Studies in the Heterocyclic and Carbocyclic Series.

THESIS

submitted by

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PREFACE.

The author would like to express his warm appreciation for the constant advice and encouragement, tendered by Professor J.W. Cook, F.R.S., during the period when the work herein recorded was being carried out.

Thanks are also due to Mr. J.M.L. Cameron, Miss R.H. Kennaway and Miss Christie for carrying out the necessary micro-analyses and to the Department of Scientific and Industrial Research for a Maintenance Grant held for one year by the author.

SUMMARIES.

PART I.

Catalytic hydrogenation of 2-9'-fluorenyl*cyclo*hexanone, prepared by the reaction of 9-bromofluorene and the sodio-derivative of ethyl *cyclo*hexanone carboxylate and decarbethoxylation of the product, has resulted in the isolation of two stereoisomeric alcohols, *cis*- and *trans*-2-9'-fluorenyl*cyclo*hexanol, and a hexahydride of one of these. Both carbinols yield the same product on dehydration with phosphoric acid. The structure of this product is established as 9-*cyclo*-hexΔ_1-enylfluorene by the following series of steps: microhydrogenation and double bond estimation with perphthalic acid indicate the presence of one double bond, as does the isolation of an epoxide from the perphthalic acid oxidation and a dihydroxy-derivative via the osmium tetroxide-pyridine complex; the position of the double bond is established by the formation of the same product by the dehydration of 1-9'-fluorenyl*cyclo*hexanol; the possible alternative structure of *cyclo*hexylidenefluorene (formed by double-bond migration) is excluded by the fact that this compound, prepared by the dehydration of 9-*cyclo*hexylfluoren-9-ol, is distinct from the product. The absorption spectra of these various dehydration products and their hydrogenation product 9-*cyclo*hexylfluorene, have been recorded and shown to be in accord with the structures variously assigned to them.

This work extends and corrects that of Hurd and Mold (J.Org.Chem.,1948, **13**, 339) who isolated one alcohol from the hydrogenation of 2-9'-fluorenyl*cyclo*hexanone and regarded its dehydration product as 1:9-*cyclo*hexylenefluorene.

PART II.

The maleic anhydride adduct with 9:10-diphenylanthracene has been prepared (a) according to the procedure of Bachmann and Kloetzel (J.Amer.Chem.Soc.,1938, **60**, 481) by refluxing the hydrocarbon in xylene with a thirty mole excess of maleic anhydride, and (b) according to the procedure of Dufraisse, Velluz and Velluz (Bull.Soc.chim.,1938, **5**, 1073) by fusing equal weights of the same two reactants. The adducts are shown to be identical by comparison of their melting points and absorption spectra, and by comparison of three derivatives, their diethyl esters, their dimethyl esters and the *trans*-dimethyl esters obtained by isomerisation. The suggestion of Dufraisse, Velluz and Velluz (loc.cit.) that the widely different melting points recorded for the adduct prepared by the two methods are due merely to the different procedures adopted in taking the melting points has been experimentally confirmed. The absorption spectra are in agreement with that recorded for the Dufraisse adduct by

Gillet (Bull. Soc. chim., 1950, 17, 1141) who demonstrated that its similarity to the absorption spectrum of 1:4-diphenylnaphthalene indicated that 1:4-addition of maleic anhydride had taken place instead of the 9:10-addition, normal with other anthracene derivatives.

Chemical confirmation of Gillet's structure for the adduct has now been obtained by an estimation with perphthalic acid which showed the presence of an ethylenic double bond and by the characterisation of the epoxides prepared by perphthalic acid oxidation of the diethyl and dimethyl esters of the adduct. No pure products could be isolated when permanganate oxidation and ozonisation were used similarly to attack the isolated double bond.

PART III.

The structure of the product of the reaction of *o*-nitroaniline with 1-naphthylamine, first prepared by Wohl and Lange (Ber., 1910, 43, 2186) and described by them as an "amino-naphthophenazine" without assigning it any definite structure, has been established as 5-amino-*ang*-benzophenazine and not 7-amino-5:12-diazanaphthacene as suggested by Allen and Webster (Six-membered Heterocyclic Nitrogen Compounds with four condensed Rings, p. 59; New York, 1951). Deamination to *ang*-benzophenazine shows the compound to possess that ring system and not the ring system of *lin*-benzophenazine (i.e. 5:12-diazanaphthacene). Comparison (absorption spectrum and melting point) with an authentic sample of 5-amino-*ang*-benzophenazine shows that the two compounds are identical.

PART IV.

The Friedel-Crafts reaction of quinolinic anhydride with naphthalene has been thoroughly investigated and found to give poor results under all the experimental conditions which were tried. Two products were isolated; β-naphthoylpicolinic acid, so designated because it has a melting point in agreement with that recorded by Jephcott (J.Amer.Chem.Soc., 1928, *50*, 1189) for the compound which he proved to have this structure and which he prepared by a similar Friedel-Crafts reaction, and α-naphthoylpicolinic acid whose structure was proved by potassium hydroxide fusion and by a positive Skraup test for a picolinic acid. Numerous attempts to cyclise this α-naphthoylpicolinic acid or its zinc dust and ammonia reduction product, α-naphthylmethylpicolinic acid, using a wide variety of cyclising agents have all proved unsuccessful. From the few examples present in the literature of cyclisations in which the carboxyl group is attached to the nitrogen ring, evidence is adduced in support of the claim that compounds containing a carboxyl group in the α-position to the ring nitrogen atom are peculiarly difficult to cyclise and a possible explanation for this phenomenon is suggested.

Contents.

PART I. Page.

PART II.

PART III.

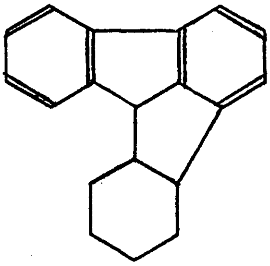
PART IV.

PART ONE.

PART. I.

Introduction.

Hurd and Mold have recently described (1) the formation of a compound to which they assign the structure (I) of 1:9-*cyclo*hexylenefluorene. They claim to have synthesised this compound by the cyclodehydration of 2-9'-fluorenyl-*cyclo*hexanol (II). Their claim was supported by the statement that the hydrocarbon was inert towards bromine and towards potassium permanganate and was therefore saturated. They noted that it was dehydrogenated to 9-phenylfluorene by heating it with palladium-charcoal or with selenium but attributed this to a pyrolytic fission of a carbon-carbon bond.



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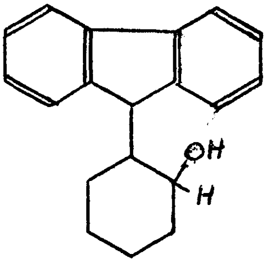

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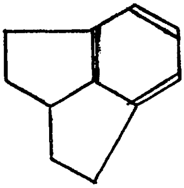
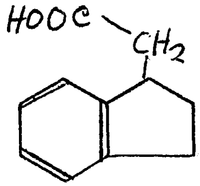


III

This claim, if upheld, would be of considerable importance, representing, as it does, one of the few successful attempts to prepare a compound containing the highly strained ring system (III). Several attempts by von Braun to prepare compounds containing two fused five-membered rings mutually fused to a benzene nucleus have all proved unsuccessful. For example, he found that the chloride of 1-hydrindylacetic acid (IV) would condense readily with aromatic hydrocarbons but would not undergo internal condensation under the influence of aluminium chloride (2). The chloride of tetraphthylacetic acid (V) also refused to undergo an intramolecular Friedel-Crafts reaction although the next higher homologue, tetraphthylpropionyl chloride (VI) readily ring-closed with aluminium chloride (3).



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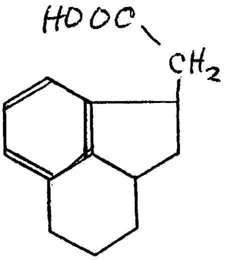

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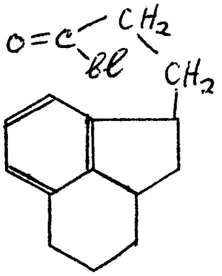
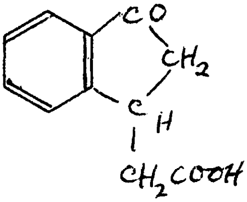


VI

Again Jackson and Kenner (4) found it impossible to convert 1-ketohydrindene-3-acetic acid (VII) or indoxylacetic acid (VIII) into the tricyclic compounds (IX) and (X) respectively.



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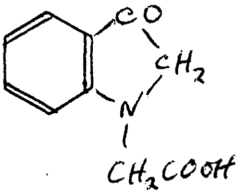

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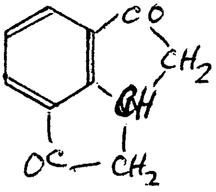

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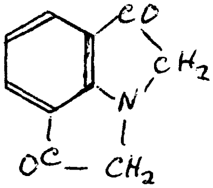
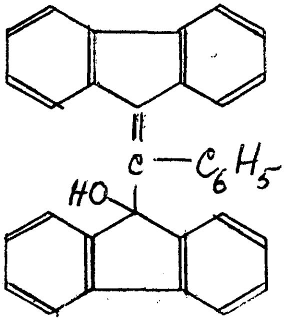


X

One apparently well authenticated case of the formation of this type of ring system occurs in the published work of Koelsch (5) who found that the acetic acid solution of the halochromic sulphate of α:γ-bisphenylene-β-phenylallyl alcohol (XI) decomposed to give a hydrocarbon which proved to be 1-diphenylene-2-phenyl-3:4-phenyleneindene (XII).



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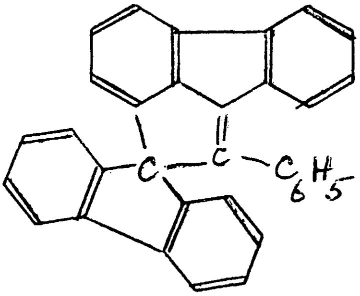
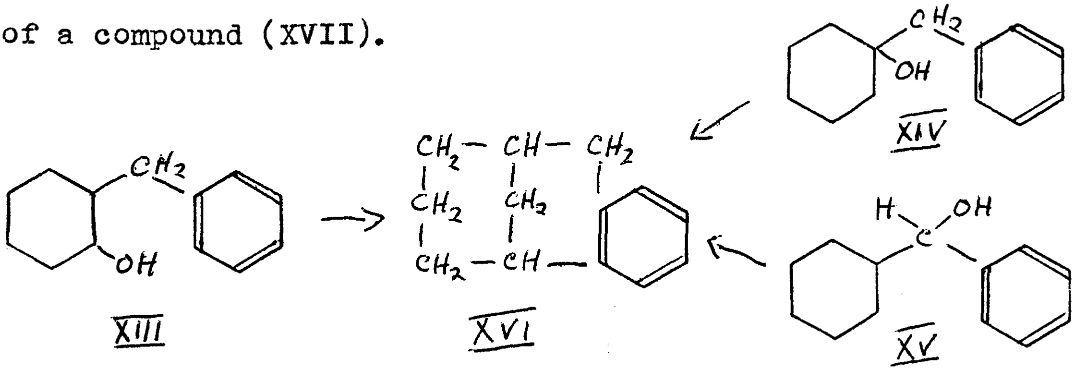
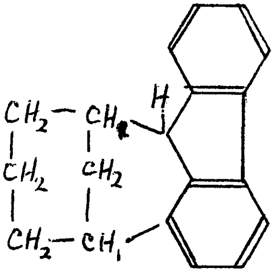


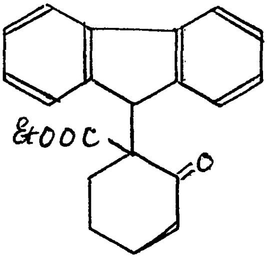
XII

A further doubt as to the correctness of the structure assigned by Hurd and Mold to their compound was raised by the suggestion of Cook (6) that the dehydration of Hurd and Mold's carbinol might be analogous to the dehydration of 2-benzyl*cyclo*hexanol (XIII), which produces, as does the dehydration of 1-benzyl*cyclo*hexanol (XIV) and of phenyl*cyclo*hexylcarbinol (XV), the benz-bi*cyclo*nonene (XVI) (7). This would lead in the present instance to the formation of a compound (XVII).





XVII



XVIII

Discussion.

As a preliminary step in the reinvestigation of the structure of Hurd and Mold's hydrocarbon (I) the synthesis of the compound was undertaken. The route followed by Hurd and Mold (1) involved, first, the condensation of the potassio-derivative of ethyl 2-*cyclo*hexanone carboxylate with 9-chlorofluorene, which had been prepared from fluorene by oxidation of the latter to fluorenone, reduction to fluorenol and reaction with hydrochloric acid. This gave 2-carbethoxy-2-9'-fluorenyl*cyclo*hexan-1-one (XVIII) which was decarbethoxylated to 2-9'-fluorenyl*cyclo*hexanone and the latter compound hydrogenated catalytically to give 2-9'-fluorenyl*cyclo*hexanol (II). Dehydration of the carbinol with syrupy phosphoric acid gave "1:9-*cyclo*hexyl-enefluorene".

Whilst the present synthesis of the hydrocarbon followed, in broad outline, the above route, certain modifications were introduced which resulted in greatly increased yields at certain stages. Thus the sodio-derivative of ethyl

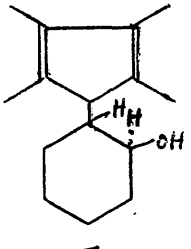
2-cyclohexanone carboxylate was used in place of the potassio-compound and to compensate for any reduced activity in this compound, it was condensed with 9-bromofluorene, prepared either via 9-fluorenol obtained from 9-fluorenone by hydrogenation with Raney nickel, or by direct bromination of fluorene with N-bromosuccinimide. The yields of 2-carbethoxy-2-9'-fluorenylcyclohexanone obtained were as high as 75% compared with the reported yield of 35% from the reaction of the potassio-derivative and chlorofluorene.

The 9-bromofluorene prepared via 9-fluorenol was found to exert a severe skin irritant action which necessitated the wearing of rubber gloves whenever the compound was handled. This property has previously been noted in the journal, "Science", (8) where the irritation is attributed to the presence of a by-product, 9:9-dibromofluorene.

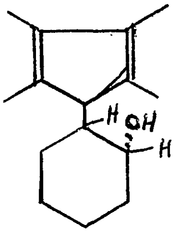
Decarbethoxylation of the above keto-ester was far more satisfactory when barium hydroxide was used instead of potassium hydroxide. The resulting ketone and its semicarbazone analysed correctly but the melting point of the semicarbazone was some 15° higher than that recorded by Hurd and Mold.

Attempts were made to hydrogenate the fluorenylcyclohexanone at ordinary pressures using Raney nickel and Adams catalyst. With Raney nickel the ketone was recovered unchanged. With Adams catalyst there was an extremely slow uptake of hydrogen which yielded a mixed product similar to that more readily obtained by high pressure hydrogenation (see below). The hydrogenation was therefore carried out exactly as described by Hurd and Mold (1) using copper chromite catalyst and hydrogen under pressure at 150°.

Instead of the single pure product, melting point 122.5° obtained by the American workers, a product was obtained which was obviously a mixture - the melting point was low and over a considerable range. Several crystallisations resulted in a very gradual rise in melting point concomitant with a large drop in the quantity of material. It seemed probable that the two stereoisomerically possible alcohols (XIX) and (XX) had been formed.



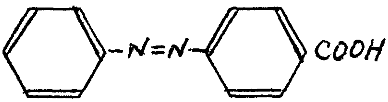
XIX



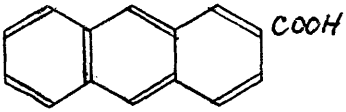
XX

Assuming that cyclodehydration had taken place either along the lines indicated by Hurd and Mold (1) or according to the alternative scheme suggested by Cook (6) it was obviously of importance to determine whether pure samples of each isomer would give the same product on dehydration.

Various attempts were therefore made to separate the products of the hydrogenation. One of these involved the chromatography of the coloured esters formed by the esterification of the alcohol mixture with the acid chloride of *p*-azobenzenecarboxylic acid (XXI), which was obtained by the reaction of *p*-aminobenzoic acid with nitrosobenzene according to the procedure of Angeli and Valori (9).



XXI



XXII

This attempted separation met with no success, there being no worthwhile separation on the acid-washed alumina columns which were used.

Work was in progress on the chromatographic separation of the fluorescent esters which were obtained with β-anthroic acid (XXII) when it was found that both the stereoisomeric alcohols, small samples of which had meanwhile been prepared by a laborious series of crystallisations, formed the same dehydration product. This, coupled with the fact that a hydrogenation at a lower temperature readily gave the pure ?*cis*-alcohol, melting point 122-123°, led to the abandonment of any further work on the separation of the stereoisomers.

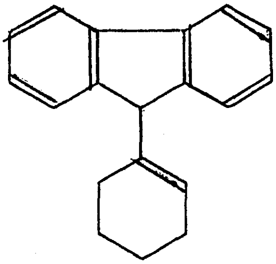
Results of the work on this stage of the synthesis of Hurd and Mold's hydrocarbon may be summarised as follows: high pressure hydrogenation according to Hurd and Mold's procedure (1) gave a mixed product from which were isolated three compounds, *cis*-2-9'-fluorenyl*cyclo*hexanol (the isomer isolated by Hurd and Mold), *trans*-2-9'-fluorenyl*cyclo*hexanol and a third substance which analysed for a hexahydrofluorenyl*cyclo*hexanol. Using a very active copper chromite catalyst the hydrogenation could be carried out at a much lower temperature (80°) and this gave the *cis*-isomer alone. Reversion to the higher temperature with this catalyst gave once more the mixed product.

As mentioned above dehydration of both the *cis*- and *trans*-alcohols with phosphoric acid gave a product agreeing in melting point and analysis with Hurd and Mold's hydrocarbon. The same compound was later found to be obtained much more readily by potassium bisulphate dehydration.

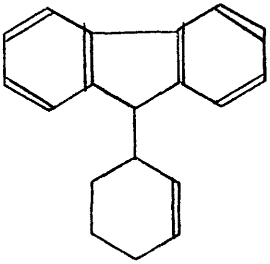
As a first step in the investigation of the structure of the hydrocarbon and to ascertain the points of attachment of the *cyclo*hexane ring to the aromatic fluorene system a chromium trioxide oxidation was carried out. The product of the oxidation proved to be fluorenone and not fluorenone-1-carboxylic acid which should have been obtained from a hydrocarbon either with Hurd and Mold's proposed structure or with the alternative structure suggested by Cook (6). The appearance of fluorenone as an oxidation product gives rise to a third possible structure for the hydrocarbon, a structure in which no cyclisation has taken place but instead a simple dehydration with the formation of an ethylenic double-bond. Confirmation of this was immediately obtained through a double-bond estimation with perphthalic acid and a micro-hydrogenation, both of which showed the presence of one ethylenic double-bond. Moreover the hydrogenation product proved to be identical with a sample of 9-<u>cyclo</u>hexylfluorene prepared from <u>cyclo</u>hexyl magnesium bromide and 9-bromofluorene by the method of Miller and Bachman (10), who, using chlorofluorene instead of bromofluorene, obtained a compound, melting point 102-103°, which they claimed to be 9-<u>cyclo</u>hexylfluorene. In the present case the product isolated from this reaction melted at 115° and analysed correctly for 9-<u>cyclo</u>hexylfluorene. This is in agreement with the melting point quoted (115-116°) by Brown and Bluestein (11) for their preparation of <u>cyclo</u>hexylfluorene from 9-formylfluorene and <u>cyclo</u>hexyl bromide.

The epoxide and the dihydroxy compound from Hurd and Mold's hydrocarbon were also isolated and analysed, the former being obtained from the perphthalic acid oxidation and the latter from the osmium tetroxide-pyridine complex with the hydrocarbon.

