid (20 c.c.) on the steam-bath for 30 minutes. After 5 minutes, a green oil is observed to be replacing the yellow crystals of the starting material. On cooling and scratching, at the end of the reaction, the green oil gives a white solid. This is filtered off, washed with water, and recrystallized from water with a hot filtration. The white powder melts at  $191^\circ\text{C}$ .

Yield 75%.

A mauve colour is obtained in Knorr's test. Exposure to bromine vapour causes immediate colour change to blue. The hydrochloride is not very soluble in water, but is readily soluble in cold alcohol. It has

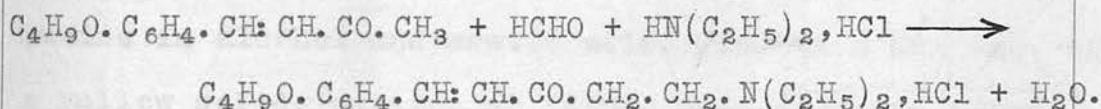
a powerful local anaesthetic effect on the tongue.

Found: N, 9.87%, 9.51%; Cl, 7.9%.

Calculated for  $C_{26}H_{36}ON_3Cl$ : N, 9.50%; Cl, 8.0%.

1-Phenyl-3-( $\beta$ -diethylaminoethyl)-5-(2'-n-butoxyphenyl)-pyrazoline Hydrochloride.

\* (a.) 1-Diethylamino-5-(2'-n-butoxyphenyl)- $\Delta^4$ -penten-3-one Hydrochloride.



7.3 gm. o-n-butoxybenzylidene-acetone.

3.7 gm. diethylamine hydrochloride.

1 gm. paraformaldehyde.

3 c.c. absolute alcohol.

The mixture is warmed until reaction sets in, and is then refluxed for 10 minutes to give a homogeneous solution. To this, 0.5 gm. paraformaldehyde is added, and heating is continued 10 minutes longer.

The sticky solid which separates on cooling in the ice-chest is freed from liquid as far as possible by filtration, smeared on a porous plate to dry, and washed very cautiously with alcohol, and then thoroughly with ether. From absolute alcohol, white crystals, melting

at 115°-116°C., are obtained.

Yield 5% to 10%.

The compound is very soluble in alcohol and in water, but insoluble in ether. It is not hygroscopic.

Found: C, 66.35%; H, 8.51%; N, 4.08%.

Calculated for  $C_{19}H_{30}O_2NCl$ : C, 67.06%; H, 8.82%; N, 4.12%.

\* (b.) Phenylhydrazone:

The first attempt to prepare this compound, using equimolecular proportions of the ketone and phenylhydrazine in alcohol and acetic acid, yielded a few mgm. of a yellow solid, melting at 141°C. when recrystallized from alcohol. This solid did not answer Knorr's test for pyrazolines. It dissolved in hot dilute hydrochloric acid, and on cooling a white solid was observed to separate. On standing for some time, the yellow crystals decomposed.

Found: N, 9.63%.

Calculated for  $C_{25}H_{36}ON_3Cl$ : N, 9.79%.

All subsequent attempts to prepare the phenylhydrazone resulted in a white solid which remains unidentified. It recrystallized from alcohol in needles, m. pt. 178°C. Neither Knorr's test nor the bromine vapour test for pyrazolines was answered. The compound was readily soluble in water. The following figures were obtained: C, 52.23%; H, 5.86%; N, 9.87%.

Attempts to Prepare other  $\beta$ -Amino-ketones from o-n-Butoxy-benzylidene-acetone.

Several unsuccessful efforts were made to condense dimethylamine, di-n-propylamine, di-n-butylamine, and di-( $\beta$ -hydroxyethyl)-amine hydrochlorides with formaldehyde and o-n-butoxy-benzylidene-acetone, to give analogous compounds to those already obtained by condensations with piperidine and diethylamine hydrochlorides.

The quantities of solvent used in the preparations were varied, and the reaction mixtures heated for widely different times. In some cases, a few drops of concentrated hydrochloric acid were added. In no attempt did the required  $\beta$ -amino-ketone hydrochloride crystallize out on cooling, nor on evaporation to dryness on the steam-bath and in a vacuum desiccator for a long period. Frequently, however, large amounts of the amine hydrochlorides used were recovered.

Treatment of the reaction mixtures with alkali, followed by extraction with ether, yielded in no case anything resembling the  $\beta$ -amine-ketone base.

Attempts were also made to isolate any condensation product present as its phenylhydrazone. For this, the reaction mixture was taken to dryness and washed thoroughly with ether to remove butoxy-benzylidene-acetone. The remaining oil was then treated with phenylhydrazine in acid solution. Neither the phenylhydrazone nor the corresponding pyrazoline (under conditions for conversion), as hydrochloride or base, was obtained in any case.

Buffolk, and to those who volunteered for intradermal tests.

