SOME INDIAN MEDICINAL PLANTS, THEIR PHARMACOLOGICAL ACTION and SYNTHESIS OF EMBELIC ACID.

by

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Contents.

I. INTRODUCTION.

From the earliest times medicine has been a curious blend of superstition, empiricism and of sagacious observation out of which ultimately science is made. Of these three strands, superstition, empiricism and observation, medicine was constituted in the days of the priest physicians of Egypt and Babylonia; of the same three strands it is still composed. The proportions have, however, varied significantly. An increasingly alert and determined effort, running through the ages, has endeavoured to expel superstition, to narrow the range of empiricism and to enlarge, refine and systematise the scope of observation. Superstition is easily recognisable, but the line between an empirical and scientific observation is not so clear. Empiricism does not endeavour to penetrate more deeply and gets no further. On the other hand a scientific observer is not content with mere facts; he asks the reasons and seeks to establish/

establish further relationships, while the empiricist practising his rule of thumb works disjointedly and tends to remain in reference to any particular observation just where he is. This difference between empiricism and a sustained scientific research of known facts in short is the subject of these investigations.

(a) Early History.

From the earliest times the human races by instinct relied on plants and herbs to cure their diseases and it is an interesting fact that the Anglo Saxons, the Druids and the North American Indians employed most of the plants we are now using for identical complaints. It is to the Egyptian Papyri, however, that we must go for the earliest mention of onions, garlic, pomegranates, gentian, squills and castor oil as curatives. In the East it was not till about 2100 B.C. that the city of Babylon, under the leadership of Hammurabi, a Semitic king (Amorite) gained ascendancy over the Sumerian cities that an authentic record is available. From the cuneiform library of Assurbanipal (668-126 B.C.) one of the Assyrian kings who recorded the code of Hammurabi, information about the/

the Babylonian medicine is available. In the text book literature of the library of Assurbanipal are found long lists of drugs which are divided into organic and inorganic substances. Among the latter are found alkalies and salts,as well as a number of stones,efficacious as amulets; anise, cumin, colocynth, juniper and oleander are amongst the identified organic substances.

Records of Indian and Chinese medicine are less clear, though from the latest archaeological finds in Sindh there is evidence of civilisation as old as of Sumeria. From the Hindu Vedas it is clear that theurgic medicine prevailed in India and their skill in surgery was unequalled at that time.

The earliest record of Greek medicine is found in the Odyssey where we are told that Aesculapius had been instructed in medicine by Chiron in the eighth century B.C.

(b) History of Unani Medicine.

The knowledge of the curative properties of plants as we now know it, more or less freed from superstition, may be said to have started in Greece/

Greece four centuries B.C. with the greatest doctor of all time, Hippocrates. After the destruction of the Roman Empire, the only civilisation was to be found in the East and before the death of Paul of Aegina, the translation of Greek and Syriac medical works into the language of the Mohammedan conquerors of Asia Minor had begun. And even before the end of the fifth century, the medical science of Constantinople had been carried as far east as the Persian Province of Khorasan. At the school and hospital of Gondisapor was educated the Arab physician Harets-bin-Kaladah. The rapid progress of the Saracens in the realms of art and science is one of the most remarkable features of history.

There are six outstanding names in the history of Unani medicine, three of them, Rhazes, Haly Abbas and Avicenna, belong to the Eastern Caliphate 750-1258, and the names of Albucasis, Avenzoar and Moses Maimonides to the Western Caliphate.

The most consulted authorities of the middle ages on drugs were the works "Jami" of Ibu Baitar (a botanist who travelled through Asia in pursuit of medical plants), the Qrabadin of Sabor-ibu- /

ibn-Sahil, the Persian Materia Medica of Abu Mansur and the pharmaceutical works of Jabir Ibn Haiyan. And even to this day these works form the text books for the student of Unani medicine in India, Persia and Arabia.

(c) Present Position.

Of the many systems of medicine practised in India to-day, it is probably true that some nine-tenths of the masses of the Indian population depend on Unani and Ayurvedic medicine in some form or another, and that western medicine only reaches about one-tenth of the population despite the network of hospitals and dispensaries with which the land is covered. And of recent years the claims of indigenous systems which had so far slumbered have been brought forward. At last three provincial governments have appointed committees to investigate them. The practioner of western medicine is wont to hold the indigenous system in contempt, but that is simply on account of his ignorance of it. Its anatomy and physiology are crude, and it has no pharmacology, as/

as was the case withwestern medicine until a few decades ago. Yet its merits are greater than its demerits; it and not western medicine is the medicine of the people. It has long tradition, it is deep rooted in the customs and habits of the people, its dietetics especially are based on Indian dietaries and meet Indian requirements.

In view of the great cheapness and unchallenged efficacy of some of the indigenous drugs,as testified by several eminent British authorities, a vast amount of medical relief could be given to the masses of India at a very little cost if the dispensaries can use them intelligently. With the inauguration of reforms in 1924 when members of the Indian legislature and local bodies pressed for the encouragement and investigation of indigenous systems of medicine the government of India took steps in the right direction to appoint committees to investigate their claims.

These committeed chiefly consisted of Allopaths, Hakims and Vaids and scareely any other scientific interest was represented; their admirable reports, although viewing the subject in the right perspective, failed to appreciate the/

the help that a chemical investigation can give.

(d) Order of Future Research.

It is therefore suggested that any future investigation of the indigenous systems of medicine should be as follows:-

1. Examination of the drugs by pharmacologists.
2. Isolation and chemical investigation of the active principles.
3. Physiological tests on the pure active principles.
4. Clinical trials of drugs of potential value.

Searching through the ancient and the modern literature on herbs and medicinal plants of India one's attention is irresistibly drawn to many that possess reputed curative properties, but that such search yields no clue as to whether a scientific investigation has ever been made with regard to their nature or not. In going through the pages of one of the latest authoritative works on "Medicinal Plants of India" by Colonels Basu and Kirkpatrick, both members of the Indian Medical Service, a list of drugs was compiled for the purposes of studying their chemical nature provided they proved pharmacologically active according to the present day technique. Out of this list four such drugs were selected which possessed the greatest curative powers and were easily procurable in sufficient quantities.

II. /

II. DRUGS FOR INVESTIGATION.

According to the authors' descriptions.

1. Cassia absus (n.o. Leguminoseae), Indian name Chaksu. Seeds and leaves of this plant are used. Seeds are recommended as attenuant and astringent to wounds and sores. In purulent ophthalmia about a grain of the powdered seeds, after being baked, is introduced beneath the eyelids. The receptacle of the seed possesses diuretic and stimulant properties. It is used as a cathartic in habitual constipation (dose $\frac{i}{8}$ - 3 drams). Seeds are also efficacious in ringworm.

2. Sphaeranthus indicus (n.o. Compositae). Indian name Mundi. Parts used are seeds, root, bark and flowers. The seeds are considered to have anthelmintic properties. The powder of the root is considered stomachic and ground bark mixed with whey is a valuable remedy for piles. In the Punjab the flowers are highly esteemed as alterative, depurative, cooling and tonic.

3./

3. Plantago lanceolata (n.o. Plantigmae). Indian name Bartang. Parts used are leaves and seeds. Leaves are used as an application to wounds, inflamed surfaces and sores. The seeds are used with sugar as a drastic purgative.

4. Embelia ribes (n.o. Myrsinae). Indian name Baibarang Kabli. Seeds are reputed anthelmintic, stomachic and useful against intestinal worms and tape worms.

It was deemed highly desirable first to test these drugs pharmacologically and if found active to undertake their chemical investigation.

According to our present knowledge of pharmacology, it is noticed that some of the medicinal terms applied for the virtues of these drugs are vague and uncorrelated. Hence it is not always possible to test every describable property of a medicine on animals. Therefore during these investigations Cassia absus and Plantago lanceolata were tested for their purgative and cathartic actions and Spheranthus indicus/

indicus and Embelia ribes for their anthelmintic properties.

III. PHARMACOLOGICAL TESTS.

1. Purgative Action on Mice.

Seeds of Cassia absus and Plantago lanceolata were tested on a number of mice with negative results. For this purpose 8 mice were prepared by feeding them on breadcrumbs moistened with water for 3 days. On the 4th day, two mice were given 30 mgm. of each substance in the form of powder mixed with breadcrumbs. Six mice served as controls. No purgative action was noticed. In the next experiment two more mice out of the controls were given the substances, but no effect was noticed. In the same way all the mice were fed on the substances with negative results. The increase in dose did not produce the purgation.

2. Purgative Effect on Rats.

Two rats were fed on the powdered seeds mixed with Indian meal and the dung weighed every day/

day for a fortnight in the case of the first rat and three weeks in the case of the second rat. No increase in the weight of the dung was noticed.

Cassia absus and Plantago lanceolata were therefore considered negative in their purgative properties.

3. Anthelmintic Action of Spheranthus indicus.

On earth worms. According to the technique of Sollman (Textbook on Pharmacology) a number of freshly dug up earth worms are suspended in the bile bicarbonate solution (containing 1% $NaHCO_3$ and 0.04% sodium tauroglycholate), the substance to be tested is added and the mortality of worms observed during 24 hours. The experiment is controlled by suspending the same number of worms in sodium tauroglycholate solution and water respectively.

Table I. /

Table I.

Spheranthus indicus (whole flowers).

B.B. = bile bicarbonate solution; F = fatality;

I.R. = irritability reduced; N = normal.

	After 1 hr.	3 hrs.	6 hrs.	24 hrs.
100 c.c. B.B. soln. + 4 gm. subs. + 4 worms	all N	all N	1 F, 3 I.R.	2 F, 2 I.R.
100 c.c. B.B. + 2 gm. subs. + 4 worms	do.	do.	all I.R.	1 F, 3 N.
100 c.c. B.B. + 1 gm. subs. + 4 worms	do.	do.	all N	1 F, 3 N
100 c.c. soln. + 4 worms	do.	do.	do.	all N
100 c.c. water + 4 worms	do.	do.	do.	do.

In another experiment very finely crushed flowers of Spheranthus indicus were used with the following results:

Table II. /

Table II.