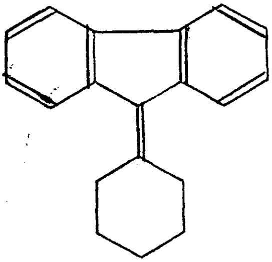
Having proved the presence of a double-bond in the hydrocarbon, the precise position of this bond remained to be ascertained. Migration of the bond seemed quite within the bounds of possibility, analogous to the migration of the double-bond obtained by dehydration of 1-benzyl*cyclo*hexanol (XIV) and phenyl*cyclo*hexylcarbinol (XV) to the most suitable position to effect cyclisation (7). Of the three possible positions two are within the *cyclo*hexane ring (XXIII) and (XXIV) and the third lies between the ring systems (XXV).



XXIII

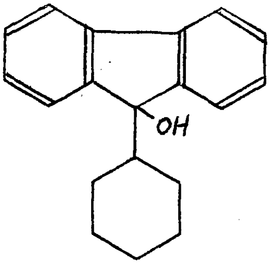


XXIV

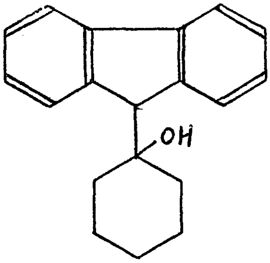


XXV

At first, the structure of *cyclo*hexylidenefluorene (XXV) seemed most likely as such a double bond shift would lead to conjugation with the double bond system in the fluorene nucleus. However, the absorption spectrum (fig 1, p 14) of Hurd and Mold's hydrocarbon proved to be very similar to that of fluorene itself whereas one would expect a compound with a double-bond in the fluorene 9-position to have a completely different spectra, as is the case with 9-ethylidenefluorene (12) (fig 2, p 15). This assumption was verified by the synthesis of 9-*cyclo*hexylidinefluorene by the dehydration of 9-*cyclo*hexylfluoren-9-ol (XXVI) which had been prepared from *cyclo*hexylmagnesium bromide and fluorenone. This hydrocarbon hydrogenated to give 9-*cyclo*hexylfluorene, decomposed readily on standing in air giving a yellow gum as do other fluorene compounds with a 9-double bond (13), was not identical with Hurd and Mold's compound and had an absorption spectrum (fig 2, p 15) completely different from that of fluorene while the absorption spectrum (fig 3, p 16) of its hydrogenation product (i.e. 9-*cyclo*hexylfluorene) was again very similar to that of fluorene. It is of interest to note that when an attempt was made to construct a Stuart model of 9-*cyclo*hexylidenefluorene it was found impossible to link the fluorene and *cyclo*hexane systems with a double-bond due to the interference of the hydrogen atoms in the 1- and 8-positions in the fluorene nucleus with hydrogen atoms in the cyclohexane ring. During the formation of Hurd and Mold's hydrocarbon this steric effect probably tends to counteract any tendency towards a double-bond shift leading to conjugation with the double-bond system of the fluorene nucleus.

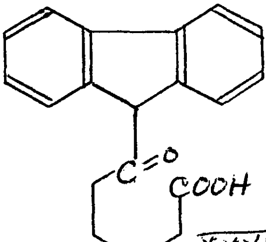


XXVI

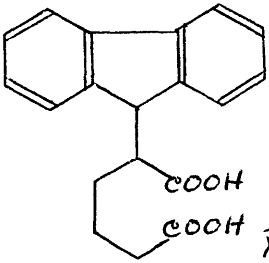


XXVII

There remained the question of decidimg which of the two cyclohexenylfluorenes (XXIII) or (XXIV) represented the structure of Hurd and Mold's hydrocarbon. An attempt was made to settle this by a degradation involving lead tetra-acetate cleavage of the dihydroxy derivative of the hydrocarbon, followed by silver oxide oxidation of the product. As will easily be seen this should lead in the case of (XXIII) to the formation of a keto-acid (XXVIII) while, if (XXIV) represented the structure of Hurd and Mold's hydrocarbon, a dicarboxylic acid (XXIX) would be formed. Unfortunately no pure analysable material could be isolated from the intractable gum which was obtained. The one piece of evidence which seemed to favour the structure of (XXIII) was the apparent formation of an impure 2:4-dinitrophenylhydrazone from the gummy reaction product.



XXVIII

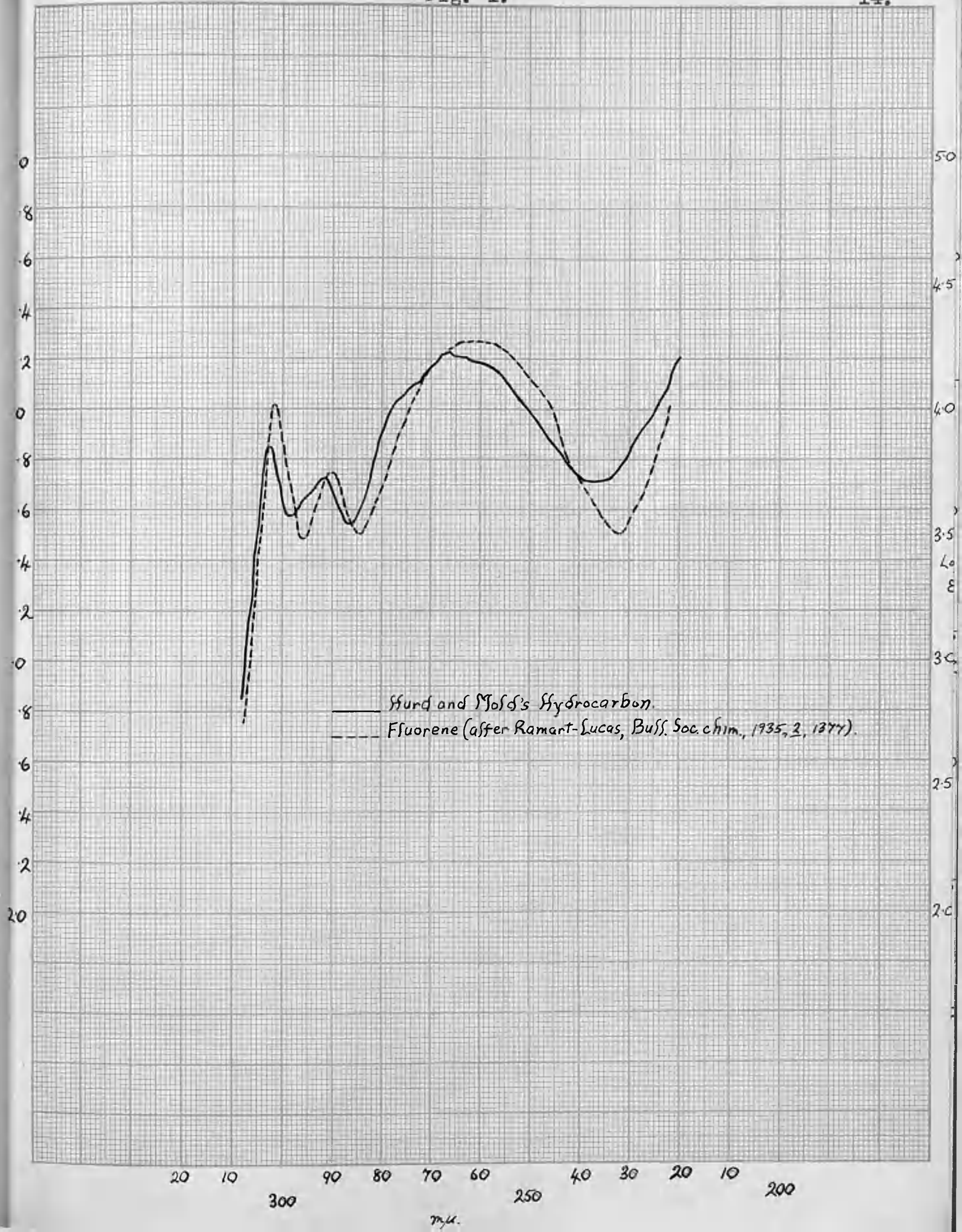


XXIX

The problem was finally cleared up by the preparation of 1-9'-fluorenyl*cyclo*hexan-1-ol (XXVII) from fluorenylmagnesium bromide and *cyclo*hexanone. This alcohol was prepared quite readily and analysed correctly but could not be induced to form any of the usual alcohol derivatives such as the phenylurethan, the acetate or the 3:5-dinitrobenzoate. This is very probably due to the extremely cramped position of the hydroxyl group (as can be seen if a Stuart model of the molecule is constructed). This leaves no room for the addition of the bulky groups necessary for the formation of these derivatives.

Dehydration of the carbinol (XXVII) with potassium bisulphate took place quite smoothly and gave a product which proved to be identical with Hurd and Mold's hydrocarbon. The latter is thus shown to be 9-*cyclo*hex-Δ_1-enylfluorene (XXIII).

Fig. 1.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Hurd and Mold's Hydrocarbon.
Fluorene (after Ramart-Lucas, Bull. Soc. chim., 1935, 2, 1377).
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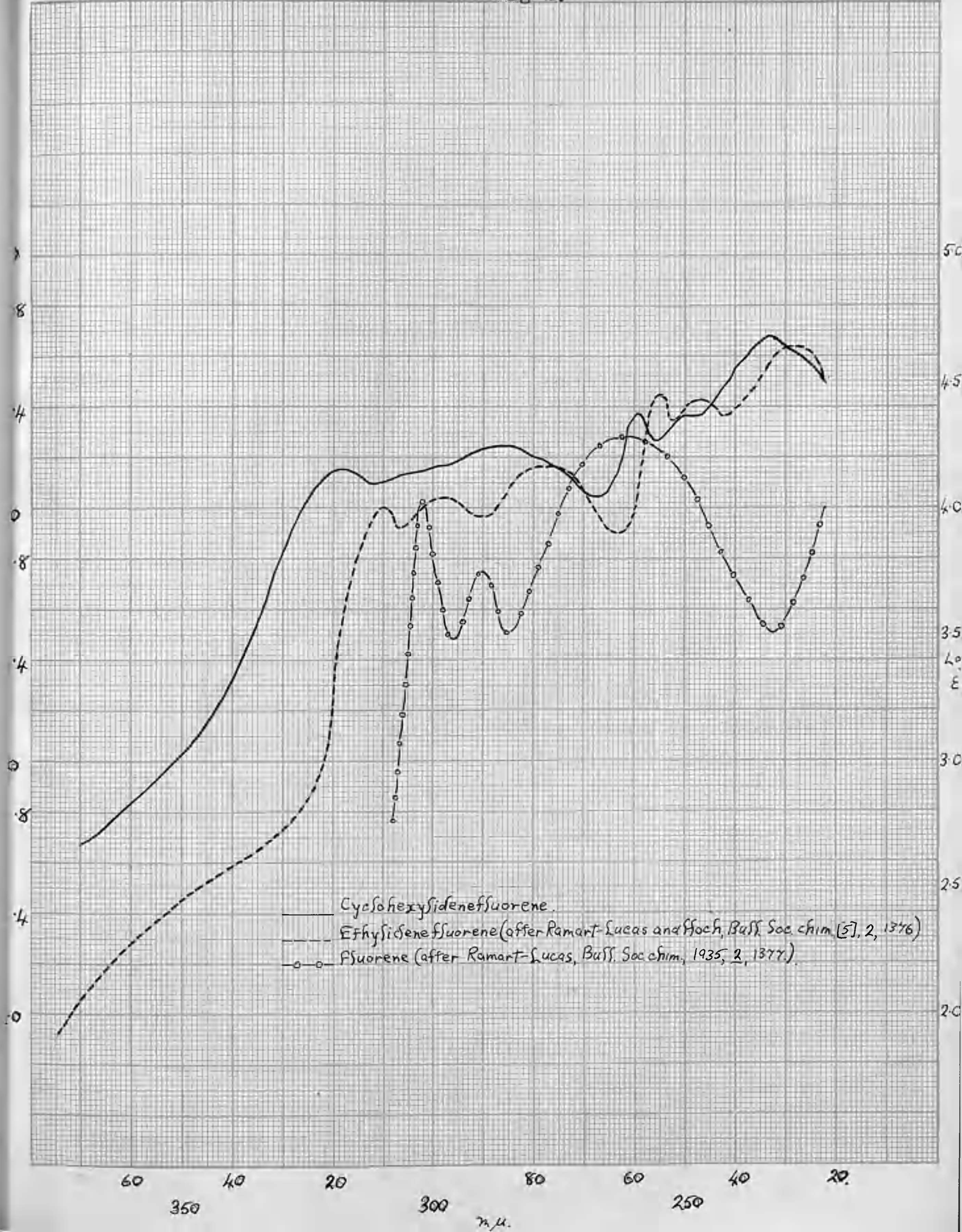
Fig 2.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Cyclohexylidenefluorene.
Ethylidenefluorene (after Ramart-Lucas and Hoch, Bull. Soc. chim. [5], 2, 1376)
Fluorene (after Ramart-Lucas, Bull. Soc. chim., 1935, 2, 1377.)
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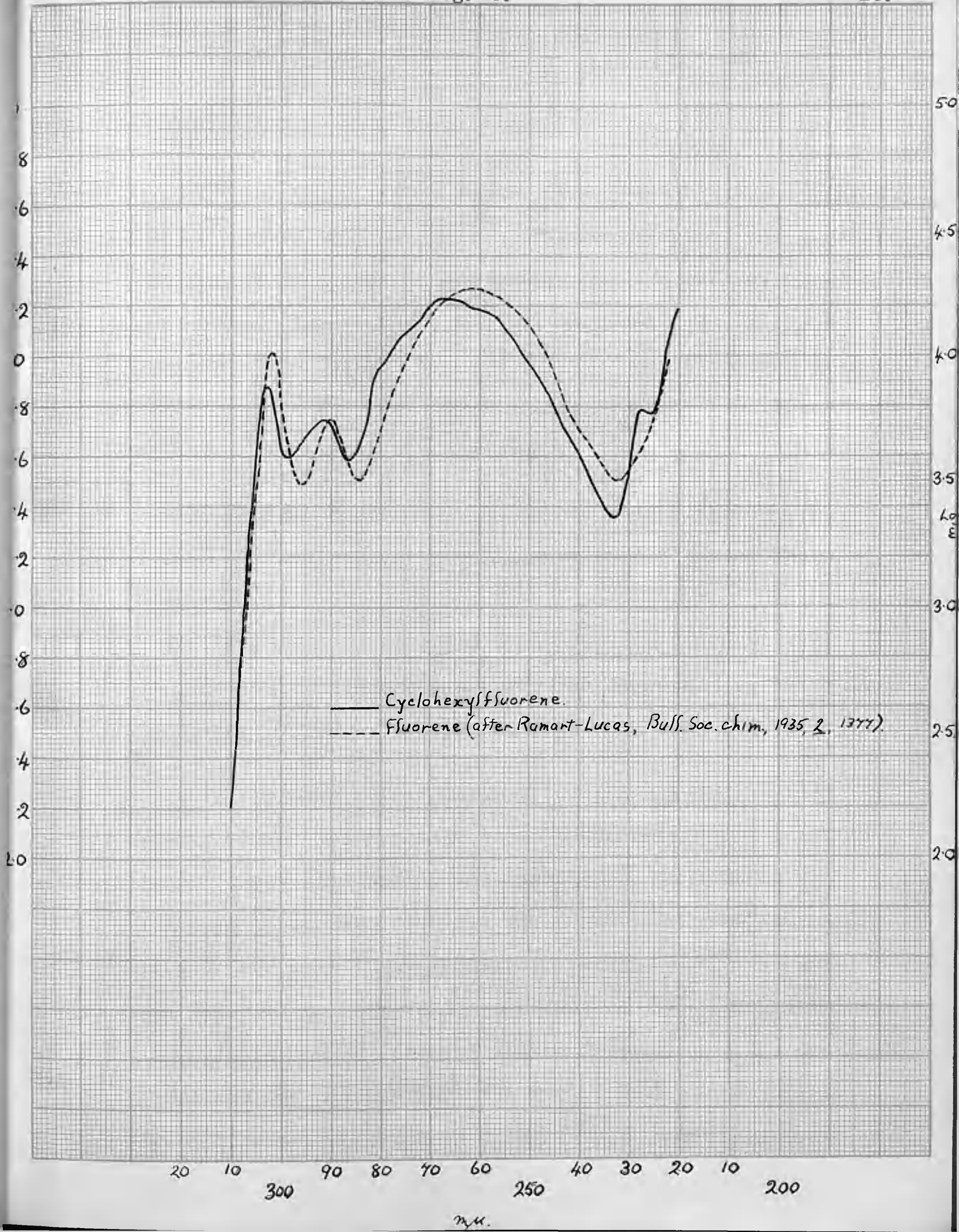
60
40
20.
350
300
250
mμ.

Fig. 3.


·1
·8
·6
·4
·2
0
·8
·6
·4
·2
·0
·8
·6
·4
·2
1.0
5.0
4.5
4.0
3.5
Log ε
3.0
2.5
2.0
—— Cyclohexylfluorene.
- - - Fluorene (after Ramart-Lucas, Bull. Soc. chim., 1935, 2, 1377).
20
10
300
90
80
70
60
250
40
30
20
10
200
mμ.

Experimental.

9-Fluorenol. Raney nickel (5g) (14) in ethanol (250 ml) was saturated with hydrogen. Fluorenone (20g) was added. The theoretical uptake of hydrogen was reached after 10-15 hours. The solution was filtered hot, the filtrate evaporated to dryness and the residue recrystallised from benzene to give a white crystalline product, m.p. 152.5-153.5°. The yield was 18g (89%).

9-Bromofluorene. (a) Using Bachmann's method (15) yields of 75-80% of 9-bromofluorene were obtained from 9-fluorenol.

(b) 9-Bromofluorene was also prepared directly from fluorene using N-bromosuccinimide as described by Wittig and Felletschin (16). 65% yields were obtained.

2-Carbethoxy-2-9'-fluorenylcyclohexan-1-one (XVIII). Sodium (2.2g) was atomised in toluene, previously purified by refluxing with sodium and distilling, and the toluene replaced by benzene (140 ml) which had been purified similarly. 2-Carbethoxycyclohexanone (15.9g) (17) was added and the mixture left to stand overnight when a bulky white precipitate was obtained. 9-Bromofluorene (23.7g) was then added and the mixture refluxed for 24 hours on an oil-bath. The cloudy orange-coloured solution obtained was poured slowly into water and the benzene layer washed several times with water before drying over anhydrous sodium sulphate. The benzene was removed in vacuo and the orange-coloured residue ground up in a mortar with a little petroleum ether (b.p.60-80°) and filtered. This removes the orange colour by solution in the petroleum ether in which the carbethoxyfluorenyl*cyclo*hexanone is practically insoluble. The off-white solid thus obtained was dissolved in hot acetic acid and recrystallised by quick cooling and rubbing with a glass rod. M.p. was 133-134°. Yield was 23.8g (74.5%). Hurd and Mold (1) give m.p. 133-133.5° with a 35% yield. A small amount of unchanged 9-bromofluorene was recovered from the petroleum ether washings.

It should be noted that Hurd and Mold carried out this reaction with 0.023 mole of 2-carbethoxy*cyclo*hexanone and an excess of potassium (0.033 mole). In the present instance experiments carried out using these proportions of the ketone and sodium gave poor yields of the required product together with a quantity of difluorenyl. This observation seems to explain the poor yield reported by the American workers.

2-9'-Fluorenyl*cyclo*hexanone. (a) Decarbethoxylation of the carbethoxyfluorenyl*cyclo*hexanone with aqueous-alcoholic potassium hydroxide as described by Hurd and Mold was found to be unsatisfactory, a yield of less than 20%

of solid product being obtained, accompanied by an intractable gum.