Several  $\beta$ -dialkylaminoethyl ketones and  $\beta$ - $\beta$ -dialkylaminoethyl-pyrazolines have been found to be local anesthetics (see Introduction). Compounds of the latter type have also been shown to be anti-pyretic (private information). That they possess this property is

## IV.

Pharmacological Tests and Results.

The local anaesthetic properties of the new compounds prepared were examined by the author in the Department of Pharmacology, University of Edinburgh. Determination of their toxicities, for which greater biological experience is desirable, was carried out by Lord Suffolk.

Professor A. J. Clark's hospitality and advice are gratefully acknowledged. Thanks are also due to Lord Suffolk, and to those who volunteered for intradermal tests.

Several  $\beta$ -dialkylaminoethyl ketones and 3- $\beta$ -dialkylaminoethyl-pyrazolines have been found to be local anaesthetics (see Introduction). Compounds of the latter type have also been shown to be anti-pyretics (private information). That they possess this property is

hardly surprising in view of the similarity between their structures and those of antipyrin (1-phenyl-2:3-dimethyl-5-pyrazolone) and amidopyrin (1-phenyl-2:3-dimethyl-4-dimethylamino-5-pyrazolone).

To be a satisfactory local anaesthetic, a compound must cause loss of sensation for a perceptible period, without local irritation or central toxic action. The compounds were tested for these effects as follows (cf. H. K. Sinha, J. Pharm., 1936, 57, 199 and Ph.D. Thesis).

Local anaesthetic efficiency is taken to be the reciprocal of the minimum concentration producing action of a certain duration. The duration selected is 10 minutes, as sufficiently long to eliminate errors due to the transient local anaesthesia caused by saline solution. (A drug which cannot produce 10 minutes action is obviously useless.) This narrow definition of efficiency is necessary since the duration of action of a drug does not vary directly as the concentration, the relationship being different for each drug. Thus it is impossible to estimate the relative potency of local anaesthetics from the relative duration of their actions in a given concentration. Moreover, the ratio between concentrations producing an action of a given duration

will vary with the duration.

The use of molar concentrations is pointless in view of the low standard of accuracy of the methods.

Rabbit's Cornea: This method measures the power of the drug to penetrate mucous membranes and to paralyse nerve-endings. Any irritation caused by the concentrations used is also noted. The rabbit's eye-lashes are clipped off, and the pocket formed by pulling the lower eye-lid outward and slightly upward is flooded with the aqueous drug solution. This is allowed to act for 5 minutes, being replenished at intervals, and the eye is then thoroughly washed with saline. The eye is tested from time to time for the return of the winking reflex on touching the cornea with a horse-hair, and the duration of anaesthesia is noted. Application for 5 minutes gives slower-acting drugs an opportunity to produce their full effects. When the concentration giving 10 minutes action is found, comparisons with cocaine are made by applying the two drugs alternately to the same eye. There is considerable variation in the sensitivity of eyes, even in the same rabbit. As repeated applications make the eye less sensitive to drugs, an adequate interval must be allowed between tests.

Human Wheal (Intradermal): The power to paralyse nerve-endings is measured, independently of the ability to penetrate protective tissues. Irritation is also ob-

served. Under sterile conditions, the drug, in isotonic saline solution, is injected intracutaneously on the flexor surface of the forearm. Sufficient solution to produce a wheal about 5 mm. in diameter is used (0.15 c.c.). The duration of anaesthesia is tested by marking the area surrounding the wheal in which sensation to pricking is lost. The end-point is taken when the sensitivity approaches that of the normal skin. Injections of cocaine are carried out on the same arm. In spite of the large psychological factor, the error in this method is much smaller than in the corneal test.

Toxicity: Median lethal doses, i.e. those doses causing 50% mortality, are determined by intraperitoneal injections into mice, of average weight 20 gm., 0.2% solutions being used. The doses are varied by varying the volume of fluid, and are calculated in mgm. per 20 gm. body-weight.

The di-n-propylaminoethyl ketone being extremely irritant, it was impossible to estimate its anaesthetic activity. No further tests were carried out on this group of compounds.

$\beta$ -Amino-ketones derived from 2-acetyl furanone, general

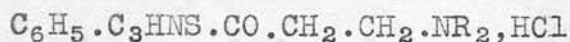
formula -



$NR_2$	$NC_2H_5$	$N(CH_3)_2$	$N(C_2H_5)_2$	$N(C_4H_9)_2$	$N(C_2H_5)(C_4H_9)$
Irritation	++	++	+++	+++	+++

RESULTS:Local Anaesthesia of Rabbit's Cornea.

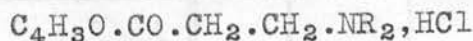
$\beta$ -Amino-ketones derived from 4-phenyl-2-acetylthiazole, general formula -



NR <sub>2</sub>	NC <sub>5</sub> H <sub>10</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	N(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub>	Cocaine
Concentration per cent causing 10 minutes anaesthesia	-	0.1	0.67	-	0.33
Relative potency compared with cocaine	-	3	0.5	-	1
Irritation .....	++	+++	+++	++++	+

In the case of the piperidino-compound, the greatest concentration possible was 0.1%. As this caused no anaesthesia, the compound is no more potent than cocaine. The di-n-propylaminoethyl ketone being extremely irritant, it was impossible to estimate its anaesthetic activity. No further tests were carried out on this group of compounds.