	After 1 hr.	3 hrs.	6 hrs.	24 hrs.
100 c.c. B.B. soln. + 4 gm. subs. + 4 worms	1 F, 3 I.R.	all F	all F	
100 c.c. B.B. soln. + 2 gm. subs. + 4 worms	all I.R.	do.	do.	
100 c.c. B.B. soln. + 1 gm. subs. + 4 worms	2 N 2 I.R.	do.	do.	
100 c.c. B.B. soln. + 0.75 gm. subs. + 4 worms	all N	do.	do.	
100 c.c. B.B. soln. + 0.5 gm. subs. + 4 worms	1 I.R. 3 N	1 F, 1 I.R. 2 N	do.	
100 c.c. B.B. soln. + 0.25 gm. subs. + 4 worms	all N	2 F, 1 I.R. 2 N	do.	
100 c.c, B.B. soln. + 0.10 gm. subs. + 4 worms	all N	all N	all I.R.	all F
100 c.c. B.B. soln. + 0.05 gm. subs. + 4 worms	all N	do.	all N.	do.
100 c.c. B.B. soln. + 4 worms	do.	do.	do.	do.
100 c.c. water + 4 worms	do.	do.	do.	do.

Results: 0.05 gm. % fatal.

Comparison/

Comparison between the powdered flowers of Spheranthus indicus with the cold extract of the flowers and Santonin. (1 gm. powdered flowers were soaked in 100 c.c. water overnight and the filtered extract used).

Table III.

	After 1 hr.	3 hrs.	24 hrs.
90 c.c. B.B. + 10 c.c. ext. + 4 worms	All N	all N	2 F, 1 I.R. 1 N.
95 c.c. " 5 c.c. " "	do.	do.	2 I.R., 2 N
97.5 c.c. " 2.5 " " "	do.	do.	1 I.R., 3 N
100 c.c. " 0.1 gm. powder + 4 worms	do.	do.	3 F, 1 I.R.
do. " 0.05 " " "	do.	do.	1 F, 3 N
do. " 0.005 " " "	do.	do.	1 I.R., 3 N
do. " 0.1 gm. Santonin + 4 worms	do.	do.	all F
do. " 0.005 " "	do.	do.	do.
do. " 0.002 " "	do.	do.	all I.R.
do. " 0.01 "	do.	do.	all N
100 c.c. B.B. + 4 worms	do.	do.	do.
100 c.c. water + 4 worms	do.	do.	do.

Results: 0.1 gm. powdered flowers 75% fatal.
10 c.c. 1% extract equivalent to 0.1 gm. powdered flowers } 50% fatal.
0.05 gm. santonin - 100% fatal.

Comparison/

Comparison of anthelmintic activity of fat from *Spheranthus indicus* with fatty acids and unsaponifiables.

1 c.c. ether solution contained 0.0054 gm. unsaponifiable.
1 c.c. " " " 0.0054 " fatty acids.
1 c.c. " " " 0.0054 " fat

Table IV.

	After 18 hrs	After 24 hrs.
100 c.c. B.B. + 0.0054 gm. unsap. + 4 worms	all N	all N
do. 0.0108 " "	all N	do.
do. 0.0216 " "	do.	do.
do. 0.0054 gm. F.acids "	do.	do.
do. 0.0108 " "	1 F, I I.R. 1 N.	2 F, 1 I.R. 1 N.
do. 0.0216 " "	all F	all F
do. 0.0054 " "	all N	all N
do. 0.0108 " "	all I.R.	1 F, 3 I.R.
do. 0.0216 " "	1 F, 3 I.R.	3 F, 1 I.R.
100 c.c. B.B. + 4 worms	all N	all N
100 c.c. water + 4 worms	do.	do.

Results: The fatty acids most active and unsaponifiables practically inactive.

In a number of experiments on worms, it was found that (a) hot water extraction did not increase the potency of the extract, (b) concentration in vacuo destroyed the activity to a considerable extent and (c) the residue left from 50% alcoholic extract was more active than aqeuous extract, (d) the residue from the ethereal extract was more active than the residue from the alcoholic extracts, (e) the fatty acids obtained after saponification of the fat retained all the activity, (f) the unsaponifiable possessed practically no activity.

Anthelmintic activity of Spheranthus indicus on dogs.

Testing of an anthelmintic on earth worms provides only an arbitrary guide to its activity. A substance may be found to be active against earth worms but may not expel worms from the intestines, but when a substance has been found to be an active anthelmintic by other trials, earth worms can be used to determine their comparative efficiency.

For pharmacological tests dogs are used and the method of preparation of the animal and the/

the administration of the drug is as follows:-

The dog was given a light meal during the day followed by a dose of 5 gm. of $MgSO_4$ in the evening and the next morning when no worms were found in the stools, a dose of the anthelmintic was administered at about 10 a.m., again followed by a dose of 5 gm. $MgSO_4$ after 6-7 hours. The stools were examined every morning for a period of one week by collecting them on a sieve of a very fine mesh, washing them under the tap and separating the worms from the solid material. After the stools had been examined for one week, a post mortem was carried on the dog and the number of worms found in the intestines counted.

Table V. /

Table V.

Spheranthus indicus, powdered flowers, fat and fatty acids.

No. of dog.	Wt. in lbs.	Sex	Dose administered	No. of worms expelled on treatment.		No. of worms found on P.M.		Efficiency %.	
				Round	Flat	Round	Flat	Round	Flat.
54	30	♂	2 gm. powdered flowers	10	-	40	7	20%	-
55	20	♂	do.	-	1	3	9	-	10%
59	17	♀	2 gm. fat	-	-	6	-	-	-
60	20	♂	do.	2	-	18	-	-	-
56	17	♀	2 gm. fatty acids	-	1	-	4	-	-
57	18	♂	do.	-	-	-	-	-	-

Remarks: In the case of dogs nos. 54 and 55, the powder was too bulky to administer. In the case of dogs nos. 59, 60, 56 and 57, the fat and fatty acids could not be retained by the animals.

Results: It was found that the powdered flowers were too bulky to be taken by the animals, and fat and fatty acids too distasteful to be retained by the animal. Fat and fatty acids were administered both/

both in capsules and by stomach tube but in no case was a satisfactory result obtained. The results obtained only showed that the substance may possess an anthelmintic property but the administering of the drug is not easily carried out.

Anthelmintic Activity of Embelia ribes Berries on Earth Worms.

Table VI.

	After 1 hr.	3 hrs.	6 hrs.	24 hrs.
100 c.c. B.B. + 4 gm. powdered berries + 4 worms	1 F, 2 I.R. 1 N	2 F, 2 I.R.	all F	-
do. + 2 gm. powdered berries + do.	2 I.R.,2N.	1 F, 2 I.R. 1 N.	all I.R.	all F
do. + 1 gm. do. + do.	all N	all N	all I.R.	all F
100 c.c. B.B. + 4 worms	all N	all N	all N	all N
100 c.c. water + do.	do.	do.	do.	do.

Results: 1 gm. 100% fatal.

Table VII /

Table VII.

	After 1 hr.	3 hrs.	6 hrs.	24 hrs.
100 c.c. B.B. + 3.5 gm. powdered berries + 4 worms	all N	1 F, 2 I.R. 1 N	1 F, 3 I.R.	all F
do. + 2.5 gm. do. + do.	all N	all I.R.	all I.R.	all F
do. + 1.5 gm. do. + do.	all N	3 I.R. 1 N	do.	do.
do. + 0.75 gm. do. + do.	all N	all N	all N	all N
do. + 0.5 gm. do. + do.	all N	all N	all N	all N
do. & 0.25 gm. do. + do.	all N	all N	all N	I I.R., 3 N
do. + 0.10 gm. do. + do.	all N	all N	all N	all N
100 c.c. B.B. + 4 worms	all N	all N	all N	all N
100 c.c. water + 4 worms	all N	all N	all N	all N

Results: 0.75 gm. 100% fatal.

0.5 gm. 75% fatal.

Table VIII.

Comparison of orange yellow crystalline substance isolated from ether extract with that of uncrystallisable portion.

A. 0.25 gm. substance dissolved in 100 c.c. B.B. solution and out of this 10 c.c. further made up to 20 c.c.

Therefore each c.c. contained 0.00125 gm. substance.

B. 1 gm. uncrystallisable material made up to 50 c.c. and 10 c.c. of this further made up to 40 c.c.

Therefore each c.c. contained 0.005 gm. substance.

	After 24 hours.	
99.5 c.c. B.B. soln. + 0.5 c.c. A + 4 worms	all F	= 0.031 gm. original subs
99 c.c. " + 1 c.c. A "	"	= 0.062 "
98 c.c. " + 2 c.c. A "	"	= 0.124 "
99 c.c. " + 1 c.c. B. "	2 F, 2 I.R.	= 0.075 "
98 c.c. " + 2 c.c. B "	1 F, 3 I.R.	= 0.15 "
90 c.c. " + 4 c.c. B "	1 F, 3 I.R.	= 0.30 "
100 c.c. B.B. soln. + 4 worms	all N	
100 c.c. water + 4 worms	all N	

Results: Crystalline material 100% fatal 1.25 pts. in 100,000.
Uncrystallisable " 25-50% fatal 1 pt. in 1,000.

In/

In a number of experiments carried out on worms it was found that (a) the aqueous extract was practically inactive, (b) the residues left after evaporating the alcoholic solution possessed considerable activity, (c) the residues left after evaporating the solution were most active, (d) that most of the activity was retained in the orange yellow crystalline material isolated from ether residues.

Anthelmintic activity of Embelia ribes on dogs.

The same method of preparation of dogs and administration of drugs were used in this case with the following results:-

Table IX. /

Table IX.

Embelia ribes powdered berries.

No. of dog.	Wt. in lbs.	Sex	Dose in gms.	No. of worms expelled on treatment		No. of worms found after P.M.		Efficiency	
				Round	Flat	Round	Flat	Round	Flat
61	25	♀	2	-	-	-	8	-	-
62	18	♂	3	9	22 pieces	5	numer-ous	64%	?
63	30	♂	4	12	6 pieces	3	3	80%	?
64	40	♀	4	9	5 pieces	12	2	42%	?
65	45	♂	4	-	-	-	numer-ous	-	-
66	35	♀	4	3	11 pieces	-	4	100%	-

Results: The substance therefore appears to possess the property of expelling round worms, but the action seems to be erratic in the case of flat worms. As it was found difficult to find heads of the flat worms, it is not possible to give percentage efficiency in their case.

Table X /

Table X.

Activity of fat and crystalline material on dogs.