(b) 2-Carbethoxy-2-9'-fluorenyl*cyclo*hexanone (10g) was refluxed with barium hydroxide (15.4g) in 90% ethanol (100 ml) for 22 hours. The solvent was distilled off under reduced pressure and hydrochloric acid added to the residue which effervesced. A white solid remained after the solution became acid. On heating for a short time the solid disappeared leaving a pale yellow oil floating on the surface. The mixture was extracted with ether , the ether extract dried over sodium sulphate and the ether removed in vacuo leaving a pale yellow solid in the flask. Two recrystallisations from aqueous ethanol gave white lustrous platelets, m.p. 111.5-112.5°, identical with the solid obtained from the potassium hydroxide decarbethoxylation. Yield was 3.91g (50%). (Found: C, 87.0; H, 6.9. Calc. for $C_{19}H_{18}O$: C, 87.05; H, 6.9%). Hurd and Mold give 112.5-113.5° for the m.p. of their product.

The semicarbazone crystallised from ethanol as a white solid, m.p. 235-238° (decomp.). Hurd and Mold's value was 220°. (Found: C, 75.4; H, 6.6; N, 13.5. Calc. for $C_{20}H_{21}ON_3$: C, 75.2; H, 6.6; N, 13.2%). The ketone was readily recovered unchanged on hydrolysis with 6N hydrochloric acid.

2-9'-Fluorenylcyclohexanol. Attempts were made to hydrogenate 2-9'-fluorenyl*cyclo*hexanone at ordinary pressures using Raney nickel and Adams catalyst with dioxan as the solvent in each case. These experiments were unsuccessful, the reaction taking place not at all or, at best, with extreme slowness. Using acetic acid as the solvent (12 ml) with Adams catalyst (0.1g) and the ketone (1g), there was a slight increase in the rate of hydrogen uptake (90 ml in 17 hours). Examination of the product indicated that it was a mixture (e.g. low m.p. 75-85°, rising very gradually during several crystallisations with a considerable reduction in the amount of solid), and, moreover, a mixture from which the isolation of pure constituents presented considerable difficulty and required, in the first instance, a fairly large quantity of the reaction product. Since the reaction was so slow and since the hydrogenation with copper chromite, described below, produced a similar mixture much more readily, the isolation of the constituents was carried out on the product of the copper chromite reduction.

(a) 2-9'-Fluorenyl*cyclo*hexanone (2.62g), dissolved in dioxan (40 ml, purified as in Fieser's "Experiments in Organic Chemistry" page 369) was placed in a steel bomb with copper chromite catalyst (1g, prepared, as was Hurd and Mold's catalyst, according to "Organic Syntheses" Coll.Vol.II, 142).

The bomb was charged with hydrogen at 90 atmospheres and heated at 150° for 1.75 hours. The catalyst was removed and the dioxan distilled off to give a viscous liquid. This procedure was repeated on another two lots of the substituted cyclohexanone. The combined products were dissolved in hot cyclohexane from which, on cooling, a white solid, m.p. 120-123° (3.3g) was obtained.

When this solid had been recrystallised eight times a pure product, ?trans-2-9'-fluorenylcyclohexanol, was obtained as a white crystalline powder, m.p. 126.5-127.5° (0.3g). (Found: C, 86.4; H, 7.6. $C_{19}H_{20}O$ requires C, 86.3; H, 7.6%). The phenylurethane was prepared by heating a mixture of phenyl isocyanate (0.05g) and the alcohol (0.1g) on the water-bath for 5 minutes. The product was recrystallised several times from petroleum ether (b.p.60-80°) to give silky white needles, m.p. 171.5-172.5°. (Found: C, 81.6; H, 6.4; N, 3.64. $C_{26}H_{25}O_2N$ requires C, 81.4; H, 6.6; N, 3.65%). Hurd and Mold (1) reported an impure product obtained by reduction of the ketone with sodium and moist ether, which gave a phenylurethane, m.p. 167.5-168.5° and is probably identical with the isomer obtained above.

The cyclohexane was distilled off in vacuo from the mother liquor from the first crystallisation of the viscous reduction product, leaving a yellow syrup (3.9g) which was dissolved up in hot 95% ethanol. On standing, a white solid came down and was filtered off, washed with a little ethanol and dried. M.p. was 146-164°. After several crystallisations from various solvents including acetone, chloroform and n-hexane in that order, a hexahydro-2-9'-fluorenylcyclohexanol was obtained as fine white needles, m.p. 177-181°. (Found; C, 84.4; H, 10.1. $C_{19}H_{26}O$ requires C, 84.4; H, 9.7%).

Concentration of the mother liquor from the first ethanol crystallisation above gave a yellowish syrup which deposited a white solid on standing. Six crystallisations from ethanol gave stellate clusters of crystals of the ?cis-2-9'-fluorenylcyclohexanol with a m.p. steady at 122.5-123°. A mixed m.p. with the ?trans-alcohol previously isolated gave a depression of 20-30°. (Found; C, 86.3; H, 7.6. Calc. for $C_{19}H_{20}O$: C, 86.3; H, 7.6%). The phenylurethane, prepared by the method already described, was recrystallised from petroleum ether (b.p.60-80°) to give silky white needles, m.p. 145-146°, in agreement with the figure (144.5-145.5°) quoted by Hurd and Mold for the phenylurethane of their alcohol, m.p. 122-122.5°.

(b) 2-9'-Fluorenylcyclohexanone (5.24g), copper chromite 2g, of the very reactive catalyst, H.J.S.2., prepared by the method of Adkins, Burgoyne and Schneider (18)) and dioxan (80 ml) were placed in a steel bomb. The bomb was charged with hydrogen at 88 atmospheres and heated at 80° for 2 hours. The catalyst was removed and the dioxan distilled off leaving a white solid which, after two crystallisations from ethanol, formed colourless narrow slabs (3.0-3.5g), m.p. 121-123°, which a mixed m.p. proved to be identical with the ?*cis*-alcohol isolated by procedure (a).

A hydrogenation, using this more reactive copper chromite catalyst but raising the temperature to 150° for 1.75 hours, again gave a mixture from which, by recrystallising from acetone, the high melting hexahydro-compound, m.p. 177-181°, was obtained, while the acetone mother liquors yielded a sample of the ?*trans*-alcohol.

Dehydration of ?cis-2-9'-fluorenylcyclohexanol.

(a) Following Hurd and Mold's method exactly, i.e. heating the alcohol at 230° for half-an-hour with phosphoric acid, diluting with water, extracting the product with benzene, removing the benzene and recrystallising the residue from methanol, a pure sample of the ?*cis*-alcohol gave a product consisting of colourless needles, m.p. 110.5-111°, agreeing with the description given by Hurd and Mold for their product.

A slight variation of the above method, involving the steam distillation of the product out of the phosphoric acid reaction mixture seemed to result in a purer "crude" product, but had the disadvantage of being rather slow, due to the low steam volatility of the hydrocarbon. The creamy coloured steam distillate, after recrystallisation from methanol, proved to be identical with the product obtained by the original method. The yield was 45%. (Found: C, 92.6; H, 7.4. Calc. for $C_{19}H_{18}$: C, 92.7; H, 7.4%). Light absorption in ethanol: $\lambda_{max.}$ 2665, 2920, 3025 Å; log ε = 4.23, 3.72, 3.85. A solution of the hydrocarbon in carbon tetrachloride reacted only slowly with bromine in the same solvent, and with aqueous permanganate in acid or neutral solution.

(b) 2-9'-Fluorenyl*cyclo*hexanol (1g) was ground to a fine powder, thoroughly mixed with powdered anhydrous potassium bisulphate (0.1g) and placed in a sublimer which was then evacuated (ca. 15 mm) and immersed in an oil bath heating gradually to 180°. The alcohol melted, bubbles of steam were rapidly given off and a product consisting of white needles sublimed on to the cold finger. One crystallisation from methanol gave needles, m.p. 108-110° (50% yield). A second crystallisation raised the melting point to 110-111° with no depression on mixing with a sample of Hurd and Mold's hydrocarbon prepared by method (a).

Dehydration of ?trans-2-9'-fluorenylcyclohexanol. The ?*trans*-alcohol (50 mg) was dehydrated with syrupy phosphoric acid (2 ml) under conditions similar to those used by Hurd and Mold for their alcohol (see (a) above). Since it seemed likely that, working with such a small quantity, it would not be possible to purify the product as thoroughly as previously done with the ?*cis*-alcohol dehydration product, a parallel dehydration was carried out with 50 mg of the ?*cis*-alcohol. Both products were steam-distilled out of their respective reaction mixtures and recrystallised three times from methanol. The m.p. of the product from the ?*cis*-alcohol (i.e. Hurd and Mold's hydrocarbon) was 107.5-109°, the m.p. of the product from the ?*trans*-alcohol was 106.5-108° and the mixed m.p. of the two was 106.5-108.5°, confirming that the ?*trans*-alcohol also gave Hurd and Mold's hydrocarbon on dehydration.

9-Cyclohexylfluorene. Using magnesium (0.79g), *cyclo*hexyl bromide (5.2g) and dry ether (50 ml), *cyclo*hexylmagnesium bromide was prepared in the usual manner in a 100ml flask fitted with a three-necked adapter to take a mercury-sealed stirrer, a reflux condenser and a dropping funnel. The ether was then replaced by dry benzene (50 ml). 9-Bromofluorene (3.9g) was added and the mixture refluxed for 3 hours before decomposing with water and dilute sulphuric acid. The benzene layer was separated off and the aqueous layer washed with a further quantity of benzene. The combined benzene solutions were washed with water, roughly dried over sodium sulphate and the benzene distilled off. The orange-coloured solid thus obtained was extracted several times with hot methanol which removed the colour but left the bulk of the material as an off-white solid which proved to be difluorenyl. When the combined methanol extracts were evaporated a viscous orange oil was obtained, the bulk of which became solid, on standing for several days. Washing with acetone removed the orange colour and with it the remainder of the oil, leaving an almost white solid which, after several crystallisations from ethanol, formed colourless needles of 9-cyclohexylfluorene, m.p. 114.5-115.5°. (Found: C, 91.8; H, 8.3. Calc. for $C_{19}H_{20}$: C, 91.9; H, 8.1%). Light absorption in ethanol: $\lambda_{max.}$ 2270, 2665, 2918, 3028 Å; log ε = 3.79, 4.24, 3.74, 3.88.

The product may also be purified by vacuum sublimation.

Oxidation of Hurd and Mold's hydrocarbon. Chromium trioxide (1.5g) in water (1.5 ml) and acetic acid (1 ml) was dropped slowly into a near-boiling solution of Hurd and Mold's hydrocarbon (0.25g) in acetic acid (6.5 ml). The mixture was then refluxed for 1.5 hours and left overnight after which it was diluted with water (50 ml) and ether extracted several times. The ether extract was shaken with sodium hydroxide solution, washed with water, dried over sodium sulphate and the ether removed to give a yellow solid, m.p. 75-80° (yield 0.052g, 32% if assumed to be fluorenone). Recrystallisation from benzene-petroleum ether gave a yellow crystalline solid, m.p. 80-81.5°, undepressed on mixing with an authentic fluorenone sample, m.p. 81-82.5°.

The oxime of the oxidation product was prepared in the usual way from the reaction of the product with hydroxylamine hydrochloride and sodium hydroxide in alcohol-water. Recrystallisation of the oxime from benzene gave a yellow solid, m.p. 192-193.5°. The oxime from an authentic sample of fluorenone, prepared in the same way and recrystallised from benzene, melted at 190-192°. A mixed m.p. gave a value of 191-193.5°, confirming that the oxidation product was fluorenone.

Hydrogenation of Hurd and Mold's hydrocarbon.

(a) A microhydrogenation carried out on a sample of the hydrocarbon (4.270 mg), using, as catalyst, palladium black in glacial acetic acid, resulted in a total uptake of 0.43 ml hydrogen at 756 mm and 17° during a period of 35 minutes. The number of ethylenic double bonds present per molecule, calculated from these figures, was found to be 1.05.

(b) Hurd and Mold's hydrocarbon (0.5g) in glacial acetic acid was hydrogenated using palladium black (0.25g) as catalyst. The slow uptake of hydrogen was complete after 12 hours. The catalyst was filtered off, the solvent was distilled off under reduced pressure and the solid residue recrystallised three times from methanol to give colourless silky needles, m.p. 115-115.5°. The melting point was depressed on mixing with a sample of Hurd and Mold's hydrocarbon but undepressed on mixing with a sample of 9-*cyclo*hexylfluorene, m.p. 114.5-115.5°. Therefore the hydrogenation product is 9-*cyclo*hexylfluorene.

Double bond estimation and preparation of epoxide of Hurd and Mold's hydrocarbon. (a) Two portions of Hurd and Mold's hydrocarbon (0.2156g and 0.1786g) were accurately weighed out into two 350 ml ground glass-stoppered conical flasks. 50 ml of an approximately 0.5% perphthalic acid solution in chloroform, prepared by the method of Stahmann and Bergmann (19) from phthalic anhydride and sodium perborate with chloroform replacing the ether from the original ether extract after the latter solvent had been removed under vacuum at room temperature, were measured out accurately into each flask. At the same time a further two 50 ml portions of perphthalic acid solution were measured out into another two flasks to give the blank titrations which would allow for the slow decomposition of the perphthalic acid on standing. The four solutions were left at room temperature for 45 hours before adding 1-2g potassium iodide in water and dilute sulphuric acid and titrating with 0.1N sodium thiosulphate solution.

Weight of hydrocarbon (flask A) = 0.2156g

Weight of hydrocarbon (flask B) = 0.1786g

Volume of 0.1N Thiosulphate equivalent to <u>reacted</u> per-acid in flask A = 16.4 ml.

Volume of 0.1N Thiosulphate equivalent to <u>reacted</u> per-acid in flask B = 13.4 ml.

1 ml. 0.1N Thiosulphate $\equiv$ 0.0091g perphthalic acid.

No. of double bonds calculated from titration of contents of flask A $= (0.0091 \times 16.4) \div 0.1594 = 0.94$

No. of double bonds calculated from titration of contents of flask B $= (0.0091 \times 13.4) \div 0.132 = 0.924$

(b) In the preparation of the <u>epoxide</u> without any attempt to follow the reaction quantitatively a sample of Hurd and Mold's hydrocarbon (0.355g) was dissolved in 60 ml of an ether solution containing about 0.6g perphthalic acid and the solution left standing for two days. It was then shaken with dilute alkali, washed with water, dried over sodium sulphate and the ether removed, leaving a white residue, m.p. 86-89° (0.369g). Several crystallisations form petroleum ether (40-60°) gave colourless prisms, m.p. 89-90° (micro). (Found: C, 86.7; H, 6.9. $C_{19}H_{18}O$ requires C, 87.0; H, 6.9%).

It is of interest to note that the sample of epoxide which could be isolated from the quantitative experiment (a) although identical (mixed m.p.) with that obtained from (b), could not readily be purified to the same degree and would not give a good analysis. This must obviously have something to do with the presence of the various reagents used in the estimation of the excess perphthalic acid, such as the potassium iodide, sodium thiosulphate, etc.

Hydroxylation of Hurd and Mold's hydrocarbon.

(a) Via the epoxide. Attempts to hydrolyse the epoxide to the corresponding dihydroxy compound by boiling 0.5% sulphuric acid (20), by heating in a sealed tube with water at 110° for 4 hours (21) and by a combination of the above two methods, heating in a sealed tube with 0.5% sulphuric acid at 110-130°, resulted in the recovery of the epoxide unchanged. However, when the epoxide was heated at 100° with glacial acetic acid, containing a trace of concentrated sulphuric acid, for 1.5 hours, a reaction did seem to take place and the solution became a pale yellow colour. On working up the product, by diluting with water, making alkaline with potassium hydroxide solution, refluxing for 1.5 hours (to hydrolyse any hydroxy-acetate that may have been formed), extracting with ether and distilling off the ether, a viscous yellow gum was obtained. By dissolving this up in petroleum ether (40-60°) and charcoaling, a colourless solution was obtained, which on evaporating down to very small bulk, gave a tiny amount of a white solid, m.p. 134-144° (after pressing on porous plate and washing with a few drops of petroleum ether).

This indicates that hydrolysis of the epoxide seems to be possible although rather poor results are obtained. No further work was done on this reaction when method (b) below was found to give a dihydroxy compound with little trouble.

(b) Via the osmium tetroxide complex. The osmium tetroxide-pyridine complex from Hurd and Mold's hydrocarbon was prepared by dissolving the hydrocarbon (0.33g) and pyridine (0.21g) in dry benzene and adding osmium tetroxide (0.34g). The dark brown solution quickly deposited the brown complex. This was filtered off, dried, and hydrolysed by dissolving in chloroform and shaking with an aqueous solution (50 ml) of mannitol (5g) and potassium hydroxide (0.5g) for 2.5 hours. The colourless chloroform layer was separated off, dried over sodium sulphate and the chloroform removed, leaving a white solid (0.3g). Recrystallisation from methanol gave the dihydroxy-compound as a finely-crystalline solid, m.p. 183-184°. (Found: C, 81.5; H, 7.2. $C_{19}H_{20}O_2$ requires C, 81.4; H, 7.2%).

Attempted cleavage of the dihydroxy derivative of Hurd and Mold's hydrocarbon and oxidation of the product.

The dihydroxy compound (50 mg) was dissolved in benzene (30 ml). A solution of lead tetra-acetate (0.1g) in benzene was added and the mixture shaken for 1 hour during which time a flocculent brown precipitate formed. Filtration gave a colourless benzene solution which was shaken with a small quantity of ethylene glycol to remove excess lead tetra-acetate and then several times with water before drying over sodium sulphate. Removal of the benzene left a pale yellow gum, presumably containing either the keto-aldehyde from (XXIII) or the di-aldehyde from (XXIV). Despite repeated attempts with various solvents and chromatography this gum could not be induced to crystallise.

The scission product was therefore oxidised with silver oxide according to the method of Delépine and Bonnet (22) which involves the preparation in situ of the silver oxide by the addition of alkali to the solution containing the aldehyde and silver nitrate.

The gum was dissolved in aqueous ethanol. Silver nitrate (61 mg) was dissolved in this solution with shaking. 0.5N sodium hydroxide (1.08 ml, the quantity calculated to convert all the silver nitrate to silver oxide without leaving an excess of alkali), diluted to about 2 ml with ethanol, was added four or five drops at a time over the course of 2 hours with shaking. Shaking was then continued for a further eighteen hours. Filtration through a fluted filter paper removed the very finely divided black suspension after which the filtrate was extracted with ether to remove any neutral material. Acidification of the aqueous layer and extraction with ether in the usual way gave 47 mg acidic material in the form of a pale yellow gum which, once again could not be induced to crystallise.

A test for a ketone with 2:4-dinitrophenylhydrazine was positive indicating that the structure of the oxidation product was (XXVIII) rather than (XXIX) or, in other words, that Hurd and Mold's hydrocarbon was (XXIII) rather than (XXIV). But a pure 2:4-dinitrophenylhydrazone could not be isolated. Again, with semicarbazide acetate, there was evidence of the formation of a semicarbazone but the solid, m.p. 125-135°, which was isolated could not be induced to yield a pure analysis sample.