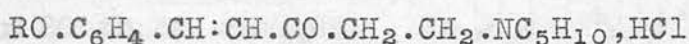
$\beta$ -Amino-ketones derived from 2-acetylfurane, general formula -



NR <sub>2</sub>	NC <sub>5</sub> H <sub>10</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	N(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub>	N(C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub>	N(C <sub>2</sub> H <sub>4</sub> OH) <sub>2</sub>
Irritation	++	++	+++	+++	++++

No local anaesthetic action was observed with any member of the furane group, the maximum concentration used in each case being 1%. The group was tested no further.

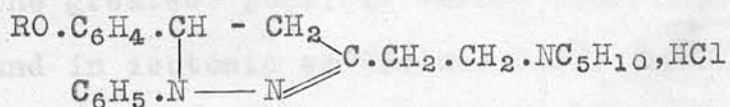
$\beta$ -Piperidino-ketones derived from o-alkoxybenzylidene-acetones, general formula -



R	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	C <sub>4</sub> H <sub>9</sub>
Concentration per cent causing 10 minutes anaesthesia....	1	1	0.1	0.1
Relative potency compared with cocaine .....	0.33	0.33	3	3
Irritation .....	++	+++	++	++

No further tests were carried out on this group of compounds.

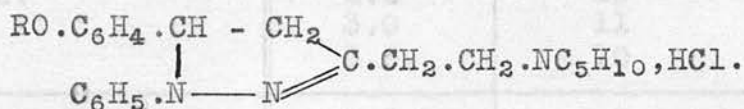
3- $\beta$ -Piperidinoethyl-pyrazolines derived from o-alkoxybenzylidene-acetones, general formula -



R	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	C <sub>4</sub> H <sub>9</sub>	Cocaine
Concentration per cent causing 10 minutes anaesthesia .....	0.1	0.1	0.33	0.16	0.33
Relative potency compared with cocaine .....	3	3	1	2	1

In the case of the methoxy- and propoxy-compounds, the concentrations shown caused anaesthesia for 30 to 40 minutes, but lower concentrations had no effect at all. Increasing the concentrations did not appreciably increase the durations of action. The minimum concentration of the butoxy-compound causing any anaesthesia acted for 20 to 30 minutes. No irritation was caused by any member of this group.

Local Anaesthesia of Human Wheal.



R	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	C <sub>4</sub> H <sub>9</sub>	Cocaine
Concentration per cent causing 10 minutes anaesthesia .....	0.01	0.01	-	0.0067	0.33
Relative potency compared with cocaine ...	33	33	-	50	1

The greatest possible concentration of the propoxy-compound in isotonic saline was 0.1%, which caused an average of 5 minutes anaesthesia. For this duration, its potency equals that of cocaine. The interval between injection and loss of sensation is much smaller with the pyrazolines than in the case of cocaine. Using solutions of three-quarters the concentrations shown,

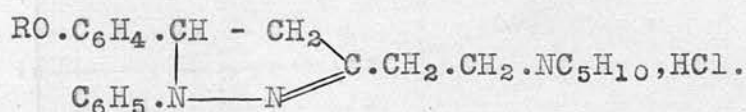
the durations of action were much less, and loss of sensation was not so clearly marked. No irritation was observed with any of the pyrazolines in this test.

Toxicity. The results obtained for three of the pyrazolines ( $R = CH_3, C_2H_5, C_4H_9$ ) and for cocaine are summarised in the following table.

Drug	Dose mgm./20 gm.	Number of mice injected	Number of deaths	Mortality %
Cocaine.	1.5	6	0	0
	2.0	10	0	0
	2.5	10	3	30
	3.0	11	6	55
	3.5	10	10	100
1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-methoxyphenyl)-pyrazoline hydrochloride	1.5	5	0	0
	3.0	5	0	0
	3.5	10	8	80
	4.0	17	12	71
	5.0	5	4	80
1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-ethoxyphenyl)-pyrazoline hydrochloride	3.0	5	0	0
	3.5	10	1	10
	4.0	15	4	27
	5.0	5	5	100
1-Phenyl-3-( $\beta$ -piperidinoethyl)-5-(2'-n-butoxyphenyl)-pyrazoline hydrochloride	2.0	5	0	0
	2.5	5	0	0
	3.0	23	2	9
	3.5	9	0	0
	4.0	15	4	27
	5.0	5	4	80

Several post-mortems were performed to ensure that death had not resulted from accidental damage of abdominal organs. Convulsions, such as were caused by cocaine, were not observed on injection of any of the pyrazolines.