No. of dog.	Wt. in lbs.	Sex	Dose in gms.	No. of worms expelled on treatment.		No. of worms found after P.M.		Efficiency	
				Round	Flat	Round	Flat	Round	Flat
67	50	♂	0.5 cryst.	4	-	-	-	100%	-
68	25	♂	0.5 "	6	-	4	-	60%	-
69	40	♂	1.0 fat	-	-	-	numer-ous	-	-
70	40	♂	1.0 fat	-	6 pieces	-	2	-	?
71	50	♂	1.0 cryst.	11	-	3	-	78%	-
72	18	♂	do.	10	41 pieces; 6 heads	-	4	100%	?
73	30	♀	do.	5	14 pieces	4	3	54%	?
74	35	♂	do.	-	-	-	numer-ous	-	?

Remarks: It was found that dogs nos. 67 and 68 were free from flat worms; dog no. 74 was free from round worms. Dog no. 69 was suffering from appendicitis.

Results:

1. The crystalline material was found to be sufficiently efficient against round worms.
2. Its efficiency against flat worms is doubtful.

Having found Embelia ribes active against intestinal worms, it was decided to isolate the active principle on a large scale and carry out the chemical investigation. But on reference to the past literature it was found that Heffter and Feurstein (Arch. Pharm., 1900, 238, 15) had to a certain extent studied the chemical constitution of the isolated product. The work was therefore started from where Heffter and his colleague left it.

The pharmacological tests and isolation of the product were carried out at the Medical School, University of Leeds, and as there were no facilities there to carry out a chemical investigation and synthesis, transfer to the Medical Chemistry Department of the University of Edinburgh was highly desirable, where the work has been completed.

IV. /

IV. CHEMICAL INVESTIGATION.

The first chemical examination of the berries of Embelia ribes was carried out by Scott (Chemist and Druggist) who isolated a substance which crystallised in the form of bright yellow scales and which he regarded as a glucoside. Scott proposed the name Embelin for this substance. Shortly afterwards Warden (Pharm. J. and Trans., 1888, 18, 601, 19, 305) similarly examined the berries and isolated a substance, probably identical with the so-called glucoside of Scott, which was found to possess acidic properties, and to which he assigned the formula, $C_9H_{14}O_2$. In view of the definite acidic properties of this substance as shown by the formation of crystalline ammonium salt as well as by its solubility in alkalies, Warden assigned the name Embelic Acid to it.

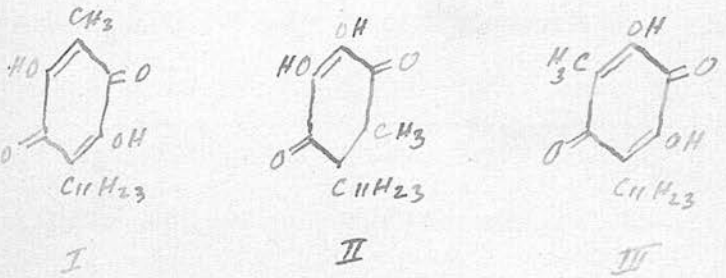
No further chemical work appears to have been done on this subject until Heffter and Feurstein (loc. cit.) submitted embelic acid to a detailed investigation. These authors confirmed both the acidic/

acidic properties of the substance and the analytical results, but they provided evidence which necessitated revising the molecular formula to $C_{18}H_{28}O_4$. Of the four oxygen atoms, two were shown to be present as hydroxyl groups, since embelic acid was found to form a dibenzoyl derivative; these hydroxyl groups were further shown to be responsible for the acidic properties of the substance. The remaining oxygen atoms could be readily reduced with the formation of dihydroembelic acid, a colourless substance which underwent spontaneous oxidation in the air to embelic acid. In view of this behaviour, coupled with the fact that embelic acid condensed readily with primary amines, such as methylamine, aniline and toluidine, Heffter and Feurstein concluded that the substance was a para-quinone.

By oxidation with alkaline permanganate the same authors succeeded in isolating lauric acid; small amounts of simpler acids were at the same time formed.

On the basis of the above results Heffter and Feurstein proposed Formula I as most probably representing the constitution of embelic acid, although/

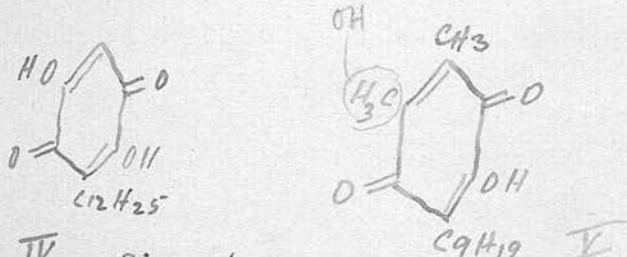
although they pointed out the possibility of a different orientation of the substituent groups.



I II III

Thus formulae II and III, although improbable are not inconsistent with Heffter and Feurstein's views.

It is clear that in devising the above formulae Heffter and Feurstein tacitly assumed that the lauric acid produced on oxidation of embelic acid was derived from the large side chain together with one carbon atom from the ring, and it was this assumption which necessitated the introduction of methyl group which is shown in their formula although no evidence was obtained of its presence. They apparently overlooked the possibility that this acid might originate entirely from the side chain, in which case the constitution of embelic acid would be represented by formula IV.



IV V

Since/

Since degradation experiments were unlikely to lead to results which would permit of a decision between the alternative formulae I and IV, the synthesis of these two compounds was undertaken. In view however of the recent work of Kaul, Dutt and Ray (J. Indian Chem. Soc., 1929, 6, 577) who have repeated Heffter and Feurstein's work on the oxidation of embelic acid and who claim to have identified the acid produced as isolauric acid, and not lauric acid, it became necessary to repeat this work. Heffter and Feurstein's results were completely confirmed. By oxidation of embelic acid either by alkaline permanganate, the method employed by Heffter and Feurstein, or by nitric acid, one of the methods used by Kaul, Dutt and Ray, a product was obtained which after distillation, conversion into its sodium salt, and regeneration from the latter by treatment with hydrochloric acid, melted at 42° and showed no depression when mixed with a pure specimen of lauric acid, obtained from the British Drug Houses Ltd. Further information was afforded by the conversion of both specimens into the amide by successive treatment with thionyl chloride and ammonia/

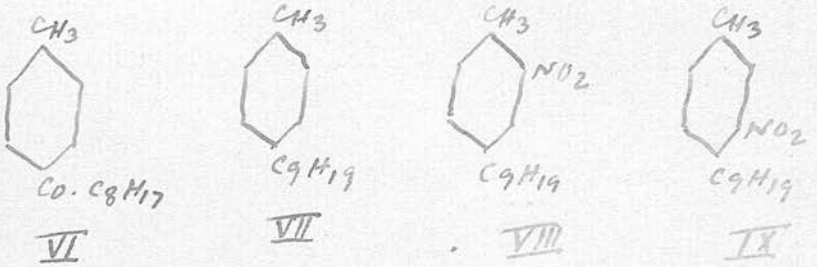
ammonia. After crystallisation from ligroin both products melted at 96° and showed no depression on mixing. Various values ranging from 96° to 110° are given in Beilstein's Handbuch for the melting point of lauramide.

In view of this result it was decided to proceed in the first place with the synthesis of 2:5-dihydroxy-3-n-undecyl toluquinone (formula I). Owing, however, to the difficulty in procuring large quantities of the undecylic acid required for the synthesis of this substance, a lower homologue, 2:5-dihydroxy-3-n-nonyl toluquinone (formula V) was first prepared in order to gain information regarding the properties of the intermediate compounds and the conditions under which the various reactions took place.

In this synthesis which is based on the methods developed by Zincke (Ber., 1885, 18, 787), Kehrmann (Ber., 1891, 23, 897) and Fichter (Ber., 1904, 37, 2388; Annalen, 1908, 361, 363) for the conversion of p-quinones into dihydroxyquinones, the easily procurable pelargonic acid could be utilised.

Toluene/

Toluene formed the starting point of the synthesis. This was condensed by Friedel and Craft's reaction with nonyl chloride to give p-n-octyl tolyl ketone (Formula VI), which on reduction

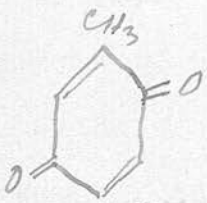


by Clemmensen's method yielded p-n-nonyl toluene (formula VII). Nitration of the latter gave a mixture of 2 and 3-nitro-p-n-nonyl toluene (formulae VIII and IX.

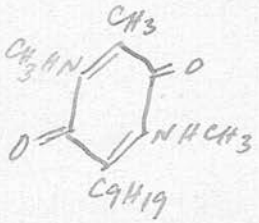
The mixed nitro compounds, without attempts at separation, were reduced with iron powder and acetic acid to the corresponding amines. Owing to the relatively large hydrocarbon residue in these amines, the salts showed anomalous behaviour. Thus, the acetates and sulphates and probably also other salts are sparingly soluble in water and readily in moist ether. These properties were therefore utilised in the isolation of the amines from the reaction mixture, as detailed in the experimental portion.

Since the two isomeric amines should yield on oxidation the same quinone, it was unnecessary from the point of view of the projected synthesis to/

to effect their separation. Nevertheless it was found possible to isolate pure specimens of the sulphates of the two isomerides. By oxidation of the amine with sodium dichromate in sulphuric acid solution p-n-nonyl toluquinone (formula X) was obtained.



X



XI

The yield of this substance never exceeded 17% of the theoretical. The difficulties experienced in this oxidation can probably be attributed entirely to the virtual insolubility of the sulphate of the amine in water. When an alcoholic solution of the above quinone was treated with alcoholic methylamine, 2:5 dimethylamino-p-n-nonyl toluquinone (formula XI) was obtained in about 30%, yield calculated on the weight of the quinone used. This corresponds entirely with theory, according to which two-thirds of the quinone are reduced to the corresponding hydroquinone.

$$3\ \begin{matrix} C_9H_{19} \\ CH_3 \end{matrix}\!>\!C_6H_2O_2 + 2NH_2\cdot CH_3 = \begin{matrix} C_9H_{19} \\ CH_3 \end{matrix}\!>\!C_6O_2(NH\cdot CH_3)_2 + 2\ \begin{matrix} C_9H_{19} \\ CH_3 \end{matrix}\!>\!C_6H_2(OH)_2$$

Hydrolysis/

Hydrolysis of the dimethylamine compound with 40% sulphuric acid yielded 2:5-dihydroxy-p-n-nonyl toluquinone(formula V). This substance exhibited properties similar to those of embelic acid. It crystallised in lustrous deep orange plates and gave a violet coloration with alkalies, due to the formation of coloured salts.

Using a series of reactions identical with those outlined above, but starting from toluene and undecoyl chloride, 2:5 dihydroxy-p-n-undecyl toluquinone (formula I) was synthesised.