9-Cyclohexylfluoren-9-ol (XXVI). Cyclohexylmagnesium bromide was prepared in the usual way from magnesium turnings

(0.7g) and *cyclo*hexyl bromide (4.4g) in dry ether (50 ml). Fluorenone (2.2g), dissolved in dry ether was slowly run into the solution of the Grignard reagent with continuous stirring, iced water being used to cool the reaction flask if necessary. The orange-coloured solution was then refluxed for three hours before cooling and pouring into aqueous ammonium chloride solution to decompose the complex. The yellow ethereal layer was separated off and the aqueous layer extracted with further small quantities of ether. From the combined ether extracts a viscous yellow liquid was obtained, which on the addition of a little petroleum ether (40-60°), yielded a precipitate of an almost white solid. After filtration and recrystallisation from aqueous methanol (75%) colourless crystals of 9-*cyclo*hexylfluoren-9-ol were obtained, m.p. 126.5-128°. (Found: C, 86.5; H, 7.6. $C_{19}H_{20}O$ requires C, 86.3; H, 7.6%). The phenyl urethane was prepared in the usual way from the alcohol (0.1g) and phenylisocyanate (0.05g) and was recrystallised from petroleum ether (80-100°) to give fine silky needles, m.p. 184-186° (decomp). (Found: C, 81.4; H, 6.7; N, 3.8. $C_{26}H_{25}O_2N$ requires C, 81.4; H, 6.6; N, 3.7%).

9-*Cyclo*hexylidenefluorene (XXV). 9-*cyclo*hexylfluorenol (0.33g) and potassium bisulphate (0.034g), powdered and mixed thoroughly, were placed in a sublimer and heated in an oil-bath to 140-150° under vacuum (ca. 15 mm). The solid melted and bubbles of steam were given off. When the oil-bath temperature was raised to 170° the product sublimed readily on to the cold finger. The sublimed material (0.27g) was recrystallised from methanol to give colourless needles of 9-cyclohexylidenefluorene, m.p. 107-108°. (Found: C, 92.6; H, 7.3. $C_{19}H_{18}$ requires C, 92.7; H, 7.4%). Light absorption in ethanol: $\lambda_{max.}$ 2330, 2500, 2595, 2870, 3185 Å; log ε = 4.67, 4.35, 4.37, 4.24, 4.14. Mixture with Hurd and Mold's hydrocarbon gave a depressed melting point. After standing for 24 hours the melting point of the pure hydrocarbon dropped to 90°. As further evidence of the instability of 9-cyclohexylidenefluorene it was noted that, on standing in air, the colourless needles slowly turned yellow and finally formed a gum.

Hydrogenation of 9-cyclohexylidenefluorene. The hydrocarbon (0.04g) in glacial acetic acid was hydrogenated using palladium black (0.05g) as catalyst. The theoretical uptake of hydrogen was completed after two hours. On working up, a slightly yellow solid was obtained which, after several crystallisations from methanol, gave colourless needles, m.p. 115-115.5°, undepressed on admixture with an authentic sample of 9-cyclohexylfluorene.

1-9'-Fluorenylcyclohexan-1-ol (XXVII). Fluorenylmagnesium bromide was prepared by refluxing fluorene (25g) with ethylmagnesium bromide (prepared in the usual way from ethyl bromide (20g) and magnesium (4.3g)) in xylene as described by Miller and Bachman (10). As much of the xylene as possible was poured off from the yellow deposit of fluorenylmagnesium bromide which was washed by adding a further quantity of xylene and pouring off the supernatant liquid again. The suspension of the Grignard reagent in the remaining xylene was heated up to 80° in a flask fitted with a reflux condenser, a mercury-sealed stirrer and a dropping funnel. Cyclohexanone (9g) in a small amount of dry benzene was slowly run in while the mixture was stirred. After stirring at 80° for 2 hours, the mixture was left to cool overnight before pouring it into cold dilute sulphuric acid and separating off the xylene-benzene layer which was washed with water and dilute sodium bicarbonate solution. The solvents were then removed under vacuum, leaving an orange brown viscous oil which gave an orange solid on rubbing with a glass rod. Recrystallisation from methanol gave an orange solid which, after several further crystallisations yielded almost colourless needles, m.p. 113-114° which proved to be fluorene. The methanol mother liquors were taken to dryness giving the orange gum which was solidified as previously described. This solid was dissolved in hot petroleum ether (60-80°) and precipitated out by rapid cooling and rubbing with a glass rod. Filtration and washing with a further quantity of petroleum ether gave a creamy solid. Two or three more crystallisations gave pure 1-9'-fluorenylcyclohexan-1-ol as colourless flat needle clusters, m.p. 130-131°. The yield was about 6g. (Found: C, 86.5; H, 7.7. $C_{19}H_{20}O$ requires C, 86.3; H, 7.6%). Various attempts to prepare the phenylurethane, the acetate and the 3:5-dinitrobenzoate all met with failure. With the first two, the alcohol was recovered unchanged while, with the last, a product was isolated which proved to be identical with Hurd and Mold's hydrocarbon.

Dehydration of 1-9'-fluorenylcyclohexan-1-ol. The carbinol (0.5g) was mixed with powdered potassium bisulphate (0.05g) and placed in a sublimation tube heated at 180° in an oil-bath. Dehydration took place and white solid sublimed on to the cold finger. This solid was recrystallised several times from methanol to yield colourless needles of 9-cyclohex-Δ_1-enylfluorene, m.p. 110-111°, undepressed on mixing with a sample of Hurd and Mold's hydrocarbon.

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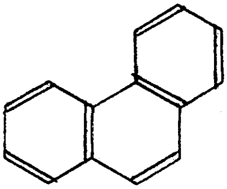
22. Delépine and Bonnet, Bull.Soc.chim.,1909, 5, 879.

PART TWO.

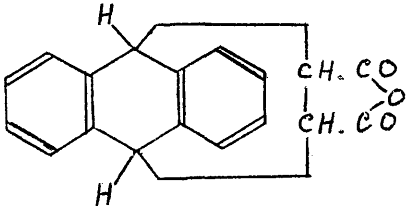
PART II.

Introduction.

Anthracene has, for some considerable time past, been known to take part in the Diels-Alder reaction (diene synthesis) and to form adducts with such dienophiles as maleic anhydride, dimethylmaleate, fumaric acid, citraconic acid, crotonic acid and dibromomaleic anhydride (1) (2). This is in accord with the fact that a pure Kekulé structure of the benzene type cannot be assigned to all the rings simultaneously as, for example, is the case with the angular system of phenanthrene (I) which is inert towards dienophiles. In consequence anthracene and in particular the central ring of anthracene seems to possess some of the properties of a diene system, notably with regard to its behaviour towards compounds like maleic anhydride.



I



II

The product (II) of the reaction of anthracene with maleic anhydride has been examined spectroscopically (3) and shown to have an absorption spectrum which clearly indicates that it is a benzene derivative. This provides evidence for the 9:10 attachment of the ethylene bridge and confirmation of this structure (II) for the adduct is obtained from the fact that oxidation leads to the formation of anthraquinone (1).

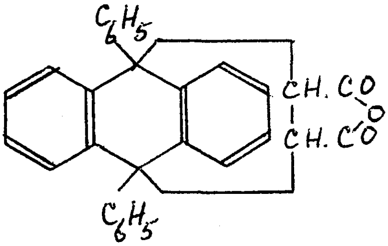
Adduct formation with anthracene, substituted in various positions, was successfully carried out by several workers. The anthracene-dienophile reaction is a reversible reaction and the position of the equilibrium and the rate of the reaction have been found to vary, not only with the dienophile used, but also with the nature of the substituents in the anthracene nucleus and their position in the three rings. Substituents, such as halogens and alkyl radicals, have been found to have little effect when their position of attachment is either of the two terminal rings. But substitution in the meso-positions has an important and widely variable effect on the course of the reaction. Thus 9:10-dialkylanthracenes react with much greater rapidity than anthracene, with the rate dropping, however, on proceeding from dimethyl to diethyl substituents (4). With 9:10-dichloroanthracene the opposite effect is found and the reaction with maleic anhydride takes much longer than does the reaction of anthracene with the latter (5).

The Diels-Alder reaction has been carried out with a considerable number of 9- and 9:10-substituted anthracenes.

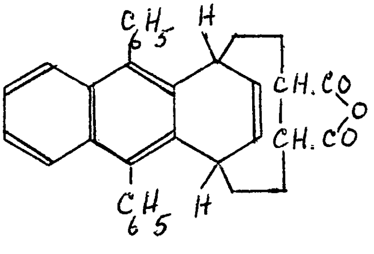
Among these are included the dialkyl- and dichloro-compounds mentioned above, 9-bromoanthracene, 9-nitroanthracene (6), 9-bromoanthracene-10-carboxylic acid (7), 9:10-dibromoanthracene (8), 9-phenyl- and 9:10-diphenylanthracene (9) (10) (11).

Until relatively recently the adducts formed from all these substituted anthracenes had been either proved or assumed to have the characteristic bridge formed across the 9- and 10-positions (12) (13), and indeed it seemed so well established that 9:10-addition of the dienophile was the usual occurrence with anthracene and its derivatives that isolation of a product with the correct analysis figures was sufficient to justify the assumption that a 9:10-adduct had been formed.

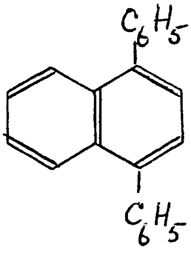
However, in 1950, Gillet published a paper (14) in which he produced evidence that 1:4-addition of maleic anhydride had taken place in an anthracene derivative. Reacting 9:10-diphenylanthracene with maleic anhydride according to the procedure of Dufraisse, Velluz and Velluz (10), Gillet obtained an adduct whose U.V. spectrum closely resembled that of 1:4-diphenylnaphthalene and was completely different from those of the corresponding adducts of anthracene and 9-phenylanthracene which in turn gave spectra in the region in which the spectra of benzene derivatives are normally found. Gillet interpreted these findings by claiming that 9-phenylanthracene formed an adduct with the "normal" 9:10-bridge as in anthracene itself and thus produced a molecule (III) which was in essence a benzene derivative and would therefore be expected to have a U.V. spectrum in the benzene portion of the absorption band. On the other hand 9:10-diphenylanthracene for some reason associated with the presence of the two phenyl groups - Gillet suggests steric hindrance - is unable to form a 9:10-bridge and instead the Diels-Alder reaction involves one of the terminal rings with the formation of a 1:4-bridge which leads to the production of a compound (IV) which is basically a naphthalene derivative and which in fact has a spectrum very closely resembling that of diphenylnaphthalene (V).



III



IV



V

Chemical confirmation of such an exceptional course for the anthracene-dienophile reaction seemed desirable and the appearance of a theoretical paper by Brown (15) added further to the necessity for such confirmation. In this paper Brown discussed the effects of substituents on the reactivity of aromatic molecules on the basis of localisation treatment of reactivities and took as his examples 9- and 9:10-diphenylanthracene and their Diels-Alder reaction with maleic anhydride. His calculations seemed to show that addition of the dienophile should take place almost exclusively at the 9:10-positions, even in diphenylanthracene. In consequence, Brown was obliged to make a distinction between the adduct made by the method of Bachmann and Kloetzel (9) who, by refluxing diphenylanthracene in xylene with a large excess of maleic anhydride obtained a product, m.p. 249-250° with decomposition, and the adduct, used by Gillet in the work outlined above, prepared by Dufraisse, Velluz and Velluz (10) who fused equal weights of the hydrocarbon with maleic anhydride to obtain a compound, with a block melting point of 315-317°. Brown suggested that at the higher reaction temperature required by this second procedure the increased vibration of the phenyl substituents about their linking bonds would prevent 9:10-addition by steric hindrance and that this factor would not be so overwhelming at the lower temperature (140°) used in the alternative preparation when an apparently different and presumably 9:10-addition product was obtained.

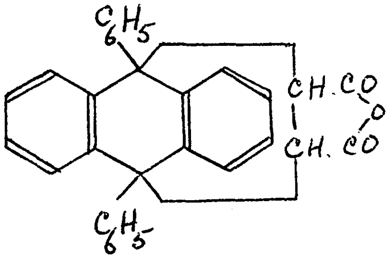
A possible explanation put forward by Dufraisse for the two quite different melting points recorded for what he obviously regarded as the same adduct, has apparently been overlooked by Brown. Dufraisse suggested (10, correction added in proof) that the lower melting point quoted by Bachmann and Kloetzel (9) was simply the melting point of diphenylanthracene formed by dissociation of the adduct on heating up in a capillary in the ordinary way whereas his melting point of 315-317° was obtained on a block which enabled him to determine the instantaneous point of fusion.

Discussion.

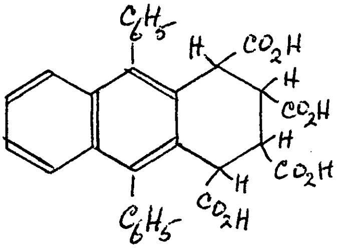
In order to clear up the confusion regarding the structure and identity of the diphenylanthracene-maleic anhydride adducts prepared by the different methods, the present investigation was undertaken.

As a first step the two adducts were proved beyond any shadow of a doubt to be identical. Diphenylanthracene, prepared via 9:10-diphenyl-9:10-dihydroxy-9:10-dihydroanthracene from anthraquinone and phenylmagnesium bromide, was reacted with maleic anhydride (a) by fusing equal amounts of the two substances for a few seconds as described by Dufraisse, Velluz and Velluz (10) and (b) by refluxing the two substances in xylene for three hours using a large excess of maleic anhydride as done by Bachmann and Kloetzel (9). This gave a yield of 80-90% in the second case as compared with 10% in the first. The melting points of the products were determined both on the Maquesne block and in a capillary. The adduct from (a) melted at 309-315° (block) and 245-247° (capillary) while the adduct from (b) melted at 310-315° (block) and 244-245° (capillary). Their U.V. absorption spectra were identical within the limits of experimental error and were similar to the curve obtained by Gillet (14). Their dimethyl esters were prepared conveniently by refluxing either the adduct anhydride or free acid with methanol containing 2% sulphuric acid. The esters had a double melting point, that from (a) at 187° and 215-216° and that from (b) at 189° and 215°, and there was no depression of these values on mixing. A sample of each dimethyl ester was converted to the corresponding trans-compound by refluxing in sodium methoxide solution and re-esterifying the free acid obtained on acidification. The trans-dimethyl ester from (a) melted at 186-187° as did its counterpart from (b) and there was no depression on admixture. An attempt was made to reconvert the trans-ester to the cis but this was unsuccessful due to the small amounts of material involved and the fact that treatment with acetic anhydride to obtain the cis-anhydride led to the dissociation of the adduct into its components. Finally the diethyl esters were prepared in a manner similar to that used for the preparation of the methyl derivatives by refluxing in ethanol-sulphuric acid solution. The melting point of the diethyl ester from (a) was 222-224°, that from (b) was 221-224° and a mixed sample gave no depression.

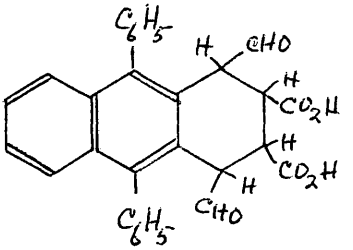
Having proved conclusively that the adducts prepared by the two methods were identical confirmation of Gillet's proposed structure (IV) for the product was now sought. The outstanding difference between this structure and what might be called the classical structure for the adduct (VI) is the presence of an unsaturated system in the former with its terminal ring containing an isolated double bond. This suggested a possible line of attack on the problem. For treatment of the adduct with one of the common reagents known to attack double bonds should lead to the formation of a product entirely different from the product, if any, which would be obtained by using such a reagent on a compound with structure (VI).



VI



VII



VIII

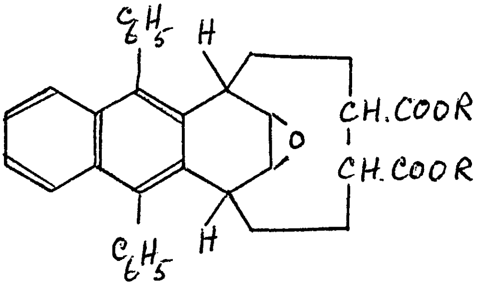
For example, double bonds are susceptible to attack by potassium permanganate with scission leading to the formation of acidic oxidation products. In the present case it was thought that such an oxidative procedure on Gillet's adduct would give 1:2:3:4-tetrahydro-9:10-diphenylanthracene-1:2:3:4-tetracarboxylic acid (VII) which would be readily analysable either as the free acid or its ester. No comparable type of product is to be expected from the permanganate oxidation of a 9:10-addition product, and thus the structural question would be very easily settled. However when a permanganate oxidation was carried out in acetone, the acidic product which was obtained could not be induced under any circumstances to yield a pure substance suitable for analysis although crystallisation from various solvents, esterification and chromatography were all tried. Decarboxylation of the acid oxidation product which might be expected to give 1:2:3:4-tetrahydro-9:10-diphenylanthracene gave as the only identifiable product a small amount of diphenylanthracene. While this might conceivably have been formed by dehydrogenation during the decarboxylation and would therefore constitute a proof of the adduct's structure, there was always the possibility that it had been present as a contaminant in the acidic oxidation product especially as it was isolated in such a small amount. Since there seemed to be little hope of success with this line of attack, attention was turned to the possibility of obtaining an analysable degradation product by ozonisation of the adduct.

Ozonisation, followed by hydrolysis of the ozonide, seemed likely to lead to the formation of a mixed product consisting of the dialdehyde-diacid (VIII) and the tetra-acid (VII). The hydrolysis was therefore carried out in the presence of hydrogen peroxide to ensure complete conversion to the tetra-acid. A glassy solid was obtained which could not be crystallised. Only partial esterification could be achieved on refluxing with methanol-sulphuric acid while treatment with diazomethane gave complete esterification. This behaviour is paralleled by that of benzene-1:2:3:4-tetracarboxylic acid (16) which esterifies only in the 1- and 4-positions using methanol-sulphuric acid. The esterified gum could not be further purified.

Ozonisations of the dimethyl and diethyl esters of the adduct were then carried out under different conditions. The danger of "over-ozonisation" (17) was avoided by testing for the presence of excess ozone in the exit gases from the bottle containing the adduct ester dissolved in ethyl acetate. The mere fact that this was possible was in some degree support for the presence of a double bond in the adduct as during ozonisation of aromatic compounds the uptake of ozone is never complete and its presence in the exit gases is detectable from the outset of the experiment (18). Decomposition of the ozonide was carried out by the hydrogenative procedure introduced by German workers (19) (20), which is claimed to give much better yields of the initially formed aldehydes. The product yielded only a very small amount of a 2:4-dinitrophenylhydrazone whose melting point and nitrogen analysis suggested that it was the hydrazone of glyoxal or some similar small molecule possibly derived from the action of the ozone on the ethyl acetate used as solvent.

With the failure of ozonisation to yield concrete evidence in favour of the presence of a double bond in the adduct molecule, it was decided to carry out a double bond estimation with perphthalic acid following a procedure which had been successfully used in Part I (page 28). On leaving the reactants (i.e. the adduct diethyl ester and perphthalic acid) together for the usual period of two days the value for the number of double bonds present per molecule was 0.65, and it was found that the reactants had to be left for fully four days before the reaction was complete. Under these conditions two separate determinations gave 1.048 and 1.025 as the number of double bonds present in the adduct.

To complete the confirmation of Gillet's structure (IV) for the adduct the epoxides (IX) and (X) of the dimethyl and diethyl esters of the adduct were isolated and characterised by melting point and elementary analysis.



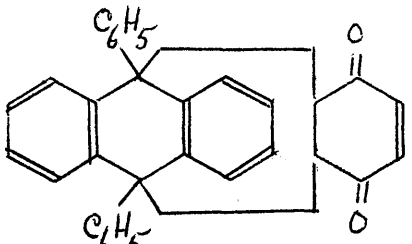
IX ; R = Me

X ; R = Et.