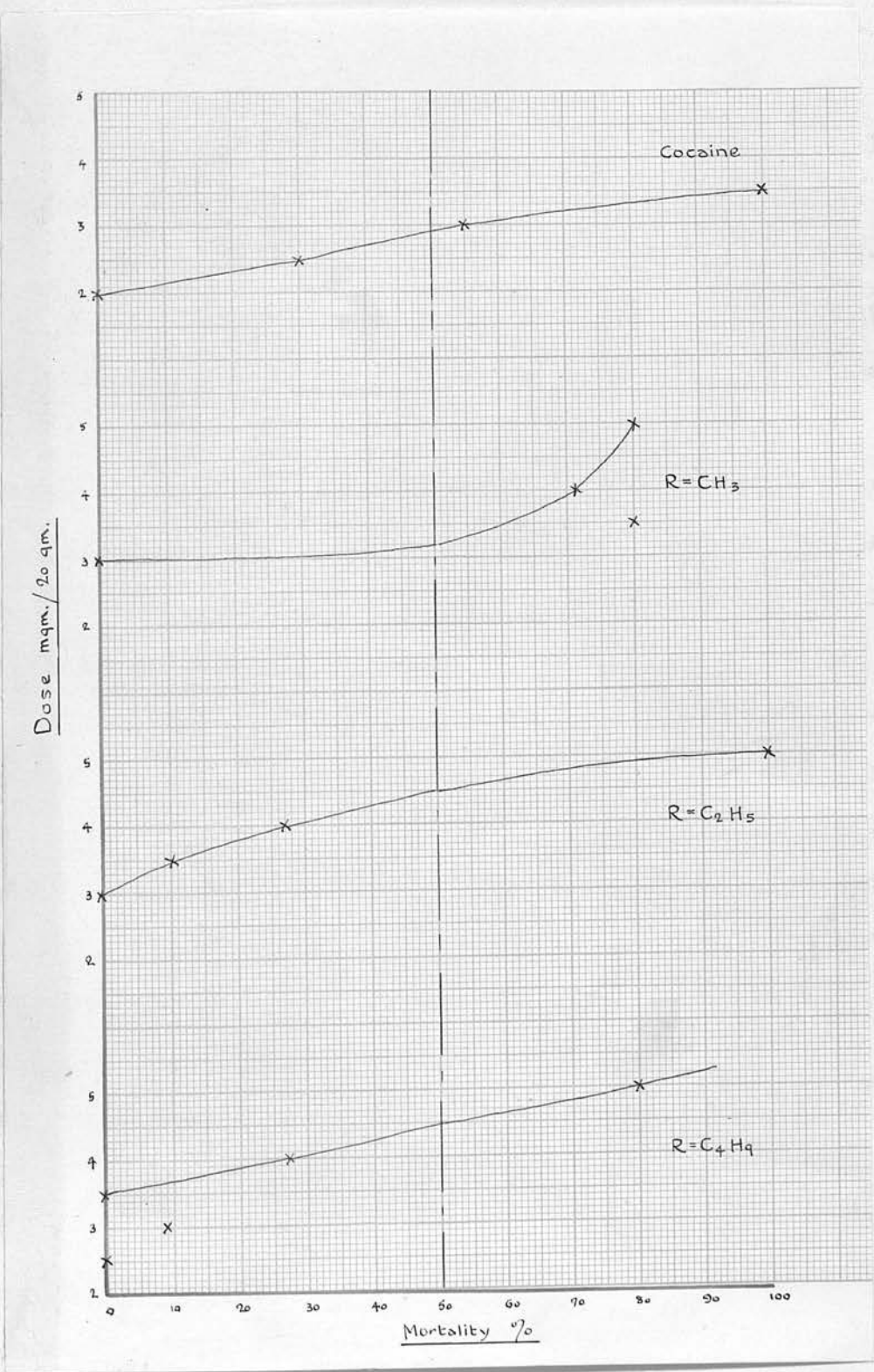
Approximate values for the median lethal doses may be conveniently found by plotting dose against percentage mortality. Although the experimental results give the lethal doses within limits close enough for present purposes, the data is in no case sufficient to justify claiming any degree of accuracy for the dose-mortality curve. Having found their relative toxicities compared with cocaine, the therapeutic values (see Introduction) of the pyrazolines may be calculated.



R	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub>	Cocaine
M.L.D. - from table .....	3.0-3.5	4.0-5.0	4.0-5.0	2.5-3.0
M.L.D. - from graph .....	3.2	4.5	4.5	2.9
Relative toxicity compared with cocaine .....	0.9	0.6	0.6	1
Therapeutic value - cornea	3.3	5	3.3	1
Therapeutic value - wheal	37	55	83	1

1-Phenyl-3-(β-piperidinoethyl)-5-(2'-methoxyphenyl)-pyrazoline hydrochloride was observed by Lord Suffolk to have an anti-pyretic action, the body temperature of a rat, in which fever had been induced with a killed culture of B. Coli, dropping much more rapidly after in-

jection of the pyrazoline than that of a control animal.



