Basic derivatives of fluorene and anthracene

and

Isomerisation reactions with hydrogen fluoride.

THESIS

submitted by

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Contents.

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Summary, Part I.

Attempts to prepare the basic esters β-diethylaminoethyl 1,2,3,4,10,11-hexahydrofluorene-9-carboxylate and β-diethylaminoethyl 1,2,3,4,9,10,11,12-octahydroanthracene-9-carboxylate for testing as antispasmodic drugs have been made. These compounds have certain structural features which, in similar compounds, have been found to enhance the antispasmodic properties of these compounds.

The reduction of fluorene-9-carboxylic acid has been studied with limited success. Hexahydrofluorene-9-carboxylic acid, an intermediate required in the synthesis of the former ester, has been obtained but only in poor yield. A further acid of unknown structure and several neutral by-products have also been isolated. Other synthetic methods failed due to the reluctance of hexahydrofluorenone to form a cyanhydrin and the ease with which 9-halogene-hexahydrofluorenes decomposed.

trans-as-hexahydroanthrone did not form a cyanhydrin so that trans-as-octahydroanthracene-9-carboxylic acid, an intermediate in the synthesis of the latter ester, was not obtained.

The basic ethers, β-diethylaminoethyl fluorenyl-9-ether, β-diethylaminoethyl hexahydrofluorenyl-9-ether and β-diethylaminoethyl trans-as-octahydroanthranyl-9-ether,

also required for testing as antispasmodic drugs, were obtained by condensation of the sodio-derivatives of the alcohols 9-fluorenol, hexahydrofluoren-9-ol and 9-hydroxy-trans-as-octahydroanthracene, respectively, with β-diethylaminoethyl chloride.

Summary, Part II.

A study of a new type of isomerisation reaction (68 , 69) using hydrogen fluoride as catalyst has been extended to durene (1,2,4,5-tetramethylbenzene) and pentamethylbenzene derivatives. It has been confirmed that migration of methyl groups in this reaction occurs only when accompanied by cyclisation.

Durene, durylcarboxylic acid and durylacetic acid were unaffected by treatment with hydrogen fluoride at room temperature. Under similar conditions β-durylpropionic acid was partially converted to a mixture of 4,5,7-trimethylindan-1-one and 4,5,6,7-tetramethylindan-1-one. The latter ketone was also obtained from β-pentamethylphenylpropionic acid under identical conditions. Similarly γ-durylbutyric acid yielded 5,6,7,8-tetramethyl-1,2,3,4-tetrahydroanphthalen-1-one. γ-pentamethylphenylbutyric acid was recovered unchanged on similar treatment.

Similarities between this type of reaction and previously described isomerisation reactions have been noted though migration in this new type of isomerisation reaction appears to be much more limited in extent. A possible mechanism for the new type of reaction, based on these similarities, has been evolved.

A partial isomerisation in the durene nucleus under the influence of aluminium chloride under mild conditions has been noted and correlated to a similar isomerisation in the s-octahydroanthracene nucleus and to the Jacobsen reaction.

Part I. Basic derivatives of fluorene and anthracene.

In recent years considerable numbers of chemical compounds have been synthesised in a search for new drugs of the antispasmodic type. The structure of most of these synthetic materials is derived from that of either atropine (I) or papaverine (II), though, as developments are made in changing the structure of the parent molecule, a stage is finally reached where there appears to be no obvious connection between the structure of the parent compound and that of the latest synthetic product developed therefrom.

Neither atropine (I) nor papaverine (II), though occurring naturally and hence relatively cheap, is a perfect antispasmodic. Atropine, for instance, produces several invidious physiological side-reactions, mydriatic action, dry mouth, etc., which detract from its serviceableness as an antispasmodic. Papaverine also produces undesirable side-effects. The main disadvantage in the use of these two compounds as antispasmodics arises, however, from the fact that each is effective against only one type of spasm and is remarkably inactive against any other type of spasm.