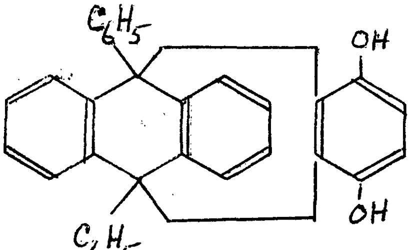
With the complete confirmation of 1:4-addition in the adduct formed by maleic anhydride with 9:10-diphenylanthracene, one or two points of interest crop up with regard to previously published work. In the first place a revaluation of the factors used by Brown in his previously mentioned paper (15) would seem desirable since they have led to the completely erroneous conclusion that 9:10-addition in diphenylanthracene should take place almost exclusively.

In an early paper by Clar (11) there is described the formation of a quinhydrone by the combination of the adduct of diphenylanthracene and p-benzoquinone and its hydroquinone. These compounds, the adduct and its hydroquinone, have been assigned the structures (XI) and (XII) respectively in the review by Norton (21). A reconsideration of this matter would now seem to be indicated.

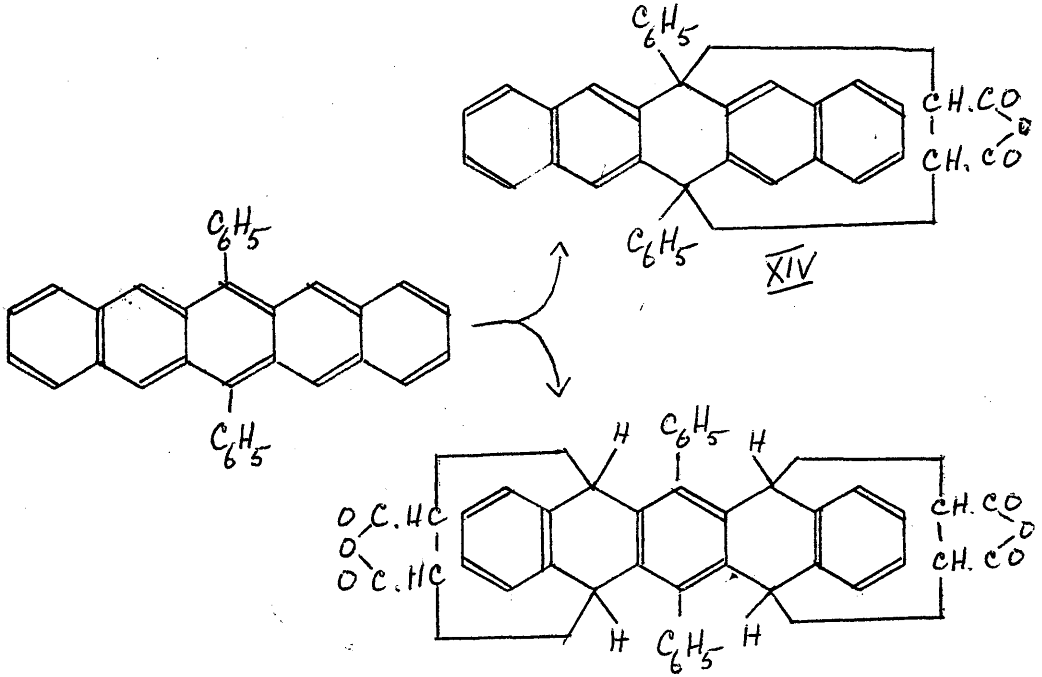
This is also the case with at least one of the products of maleic anhydride addition to 6:13-diphenylpentacene (22).



XI



XII



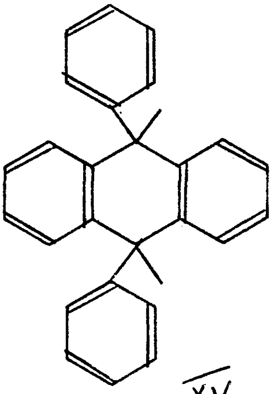
XIV

XIII

Although (XIII) may be regarded as quite feasible for the structure of the di-maleic anhydride addition product, (XIV) as the structure of the mono-addition product is now definitely under suspicion and 5:14-addition would seem to be a much more likely occurrence especially as this not only avoids the diphenyl substituents at the 6 and 13-positions but also allows addition at what is after all still a *meso*-

position.

It is interesting to note that an attempt by Clar to obtain the diphenylanthracene-maleic anhydride 9:10-adduct by a Friedel-Crafts reaction with benzene and aluminium chloride on the previously prepared 9:10-dichloroanthracene maleic anhydride 9:10-adduct gave only 9:10-diphenylanthracene (5). The reason for this can now be seen in the preference for 1:4-dienophilic addition in this 9:10-substituted hydrocarbon and in what must be the relative instability of any 9:10-dienophilic addition product such as would be obtained in the reaction undertaken by Clar.



XV

The suggestion that the slowness with which maleic anhydride reacts with diphenylanthracene (9) (23) is due to the protection afforded the trivalent carbon atoms, whose presence is postulated (24) (25) by supporters of the biradical theory of the reaction, by the compact arrangement of the benzene nuclei (XV) (24) must now be discarded and the slowness of reaction attributed merely to the fact that addition is taking place at the 1:4-positions in the anthraeene molecule, which, although a great deal less reactive than the <u>meso</u>-positions, may be compared with the 1:4-positions in naphthalene which have already been shown to add maleic anhydride (33) (34).

Experimental.

9:10-Diphenyl-9:10-dihydroxy-9:10-dihydroanthracene. This compound was prepared by the procedure of and in yields comparable with those obtained by Dufraisse and Le Bras (26) who reacted phenylmagnesium bromide with anthraquinone.

9:10-Diphenylanthracene. The diphenyldihydroxydihydroanthracene was converted to 9:10-diphenylanthracene by treatment with potassium iodide in acetic acid according to the method used by Clar (27) for the preparation of 9:10-diphenyl-1:2-benzanthracene.

The dihydroxy-compound (10g) in glacial acetic acid (220 ml) was refluxed for 10-15 minutes with potassium iodide (10g). The light brown solid obtained on cooling was filtered off, washed with acetic acid and recrystallised twice from benzene-acetic acid (50:50) to give creamy-coloured crystalline diphenylanthracene in 67% yield (6.08g).

Bachmann and Kloetzel (9) used this method to obtain 9:10-diphenylanthracene but give no practical details.

Reaction of maleic anhydride with 9:10-diphenylanthracene.

(a) Preparation of the adduct by the method of Dufraisse Velluz and Velluz (10). Diphenylanthracene (0.5g) and maleic anhydride (0.5g) were powdered, mixed thoroughly and heated to fusion. After heating for a few seconds, the product was allowed to cool, powdered and extracted with a little ether and benzene to remove unchanged maleic anhydride and diphenylanthracene. The residue was recrystallised from benzene to give colourless crystals, m.p. 309-315° (Maquesne block), 245-247° (capillary). The fact that a good analysis of the adduct could not be obtained is undoubtedly due to the ease with which dissociation takes place, for example, on crystallisation. Light absorption in ethanol: $\lambda_{\text{max.}}$ = 242*, 288, 291, (294) mμ; log ε = 4.74, 4.07, 4.06, (4.04).

Monomethyl ester. In an attempt to prepare the half-ester the adduct (1g) was refluxed in methanol for 4 hours only to be recovered unchanged.

Dimethyl ester. The adduct (0.7g) was refluxed in methanol (60 ml) containing 2% conc. sulphuric acid for 6 hours. The suspended solid gradually dissolved to give a clear solution. A portion (ca. half) of the methanol was distilled off and the remaining solution poured into water to give a white precipitate which was filtered off and recrystallised several times from methanol to give flat rectangular prisms with a blue fluorescence. The dimethyl ester seemed to have a double melting point. A definite softening occurred

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*Because of a defect in the spectrophotometer absorption in this region was not measured with the sample prepared in (b).

about 187°, but there was no further change until the final m.p. 215-216°. (Found: C, 81.1; H, 5.4. $C_{32}H_{26}O_4$ requires C, 81.0; H, 5.5).

Diethyl ester. A sample of the adduct was refluxed in ethanol containing 2% conc. sulphuric acid for 7 hours. The adduct gradually dissolved giving a clear solution from which the ester slowly precipitated. Two crystallisations of the product from benzene-ethanol (25-75) removed all traces of the blue fluorescence due to the presence of diphenyl anthracene and gave colourless crystals of the *diethyl ester*, m.p. 222-224°. (Found: C, 81.45; H, 6.05. $C_{34}H_{30}O_4$ requires C, 81.3; H, 6.0).

trans-*Dimethyl ester*. A sample (0.1g) of the dimethyl ester, prepared above, was refluxed for 15 hours in a sodium methoxide solution (2g sodium in 50 ml methanol) following a published procedure (28) (29) (35). A portion of the methanol was distilled off and the remaining solution poured into water to give a clear solution. Acidification gave the free acid which was esterified in the usual manner with methanol-sulphuric acid. Crystallisation from methanol gave the trans-*dimethyl ester* as colourless stellate clusters, m.p. 186-187°, depressed to 167-175° on mixing with a sample of the *cis*-dimethyl derivative. (Found: C, 80.75; H, 5.55. $C_{32}H_{26}O_4$ requires C, 81.00; H, 5.5%).

When an attempt was made to reconvert a small quantity of the *trans*-ester to the *cis*-derivative by hydrolysing and treating the free acid with acetic anhydride, only diphenylanthracene could be isolated in sufficient quantity for identification, because of the unfavourable equilibrium existing between the adduct (16%) and its components (9).

(b) Preparation of the adduct by the method of Bachmann and Kloetzel (9). Diphenylanthracene (10g) and maleic anhydride (80g) were refluxed for 3 hours in xylene (250 ml). A change in the working up procedure from that outlined by the above authors gave the same product much more conveniently. The reaction mixture was poured into a 40% potassium hydroxide solution and steam distilled to remove the solvent. This left the potassium salt of the adduct as a white solid suspension which was filtered off, washed with a little water and dried in a vacuum dessicator. Unchanged diphenylanthracene was removed from the material by extraction with benzene, leaving the potassium salt of the adduct as a white powder (11.4g). Diphenylanthracene (2.5g) was recovered from the benzene washings. The free x:x'-*endo*-(α:β-succinic acid)-9:10-diphenylanthracene was obtained by reflux-the potassium salt with dilute mineral acid for some time. Recrystallisation from moist ethyl acetate (to inhibit conversion to the anhydride) gave colourless crystals, m.p. 260° (resolidifies) (Maquesne block); 241-242° (capill.). (Found: C, 77.5; H, 4.75. Calc. for $C_{30}H_{20}O_4.1H_2O$:

C, 77.9; H, 4.8%).

Recrystallisation of the free acid or the potassium salt from acetic anhydride gave the anhydride as a white solid, m.p. 310-315° (Maquesne block); 244-245° (capillary), both figures in agreement with the values obtained with Dufraisse's adduct (vide supra). Light absorption in ethanol: $\lambda_{max.}$ = 288, 291, 293 mμ: log ε = 4.1, 4.08, 4.07.

Dimethyl ester. A sample of the dimethyl ester was prepared as above for the ester of Dufraisse's adduct using sulphuric acid-methanol. On crystallising the product from methanol it was noted that the compound initially crystallised in the form of stellate clusters of stout needles which were converted on standing in contact with the solution for some 30 hours into flat rectangular prisms. A double melting point was observed, softening at 189° without further change until final m.p. 215°. A sample mixed with some of Dufraisse's ester showed the same characteristic behaviour on melting with no depression.

Diethyl ester. Prepared, like the Dufraisse adduct ester, by refluxing in ethanol-sulphuric acid. Colourless crystals from benzene-ethanol, m.p. 221-224°, undepressed on admixture with a sample of the Dufraisse ethyl ester.

trans-Dimethyl ester. Prepared from the dimethyl ester of the Bachmann adduct, the trans-ester was identical (mixed m.p.) with the trans-ester prepared (vide supra) in the same way from the dimethyl ester of the Dufraisse adduct.

Permanganate oxidation of x:x'-endo-(α:β-succinic acid anhydride)-9:10-diphenylanthracene. An attempt to oxidise the anhydride with potassium permanganate in aqueous sodium carbonate solution was unsuccessful, the reaction taking place with extreme slowness, due, probably, to the insolubility of the anhydride in the aqueous solution. An oxidation in acetone seemed to offer more chance of success.

Accordingly the adduct (as free acid; 2.08g) was refluxed in acetone (250 ml) for 0.5 hours with potassium permanganate (1.98g). The precipitated "manganese dioxide" was filtered off and from the acetone filtrate a yellow-brown solid (0.26g) was obtained, which after charcoaling and crystallising from acetone gave small yellow prisms, m.p. 245-247°, identical with a sample of authentic diphenylanthracene. This compound must have come from the dissociation of the adduct on heating.

The manganese dioxide was suspended in water and treated with sulphur dioxide. This left behind an amorphous yellow solid (1.96g) which after treatment in the usual way (solution in sodium carbonate, ether extraction, etc.) to remove non-acidic material, gave an acidic product (1.76g) as an orange yellow glassy solid. Attempts to crystallise this material from a wide range of solvents and solvent mixtures met with no success. Esterification with diazomethane gave a neutral product which again resisted all attempts at crystallisation. Chromatography of the methyl ester both on alumina and silica in an effort to purify it was scarcely more profitable. Various rather ill-defined bands of differing shades of orange and yellow together with a bright blue fluorescent band which proved to be a trace of diphenylanthracene, were obtained but none of these could be induced to yield a pure crystallisable solid.

The acidic product could be converted to a neutral product, presumably an anhydride, by refluxing for 0.75 hours with acetyl chloride. A good reconversion to the acidic material (100 mg acid gave 80 mg recovered acid) was obtained on heating the "anhydride" with sodium hydroxide solution. No progress was made in the isolation of a pure product from the neutral "anhydride".

Decarboxylation. A sample of the acidic oxidation product (0.74g) which had been rigorously separated from non-acidic material as described above was heated with soda-lime (1.4g) at 350°. Decarboxylation took place, a gas was evolved and a solid (80 mg) sublimed on to the cold finger of the sublimer in which the reaction was carried out. Chromatography of this solid on alumina gave an almost colourless crystalline solid (39 mg) which proved to be diphenylanthracene. No other pure material could be isolated either from the sublimate or the soda-lime mixture. The isolation of diphenylanthracene may be of no significance but it is noteworthy that when a sample of the same acidic product as was used above was dissolved in petroleum ether and chromatographed there was no trace of the unmistakeable bright blue fluorescent band which is produced by diphenylanthracene.

Ozonisation of x:x'-endo-(α:β-succinic acid anhydride)-9:10-diphenylanthracene and its dimethyl and diethyl esters.

(a) The adduct (0.2g) in pure pyridine (30 ml) was ozonised for 2 hours. The solvent was removed under vacuum at 45° leaving a syrupy residue which was treated with water and 30% hydrogen peroxide (30 ml) and left overnight. The mixture was then heated on the water-bath for 20 minutes before acidifying and extracting with ether. The ether extract was treated with sodium carbonate solution and from this the acidic material was recovered as a pale yellow glassy solid (70 mg). All efforts to crystallise this product were unsuccessful.

Esterification by refluxing with methanol containing 2% sulphuric acid gave only a tiny amount (6 mg) of non-acidic gum. It is possible that the esterification of 1:2:3:4-tetrahydro-9:10-diphenylanthracene-1:2:3:4-tetracarboxylic acid (VII) under these conditions might only go partially as happens with benzene-1:2:3:4-tetracarboxylic acid which esterifies under similar conditions in the 1- and 4-positions only although complete esterification can be achieved using diazomethane (16). The acidic material recovered from the above esterification was therefore treated with diazomethane when an effervescence occurred and neutral material was obtained as a pale yellow gum. The product resisted all efforts at purification.

(b) In an effort to avoid the possible serious consequences of "over-ozonisation" (17) the ozonisation of the dimethylester was carried out under strictly controlled conditions in the apparatus shown in fig.1. With this apparatus it was possible to test the exit gases periodically for the presence of ozone and consequently to determine when the ozonisation of the compound was complete. In addition a reductive decomposition (19) (20) of the ozonide was used as this was more likely (than hydrolysis) to lead to the isolation of the primary aldehydic products of the reaction.

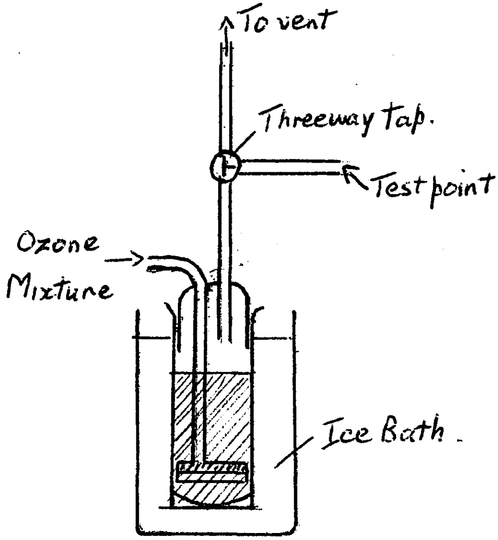

Fig. 1.

The dimethyl ester (0.5g) was dissolved in ethyl acetate (130 ml) and the solution placed in the Dreschler bottle of the apparatus illustrated. The ozone stream was bubbled slowly through the solution while the Dreschler bottle was immersed in an ice-water bath. After 100 minutes excess ozone could be detected (with potassium iodide-starch paper) in the exit gases compared with a period of 20 minutes which obtained when the solvent alone was placed in the Dreschler bottle. The gas stream was stopped and the contents of the bottle were hydrogenated using palladised calcium carbonate (0.5g) (30) and cooling the hydrogenation flask in ice-water (31) (20). After separating off the catalyst the solution was concentrated at a low temperature and divided in two parts, one of which was treated with 2:4-dinitrophenylhydrazine solution while the other, after removal of the solvent in vacuo, was treated with a solution of hydroxylamine hydrochloride and sodium acetate. No oxime was isolated from the latter reaction. With the former an orange-red precipitate slowly came down overnight. Recrystallisation from ethyl acetate gave orange-red needles, m.p. 330° (micro). A nitrogen analysis gave a value of 24.4% indicating that the compound was a derivative of an aldehyde of low molecular weight possibly glyoxal (although glyoxal-2:4-dinitrophenylhydrazone contains 26.8% nitrogen it gives a low nitrogen analysis due to the formation of a nitrogenous charcoal (32)) formed by a reaction of ozone with the solvent, ethyl acetate, and in any case of little value in the elucidation of the structure of the adduct.

(c) An ozonisation of a sample (0.5g) of the diethyl ester of the adduct under much the same conditions as described above gave almost exactly the same result, the only material which could be isolated again being a 2:4-dinitrophenylhydrazone containing a very high percentage of nitrogen.

Double bond estimation on the diethyl ester of the adduct. Two portions of the diethyl ester (A and B) were weighed out and each treated with 50 ml of an approximately 0.5% perphthalic acid solution in chloroform. The solutions together with two "blanks" of 50 ml perphthalic acid solution were left in stoppered flasks for 95 hours at room temperature before estimating the remaining perphthalic acid by adding potassium iodide and dilute acid and titrating the liberated iodine with standard sodium thiosulphate.

Weight of diethyl ester (A) = 0.3494 g
Weight of diethyl ester (B) = 0.430 g

Volume of 0.0975N thiosulphate equivalent to <u>reacted</u> per-acid in (A) = 14.95 ml
Volume of 0.0975N thiosulphate equivalent to <u>reacted</u> per-acid in (B) = 18.00 ml

1 ml 0.1N thiosulphate $\equiv$ 0.0091g perphthalic acid.