Percentage Mortality Produced by Intraperitoneal Injections in Mice.

CONCLUSIONS:

Of the  $\beta$ -amino-ketones prepared from 4-phenyl-2-acetylthiazole and from 2-acetylfurane, only one compound showed any marked local anaesthetic activity. In any case, all these compounds were too irritant to be of any use. Increase in the size of the N-alkyl radical was associated with increased irritation. Variation of R and R' in ketones of the type  $R.CO.CH_2.CH_2.NR'_2$  has thus failed to eliminate this undesirable property. Taking all the available information into consideration, it seems that their possessing this serious disadvantage will prevent any such compounds from being of clinical value as cocaine substitutes.

The 1:3:5-trisubstituted-pyrazolines studied were, on the other hand, not at all irritant. With one exception, they were more potent than cocaine in producing local anaesthesia of the rabbit's cornea, and were very powerful when injected intracutaneously. The difference between the results obtained by the two methods suggests that the pyrazolines do not penetrate mucous membranes at all readily. Apart from the remarkably low activity of the 2'-n-propoxy-compound, the differences between the activities and toxicities of the different pyrazolines were small. The therapeutic values, however, show that the combination of desirable proper-

ties is greatest in the case of the 2'-n-butoxyphenyl-pyrazoline.

For purposes of comparison, the unsaturated ketones from which the pyrazolines were prepared were also tested. Increase in size of the alkoxy-group was associated with increased activity, their being nothing exceptional in the behaviour of the propoxy member of the series. Like the other ketones examined, however, these compounds were too irritant to be of value.

Since the pyrazolines are local anaesthetics they can be of no practical use as anti-pyretics.

carry out the reaction in presence of hydrochloric acid. Both groups of  $\beta$ -aminoethyl-ketones answered the test with colour nitroprusside described by Feigl as specific for methyl-ketones.

2. The compound described by Olin and Johnson as 4-phenyl-3-acetylthiazole phenylhydrazone was shown to be the N-acetyl-phenylhydrazone.

3. The amino-derivatives of 4-phenyl-3-acetylthiazole reacted with phenylhydrazine to give 1-phenyl-3-(4-phenylthiazyl-2)-pyrazoline.

4. Owing to difficulty in obtaining a sufficient quantity of the starting material, 4-phenyl-2-furylthiazole, the synthesis of  $\beta$ -amino-ketones and related

## V.

S U M M A R Y.

1.  $\beta$ -Dialkylamino-derivatives of 4-phenyl-2-acetylthiazole and of 2-acetylfurane have been prepared as the hydrochlorides by the Mannich Reaction, the amine residues being varied in each case. In preparing the thiazole derivatives, it was found necessary to carry out the reaction in presence of hydrochloric acid. Both groups of  $\beta$ -aminoethyl-ketones answered the test with sodium nitroprusside described by Feigl as specific for methyl-ketones.
2. The compound described by Olin and Johnson as 4-phenyl-2-acetylthiazole phenylhydrazone was shown to be the N-acetyl-phenylhydrazone.
3. The amino-derivatives of 4-phenyl-2-acetylthiazole reacted with phenylhydrazine to give 1-phenyl-3-(4-phenylthiazyl-2)-pyrazoline.
4. Owing to difficulty in obtaining a sufficient quantity of the starting material, 4-phenyl-2-formylthiazole, the synthesis of  $\beta$ -amino-ketones and related

pyrazolines derived from 4-phenylthiazylidene-acetone was abandoned as impracticable with regard to its object. The preparation of the aldehyde by an analogous method to that used in synthesising 4-phenyl-2-acetylthiazole was found unsatisfactory, and an attempt to arrive at it by another method proved unsuccessful.

5. The synthesis of  $\beta$ -piperidino-ketones and related pyrazolines derived from *o*-alkoxybenzylidene-acetones was undertaken with success. Derivatives of *o*-*n*-butoxybenzylidene-acetone containing other amino-residues could not, however, be obtained. Raiford and Peterson's test with bromine vapour was found to be satisfactory for distinguishing the pyrazolines from the isomeric phenylhydrazones.
6. The local anaesthetic properties of the compounds prepared were examined. One thiazyl-ketone proved to be stronger than cocaine, but was too irritant to be of value. The derivatives of 2-acetylfurane had no anaesthetic action. Three of the pyrazolines were much more potent than cocaine, and were not at all irritant. Their toxicities comparing favourably with that of cocaine, they may be of value as substitutes for it. The unsaturated amino-ketones, from which the pyrazolines were prepared, also caused local anaesthesia, but were more irritant than cocaine.

THE DEVELOPMENT OF A RAPID MICRO-METHOD  
OF ESTIMATING SULPHUR.

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## I N T R O D U C T I O N

Sulphur in organic compounds in almost invariably determined as sulphuric acid. Several methods have been proposed for effecting quantitative oxidation and for estimating the sulphuric acid produced.