All the reactions proceeded similarly, but some difficulty was at first experienced in hydrolysing the dimethyldiamino compound. This could not be effected with 40% aqueous sulphuric acid but took place smoothly on increasing the concentration of the acid to 70% and adding alcohol. The 2:5-dihydroxy-p-n-undecyl toluquinone thus obtained resembled natural embelic acid closely in properties but the synthetic material was somewhat redder in colour and melted at 150°, i.e. 7° higher than the natural substance.

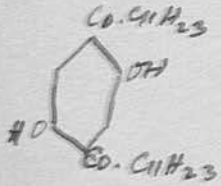
Moreover a mixture of approximately equal quantities/

quantities of the two compounds are not identical but are isomerides.

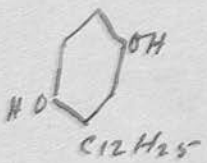
It is therefore proposed to call 2:5-dihydroxy-p-n-undecyl-toluquinone isoembelic acid.

Having thus definitely shown that the formula I proposed by Heffter and Feurstein for embelic acid was incorrect, the synthesis of the substance represented by the alternative formula IV proposed above was carried out by the following series of reactions.

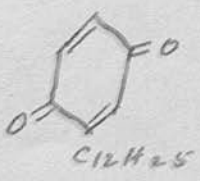
Hydroquinone was condensed by Nencki's method (J. Pr. Chem. 1881 2, 23, 546) with lauric acid. In place of the expected lauroyl hydroquinone, dilauroyl hydroquinone (probably formula XII) was obtained. This, however, on reduction by Clemmensen's method yielded the required lauryl hydroquinone (formula XIII) together with considerable quantities of hydroquinone and lauric acid.



XII



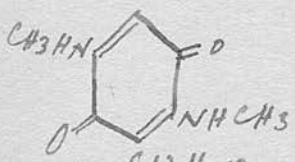
XIII



XIV

Evidently/

Evidently the reduction was accompanied by fairly extensive hydrolysis. Oxidation of lauryl hydroquinone by sodium dichromate in sulphuric acid solution readily yielded lauryl-p-benzoquinone (Formula XIV) which reacted with methylamine according to the scheme shown above in connection with the synthesis of isoembelic acid and a lower homologue, to give 2:5-dimethyl-diamino-3-lauryl-p-benzoquinone (formula XV).



XV

This on hydrolysis with sulphuric acid in the presence of alcohol yielded 2:5-dihydroxy-3-lauryl-p-benzoquinone (formula IV), which proved to be identical with natural embelic acid. Like the latter it melted at 143° and no depression was produced when the two substances were admixed.

Further confirmation of this result was afforded by the identity of the tetracetyl derivatives prepared from the two compounds by reductive acetylation. Embelic acid is thus 2:5 dihydroxy-3-lauryl-p-benzoquinone (formula IV).

V./

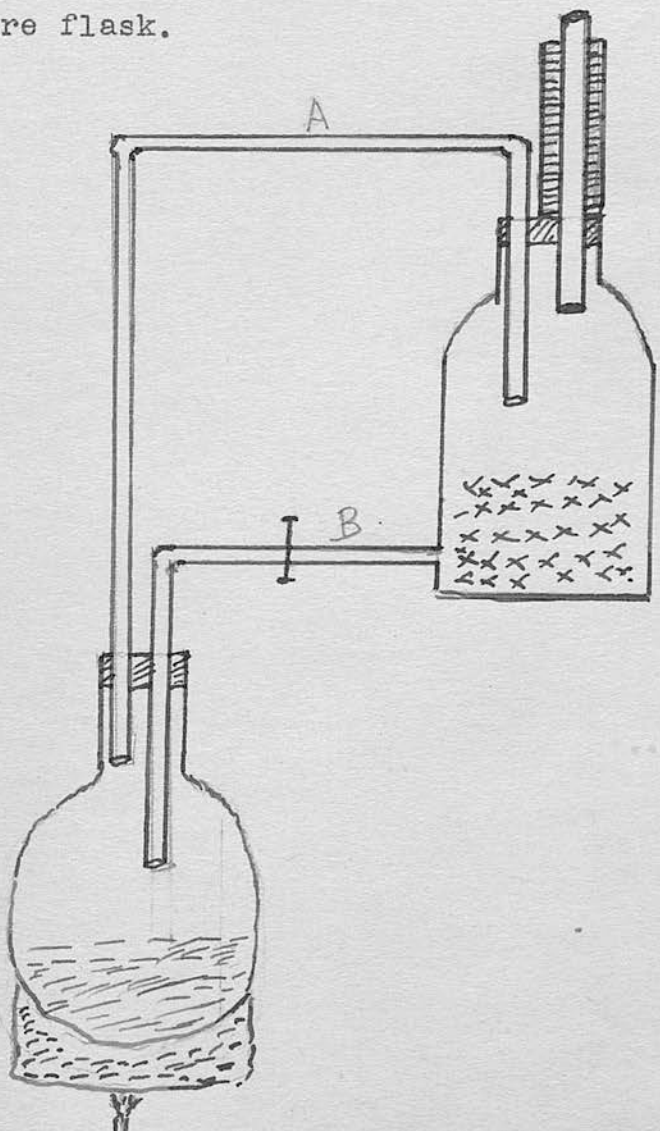
V. EXPERIMENTAL.

Section 1.

Isolation of Active Constituents of Embelia Ribes

Several methods of extraction were tried but the following was found to be the most convenient and gave the best yields.

The berries, which are quite brittle, were crushed to a fine powder and extracted continuously with ether. A semi-large scale apparatus to deal with 10 lbs. crushed material at a time was improvised, making use of a 10 litre aspirator and a 7 litre flask.



A/

A bottle shaped muslin bag of a sufficient capacity to take 10 lbs. material was first put in the aspirator and then filled with the material from outside. The mouth of the bag was tied with a piece of string sufficiently long to be pulled out of the aspirator in order to facilitate emptying the bag when extraction was complete. The mouth of the aspirator was closed with a cork carrying a large double surface condenser and a tube (A) leading from the boiling flask. The side tube of the aspirator was led a good way down into the boiling flask. Another tube B was led out of the boiling flask into the mouth of the aspirator and carried the ether vapours before condensing. Having charged the aspirator with the material, technical ether was poured in to soak thoroughly into the material and a large excess was left over. After some time the pinch cock of the tube (A) was opened and the ethereal extract transferred to the boiling flask, where it was boiled and passing through the tube (B) again condensed in the aspirator. The extraction was carried on till the ethereal extract was colourless.

After distilling off the ether a black tarry material/

material with some yellowish solid was left behind. It was dissolved in rectified spirit and allowed to crystallise slowly. Yellowish red material separated out which was filtered off and again recrystallised from absolute alcohol and finally from chloroform, when it formed golden orange plates, m.p. 143°C. Yield 2.2% on the dried substance.

The mother liquors contained a dark coloured oil which yielded no more solid material.

Section 2. /

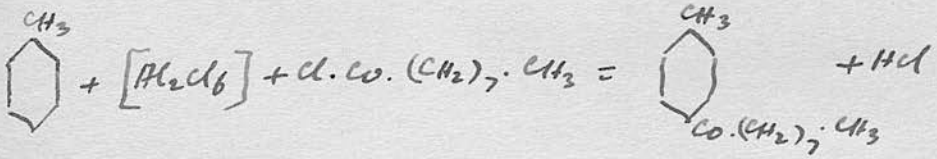
Section 2.

Synthesis of 2:5-dihydroxy p-n-nonyl toluquinone.

1. Preparation of nonyl chloride, $CH_3(CH_2)_7.COCl$.

To 158 gm. (1 mol) of pelargonic acid in a Claissen flask carrying a $CaCl_2$ tube, were added 180-185 gm. ($1\frac{1}{2}$ mols) of $SoCl_2$. The reaction started after a short time and was allowed to continue overnight. Next morning the product was distilled from an oil bath under diminished pressure. After the removal of gases a colourless liquid of characteristic odour boiling at 100°C./15 mm. passed over. Yield theoretical.

2. Preparation of N. Octyl p.tolyl ketone by Friedal and Craft's reaction.



In a round bottom flask of one and a half litres capacity provided with a condenser 177 gm. (1 mol) of nonyl chloride were mixed with 105 gm. (more than 1 mol) of sulphur-free toluene. A little more than one mol (290 gm.) of coarsely powdered Al_2Cl_6 were added at once to the mixture, and the condenser immediately replaced. A vigorous/

vigorous reaction at once started and continued for about 10 minutes and copious fumes of HCl gas were given off. When the reaction visibly subsided, the flask was heated on a boiling water bath for 2-3 hours. A slight reaction again started and HCl gas was given off. After three hours the evolution of gas ceased. The dark brown product was allowed to cool and by careful addition of small quantities of water, unchanged Al_2Cl_6 was decomposed. Copious fumes of HCl gas were given off and the flask became hot. When the decomposition of Al_2Cl_6 was complete, the product separated as an oily layer which solidified on cooling. The entire mass was repeatedly extracted with ether. The ethereal solution was first washed with water, then with dilute NaOH solution to completely remove the acid and $AlCl_3$ and finally with water, and dried over anhydrous K_2CO_3. The ether was distilled off and the residue distilled under diminished pressure. After a very small amount of unchanged toluene had passed over, the temperature gradually rose and the fraction passing over between 185° and 190°/ 15 m.m., which consisted of an almost colourless, thick oil, was/

was collected separately. On cooling this solidified to a mass of colourless wavy crystals with a characteristic odour. On redistillation, the solid product boiled constantly at 183-184° C. at 12 mm. and melted at 37°C.

Yield - 80 per cent. of the theory, i.e. 186 gm.

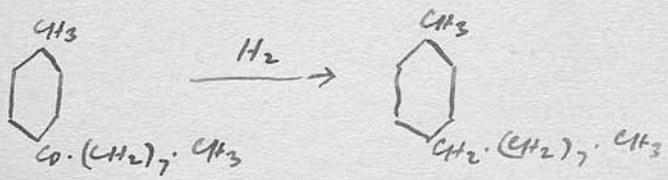
Analysis.

4.989 mgm. substance gave 15.090 mgm. CO_2 and 4.60 mgm. H_2O.

Found C = 82.5% , H = 10.2%.