Molecular Weight of diethyl ester = 502.5

No. of double bonds present calculated from titration of

$$\text{contents of (A)} = \frac{0.0091 \times 14.95 \times 0.0975}{0.1 \times 0.1266} = 1.048$$

No. of double bonds present calculated from titration of

$$\text{contents of (B)} = \frac{0.0091 \times 18.00 \times 0.0975}{0.1 \times 0.1559} = 1.025$$

The reaction of perphthalic acid with the ester was complete only after standing for 95 hours. When the reactants were left for 47 hours, a period which gave satisfactory results with the perphthalic acid oxidation of 9-*cyclo*hex-Δ_1-enylfluorene (page 28), the value obtained for the number of double bonds was 0.65.

Preparation of the epoxide of the diethyl ester of the adduct. The diethyl ester (ca. 150 mg) was dissolved in a 0.5% chloroform solution of perphthalic acid (50 ml; although this solution had been kept for over a week in the refrigerator practically no decomposition had taken place) and left for 4 days before extracting with sodium carbonate solution to remove phthalic and perphthalic acid, washing with water and drying over sodium sulphate. When the solvent was removed a very pale yellow gum was obtained which was charcoaled once and crystallised several times from petroleum ether (60-80°) to give colourless crystals, m.p. 237-238°, of the *epoxide*. (Found: C, 78.5; H, 5.75. $C_{34}H_{30}O_5$ requires C, 78.75; H, 5.8%).

A sample of the epoxide isolated from the quantitative experiment above gave a poor analysis and melted at 233-235° although apparently identical (mixed m.p.) with the product obtained in the present experiment. This confirms the observations made previously (page 30) on the "analytical" behaviour of the epoxide of 9-cyclohex-Δ_1-enylfluorene, prepared in a quantitatively followed experiment.

Preparation of the epoxide of the dimethyl ester of the adduct. A sample of the dimethyl ester was converted to the epoxide in the usual manner (see above). The product was obtained as a gum which was charcoaled and recrystallised several times from petroleum ether (60-80°) and n-hexane to give dimethyl 3:4-epoxy-1:2:3:4-tetrahydro-9:10-diphenylanthracene-1:4-endo-$\alpha:\beta$-succinate as a colourless crystalline solid, m.p. 218-219°. (Found: C, 78.45; H, 5.5. $C_{32}H_{26}O_5$ requires C, 78.34; H, 5.34%).

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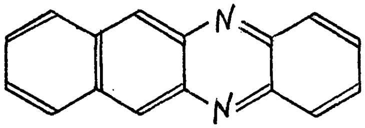
PART THREE.

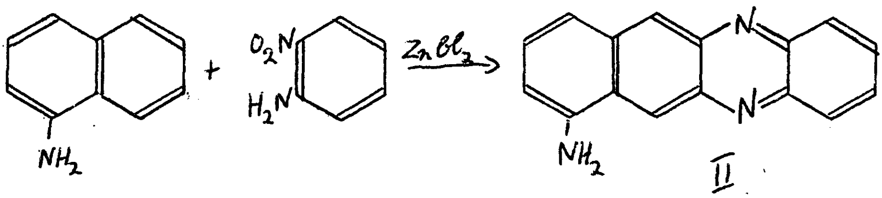
PART III.

Discussion.

Webster, in the book, "Six-membered heterocyclic nitrogen compounds with four condensed rings" (New York,1951), devotes a section to the preparation of 5:12-diazanaphthacenes (I). In this short section, short because syntheses of compounds with this type of linear ring-system occur very infrequently in the literature, Webster describes the synthesis by Wohl and Lange (1) of a 7-amino-5:12-diazanaphthacene (II) by the interaction of 1-naphthylamine with o-nitroaniline in the presence of zinc chloride.



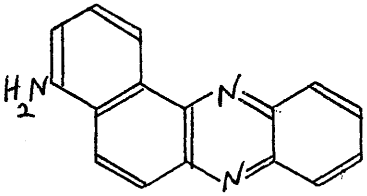
I



II

The assignment of such a structure (II) to the product of this reaction seems open to grave suspicion both on the basis of the abnormal 2:3-addition to the naphthalene nucleus and also on the grounds that substitution in the other naphthalene ring, already substituted and therefore considerably more active to further substitution, seems much more probable.

Reference to the original paper by Wohl and Lange (1) leads to the immediate conclusion that either Webster is responsible for this suggested structure or that she has gathered her facts from some intermediate and unquoted source. For Wohl and Lange give no structural formula for their compound but refer to it merely as "amino-naphthophenazine". While this name can certainly be applied to structure (II) it can equally well refer to such structurally varied compounds as (III), (IV) and (V).



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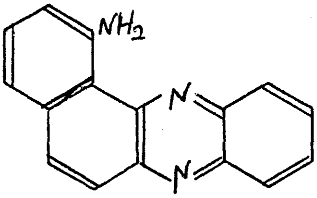
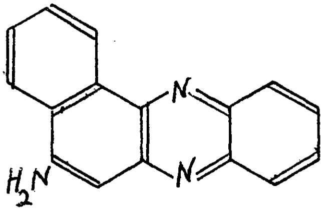
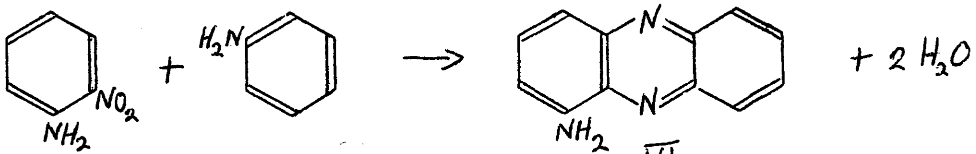


IV

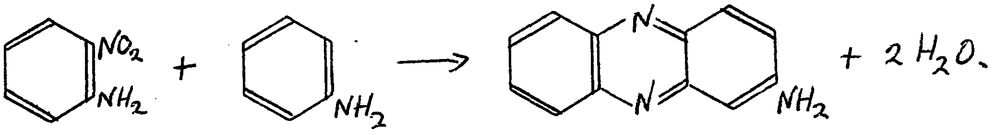


V

Moreover a brief study of the German paper should suggest quite strongly a more feasible structure. This paper is devoted to the syntheses of several phenazines by the condensation of various substituted anilines with *o*-nitroaniline in the presence of zinc chloride. Taking the "parent" reaction first, it was found that aniline and *o*-nitroaniline gave, instead of the expected α-aminophenazine (VI) and thus paralleling the reaction of nitrobenzene and aniline to give phenazine (2), the β-aminophenazine (VII). In other words both ring nitrogen atoms had come from the nitroaniline molecule, while the <u>para</u>-position in the aniline molecule had taken part in the condensation.

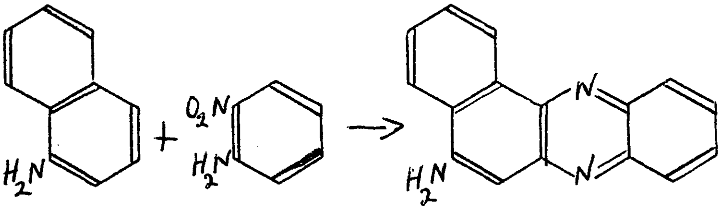


VI

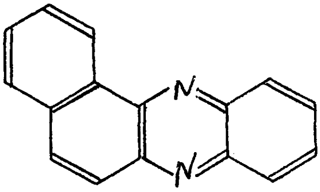


VII

Extension of this formulation to the reaction with 1-naphthylamine suggests undoubtedly that the product in this case should be (V).



V



VIII

Since Wohl and Lange do not report explicitly that (V) is the structure of their compound and since the structure cited by Webster (loc.cit.) seems so much at variance with the results of related experiments, it seemed desirable to establish conclusively the structure of Wohl and Lange's "amino-naphthophenazine".

As a preliminary step the amino-naphthophenazine was synthesised precisely as described by Wohl and Lange (1) from o-nitroaniline and 1-naphthylamine. During the final sublimation of the product, it was noted that, in addition to the small quantity of unchanged o-nitroaniline and the orange-red band of the required naphthophenazine, a small band of an orange-yellow compound melting between 130 and 140° was obtained.

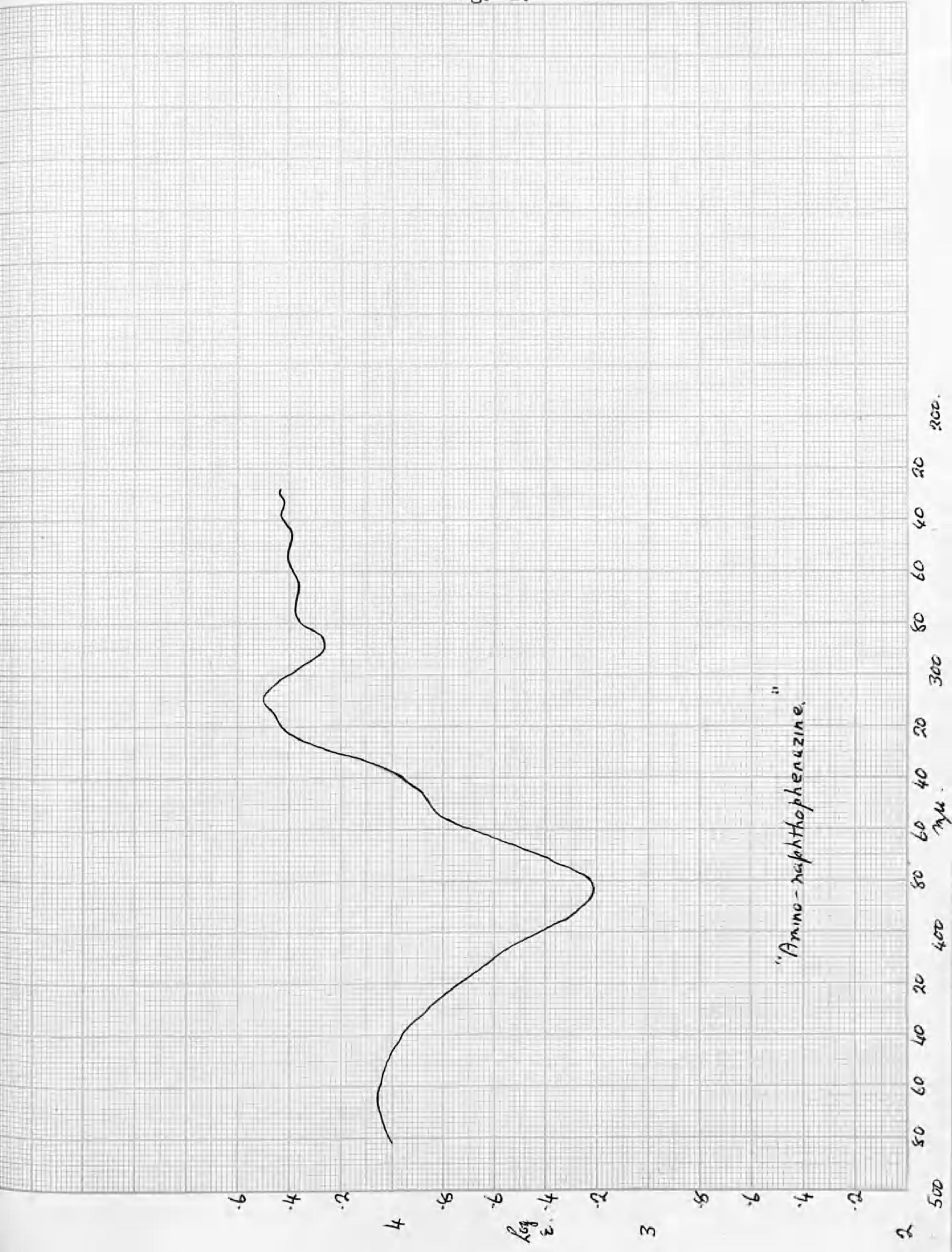
All the amino-naphthophenazines theoretically possible from this reaction (III), (IV), (V) etc., must yield, on deamination, one or other of only two parent ring systems, the linear 5:12-diazanaphthacene (I) or the angular benzophenazine (VIII). These compounds have widely differing melting points, 233° (3) and 142° (4) respectively and the identification of one or the other from the amino-compound would be invaluable in eliminating a number of possible structures.

Diazotisation of the amino-compound was carried out both in the ordinary manner by the addition of sodium nitrite solution to the amino-compound in concentrated hydrochloric acid, and also using nitrosylsulphuric acid previously prepared from sodium nitrite and sulphuric acid (5). In both cases considerable decomposition took place even during the diazotisation and this is probably the explanation for the appearance of phenolic material as the main product in each case. However from the small amount of non-acidic product chromatography yielded a pale yellow crystalline solid, m.p. 140° in agreement with the melting point for _ang_-benzophenazine. This provided confirmation for what was already the more likely ring structure for the amino-compound.

At this stage a survey of the literature dealing with the syntheses of the various amino-_ang_-benzophenazines revealed that of the three amino-compounds possible assuming the two ring nitrogens to be derived from the _o_-nitroaniline, namely, the 1-amino- (IV), the 4-amino- (III) and the 5-amino-compound (V), two were already well known, the 4- and the 5-amino-derivatives. 4-Amino-_ang_-benzophenazine was made by Ullmann and Heisler (6) who quote a melting point of 270-271° and say that the compound gives a red colour on dissolving in concentrated sulphuric acid. Fischer and Hepp (7) were the first to make 5-amino-_ang_-benzophenazine. They state that it has a melting point of 264° and gives a green colour with concentrated sulphuric acid. Now Wohl and Lange's amino-compound gives a green colour with sulphuric acid but has a melting point of 289-291° (uncorr.), which seemed to dispel any likelihood that it was the 5-amino-derivative. As this has previously been shown to be the most likely structure for the compound an exhaustive search of the literature was carried out and finally, in a paper by Kehrmann (8) in which he describes a preparation of 5-amino-ang-benzophenazine, was found the statement that "the melting point of the 5-amino-compound was 294° and not 264°", the low value previously quoted having been due to a misprint.

It was now a simple matter to prepare a sample of 5-amino-ang-benzophenazine by the reaction of 4-benzeneazo-1-naphthylamine with o-phenylenediamine according to the method of Fischer and Hepp (7). Its identity with Wohl and Lange's amino-compound was established by melting point and mixed melting point and by the determination of the U.V. absorption spectra of the two compounds which were found to be the same (figs. 1 and 2, pages 75 and 76).

Fig. 1.


"Amino-naphthophenazine."
log ε
2
.2
.4
.6
.8
3
.2
.4
.6
.8
4
.2
.4
.6
500
80
60
40
20
400
80
60
40
20
300
80
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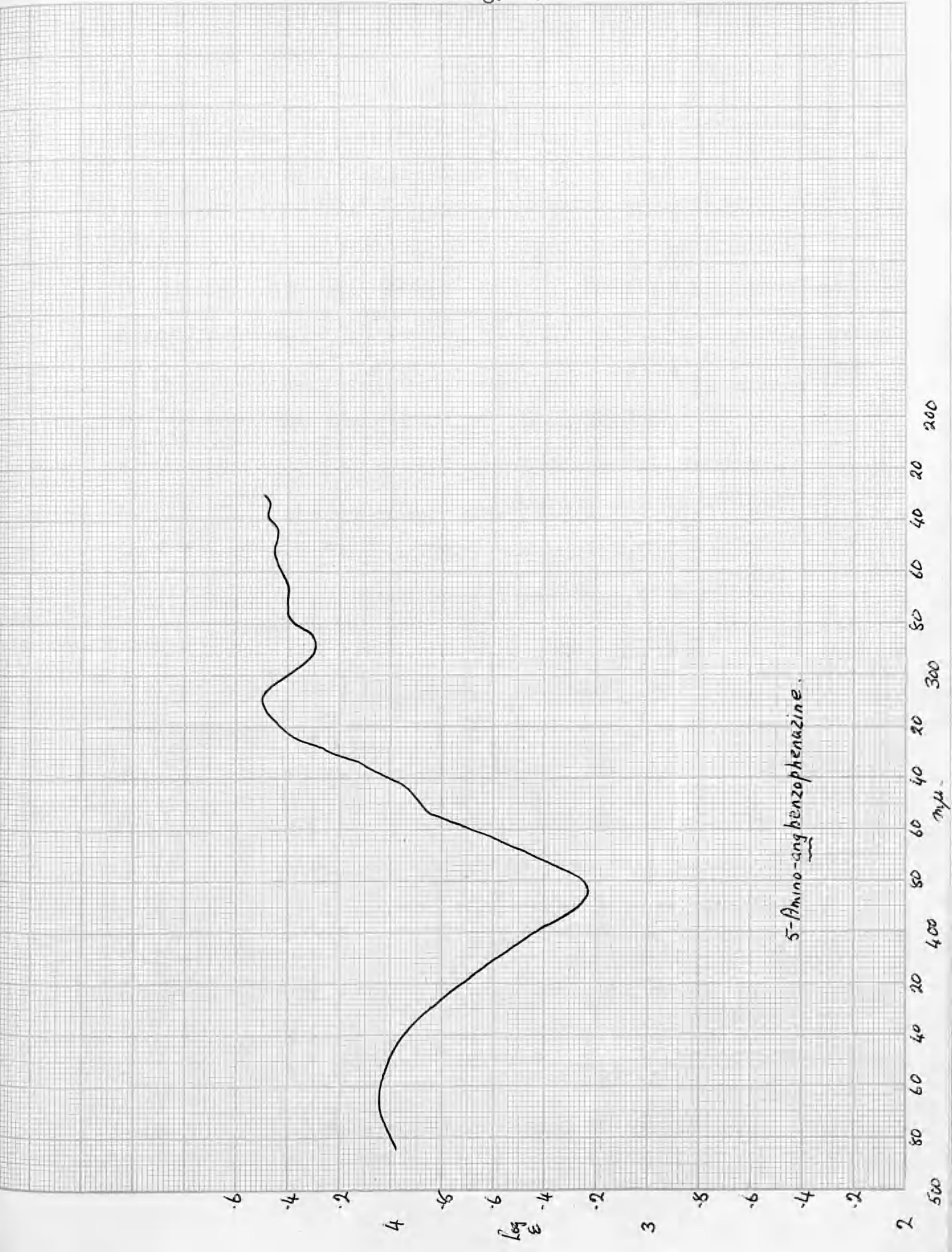
40
20
200.
mμ.

Fig. 2.



5-Amino-ang benzophenazine.

Experimental.

Amino-naphthophenazine. Prepared according to the method of Wohl and Lange (1). o-Nitroaniline (2.8g), 1-naphthylamine (2.8g) and zinc chloride (8.2g) were powdered, mixed thoroughly and heated to 150° in a boiling tube immersed in an oil-bath. At this temperature the reaction commenced, the temperature suddenly shot up to 260° and the mixture frothed up with the evolution of dense yellow fumes. When the reaction subsided the temperature was maintained at 180° for 30 minutes. After cooling the dark glassy product was powdered up, heated with a quantity of water (50 ml) and triturated with sodium hydroxide solution (30 ml). The solid obtained was filtered, washed with water and dried. The brown product was powdered and sublimed in vacuo. Unchanged o-nitroaniline sublimed at 160-180°. At 200-260° two coloured bands of sublimate were formed, a yellow-orange band of more volatile material with a m.p. 130-140° (not investigated further) and a reddish-orange band of the required product, m.p. 285-295°. The amino-naphthophenazine crystallised from xylene as a bright orange solid and finally from ethanol as fine golden yellow needles, m.p. 289-291° (uncorr.). (Found: C, 78.3; H, 4.7; N, 16.95. Calc. for $C_{16}H_{11}N_3$: C, 78.3; H, 4.5; N, 17.1%). Light absorption in ethanol: $\lambda_{\max.} = 4650, 3090, 2750, 2520, 2380\ \mathring{A}$; $\log \varepsilon = 4.05, 4.49, 4.37, 4.4, 4.43$.