Oxidation to Sulphuric Acid. Oxidation may be carried out with solid or liquid reagents, at atmospheric pressure or in a bomb-tube.

Methods of oxidation by fusion with solid reagents in an open crucible are unsatisfactory owing to uncontrollable spurning, and, unless the crucibles are of metal, breakages are frequent. Fusion-mixtures proposed include zinc oxide-potassium nitrate and potassium hydroxide-potassium nitrate. Fusion may be carried out after preliminary digestion with nitric acid at atmospheric pressure.

Nitric acid is used in all methods of wet oxidation. With this reagent alone at atmospheric pressure, oxidation of the organic compound is not complete.

In the Carius method, the activity of the nitric acid is increased by the high pressure developed on

heating in a sealed tube. Accurate results are obtained, but the bomb-tube must be heated for 3 hours at 220°.

In the rubber industry, many attempts have been made to meet the need for a rapid method of determining "total sulphur" in rubber mixes, by oxidation with nitric acid at atmospheric pressure without subsequent fusion. Various means of supplementing the activity of the nitric acid have been suggested, but, of the procedures devised, only one, first described by E. Kahane, leads to any considerable saving of time.

Using a mixture of fuming nitric acid and perchloric acid Kahane claimed that oxidation of rubber was complete in 10 minutes. The method was modified slightly by Wolessensky, who also showed that removal of nitrates by evaporation with hydrochloric acid was necessary prior to precipitation of barium sulphate. J. G. Mackay (1930) tested Kahane's method on rubber mixes, the sulphur contents of which were known from Carius estimations, and found it to give low results. Any loss of sulphuric acid on boiling off excess nitric and perchloric acids was shown to be negligible. There remained the possibility of sulphur escaping as sulphur dioxide, and on addition of bromine to the oxidising agent to prevent such losses good results were obtained. The use of a condenser to prevent mechanical removal of sulphur with

the gaseous products of oxidation was found to be unnecessary, provided that the long neck of the Kjeldahl flask, in which the heating was carried out, was kept cool. The new procedure yielded results comparable in accuracy with those obtained by the Carius method, the Kjeldahl flask being warmed for about 40 minutes in all.

For the determination of sulphur in organic compounds on the micro-scale, two methods of carrying out the oxidation are in general use.

The Carius method was first used on the micro-scale in 1909 by Emich and Donau. Modifications have been introduced by Pregl (1930), Friedrich (1933) and Friedrich and Mandl (1937). The procedure is suited to carrying out a large number of analyses simultaneously, but heating at  $340^{\circ}$ - $350^{\circ}$  must be continued for 4 hours.

In 1912, Pregl worked out a method for the estimation of sulphur, in which the products of combustion of the organic compound in a current of oxygen are passed over red-hot platinum and absorbed in a solution of hydrogen peroxide. The combustion occupies only 45 minutes, and the sulphuric acid is obtained directly in a medium suitable for precipitation of barium sulphate: in absence of halogen and nitrogen, the sulphuric acid may be estimated by titration with alkali. The method is, however, suitable for individual estimations only. It is not reliable for the analysis of certain types of

compounds.

Estimation of Sulphuric Acid. The standard method for estimating the sulphuric acid produced on oxidation of a sulphur-containing compound is gravimetrically as barium sulphate. In practice, this is a tedious operation, and there are many sources of error against which precautions have to be taken. Attempts have been made to determine the amount of barium sulphate by a turbidimetric method, without much success. Titration of the sulphuric acid with barium chloride, using sodium rhodizonate as indicator, has also been tried, but the degree of accuracy was poor.

Many volumetric processes have been proposed, but of these only the benzidine sulphate method, first studied by Raschig in 1903, is of any practical value. Benzidine reacts with sulphuric acid to form benzidine sulphate which is very sparingly soluble. Having washed the precipitate free from other acids, the sulphuric acid can be titrated directly with hot alkali, benzidine being a very weak base and neutral to phenolphthalein. Alternatively, the benzidine may be titrated with potassium permanganate. The most important sources of error are the slight solubility of benzidine sulphate in water and the adsorption of the precipitating agent, benzidine hydrochloride, by the precipitate.

Having found it possible, when sulphate was esti-

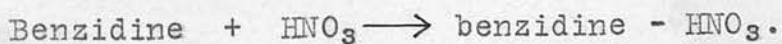
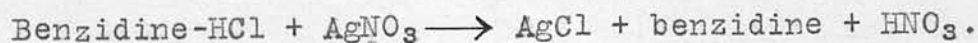
mated as barium sulphate, to obtain accurate results by his modification of Kahane's process for the oxidation of rubber, Mackay worked out a procedure for the alkalimetric determination as benzidine sulphate of the sulphuric acid produced. In using his method of oxidation in routine analyses, however, the sulphuric acid is usually estimated as barium sulphate.

None of the many other procedures described for the determination of sulphate as benzidine sulphate has yet come into general use.