$CH_3.C_6H_4.CO.C_8H_{17}$ requires C = 82.8%, H = 10.3%

3. Reduction of N. octyl p-tolyl ketone to p-N. nonyl toluene.by Clemmensen's method.



For every 100 gm. of ketone 400-500 gm. zinc wool were amalgamated with 800-1000 c.c. of a cold solution of 5% $HgCl_2$ by allowing them to remain in contact for 1 - 1¼ hours. The solution was decanted/

decanted and without washing the zinc wool, the ketone was added and the flask, provided with a good condenser. 50 c.c. of 1:1 HCl were poured on the mixture and the whole mass briskly boiled. To keep the ketone always in contact with zinc wool a steady and vigorous boiling is necessary. From time to time 10-20 c.c. HCl solution were added, the total volume employed for 100 gm. of ketone being 400-500 c.c. The reduction was continued for 6-7 hours. As the reduction proceeded, the slightly coloured oily layer became quite colourless. The flask was allowed to cool and the contents extracted three times with ether, the combined ethereal solution washed successively with water, dilute NaOH and dried over anhydrous K_2CO_3. The ether was removed and the colourless residue distilled. under diminished pressure. The distillation commenced at 155°/12 mm. and was continued up to 170°/12 mm. The bulk of this fraction, however, passed over at 160-162°/12 mm.

On redistillation the colourless liquid boils constantly at 160-161°/ 12 mm., possesses a characteristic odour and shows a slight blue fluorescence. It is much more mobile than the ketone/

ketone in the liquid state and does not solidify even in a freezing mixture.

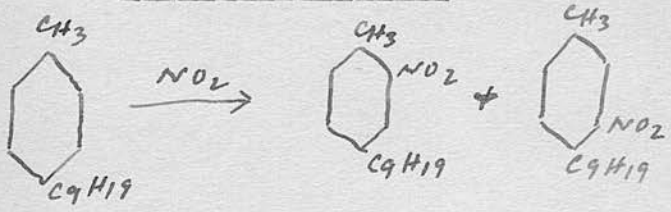
Yield - 70% of the theory, i.e. 70 gm.

Analysis.

5.20mgm. substance gave 16.720 mgm. CO_2 and 5.540 mgm. H_2O.

Found: C = 87.7%, H = 11.9%; $CH_3.C_6H_4.C_9H_{19}$ requires C = 88.1%, H = 11.9%.

4. Nitration of p. N. nonyl toluene to 2 and 3 nitro p. nonyl toluene.



To one part by weight of hydrocarbon under good stirring was slowly added a cold mixture of one part concentrated HNO_3 and two parts concentrated H_2SO_4 and the temperature kept constant at 15°C. After the addition of the nitrating mixture, the stirring was continued for a further hour and the temperature was allowed to rise to 20°C. The mixture was poured into a large excess of water, and after standing for 30 minutes, extracted three times with/

with ether. The combined ethereal extracts were washed twice with water, then repeatedly with dilute NaOH solution till the reaction of the washings remained alkaline and finally again with water. The ethereal solution was dried over anhydrous K_2CO_3, the ether removed and the dark brown residue distilled under diminished pressure. A faintly coloured liquid consisting mainly of unchanged hydrocarbon distilled at 160°/ 12 m.m. and then the temperature rapidly rose and the fraction passing over between 190-200°/12 m.m. was collected separately. On redistilling the last fraction a rather viscous yellow liquid with slightly pungent odour was obtained which boiled constantly between 198-200°/12 m.m.

Analysis.

4.928 mgm. substance gave 13.190 mgm. CO_2 and 4.09 mgm. H_2O.

3.709 mgm. substance gave 0.176 c.c. N at 23°C. and 749 mm.

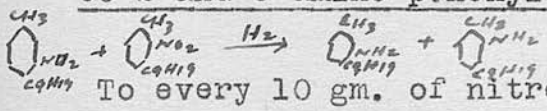
Found: C, 72.9%; H, 9.3%; N, 5.24%.

$CH_3.C_6H_3 \begin{matrix} NO_2 \\ C_{19}H_{19} \end{matrix}$ requires C, 73.0%; H, 9.3%; N,5.32%

Note/

Note:- Despite the almost constant boiling point of the nitration product, this must have consisted of a mixture of two isomeric nitro compounds since reduction yielded two isomeric amines.

5. Reduction of 2 and 3 nitro p.N. nonyl toluene to 2 and 3 amino p.nonyl toluene.



To every 10 gm. of nitro compound contained in a wide-mouthed round bottom flask fitted with a mercury sealed stirrer and water condenser, were added 12 gm. of reduced iron powder. 10 c.c. of 50% acetic acid solution were poured on to the mixture and the whole heated on a water bath with stirring. Usually there was a considerable evolution of heat, in which case heating was discontinued. After some time when the temperature had fallen, another 10 c.c. of the acid solution were added and the water bath again heated. In all 100 c.c. of the acetic acid solution were added and the reduction continued for three hours. When cool, the mixture ~~is~~ was filtered at the pump. The filtrate and the solid residue were repeatedly and separately extracted with ether, the extracts combined, shaken with strong aqueous NaOH, the aqueous layer run off, and/

and the ethereal layer, after thoroughly washing with water, dried over anhydrous K_2CO_3. The ether was then evaporated and the viscous residue distilled under diminished pressure. The fraction boiling between 180-190°C./12 mm. was collected separately. On redistillation of this fraction a viscous colourless liquid boiling between 182-186°/12 mm. was obtained. It possessed an odour similar to but much less pungent than the nitro compound.

25 gm. of nitro compound gave 20 gm. of the mixed amines; yield 90% of the theoretical.

Separation of the isomeric amino compounds.

On account of the close boiling points of the isomeric amines it was not possible to carry out their separation by fractionation. An attempt to separate their crystalline sulphates proved more satisfactory.

To a portion of the amine excess of dilute H_2SO_4 was added, when a pasty mass at once separated. This was filtered, dried and ground up with ether which partly dissolved the solid mass. After filtration the solid proved to be much less pasty.

It/

It was removed from the filter and ground up with a little more dilute H_2SO_4 and then thoroughly washed with water. After plating the solid mass, the dried material was crystallised once from acetone and twice from alcohol, when it formed white plates, m.p. 178°C, and represented the major portion of the amine.

The above ethereal filtrate was evaporated and the residue crystallised several times from alcohol, from which it was obtained in needle shaped white crystals, m.p. 144°C.

Analysis.

m.p. 170° - 4.457 mgm. substance gave 11.095 CO_2 and 3.92 mgm. H_2O
m.p. 144° - 4.795 " " " 11.995 " 4.21 " "

m.p. 178° - 2.908 " " " 0.124 c.c. N at 20°C. and 754 mm.

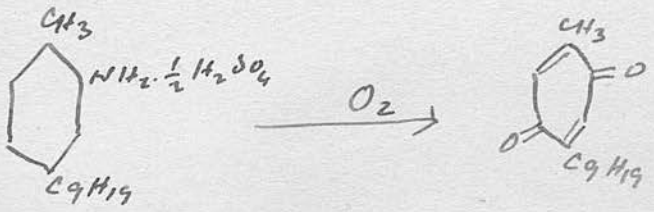
m.p. 144° - 2.863 " " " 0.123 " " " and 766 mm.

m.p. 178° - 12.142 " " " 5.050 mgm. $BaSO_4$
m.p. 144° - 10.165 " " " 4.290 " "

		C	H	N	S
m.p. 178°C.	found	67.9%	9.8%	4.8	5.7
m.p. 144°C.	"	68.0	9.8	5.0	5.8
$CH_3.C_6H_3<^{NH_2\,\frac{1}{2}H_2SO_4}_{C_9H_{19}}$ Requires -		68.1	9.9	5.0	5.7

6. /

6. Oxidation of 2 and 3 amino p.n. nonyl toluene to p. N. nonyl toluquinone.



2 Gm. of amine sulphate were finely ground with a mixture of 60 c.c. water and 16 gm. concentrated H_2SO_4 and stirred and cooled to 10°C.

1st Stage - A solution of $Na_2Cr_2O_7$ prepared by dissolving 0.75 gm. $Na_2Cr_2O_7$ in 10 c.c. water was added drop by drop to the mixture, keeping the temperature constant at 10°C. and stirring vigorously. During the addition of the chromate solution, the colour changed to yellow, then to violet and finally to black, corresponding to the aniline black stage and the whole mass became sticky. When the addition of the chromate solution was complete, the mixture was stirred for a further two hours and allowed to stand overnight in a cool place. Next morning brownish crystals were found floating on the surface, and the liquid possessed a characteristic quinone odour.

2nd/

2nd Stage - 1.5 gm. $Na_2Cr_2O_7$ were dissolved in 20 c.c. water and under exactly the same conditions were added slowly to the partially oxidised mixture, and again allowed to stand overnight. The black compound became more brown and gave a stronger smell of quinone, but remained sticky and difficult to filter. The whole mixture was shaken up with ether which dissolved the quinone and left the sticky mass undissolved. The brown ethereal solution was washed free from acid and dried with $CaCl_2$. The ether was removed and the residue treated with a small quantity of absolute alcohol and boiled on the water bath. The alcoholic solution was filtered from undissolved material whilst hot. On cooling reddish yellow plates of quinone were deposited. On recrystallisation from alcohol beautiful golden yellow plates of quinone, m.p. 53°C. separated.

Yield 0.28 gm. - 17% of the theoretical.

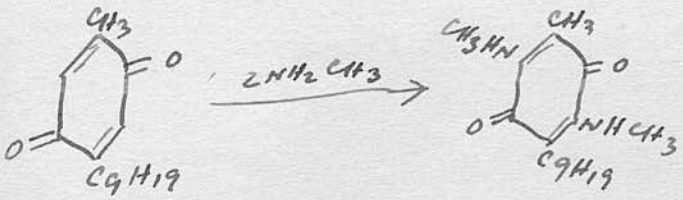
Analysis.

4.769 mgm. substance gave 13.810 mgm. CO_2 and 41.2 mgm. H_2O.

$O:CH_3.C_6H_2C_9H_{19}:O$ found C, 77.3%; H, 9.6%.
requires C,77.4%; H, 9.7%.

Note:- It was not possible to improve the yield of quinone by any modification of the above method.

7. Preparation of 2:5 dimethyl diamino p.N. nonyl toluquinone.



0.2 gm. quinone was dissolved in a small quantity of absolute alcohol and a 33 per cent. alcoholic solution of methylamine was added in slight excess and the whole solution shaken vigorously for a few minutes. After a short time a violet red precipitate separated which was filtered off, washed with alcohol, and recrystallised from alcohol when it formed steely microscopic needles, m.p. 167°C.