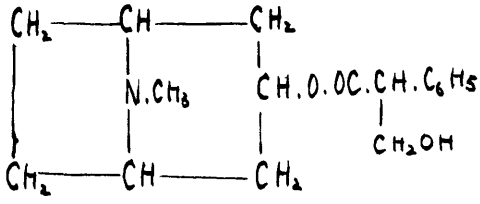
Two types of smooth muscle spasm are recognised medically. Musculotropic spasm is produced by direct stimulation of smooth muscle tissue; neurotropic spasm is produced indirectly through the nerve endings connected with the smooth muscle. Most of the antispasmodic drugs

synthesised so far have been effective against one or both of these types of spasm only when the spasm occurred in the gastrointestinal tract. (For review see Blicke[1]). Smooth muscle spasms in other organs are relieved only to a negligible extent by the synthetic antispasmodics known at the moment. Therefore, in preliminary tests on compounds likely to show antispasmodic activity one uses living, isolated, animal intestinal tissue. The spastic state is artificially induced in the isolated tissue by addition of barium chloride, histamine, acetylcholine, etc. Barium chloride and histamine produce musculotropic spasm, whereas acetylcholine and several of its derivatives produce neurotropic spasm.

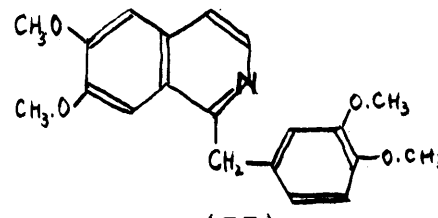
Atropine is found to relax tissue in which neurotropic spasm has been induced by the addition of acetylcholine. Larger doses of atropine are required, however, before a comparable effect is noted in tissue in which musculotropic spasm is present. Atropine is therefore a neurotropic antispasmodic, or, as it is occasionally alternatively named, an anti-acetylcholine compound. Papaverine, on the other hand, relieves musculotropic spasm induced by either histamine or barium chloride and is relatively ineffective against acetylcholine-induced neurotropic spasms. Papaverine is therefore a musculotropic antispasmodic or alternatively an anti-histamine and anti-barium chloride compound.

The above discussion illustrates some of the clinical difficulties involved in the use of both atropine and papaverine. A compound is required, therefore, which will be effective, in reasonable dose, in alleviating symptoms of both types of spasm without showing the undesirable side effects of atropine and papaverine and having no new undesirable side effects of its own. The perfect antispasmodic should be equally effective against smooth muscle spasms in all organs. Some of the compounds described below have one or more improvements on the parent compound. The greatest advance has been made in the field of compounds capable of alleviating both types, neurotropic and musculotropic, of spasm simultaneously. Most new synthetic products have original or novel side-effects and, in general, alleviate spasms present in one organ whilst remaining relatively inactive against spasms in other organs.

A consideration of the structure of atropine (I)

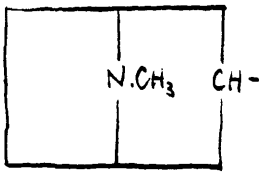


(I)



(II)

shows that it is an ester derived from the alcoholic tropyl (III) residue and the acidic tropic (IV) residue. The tropyl residue is a strongly basic, bicyclic, alcoholic residue, which suggested the first modification in the



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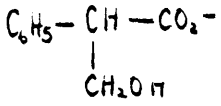

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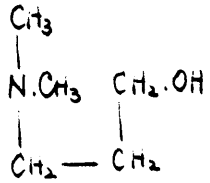


(V)

structure of atropine to be tried. A series of tropic acid esters of readily synthesised alcohols with tertiary nitrogen groups, e.g., β-diethylaminoethanol, γ-dimethylaminopropanol (V), showed undoubtedly that the complicated tropyl residue could be replaced without deleterious effect by a simpler basic alcoholic residue (2). This type of ester is better known, however, for its mydriatic and local anaesthetic properties though some antispasmodic activity was noted (2).

Very little work has been done on compounds where the tropyl residue (III) was retained and tropic acid replaced by other acid groups, e.g., benzilic. Again, though the principal activities were mydriasis and local anaesthesia, some considerable antispasmodic properties were present (3).

The antispasmodic activity of both of these types of ester indicated that neither the tropyl (III) nor tropic (IV) residue was a necessary structural factor for the production of a chemical compound showing equal or superior antispasmodic reactions to those of atropine. A

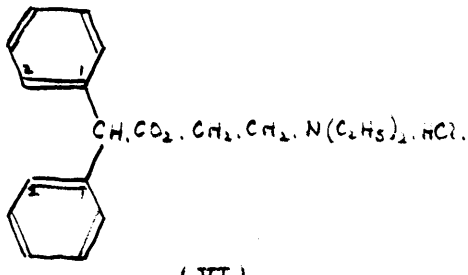
series of compounds has been described[1], in which neither the tropyl (III) nor tropic (IV) residue was present. The tropyl residue has been replaced by a much simpler residue whose only necessary features appear to be a bulky aliphatic or carbocyclic skeleton and a tertiary strongly basic nitrogen atom.