On the micro-scale, after oxidation by the Carius method, sulphur is usually estimated gravimetrically in accordance with a procedure described by Pregl (1930). If a substance free from halogen and nitrogen has been combusted by Pregl's method, the sulphuric acid produced may be titrated directly with alkali: volumetric procedures for use with compounds containing halogen and/or nitrogen have been described by Friedrich and by Gibson and Caulfield (Analyst, 1935, 60, 522).

Friedrich and Mandl (1935) carried out an exhaustive examination of the alkalimetric estimation of sulphate as benzidine sulphate, and devised a procedure for working on the micro-scale. They recommend its use in conjunction with the micro-Carius (1937). Loss of sulphate through the solubility of the precipitate in water was guarded against by saturating the precipitation re-

agent and the wash liquid with benzidine sulphate, and by using a definite volume of sulphate solution for which a correction could be made. It was found impossible to eliminate the error due to occlusion of benzidine hydrochloride by varying the conditions of precipitation or by washing of the precipitate. For the removal of hydrochloric acid, these authors therefore treated the precipitate with alcoholic silver nitrate solution. Silver nitrate reacts with benzidine hydrochloride to give silver chloride, benzidine and nitric acid. Formation of benzidine nitrate is said to be prevented by the excess of silver nitrate, which forms a complex with benzidine.



The precipitate may be then washed free from nitric acid, present in equivalent quantity to the hydrochloric acid originally adsorbed as the benzidine salt. Before the titration, potassium iodide was added, as otherwise silver oxide separated at the end-point.

For the determination of sulphur in soil solutions, Marsden and Pollard (1937) have developed a method whereby 1 mgm. or less of sulphate may be estimated by titrating benzidine sulphate with potassium permanganate solution. The empirical relationship between the volume of potassium

permanganate and the amount of sulphate was found to be constant for the range studied.

It was proposed to apply the process for the wet oxidation of rubber described by Mackay to the estimation of sulphur in organic compounds on the micro-scale, with a view to meeting the need for a rapid method of carrying out series of determinations. Preliminary to this, Friedrich and Mandl's procedure for the micro-estimation of sulphuric acid as benzidine sulphate was examined, as it appeared to have many advantages compared with the gravimetric method.

#### References:

- J. G. Mackay, J.S.C.I., 1930, 49, T 233.
- F. Pregl, "Quantitative Organic Micro-Analysis" (2nd. Eng. edition), 1930.
- A. Friedrich, "Die Praxis der Quantitativen Organischen Mikroanalyse", 1933.
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- Marsden and Pollard, J.S.C.I., 1937, 56, T 464.

iodate. In a quartz flask, 20 c.c. water containing 0.1 c.c. methyl red (dissolved in alkali) was brought to neutrality. The neutral solution was transferred to another flask, into which had been previously weighed about 30 mgm. of solid biiodate. This was then titrated to canary-yellow.

The concentration of the sodium hydroxide solution is expressed in terms of 0.02 normal.

log factor  $N/50 = \log \text{mgm. biiodate} - (\log \text{c.c. alkali} + 0.89204)$ .

Standardisation of 0.02 N  $\text{H}_2\text{SO}_4$ :

After bringing 15 c.c. water containing 0.1 c.c. methyl red indicator to neutrality, about 5 c.c. acid was added and the solution again titrated to canary-yellow.

The concentration is most conveniently expressed as a ratio of that of the alkali.

#### Results:

The method was first of all tested by titrating the benzidine sulphate precipitated from measured volumes of the standard sulphuric acid solution. Corrections were made for the loss of benzidine sulphate through solubility in water.

It was thought that these errors were caused by due to adsorbed benzidine sulphate and treatment with alcoholic silver nitrate solution.

<u>C.c. H<sub>2</sub>SO<sub>4</sub> taken</u>	<u>C.c. H<sub>2</sub>SO<sub>4</sub> found</u>	<u>Error in c.c.</u>
2.00	2.01	+0.01
2.82	3.06	+0.24
2.99	3.32	+0.33
3.43	3.59	+0.16

The high results found for measured volumes of standard sulphuric acid could have been due to the presence in the solution of sulphate other than sulphuric acid, although it is very unlikely that such an impurity could be the cause of errors of the magnitude observed.

Estimations were next carried out using weighed amounts of A.R. potassium sulphate, dissolved in 2 c.c. water. The loss of benzidine sulphate in this volume is equivalent to 0.05 c.c. 0.02 N alkali.

Theoretical percentage of sulphur = 18.36.

$\log \% S = \log \text{c.c. alkali} + \log \text{factor } N/50 + 1.50596$

-log mgm. substance.

<u>Mgm. K<sub>2</sub>SO<sub>4</sub> taken</u>	<u>Percentage sulphur found</u>	<u>Error</u>
6.684	19.55	+1.19
6.916	19.85	+1.49
8.576	19.87	+1.51
11.651	19.72	+1.36

It was thought that these positive errors might be due to adsorbed benzidine hydrochloride, the treatment with alcoholic silver nitrate solution for 30 seconds

described by Friedrich and Mandl being insufficient for its complete removal.