Yields?

Analysis.

2.917 mgm. substance gave 0.228 c.c. N at 23°C. and 757 mm.

$(NH.CH_3)_2.C_6O_2\begin{matrix}CH_3\\C_9H_{19}\end{matrix}$

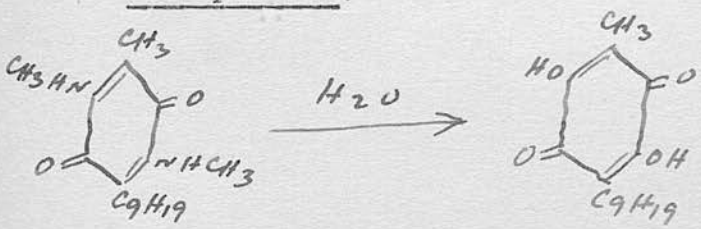
Found N, 7.6%.

Requires N, 7.9%

Note:- On allowing the filtrate to stand for a longer time, a further quantity of the methylamino compound separated, which is quite in accordance with the theory that only one third of the quinone condenses/

condenses with the methylamine, the remaining two-thirds being reduced to hydroquinone. The latter then gradually oxidises to quinone again and yields more methyl amino compound.

8. Hydrolysis of 2:5 di-methyl-diamino p.N. nonyl toluquinone to 2:5 dihydroxy p.N. nonyl toluquinone.



The methylamino compound was dissolved in a very small quantity of absolute alcohol and refluxed with 25 c.c. of dilute H_2SO_4 solution (1 part H_2SO_4 and 2 parts water). During the course of 15 minutes, the solution lost its violet appearance and became yellow and after a short time an orange yellow precipitate separated. After refluxing for an hour the solution was cooled and the yellowish orange solid filtered off, washed with water and crystallised from absolute alcohol. On slow crystallisation beautiful shining orange red plates, m.p. 154°C. separated. Yield theoretical.

Quantity?

Analysis/

Analysis.

4.764 mgm. substance gave 12.0 mgm. CO_2 and 3.71 mgm. H_2O.

$CH_3.C_6O_2\begin{matrix}(OH)_2\\ C_9H_{19}\end{matrix}$ Found C, 68.7%; H, 8.6.

Requires C, 68.6%; H, 8.6.

Section 3 /

Section 3.

Synthesis of Isoembelic Acid.

1. Ethyl undecylenate. $CH_2:CH(CH_2)_8.COOC_2H_5$

118 gm. undecylenic acid were esterified by using 454 gm. 96 per cent. alcohol and 40 gm. concentrated H_2SO_4, according to Fischer and Spier's method. On cooling the whole mass was poured into water and extracted repeatedly with ether. The ethereal extracts were dried and after removing the ether, the residue was distilled under diminished pressure. A colourless pleasant smelling liquid boiling constantly at 131°C./12 mm. was collected. Yield 130 gm., nearly theoretical.

2. Reduction of ethylundecylenate to ethyl undecylate.

$$CH_2:CH(CH_2)_8.COOC_2H_5 \xrightarrow{H_2} CH_3(CH_2)_9.COOC_2H_5$$

As large quantities of this ester were needed Dr Hilditch kindly reduced it by his special process, which consists mainly in passing the unsaturated ester/

(Hitherto)

ester over reduced nickel, at 180°C. The loss amounted to 10-12% and the saturated ester, ethyl undecylate, boiled constantly at 140°C./20 mm.

3. Undecylic acid. $CH_3(CH_2)_9.COOH$.

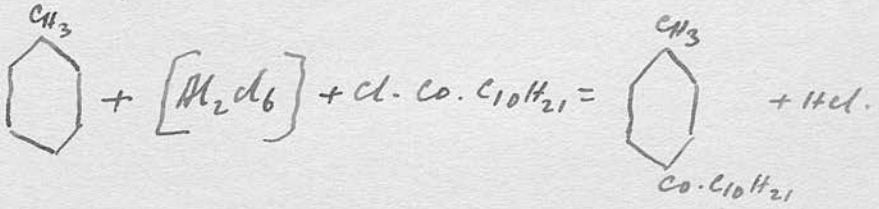
107 gm. of ester were refluxed for 4 hours with an alcoholic solution of 56 gm. KOH dissolved in 20 c.c. water and 250 c.c. absolute alcohol. As much alcohol as possible was distilled off and the residual soap was dissolved in a small quantity of hot water and acidified with strong HCl. On cooling an oily layer separated, which was extracted three times with ether, the extracts washed several times with water and dried over anhydrous Na_2SO_4. The ether was evaporated and the residue distilled under reduced pressure. A colourless oily liquid, boiling constantly at 158-159°C./12 mm., was obtained. Yield 89 gm. - 96% of the theoretical.

4. Undecoyl chloride. $CH_3.(CH_2)_9.COCl$.

93 gm. of undecylic acid were left in contact overnight with 1½ times its weight of $SOCl_2$ in a Claisen flask. By next morning the reaction was found/

found to be complete. The acid chloride was distilled under diminished pressure. A colourless liquid of characteristic smell boiling constantly at 126°C./14 mm. was collected. Yield 85 gm., i.e. 87% of the theoretical.

5. Preparation of N. decyl p. tolyl ketone by Freidal and Craft's reaction.



This Freidal and Craft's reaction was carried out in exactly the same way as in the case of the lower homologue. 102 gm. ($\frac{1}{2}$ mol) of undecoyl chloride and 69 gm. ($\frac{3}{4}$ mol) of toluene were placed in a round bottom flask of large capacity which was fitted with a condenser, and 160 gm. (more than $\frac{1}{2}$ mol) of coarsely powdered Al_2Cl_6 at once added and the condenser replaced. A vigorous reaction at once started and continued for 10 minutes. When the reaction visibly subsided, the flask was heated on a boiling water bath for 2-3 hours. A slight reaction again started and HCl gas was given off. After 3 hours when no more evolution of gas took place/

place, the dark brown product was allowed to cool. Water in small quantities was carefully added to decompose unchanged Al_2Cl_6. Copious fumes of HCl gas were given off and the flask became hot. When the decomposition of the Al_2Cl_6 was complete, the product separated as an oily layer which solidified on cooling. The whole mass was repeatedly extracted with ether, the combined ethereal extracts were first washed with water, then thoroughly with dilute NaOH and finally with water and dried over anhydrous K_2CO_3. After removing the ether the residue was distilled under diminished pressure. A small amount of unchanged toluene first distilled, then the temperature rose rapidly and a colourless thick liquid with a characteristic odour was collected between 190-200°C./12 mm., which on redistillation boiled constantly at 196.5°C./12 mm. and solidified on cooling to a crystalline waxy mass, m.p. 42°C. Yield 104 gm., i.e. 80% of the theoretical.

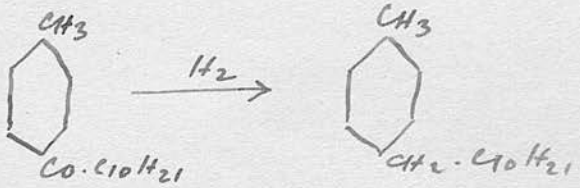
Analysis.

4.609 mgm. substance gave 13.985 mgm. CO_2 and 4.46 mgm. H_2O.

Found C, 82.8%; H, 10.8%.

$CH_3.C_6H_4.CO.C_{10}H_{21}$ Requires C, 83.1%; H, 10.8%.

6. Reduction of N. undecyl p.tolyl ketone to p.N. undecyl toluene by Clemensen's method.



As in the case of the lower homologue Clemensen's method was again used for the reduction of this ketone. In a round bottom flask fitted with a condenser 430 gm. zinc wool were amalgamated with 860 c.c. of 5% $HgCl_2$ solution for one hour. After decanting the liquid the solid ketone was added and 50 c.c. of 1:1 HCl were poured on to it, and the flask was heated in an air bath. To keep the ketone in contact with the zinc wool a vigorous boiling was maintained. From time to time another 25-30 c.c. of HCl solution were added. During the course of seven hours, 450 c.c. of HCl solution were used. The flask was allowed to cool and the product extracted three times with ether. The combined ethereal extracts were first washed with water and then with dilute NaOH and then again with water, and dried over anhydrous K_2CO_3. After distilling off the ether, the colourless residue was distilled under diminished pressure. A

colourless/

colourless mobile liquid with a faint blue fluorescence and a characteristic odour was collected between 160-185°/12 mm. On redistillation a fraction boiling constantly at 171-172°/12 mm. was collected separately. The fraction which was collected between 173-190°/12 mm. was again reduced and on redistillation yielded a further quantity of the constant boiling fraction.

Total yield, 59 gm., i.e. 73% of the theoretical.

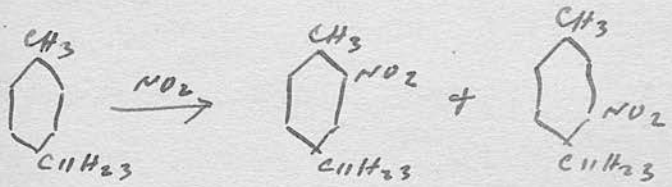
Analysis.

4.70 mgm. substance gave 15.025 mgm. CO_2 and 4.91 mgm. H_2O.

$CH_3.C_6H_4.C_{11}H_{23}$ Found C, 87.3%; H, 11.8%.

Requires C, 87.8%; H, 12.2%.

7. Nitration of p-n- undecyl toluene to 2 and 3 p-n- undecyl toluene.



To one part by weight of hydrocarbon was very slowly added, with vigorous stirring, a cold mixture of one part concentrated HNO_3 and two parts concentrated H_2SO_4 and the temperature kept at 15°C.

After/

After the addition of the nitrating mixture was complete, the stirring was continued for a further hour and the temperature allowed to rise up to 20°C. The mixture was poured on to a large excess of water and after standing for half an hour extracted three times with ether. The combined extracts were washed twice with water, then repeatedly with dilute NaOH till the washings were alkaline, and finally with water. The ethereal solution was dried over K_2CO_3 and after removing the ether, the dark orange coloured residue was distilled under diminished pressure. 25 gm. hydrocarbon gave an orange coloured viscous liquid boiling between 208-220°/12 mm. which on redistillation yielded 21 gm. of a fraction boiling at 215-216°/12 mm. Yield 72% of the theoretical.

Note:- The peculiar odour characteristic of the large undecyl molecule was persistant throughout the various stages of the synthesis.