Deamination of amino-naphthophenazine. (a) The amine (0.25g) and conc. hydrochloric acid (2 ml) in a small flask were cooled to -5° and treated drop by drop with an aqueous solution of sodium nitrite also cooled to -5°. Even at this low temperature a gas was evolved during the addition of the sodium nitrite. The solid hydrochloride did not go into solution in the normal way as the diazonium salt was formed. A solid material still remained when a definite excess of nitrite had been added.

On the supposition that at least some of the amine had undergone diazotisation and was still present as the diazo-compound, deamination was carried out by the addition of 30% hypophosphorous acid (1.8 ml) (9). The mixture was left overnight in the refrigerator and then for several hours at room temperature. The reaction mixture with solid material still present was diluted down with water and extracted several times with ether leaving an orange-yellow aqueous layer presumably containing unchanged amine. The reddish-brown ether extract was shaken with dilute sodium hydroxide solution which became an orange-red colour as phenolic material was extracted (70 mg). The ether was now extracted with dilute sulphuric acid and washed with water. The procedure applied by Kehrmann and Mermod (4) to the isolation of ang-benzophenazine from the condensation of β-naphthoquinone and o-phenylenediamine was tried out at this stage. This method involved extraction of the phenazine from the ether solution with conc. sulphuric acid. It proved unsatisfactory as a basis for isolation, the acid and the ether being completely miscible unless successive small quantities of water were added. These resulted each time in a separation into two layers with a division of the weakly basic material between them.

Instead, therefore, the ether layer, after drying, was evaporated to dryness leaving an orange-brown residue (ca. 20 mg). Unsuccessful attempts were made to crystallise this material from ethanol or acetic acid. The solid was then chromatographed on alumina using benzene as solvent. The pale yellow band passing first down the column contained the bulk of the material (ca. 10 mg). The solid obtained after removing the solvent was washed on porous plate with small quantities of petroleum ether and ethanol and had a m.p. of 140-143°, clearly agreeing with the literature record (4) of 142° for ang-benzophenazine and differing widely from the value (233°) quoted for the m.p. of lin-benzophenazine.

(b) In this experiment the diazotisation of the amine (o.1g) was carried out using nitrosylsulphuric acid, according to the method described by Cook and Moffat (5). This was prepared from sodium nitrite (60 mg), water (0.85 ml) and conc. sulphuric acid (d. 1.84; 1.7 ml), and added drop by drop to a solution of the amino-naphthophenazine in pyridine (5 ml). Deamination was again carried out with ice-cold hypophosphorous acid (3 ml), the mixture being kept at 0° for 24 hours before diluting with water and extracting with ether. From the ether extract, after treating as in (a) with alkali and acid, 10 mg of brown coloured material were obtained, from which a small quantity of a product identical with that obtained by method (a) was isolated by chromatography. The alkaline phenolic extract contained some 45-50 mg material.

<u>4-Benzeneazo-1-naphthylamine</u>. This compound was obtained in almost theoretical yield by the method of Fischer and Hepp (10) who followed the procedure used by Bamberger and Schieffelin (11) to obtain the 2-naphthylamine compound.

<u>5-Amino</u>-ang-<u>benzophenazine</u>. Prepared by the reaction of 4-benzeneazo-1-naphthylamine hydrochloride with <u>o</u>-phenylenediamine according to the procedure of Fischer and Hepp (7).

<u>o</u>-Phenylenediamine (0.073g), benzeneazo-1-naphthylamine hydrochloride (0.167g) and ethanol (3 ml) were heated

in a sealed tube at 160° for 6 hours. After allowing to cool, the tube was opened and the liquid poured off leaving a dark coloured solid. Treatment of the latter with ammonia gave a brown amorphous solid. Sublimation in vacuo gave, first, at 180-200° a red powdery sublimate, followed, at 200-230°, by the 5-amino-ang-benzophenazine as an orange coloured crystalline solid. Two recrystallisations from ethanol gave fine golden yellow needles, m.p. 289-291° (uncorr.) which did not depress on mixing with a sample of Wohl and Lange's amino-naphthophenazine. Light absorption in ethanol: $\lambda_{max.}$ = 4660, 3090, 2730, 2520, 2370 Å; log ε = 4.04, 4.5, 4.4, 4.45, 4.48, in good agreement with the figures obtained with Wohl and Lange's compound (vide supra).

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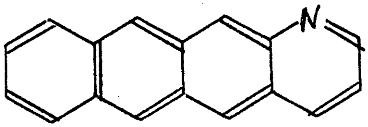
PART FOUR.

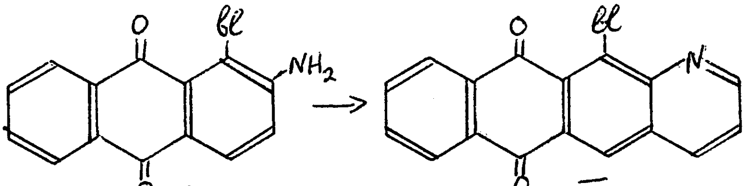
PART IV.

Introduction.

Compounds containing the 1-azanaphthacene ring skeleton (I) have been prepared by only two routes. One involves the Skraup reaction with 1- or 1:4-substituted 2-aminoanthraquinones such as 1-chloro-2-aminoanthraquinone (II) which gives the chloro-compound (III) (1). Dehalogenation of the latter provides the best route to the preparation of 1-azanaphthacene-6:11-dione. The only other method of preparation of compounds with this ring system is analogous to the formation of anthraquinone derivatives by the phthalic anhydride synthesis. Raudnitz (2) found that, using an aluminium chloride-sodium chloride melt, he could condense quinolinic anhydride with 1:4-dihydroxynaphthalene to give 6:11-dihydroxy-1-azanaphthacene-5:12-dione (IV).

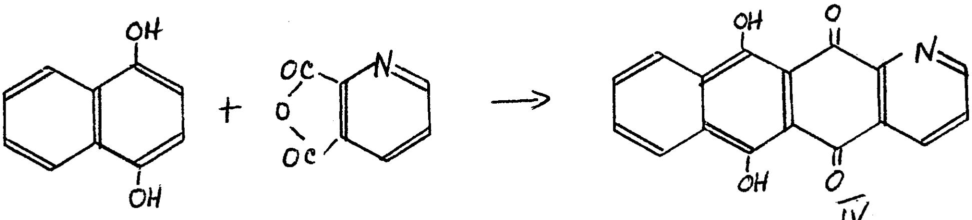


I



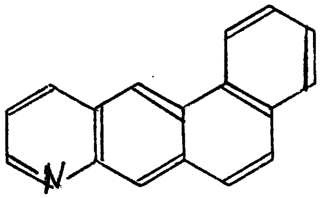
II

III



IV

Again the synthesis of the 8-azabenz[a]anthracene ring system (V) has been achieved in only a small number of cases. By applying the Skraup reaction to 2-amino-9:10-dihydrophenanthrene Mosettig and Krueger (3) obtained 5:6-dihydro-8-azabenzanthracene (VI) which could be dehydrogenated to give the fully aromatic parent compound. Johnson, Woroch and Mathews (4) are thought to have obtained a compound with this ring system by the cyclisation of (VII) with hydrogen fluoride which generally effects linear cyclisations.



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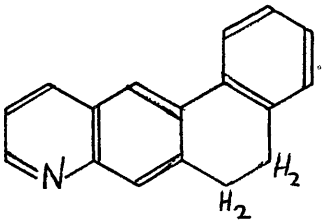
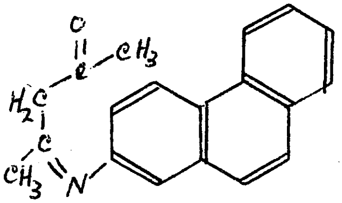
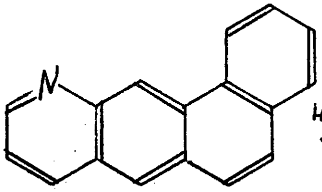


VI

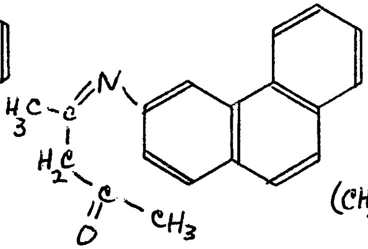


VII

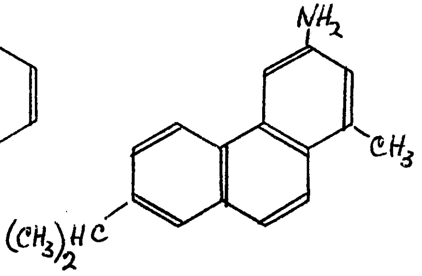
A similar cyclisation with hydrogen fluoride of the anil of 3-aminophenanthrene and acetylacetone (IX) (4) provides one of the few recorded cases of the synthesis of a compound containing the 11-azabenz[a]anthracene skeleton (VIII). There is a possibility that Cassaday and Bogert (5) may have prepared a compound with the basic structure of an 11-azabenzanthracene by the Skraup reaction on 3-aminoretene (X) although cyclisation in the 4- rather than the 2-position is favoured by the American workers.



VIII

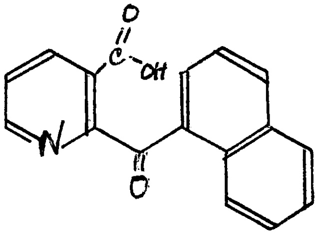


IX

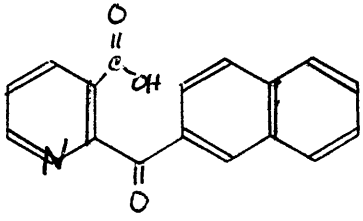


X

Now Jephcott (6) has reported the preparation of the α- and β-naphthoylpicolinic acids (XI) and (XII) by the Friedel-Crafts reaction of naphthalene with quinolinic anhydride. No ring closure, successful or otherwise, was recorded by the Canadian author but Webster (7) suggests the use of the β-naphthoylpicolinic acid as an intermediate in the synthesis of the 1-azanaphthacene ring system (I). An extension of this to the possible synthesis of compounds containing the ring systems of the two azabenzanthracenes, 8- and 11-, (V) and (VIII), from the β-naphthoyl- and α-naphthoylpicolinic acids respectively, is obvious. With these considerations in mind, the situation called for a further examination of the preparation of the two substituted picolinic acids and the possibility of obtaining cyclised compounds from them.



XI



XII

Discussion.

Jephcott (6) carried out the Friedel-Crafts reaction by refluxing quinolinic anhydride, naphthalene and aluminium chloride in benzene for 24 hours. The product, consisting of a mixture of α-naphthoylpicolinic acid (m.p. 155°) and β-naphthoylpicolinic acid (m.p. 145°) in total yield of 22%, was obtained by addition of cupric chloride solution to a hydrochloric acid extract of the crude tarry reaction product after steam distillation. This procedure, according to Jephcott, gave an immediate precipitate of the copper salts of these picolinic acids whereas the copper salt of any unchanged quinolinic acid came down only after standing for a time.

When attempts were made during the present investigation to repeat this precedure considerable uncertainty was caused by the unreliability of the copper salt precipitation. After a series of trials with quinolinic anhydride and the reaction product it was found that the rates of deposition of their respective copper salts varied over a wide range as the acidity of the solution was changed. For example, an immediate precipitate was obtained with both the anhydride and the product in dilute hydrochloric acid whereas, with increasing acidity, neither gave an immediate precipitate and, in fact, under certain conditions the anhydride could be made to precipitate more quickly than the product.

This procedure was therefore abandoned and instead the product was isolated by simply allowing it to crystallise out from the hydrochloric acid extracts of the tarry reaction product. However, even using this new method of isolation, Jephcott's reported yield could not be attained by following his reaction conditions. Consequently, in an effort to equal and indeed improve what was after all a poor yield the condensation of quinolinic anhydride and naphthalene in the presence of aluminium chloride was carried out under a wide variety of conditions of temperature and reaction time and with several solvents, including benzene, tetrachloroethane, _o_-dichlorobenzene, nitrobenzene, and naphthalene. In benzene, in addition to the isolation of a crystalline solid with a melting point (146-148°) in agreement with that quoted by Jephcott for his β-naphthoylpicolinic acid, a compound was obtained which proved to be α-naphthoylpicolinic acid (by analysis, by the Skraup test for pyridine-α-carboxylic acids (8) and by fusion with potassium hydroxide to give α-naphthoic acid) although its melting point (165-167°) differed from that reported by Jephcott for his α-naphthoylpicolinic acid, viz. 155°. Both products were obtained in very small yield.

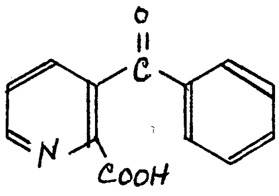
Tetrachloroethane as solvent gave no yield at all, while with o-dichlorobenzene there was some indication of a small amount of product accompanied by a large amount of unchanged quinolinic acid. Using nitrobenzene as solvent a small amount of α-naphthoylpicolinic acid could be isolated from the reaction mixture. Finally the most successful method was found to be that in which excess naphthalene was used as solvent and the mixture was heated at 90° for seven hours. Under these conditions a yield of some 27% mixed product was obtained on occasion. From all these preparations only the α-naphthoylpicolinic acid could be obtained pure and in sufficient quantity by recrystallisation for it to be used for further investigation.

The direct cyclisation of the α-naphthoylpicolinic acid was first investigated. Repeated attempts were made to carry out the condensation using a wide variety of cyclising agents including sulphuric acid, sulphuric acid with the addition of boric acid to discourage sulphonation, benzoyl chloride with a catalytic amount of sulphuric acid, fluoresulphonic acid and finally an aluminium chloride-sodium chloride melt. On no occasion was any conclusive evidence for the formation of a cyclised product obtained.

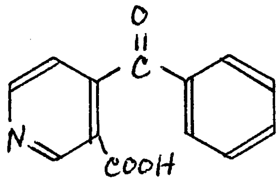
By reduction of the keto-group with zinc dust and ammonia the α-naphthoylpicolinic acid was converted to α-naphthylmethylpicolinic acid. Attempts were made to cyclise this latter compound using a variety of reagents including polyphosphoric acid, hydrofluoric acid, phosphorus pentoxide in benzene and aluminium chloride with the acid chloride. None of these gave a satisfactory product. In some cases a small amount of a brown powder was isolated which proved to be complex. Chromatography revealed a series of coloured bands none of which produced a workable amount of material. Various solvents used in turn on the brown powder would extract some colour but proved to contain only a tiny amount of amorphous non-crystallisable material.

From the results of the above experiments it can be concluded that the Friedel-Crafts reaction of naphthalene and quinolinic anhydride is not a suitable route to the formation of mono-azabenzanthracenes. In the first place because of the poor yield in the Friedel-Crafts reaction itself and secondly because of the resistance to cyclisation of both the Friedel-Crafts product and its reduction product, α-naphthylmethylpicolinic acid. It should be noted that in order that a full range of cyclisation procedures could be tried with the relatively small amount of material available (because of the yield in the Friedel-Crafts reaction) only small portions of the substituted picolinic acid could be used in each experiment and it is therefore possible that cyclisation may have taken place to a small (and synthetically worthless) extent.

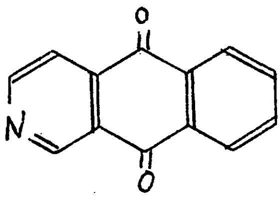
From the literature it can be seen that only a few cyclisations have been attempted in which the carboxyl group has been attached to the ring containing the nitrogen atom. It is noteworthy that in most of the cases where the carboxyl group has been attached in the α-position to the nitrogen atom and where there has been no other substituent, apart from the group taking part in the cyclisation, the cyclisation has either failed or at best taken place in much reduced yield. For example, Bernthsen and Mettegang (9) were unable to achieve the ring closure of 3-benzoylpicolinic acid (XIII), only a tiny amount of solid being obtained whose structure was not established. Philips (10) in experiments with the same compound was able to isolate only a tiny amount of the cyclised product, 1-azaanthraquinone, whereas cyclisation of 4-benzoylnicotinic acid (XIV) under the same conditions (conc. sulphuric acid at 270°) gave a far better yield of 2-aza-anthraquinone (XV).



XIII



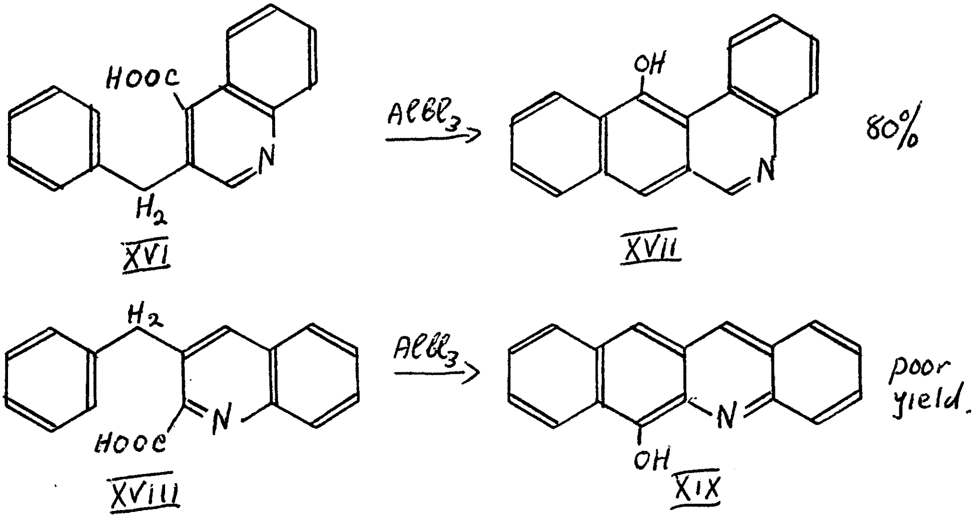
XIV



XV

Compounds in which the keto-group has been reduced still cause difficulty when they contain an α-carboxyl group.

Thus 3-benzylquinoline-4-carboxylic acid (XVI) is ring-closed readily to (XVII) in 80% yield by the action of aluminium chloride on its acid chloride (11) whereas the same reagent with the acid chloride of 3-benzylquinaldinic acid (XVIII) gives only a poor yield of the product (XIX) as a stable aluminium salt (12).



Philips (10) accounts for the comparative failure to cyclise 3-benzoylpicolinic acid by stating that the attraction between the nitrogen atom and the adjacent carboxyl group makes the condensation difficult to achieve and indeed it seems quite feasible that the positive charge induced on the nitrogen atom under the acid conditions which are common to all the cyclisation procedures will by an inductive effect tend to withdraw electrons from the carboxyl group and in so doing enhance in the -OH portion of that group the tendency for a split between the oxygen and hydrogen atoms (i.e. increasing the acidity of the compound) at the expense of the tendency to split between the carbon and oxygen atoms, which process, for lack of a complete reaction mechanism, may reasonably be assumed to take place during cyclisation. The effect may be considered as analogous to the enhancement of the acidity of acetic acid by the progressive substitution of chlorine atoms for the hydrogen atoms of the methyl group, the electronegative chlorine atoms attracting the electrons and increasing the tendency for proton dissociation to take place rather than hydroxyl dissociation.

Such an inductive effect would naturally become dissipated on progressing around the ring with the result that cyclisation of a compound containing a γ-carboxyl group would be more likely to meet with success.

Experimental.

Pyridine-2:3-dicarboxylic acid (quinolinic acid). This compound was prepared by the method of Sacharda (13) which involves the oxidation of 8-hydroxyquinoline by the addition of successive quantities of concentrated nitric acid over several days. It was found advantageous to modify Sacharda's working up procedure which involved filtering off the crude product from the nitric acid mother liquors, washing with 30% nitric acid, then with water and recrystallising the crude acid from aqueous acetic acid. Instead, the crude acid, after filtering, was dissolved up in hot water and crystallised by quick cooling to give a yellow solid. This serves to remove the very considerable quantity of nitric acid contained in the crude product and not readily removed merely by washing with water. The yellow acid was then redissolved in boiling water, charcoaled, filtered and allowed to cool when it crystallised out as a white solid. The yield of pure acid obtained was less than half the yield claimed by Sacharda (500-550g from 500g 8-hydroxyquinoline). However Sacharda's figure may have been based on the crude acid which is very considerably reduced in amount on purification. Also, a technical grade of 8-hydroxyquinoline was used in the present preparation and this gave a poor additional recovery of quinolinic acid from the nitric acid mother liquors on concentration, a syrup being obtained which did not readily deposit more solid material.