In the next series of determinations, the precipitate was treated three times with silver nitrate solution, which was allowed to act for 2 minutes on each occasion. This was followed by six washings with saturated benzidine sulphate solution.

<u>Mgm. K<sub>2</sub>SO<sub>4</sub> taken</u>	<u>Percentage sulphur found</u>	<u>Error</u>
6.722	19.26	+0.90
7.667	18.17	-0.19
7.905	19.28	+0.92
9.408	18.87	+0.51
10.224	18.42	+0.06
10.344	17.81	-0.55
10.737	17.74	-0.59

On treating the precipitate with silver nitrate for 30 seconds, it was observed to darken in colour. When the action was continued for 6 minutes, a copious black deposit was formed.

Some pure benzidine sulphate, such as was used in preparing the wash liquid, was shaken in a test-tube with alcoholic silver nitrate solution. In a few seconds, the solid became quite black.

It appears that silver nitrate reacts with the benzidine radical, irrespective of the acid with which it is combined. Correct results may then be imagined to occur

through compensation between two sources of error:

(1.) adsorption of benzidine hydrochloride by the precipitate; (2.) liberation and consequent loss of acid through the action of silver nitrate on the precipitate. Such an explanation is in agreement with the last series of results.

In view of the unreliability of the above procedure, it was decided, while carrying out preliminary tests of the proposed method of oxidation, to estimate the sulphuric acid produced gravimetrically as barium sulphate.

#### Estimation of Sulphuric Acid as Barium Sulphate.

Full experimental details for carrying out the estimation by Pregl's method are given in his text-book. Use was made of Wintersteiner's apparatus for the automatic transfer of the precipitate to the micro-Neubauer crucible.

From previous experience, the gravimetric determination was known to be reliable. After a little practice, quantitative transfer of the precipitate to the crucible could be readily accomplished automatically. To test the filter-bed in the crucible, estimations were carried out of the barium sulphate precipitated from a solution of magnesium sulphate, to which had been added a few drops of dilute hydrochloric acid. A standard 4 c.c.

pipette was used to measure out the sulphate solution.

<u>Mgm. BaSO<sub>4</sub> calculated</u>	<u>Mgm. BaSO<sub>4</sub> found</u>	<u>Error in mgm.</u>
11.435	11.388	-0.047
11.435	11.465	+0.030
11.435	11.442	+0.007

For 5 mgm. of substance, 0.05 mgm. BaSO<sub>4</sub> corresponds to 0.14% sulphur.

### The Oxidation.

#### Procedure:

The oxidation was performed in a clean, dry micro-flask Kjeldahl, into which was weighed about 5 mgm. of the organic compound. It was found convenient to use a long-handled weighing-stick, such as is recommended by Pregl for molecular weight determinations (text, p. 213), so as to be able to introduce the solid to the bottom of the flask without leaving any sticking to the sides of the long neck.

The oxidising mixture consisted of 1 c.c. fuming nitric acid, 0.5 c.c. perchloric acid (density 1.54), and one drop of bromine (H<sub>2</sub>SO<sub>4</sub> free). It was prepared in a clean dry boiling-tube and then poured into the Kjeldahl flask.

Heating was carried out on a stand of the type used for multiple Kjeldahl determinations. The contents of the flask were gently warmed for 10 to 15 minutes, by

which time the evolution of red fumes had ceased, and heating was then increased to produce gentle boiling. When dense white fumes were given off, the flame was removed.

The flask was rinsed down and the clear liquid was evaporated to dryness with 0.1 gm. pure sodium chloride and again with 1 c.c. concentrated hydrochloric acid, to remove chloric and nitric acids. Prior to the estimation of sulphate as barium sulphate, the residue was taken up in 5 c.c. very dilute hydrochloric acid (1 c.c. conc. HCl to 100 c.c. water).

**Results:**

About thirty estimations were performed in testing this method of oxidation. The results obtained with pure sulphonal and thiourea were very low, the error being 20% to 50% of the theory. When 4-phenyl-2-acetylthiazole or benzoylhydroxythioacetamide was used, a suspension of sulphur formed on the addition of acidified water to the residue from the oxidation.

No improvement resulted when the warming of the oxidising mixture was continued for 30 minutes, more bromine being added as that present volatilised. Precautions were taken throughout against likely mechanical sources of error.

It was finally concluded that it was impossible by this method to effect the quantitative oxidation of sulphur in organic compounds to sulphuric acid.

S U M M A R Y

The method described by Friedrich and Mandl for the volumetric estimation of sulphuric acid as benzidine sulphate was examined and found to yield high results. When the procedure was slightly modified, figures approximating more closely to the actual were obtained, but the degree of accuracy was still low.

Estimating the sulphuric acid produced gravimetrically, the possibility was investigated of determining sulphur in organic compounds on the micro-scale by a method of wet oxidation at atmospheric pressure. The conversion of sulphur to sulphuric acid was found to be far from complete.

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