Analysis.

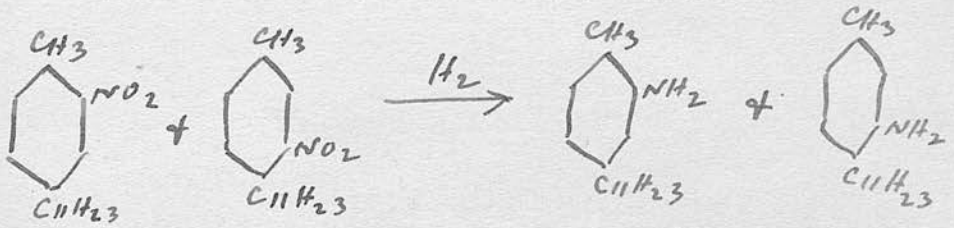
4.605 mgm. substance gave 12.495 mgm. CO_2 and 4.06 mgm. H_2O.

3.692 mgm. " " 0.114 c.c. N at 22°C. and 760 mm.

$CH_3.C_6H_3\begin{cases}NO_2\\C_{11}H_{23}\end{cases}$ Found C, 74.0%; H, 9.8%; N, 4.8%.

Requires C, 74.2%; H, 10.0%; N, 4.8%

8. Reduction of 2 and 3 nitro p-n-undecyl toluene to 2 and 3 amino p-n-undecyl toluene.



To 22 gm. of nitro compound contained in a wide mouthed round bottom flask provided with a mercury sealed stirrer and a condenser, were added 33 gm. of reduced iron powder. 20 c.c. of 50 per cent. acetic acid were poured in and the whole mixture gradually brought to the boil, whilst stirring, on a water bath. When the reaction mixture became too hot the flask was removed from the bath. In all 200 c.c. of the acetic acid solution were used and the reduction continued for three hours. On cooling the mixture was filtered at the pump. The filtrate and the solid residue were extracted separately with ether. The extracts were combined and made strongly alkaline with NaOH solution, the aqueous layer was run off and the ethereal layer after thorough washing with water dried over K_2CO_3. The ether was distilled off and the viscous residue subjected to distillation under diminished pressure. The fraction boiling between 196-210°/12 mm. was collected/

collected separately and on redistillation gave an oily liquid of characteristic odour boiling between 198-200°/12 mm. Yield 16 mg., i.e. 80% of the theory.

Note:- A small residue remained in the flask and probably contained some decomposition products.

The sulphate was prepared according to the methods already described but it was not possible to separate the two isomers. The mixture of sulphates crystallised from acetone in colourless leaflets melted at 177°C.

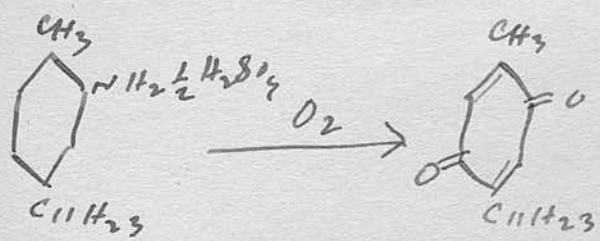
Analysis.

10.20 mgm. substance gave 3.845 mgm. $BaSO_4$.

$CH_3.C_6H_3(NH_2)C_{11}H_{23}$ $\frac{1}{2}H_2SO_4$ Found S, 5.2%.

Requires S, 5.2%.

9. Oxidation of 2 and 3 amino p-n-undecyl toluene to p-n-undecyl toluquinone.



4/

4 gm. of finely crushed amine sulphate were suspended in 140 c.c. of dilute H_2SO_4 acid (120 c.c. water, 30 c.c. concentrated H_2SO_4) and the suspension stirred and cooled to 10°C.

First Stage. A solution of $Na_2Cr_2O_7$ prepared by dissolving 1.5 gm. $Na_2Cr_2O_7$ in 20 c.c. water was slowly added drop by drop from a separating funnel, the temperature was maintained at 10°C. and the whole stirred vigorously. During the addition of the chromate solution the colour changed to yellow, then to violet and finally to black, corresponding to aniline black. When all the chromate solution had been added the mixture was stirred for a further two hours and then allowed to stand in a cool place overnight. Next morning brownish crystals of quinone with a characteristic quinone odour were found floating on the surface of the liquid.

Second Stage. 3 gm. $Na_2Cr_2O_7$ were dissolved in 40 c.c. of water and added under the same conditions to the partially oxidised mixture which was then again allowed to stand overnight. The black compound became more brown and smelt strongly of quinone. As it was found difficult to separate by filtration, the whole mixture was extracted with ether/

ether which did not dissolve the sticky material. The ethereal solution was washed free from acid and dried over $CaCl_2$. The ether was removed and the residue crystallised first from aqueous alcohol and finally from absolute alcohol when it formed golden yellow lustrous plates, m.p. 64°C. Yield 0.8 gm., i.e. 22.5% of the theory.

Analysis.

4.606 mgm. substance gave 13.205 mgm. CO_2 and 4.08 mgm. H_2O.

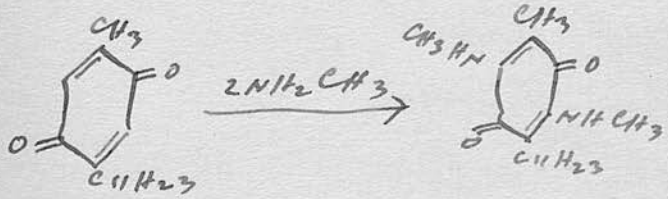
$O:CH_3.C_6H_2.C_{11}H_{23}:O$

Found C, 78.2%; H, 9.8%.

Requires C, 78.3%; H, 10.1%.

Note:- Various modifications of the above procedure were tried but it was not found possible to improve the yield of quinone.

10. Preparation of 2:5 di-methyl-di-amino p-n-undecyl toluquinone.



0.5 gm. of quinone was dissolved in a small quantity of alcohol and excess of a 33% alcoholic solution of methylamine was added. The flask was/

flask was shaken vigorously for a few minutes and allowed to stand. After a short time a violet red precipitate separated which was filtered off, washed with alcohol and crystallised from absolute alcohol when it formed violet microscopic needles, m.p. 158°C. Yield is practically theoretical.

Analysis:

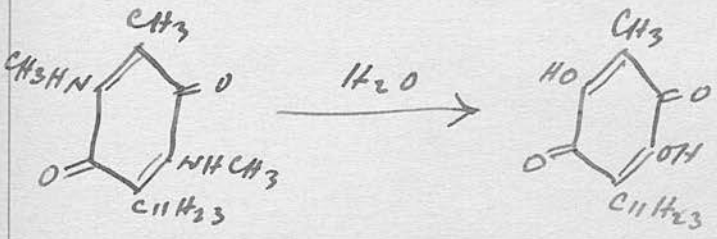
3.155 mgm. substance gave 0.227 c.c. N at 23°C. and 758 mm.

$CH_3.C_3O_2\begin{cases}(NHCH_3)_2 \\ C_{11}H_{23}\end{cases}$ Found N, 8.1%.
Requires N, 8.4%.

Note:- The filtrate on standing deposited some more precipitate which was rather red than violet. As in the case of the lower homologue it is in accordance with theory that only one third of the quinone is converted into the methylamino-compound, the remaining two thirds forming a hydro-quinone which undergoes oxidation in the air and yields further quantities of the required compound.

11./

11. Hydrolysis of the methylamino-compound to 2:5-dihydroxy p-n-undecyl toluquinone.



The hydrolysis of this compound was carried out in the same way as that of the lower homologue but with the difference that larger quantities of alcohol were required owing to the smaller solubility of the methylamino-compound. It was further necessary to employ a more concentrated solution of H_2SO_4 (viz. 1 part water to 2 parts concentrated H_2SO_4) for hydrolysis. After refluxing for an hour the violet colour of the solution changed to orange yellow from which an orange yellow solid gradually separated. After cooling the solid was filtered and washed and then crystallised first from absolute alcohol and finally from chloroform. Golden orange yellow plates, m.p. 150°C., separated out slowly. Yield theoretical.

Weight?

Analysis.

4.603 mgm. substance gave 11.835 mgm. CO_2 and 3.74 mgm. H_2O.

$CH_3.C_6O_2\begin{matrix}(OH)_2\\ C_{11}H_{23}\end{matrix}$ Found C, 70.1%; H, 9.0%.

Requires C, 70.1%; H, 9.1%.

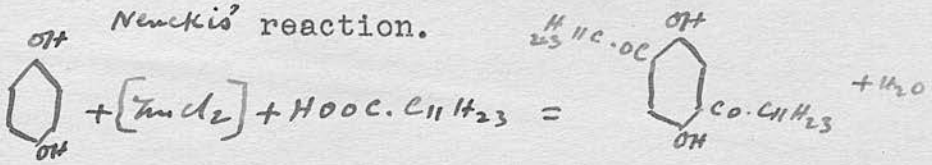
In physical appearance and crystalline form under the microscope the above compound closely resembled natural embelic acid. Its melting point, however, was 7° higher than that of the latter and an intimate mixture of approximately equal quantities of the two substances was found to melt at 125°, i.e. there was a depression of 18-25°. This obviously points to the conclusion that the synthetic compound is not identical with embelic acid.

Section 4 /

Section 4.

Synthesis of Embelic Acid.

1. Preparation of di-lauroyl hydroquinone by Neuckis' reaction.



68 gm. ($\frac{1}{2}$ mol) of anhydrous $ZnCl_2$ were dissolved by vigorous shaking and heating in 300 gm. ($1\frac{1}{2}$ mols) of lauric acid contained in a round bottom flask and filter with a loose cork and a thermometer. To the dissolved mass were added gradually 55 gm. ($\frac{1}{2}$ mol) of hydroquinone. After each addition the flask and its contents were shaken vigorously. The temperature was maintained between 130-140°C. during the course of the reaction. After all the hydroquinone had been added, the solution was stirred for two hours and the temperature maintained at 130-140°. At the end of the time the colour of the solution remained dark brown. It was allowed to cool and a large excess of water added. The solid mass which separated was thoroughly washed with water to remove unchanged hydroquinone and then a saturated solution of Na_2CO_3 was added to/

to neutralise the unchanged lauric acid. The whole mass was then repeatedly extracted with ether which dissolved the lauroyl hydroquinone and left behind the sodium salt of the acid. The ethereal solution was washed with water, which caused a small quantity of zinc laurate to separate, and dried over $CaCl_2$. The ether was distilled off and the residual solid crystallised from methyl alcohol with the addition of animal charcoal. A second crystallisation from methyl alcohol gave colourless wavy plates, m.p. 68°C. Yield 80 gm., i.e. 54% of the theory.