Pyridine-2:3-dicarboxylic acid anhydride. The anhydride was prepared by the procedure of Dox (14), namely refluxing the free acid for 5 minutes with acetic anhydride in the proportion of 1 part acid to 2 parts acetic anhydride and washing out the acetic acid and excess acetic anhydride with carbon tetrachloride when the anhydride crystallises out on cooling.

The necessity for purification of the quinolinic acid was amply demonstrated when the above reaction was attempted using the uncrystallised acid (but which had been washed with water). On warming with acetic anhydride the solution suddenly became very dark, the temperature rose sharply and there was a considerable evolution of nitrous fumes. Only a small quantity of the acid anhydride was isolated.

Condensation of pyridine-2:3-dicarboxylic acid anhydride with naphthalene. Jephcott (6) heated a mixture of the anhydride, naphthalene and aluminium chloride in benzene on the steam-bath for 24 hours. After removing the solvent and excess naphthalene by steam distillation the tarry product was extracted several times with hydrochloric acid. Isolation of the product was effected by the addition of cupric chloride solution which, according to Jephcott, gave the copper salts of the products of the Friedel-Crafts reaction as an immediate precipitate while the copper salt of the unreacted quinolinic acid came down only on standing for a time. The bright blue precipitate, on treatment with hydrogen sulphide, gave quinolinic acid while similar treatment of the immediately formed blue-grey precipitate gave a product which was separated, by using dilute acetic acid, into two components, a soluble portion, m.p. 145°, and an insoluble portion, m.p. 155°, in total yield of 22%. The compound, m.p. 145°, was proved to be β-naphthoylpicolinic acid and consequently the other compound, m.p. 155°, was assumed to be α-naphthoylpicolinic acid.

After a considerable number of experiments had been carried out on this reaction much doubt was cast on the efficacy of the cupric chloride method of separating the product from unchanged quinolinic acid. As a result a series of tests were carried out on solutions separately containing quinolinic acid and the Friedel-Crafts product. It was found that the rate at which the copper salts of both quinolinic acid and the reaction product precipitated out of solution varied considerably as the acidity of the solution was altered. With dilute hydrochloric acid <u>both</u> gave an immediate precipitate, bright blue in the case of the quinolinic acid and pale blue with the Friedel-Crafts product, while, as the strength of the acid was increased, no immediate precipitate was obtained with either and in fact, with a moderately strong acid (50:50), the bright blue precipitate of the quinolinic acid salt, although delayed, came down more quickly, a fact which conflicts directly with Jephcott's observations. Cupric chloride would thus seem to be a most unsuitable reagent for the present purpose and its use was discontinued.

The condensation was carried out a large number of times with many variations of reaction conditions, solvents, etc. Only by using excess naphthalene as solvent was it possible to exceed the yield of 22% reported by Jephcott and then only by a relatively small amount. A representative example of each type of condensation is included below.

(i) With aluminium chloride. (a) In benzene. Carrying out the reaction exactly as described by Jephcott (6) gave no immediate precipitate of a copper salt and only a very small precipitate after standing for some time. Using the following variation at least a small amount of product could be obtained.

Quinolinic anhydride (2.5g) and naphthalene (2.5g) in benzene (18 ml) were stirred vigorously and heated (oil-bath) until the benzene was on the point of refluxing. Aluminium chloride (9.5g) was added gradually with the immediate evolution of heat and hydrogen chloride. The mixture was then refluxed for 5 hours before cooling and pouring into dilute hydrochloric acid. The benzene was removed by steam distillation and the tarry residue extracted several times with dilute acid. The combined extracts were charcoaled and allowed to stand overnight when a crop of colourless needles (0.22g) were obtained, melting over a range between 130-159°. A series of crystallisations from aqueous ethanol (50:50) gave silky needles, m.p. 165-167°, of α-naphthoylpicolinic acid (see potassium hydroxide fusion, p 101). (Found: C, 73.3; H, 4.05; N, 5.1. Calc. for $C_{17}H_{11}O_3N$: C, 73.6; H, 4.00; N, 5.05%).

Concentration of the hydrochloric acid filtrate obtained above, gave a pale yellow solution which, on prolonged rubbing with a glass rod, deposited a considerable quantity of a fine white solid (2.04g) with an indefinite m.p. above 200°, indicating that the bulk of it was probably quinolinic acid. After a number of crystallisations from aqueous ethanol (75%) a white crystalline solid was obtained m.p. 146-148° (0.132g) in agreement with the figure quoted by Jephcott for β-naphthoylpicolinic acid (145°). A further quantity (0.12g) of this compound was obtained from the mother liquors of the above recrystallisations by precipitation with copper sulphate solution after the addition of dilute hydrochloric acid.

(b) In tetrachloroethane. Aluminium chloride (2.63g) was added gradually to a partially dissolved mixture of quinolinic anhydride (1.05g) and naphthalene (1.05g) in tetrachloroethane (30 ml). This gave a brownish residue instead of the deep red solution and viscous brown oil usually obtained with other solvents. After standing at room temperature for several hours with occasional shaking the reaction mixture was worked up in the usual manner. Copper chloride solution gave no immediate precipitate and the bright blue precipitate which came down on standing overnight proved to be the salt of unchanged quinolinic acid.

(c) In o-dichlorobenzene. Aluminium chloride (12.5g) was added to quinolinic anhydride (5g) and naphthalene (5g) in o-dichlorobenzene (40 ml) and the mixture was heated on the oil-bath at 70-75° until evolution of hydrochloric acid had ceased (4 hours). The dark brown mixture was worked up in the usual way and copper chloride solution was added to the hydrochloric acid extract. A considerable quantity of a fine blue precipitate formed almost immediately. The usual treatment of this material with hydrogen sulphide gave a creamy white solid which, after recrystallisation from aqueous acetic acid, softened at 140-150° but did not melt completely below 200°. Analysis showed the product to be quinolinic acid.

Considering the results of the tests on the precipitation of the copper salts (p. 95) it now seems possible that a small quantity of the product had been formed in this reaction but was completely swamped by the coprecipitation of the copper salt of quinolinic acid present in much larger amount.

(d) In nitrobenzene. The reaction was tried in this solvent both at room temperature and at 50-60°. At room temperature and after a reaction time of 28 hours only quinolinic acid could be recovered from the mixture. Under more vigorous conditions (50-60°) it was found that a prolonged reaction period led to an improvement in the yield.

A solution of quinolinic anhydride (5g) in nitrobenzene (40 ml) was cooled in ice and a solution of aluminium chloride (18.5g) in nitrobenzene was run in slowly with stirring. The solution was allowed to warm up and heated on an oil-bath at 50-60° for 1.5 hours. After cooling once more in ice,a solution of naphthalene (5g) was run in. After standing at room temperature for a time, the reaction mixture was heated at 50-60° for 48 hours. The first hydrochloric acid extract, after removal of the solvent, was charcoaled and filtered. No solid crystallised out even on standing for several days. Addition of copper chloride solution gave a considerable quantity of precipitate which yielded quinolinic acid. A second acid extract of the reaction tar yielded small warty masses of a yellow solid (0.75g). Recrystallisations from aqueous acetic acid and aqueous ethanol gave pale yellow silky needles, m.p. 162-164°, identical with the α-naphthoylpicolinic acid obtained from (a). A further two acid extractions gave smaller quantities of the same product.

(e) In naphthalene. The use of naphthalene in excess as the solvent led to the highest yield obtained in this series of experiments, namely, 27%. No increase in the yield occurred when the reaction time was increased to 22 hours. Repeating exactly the conditions found to give the best yield, a series of seven experiments met with varied success recording yields as low as 7% and as high as 25 and 27%.

Powdered aluminium chloride (28g) and quinolinic anhydride (10g) were thoroughly mixed and added to naphthalene (90g). The homogeneous powder was now heated to 90° when the reaction set in, the mixture melting with the evolution of hydrogen chloride. The temperature was maintained at 90° for 7 hours, after which the flask was cooled, water and hydrochloric acid were added and the naphthalene removed by steam-distillation. Several separate extractions of the tarry reaction product with hydrochloric acid gave deposits of colourless needles (m.p. 147-154°) on standing overnight. The total yield was 5.07g (27.2%, if assumed to consist of naphthoylpicolinic acids). Repeated recrystallisation from aqueous ethanol gave colourless needles, m.p. 164-166°, identical with α-naphthoylpicolinic acid obtained from (a).

No further precipitate was obtained from the acid mother liquors on concentration and copper chloride solution gave a negligible amount of copper salt.

(ii) With stannic chloride. Quinolinic anhydride (2.5g) and naphthalene (30g) were powdered together and placed in a flask. Stannic chloride (8.7g; 3.9 ml) was dropped in and the mixture heated on an oil-bath to 90-95°. The solid melted very gradually and little hydrogen was evolved. After heating for 3 hours the mixture was left overnight and worked up in the usual way. The reaction product was a black carbonaceous solid rather than the tar usually obtained with aluminium chloride. No product was isolated from the acid extracts of this material.

Potassium hydroxide fusion of Friedel-Crafts product, m.p. 165-167°. Following the method used by Cook (15) the Friedel-Crafts product, m.p. 165-167°, (0.7g) was added in small portions with stirring to fused potassium hydroxide (5g) at 260°. Heating at 260-280° was continued for 15 minutes while the material effervesced and a dark oil floated to the surface of the molten alkali. After cooling, the melt was dissolved in water and acidified to give a light brown precipitate which was filtered off, dried and recrystallised three times from benzene to give colourless needle clusters, m.p. 159-161°. There was no depression of the melting point on mixing with an authentic sample of 1-naphthoic acid, m.p. 158-160°.

The Skraup test (6) (8) which is used to distinguish picolinic acids from both nicotinic and isonicotinic acids by virtue of the red solution which only the former series of acids give with aqueous or alcoholic ferrous sulphate solution, was also carried out on the Friedel-Crafts product and gave a positive red colouration, confirming that the reaction product was α-naphthoylpicolinic acid.

Attempted cyclisation of α-naphthoylpicolinic acid.

(a) With sulphuric acid. The reaction was carried out at 270° following the procedure used by Philips (10) for the cyclisation of benzoylpicolinic acid. α-Naphthoylpicolinic acid (0.8g) was heated with conc. sulphuric acid (8 ml) at 270° for just over an hour. The initially red solution gradually became a dark reddish-brown. After cooling, the solution was poured into water, giving a reddish-brown solution which was saturated with ammonia gas and extracted with benzene. The pink benzene extracts were dried and the solvent removed, leaving less than 6 mg of a reddish amorphous solid. An attempt to sublime this material gave a tiny amount of a gummy yellow solid which may have been the required quinone but which was present in such small quantity as to preclude any further investigation.

(b) With sulphuric acid and boric acid. This method was used by Groggins and Newton (16) for the cyclisation of α-naphthoylbenzoic acid, the boric acid being added to prevent sulphonation. α-Naphthoylpicolinic acid (0.2g) was mixed with boric acid (0.2g). 95% sulphuric acid (0.7 ml) was added and the mixture heated to 80° to give a clear orange red solution. Heating was continued at 80-90° for 8 hours by which time the colour had deepened to nut-brown. On working up by pouring into ice a white solid was obtained which proved to be unchanged starting material (0.085g). Neutralisation of the filtrate from the above white solid with ammonium hydroxide gave no precipitate and the addition of copper sulphate solution to another sample of the filtrate gave only a minute amount of a blue precipitate. The considerable loss of starting material despite the absence of quinone formation seems to indicate that a good deal of sulphonation has taken place.

(c) With benzoyl chloride and sulphuric acid (17). The substituted picolinic acid (0.2g) was gradually heated up with benzoyl chloride (3 ml). When the temperature reached 100° a catalytic amount of conc. sulphuric acid was introduced and the temperature slowly raised to 130°. Bubbles of gas came off and the rate of evolution increased as the temperature was raised. After 1.25 hours the evolution of hydrochloric acid had practically ceased and the solution had become a brown colour. On pouring into 6N sodium hydroxide and boiling, the bulk of the material dissolved leaving a very small amount of a tarry material (20 mg) which failed to yield a pure compound.

(d) With fluorosulphonic acid (18). Cyclisation with this reagent was attempted at room temperature and at 80° using in both cases, α-naphthoylpicolinic acid (0.5g) and fluorosulphonic acid (2 ml). The experiment carried out at room temperature was left overnight before pouring into cold water. This gave an off-white precipitate which largely redissolved however, indicating that considerable fluorosulphonation had taken place. On addition of dilute sodium hydroxide a small amount of solid appeared but dissolved on warming. No quinonoid material could be isolated.

The second experiment was maintained at 80° for 5 hours before cooling and working up as above. Once again the bulk of the material dissolved in sodium hydroxide solution leaving only a negligible amount of an amorphous brown solid.

(e) With a sodium chloride-aluminium chloride melt. This procedure was used by Raudnitz (2) for the direct condensation of quinolinic anhydride with 1:4-dihydroxynaphthalene. The substituted picolinic acid (0.68g) was dropped into fused aluminium chloride-sodium chloride (4.2g:0.83g) at 180°, with stirring. Fumes were given off and a deep red solution was formed. The temperature was raised to 200° and maintained at this value for 15 minutes before cooling and decomposing with ice-water. The greenish-brown precipitate obtained was filtered off, giving a pale yellow filtrate which gave practically no precipitate on treatment with dilute alkali. Treatment of the solid obtained with sodium hydroxide solution gave a black tar which largely dissolved in water giving a reddish-brown solution from which unchanged acidic material could be recovered, and leaving behind undissolved a small amount of a dark brown residue (30 mg) which was filtered off.

This non-acidic residue proved to be a complex mixture. Only about half of it was dissolved by boiling benzene, leaving an almost black powder. Chromatography of the benzene solution on alumina gave a series of pale yellow and orange bands, each of which yielded up only a tiny amount of material completely inadequate for further investigation.

α-Naphthylmethylpicolinic acid. The reduction of the α-naphthoylpicolinic acid was carried out with zinc dust and ammonia following the procedure used Scholl and Seer (19) for the reduction of *o*-benzoylbenzoic acid.

α-Naphthoylpicolinic acid (4g), conc. ammonium hydroxide (160 ml), zinc dust (8g) and a little copper sulphate solution were refluxed for 3-4 days with the periodic addition of further quantities of ammonium hydroxide. It was noted that as the ammonia gas boiled off, and the strength of the ammonium hydroxide solution dropped correspondingly, a white solid precipitated out of solution only to redissolve on the addition of the next portion of ammonium hydroxide. Consequently at the end of the reflux period conc. ammonium hydroxide was added and the warm solution filtered. The strongly ammoniacal solution was heated on the steam bath until an off-white precipitate was obtained (3.1g). This was filtered off and ground in a mortar with a small amount of dilute sulphuric acid in which it initially dissolved only to give shortly afterwards a finely-divided white precipitate (2.9g), consisting of the product, contaminated with ammonium sulphate. Several crystallisations from ethanol gave α-naphthylmethylpicolinic acid (1.31g) as colourless plates, m.p. 170-171°. (Found: C, 77.7; H, 4.75; N, 5.5. $C_{17}H_{13}O_2N$ requires C, 77.5; H, 5.0; N, 5.3).

An attempt to isolate the product by simply acidifying the ammoniacal extract with dilute sulphuric acid gave an off-white precipitate. Several crystallisations of this material, even with charcoaling, gave only gummy products.

Attempted cyclisation of α-naphthylmethylpicolinic acid.

(a) With polyphosphoric acid. The substituted picolinic acid (0.11g) was powdered and added in portions to polyphosphoric acid (4 ml 85% phosphoric acid + 6g phosphorus pentoxide). The mixture was heated in an oil-bath at 100° for 2.5 hours. The solution, initially a pale yellow colour, gradually darkened to a reddish-brown. After cooling it was poured into water to give a white precipitate which was filtered off. The filtrate gave practically no precipitate on the addition of dilute alkali. The white precipitate dissolved completely in alkali and proved to be unchanged starting material.

(b) With hydrofluoric acid. The acid (0.385g) was treated with liquid hydrofluoric acid (10-15 ml) and left overnight. The glassy amber-coloured solid thus obtained was shaken with sodium carbonate solution and benzene to separate the acidic and non-acidic products. The benzene layer which should contain any cyclised material was washed with water, roughly dried with sodium sulphate and the solvent removed leaving a small amount of a white solid. Recrystallisation from ethanol gave colourless plates, m.p. 170°, which proved to be unchanged starting material.

(c) With aluminium chloride on the acid chloride (11). The acid chloride was prepared by the method used by Graf and Zettl (20) to obtain the acid chloride of 6-methylpicolinic acid.

Finely powdered α-naphthylmethylpicolinic acid (0.763g) was dissolved in purified thionyl chloride (5 ml). A white solid soon precipitated out. The mixture was heated at 65-75° for 2 hours then refluxed for 1 hour. The solid gradually dissolved, hydrochloric acid fumes were evolved and a pale yellow solution was obtained. The product was thrown out of solution by the addition of ether, filtered and dried in a vacuum dessicator.

The acid chloride was partially dissolved in nitrobenzene (7 ml) and powdered aluminium chloride (0.45g) was added in small portions with shaking, until a clear red solution was obtained. After warming on a water-bath (40-50°) for three hours the solution was poured into 2N hydrochloric acid and steam distilled to remove the nitrobenzene. The solution was extracted with benzene and the benzene extract washed with sodium carbonate solution. A small amount of unchanged acid was recovered from the sodium carbonate solution. When the benzene was removed in vacuo and the residue recrystallised from ethanol it melted at 169.5-171° and proved to be unchanged α-naphthylmethylpicolinic acid.

(d) With phosphorus pentoxide in benzene. This follows a procedure used by Badger, Carruthers and Cook (21).

Phosphorus pentoxide (5g) was added to α-naphthylmethylpicolinic acid (1g) partially dissolved in dry benzene (15ml). The mixture was refluxed on an oil-bath for a total of 36 hrs over a period of three days. The reaction mixture gradually assumed an orange colour. With a shorter reflux period unchanged starting acid could be detected as colourless crystals on cooling. The benzene was removed in vacuo and water added to the residue, giving a greenish-black solid which was filtered off. Treatment with strong sodium hydroxide solution gave a considerable amount of a brown powder. The orange coloured filtrate from this gave, on cautious acidification, an orange-brown crystalline solid. Recrystallisation from ethanol gave prismatic crystals which still retained their orange colour even after several crystallisations. The crystals melted at 110-115°, resolidifying, then melting finally at 170°. A sample which had been melted and resolidified gave no depression of the melting point on mixing with a sample of the starting acid, and would thus appear to be unchanged acid in a different crystalline form, probably resulting from the presence of the small amount of impurity causing the orange colour.

The brown powder obtained by the addition of the sodium hydroxide solution proved to be largely soluble in water. When the reddish-brown solution so obtained was treated with a few drops of dilute hydrochloric acid a flocculent brown precipitate was immediately formed. The pale yellow filtrate from this deposited pale yellow crystals which proved once more to be unchanged starting material. The precipitated brown powder refused to sublime at temperatures up to 300° and a pressure of 0.15 mm. It dissolved only partially in boiling xylene giving a reddish-brown solution which deposited a similar amorphous brown powder on cooling. No single pure compound could be isolated from it.

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