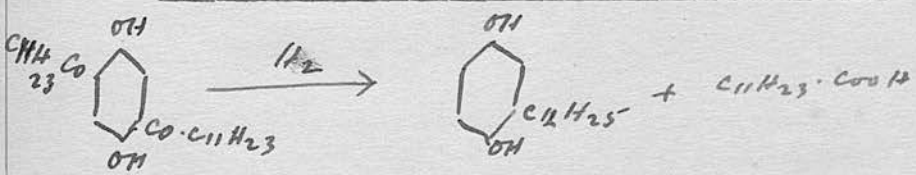
Analysis.

4.629 mgm. gave 12.820 mgm. CO_2 and 4.35 mgm. H_2O.

Found: C = 75,5; H = 10.4%.

$(HO)_2C_6H_2(CO.C_{11}H_{23})_2$ requires C = 75.9; H = 10.6%

2. Reduction of di-lauroyl hydroquinone to lauryl hydroquinone by Clemmensen's reduction.



200 gm. of granulated zinc were amalgamated for one hour with 400 c.c. of 5% cold $HgCl_2$ solution in/

in a round bottom flask. The liquid was decanted off and 40 gm. of di-lauroyl hydroquinone and 50 c.c. of 1:1 HCl were added. The flask was fitted with a mercury-sealed stirrer and a condenser, and the whole boiled briskly on a flame. From time to time further portions of 20-30 c.c. of HCl were poured in, a total volume of 450 c.c. being employed. Usually 6-8 hours were required for complete reduction. The reduced product was extracted in ether; after drying the ether and distilling it off, the residue was washed thoroughly with water to remove hydroquinone. A strong solution of Na_2CO_3 was then added to neutralise the lauric acid which had split off during the reduction. The whole mass was again extracted with ether; after washing with water, the ethereal solution was dried over $CaCl_2$. On removing the ether a light brown residue was left behind which crystallised from benzene in colourless square plates, m.p. 109°C. Yield, 11 gm., i.e. 47% of the theoretical.

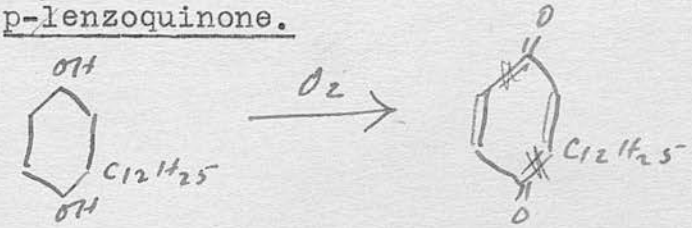
Analysis.

4.76 mgm. gave 13.51 mgm. CO_2 and 4.56 mgm. H_2O.

Found: C = 77.4; H = 10.6%.

$(HO)_2C_6H_3.C_{12}H_{25}$ requires C = 77.7; H = 10.8%.

3. Oxidation of lauryl hydroquinone to lauryl-p-benzoquinone.



5 gm. of lauryl hydroquinone were suspended in 50 c.c. dilute H_2SO_4 (10 c.c. concentrated acid plus 40 c.c. water) and the temperature cooled to 10°C. And to that with good stirring was slowly added a solution of 2.5 gm. $Na_2Cr_2O_7$ (slight excess) dissolved in 20 c.c. water and the temperature maintained. The colour of the mixture at once changed to deep blue and no further change in colour was noticeable even after two hours further stirring. The mixture was left overnight. By next morning a faint odour of quinone was noticed. The mixture was transferred to a round bottom flask and refluxed for half an hour. On heating, the blue colour changed to yellow and the quinone partly sublimed on to the cooler parts of the condenser. On cooling the solid quinone was filtered, washed free from acid and crystallised from absolute alcohol when it formed pale yellow plates, m.p. 81°C. Yield 4.4 gm., i.e. 90% of the theoretical.

Analysis/

Analysis.

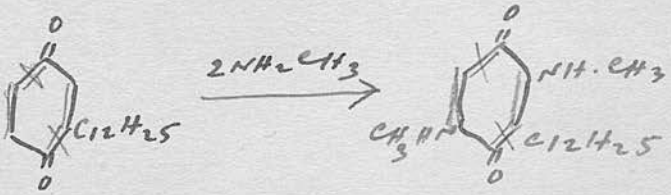
4.968 mgm. gave 14.16 mgm. CO_2 and 4.54 mgm. H_2O.

Found: C = 77.7; H, = 10.1%.

$C_6H_3O_2.C_{12}H_{25}$ requires C = 78.3; H = 10.1%.

Note:- In later experiments it was observed that treatment in the cold was not necessary. When the hydroquinone was boiled with the required amount of $Na_2Cr_2O_7$ and H_2SO_4, it directly yielded the quinone.

4. Condensation of lauryl benzoquinone with methyl amine and preparation of 2.5 di-methyl-di-amino-3-n-undecyl-p-benzoquinone.



3 gm. of lauryl benzoquinone were dissolved in 20 c.c. of absolute alcohol with slight warming and an excess of 33% alcoholic methylamine was added. After shaking the flask for a few minutes, it was left/

left overnight. A violet coloured precipitate separated, which was filtered off and recrystallised from absolute alcohol when it formed violet-red microscopic needles, m.p. 147°C.

Yield theoretical, i.e. one third of the benzoquinine used.

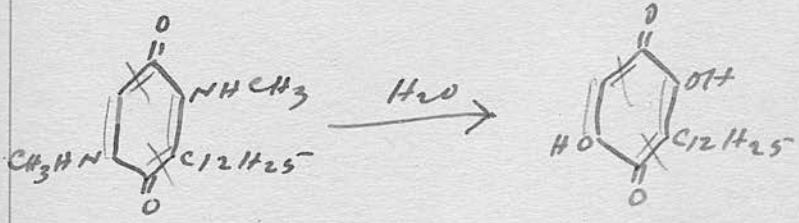
Analysis.

2.927 mgm. gave 0.223 c.c. N_2 at 24.5° and 748 mm.

Found N = 8.4%.

$C_6H.O_2(NHCH_3)_2C_{12}H_{25}$ requires N = 8.4%.

5. Hydrolysis of the methylamino compound to 2:5-dihydroxy 3-n-lauryl-p-benzoquinone.



0.5 gm. of the methylamino compound was dissolved in a small quantity of alcohol contained in a round bottom flask and 50 c.c. of 65% H_2SO_4 were added. On the addition of the H_2SO_4 solution the methyl amino compound was thrown out of solution and it was found necessary to add a larger quantity of/

of alcohol to keep it dissolved. The solution was refluxed for three hours. The violet colour gradually changed to yellow on heating and the reaction was considered complete when no more change in colour was noticed. On cooling, a yellow precipitate separated which was filtered, washed free of acid and twice crystallised from alcohol and finally from chloroform when it formed lustrous golden square plates, m.p. 143°C.

Analysis.

4.857 mgm. gave 12.43 mgm. CO_2 and 3.96 mgm. H_2O.

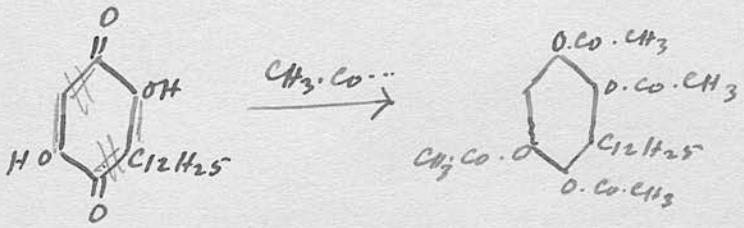
Found C = 69.8%; H = 9.1%.

$C_6HO_2(OH)_2C_{12}H_{25}$ requires C = 70.1; H = 9.1%.

The colour and crystalline form, as seen under the microscope, of the synthetic embelic acid closely resembled that of the natural substance. The melting points of both were, moreover, the same. An intimate mixture of approximately equal quantities of the two products showed no depression in the melting point. Hence it is concluded that the synthetic product is identical with the natural embelic acid.

As additional confirmation the tetracetyl derivatives of natural and synthetic embelic acid were prepared and compared as follows:-

6. Preparation of tetracetyl embelic acid (natural) by reductive acetylation.



A small quantity of natural embelic acid was dissolved in boiling acetic anhydride and small amounts of zinc dust were added gradually during boiling, till the solution became quite colourless. This solution was poured into a large excess of water, which solidified on stirring. After some time the solid was filtered, washed free from acid and once crystallised from aqueous acetone and finally from aqueous alcohol when it formed colourless needles melting at 116.5°C.

Analysis.

4.939 mgm. substance gave 11.78 mgm. Cr_2 and 7.37 mgm. H_2O.

Found: C, = 65.1%; H = 7.6%.

$C_6H\begin{cases} C_{12}H_{25} \\ (O.CO.CH_3)_4 \end{cases}$ requires C = 65.3%; H = 7.9%.

7/

7. Preparation of tetracetyl of synthetic embelic acid was carried out in exactly the same way and had a m.p. of 121°C.

An intimate mixture of approximately equal quantities of both tetracetyl compounds had a m.p. of 118°C., i.e. a decrease of 3° from the m.p. of the synthetic embelic acid and an increase of 1.5° over the m.p. of natural embelic acid. A number of recrystallisations of the natural substance made no difference in its m.p. Since there is a slight increase in the m.p. of the natural and a decrease in the m.p. of the synthetic substance in mixed melting points, it is concluded from these observations that the natural product is contaminated with a very small amount of impurity which it had not been possible to remove by several crystallisations and that both products are identical. In connection with the slightly low melting point of the derivative from natural embelic acid, it should be mentioned that Kaul, Dutt and Ray have already prepared this substance and state that it melts at 124°. This is 7.5° higher than the m.p. of the tetra acetyl derivative prepared in this investigation from natural embelic acid and 3° higher than that prepared from synthetic embelic acid.

In conclusion I wish to express my deep sense of gratitude to Professor Barger for his kind interest and guidance in this investigation, and to Dr Stedman but for whose generous aid and continual inspiration it would have been difficult to complete.

My sincere thanks are also due to Dr Hilditch for reducing the unsaturated undecylenic acid, and to the Earl of Moray Research Fund of Edinburgh University for a grant which has defrayed a small part of the expenses of this research.