It was, in fact, in this series that the major part of the synthetic work on antispasmodics has been described and in which some considerable success has been achieved. Of this series a very large number may be described as basic ethyl, propyl, etc. esters of disubstituted acetic acids; tropic acid is itself a disubstituted, i.e., α-phenyl-α-hydroxymethyl-, acetic acid. Most of the acyl residues used have been dialkyl-, arylalkyl- or diaryl-acetic residues which are more readily obtained than hydroxy-methyl substituted derivatives.

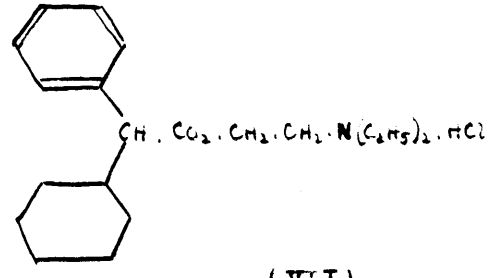
It was Halpern[4] who first demonstrated the especially potent antispasmodic effect shown by a basic ester of a substituted phenylacetic acid. The most efficient ester prepared by Halpern was β-diethylaminoethyl phenylpropylacetate which was extensively studied[5]. He, it was, who showed that the two separate entities in the molecule, β-diethylaminoethanol and phenylpropylacetic acid were, separately, completely useless in relieving

spasms, either neurotropic or musculotropic, when tested on animal intestine.

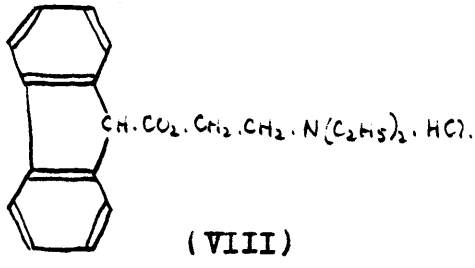
In 1936, there was described a relatively simple basic ester, β-diethylaminoethyl diphenylacetate, whose hydrochloride (VI), trasentin[6], was found to alleviate both musculotropic and neurotropic spasms to a very considerable degree[7,8]. A hexahydro-derivative of (VI),



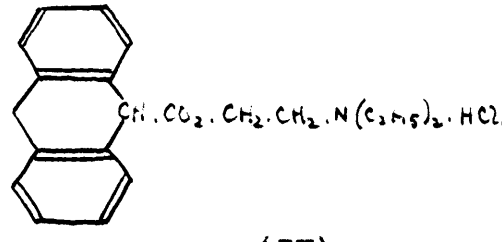
(VI)



(VII)



(VIII)



(IX)

i.e., β-diethylaminoethyl phenylcyclohexylacetate hydrochloride (VII), trasentin 6H[6], has received considerable study and has been compared with trasentin, atropine and papaverine. Graham and Lazarus[8] found that (VII) was more active than (VI) both on the isolated and intact intestine. (VII) showed activity on a level with that of atropine against neurotropic spasm and was more potent than papaverine in alleviating musculotropic spasm[12].

Though somewhat more toxic than (VI) and atropine, (VII) benefited from the fact that it was relatively free from side-effects, i.e., on the salivary and sweat glands and pupil. Both (VI) and (VII), though especially (VI) were comparable with cocaine as local anaesthetics[9]. Hoffmann[10] prepared a series of nuclear substituted alkyl and basic alkyl esters of phenylcyclohexylacetic acid, which did not, however, enhance the antispasmodic activity of (VII).

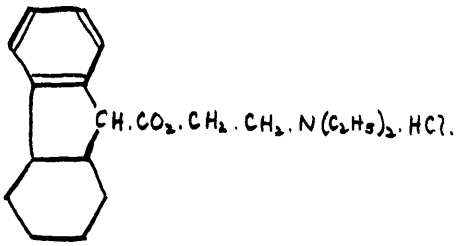
A study by Meier and Hoffmann[11] of various esters and the corresponding amides of substituted acetic acids demonstrated that the hydrochlorides of the bases were more active musculotropically but less active neutrotropically than the corresponding methochlorides. The methochlorides were, however, more toxic and therefore could not be administered in such large doses as the hydrochlorides. No remarkable improvement or disadvantage was found by substituting other similar basic radicals for the β-diethylaminoethyl group. The amides, provided no great improvement on the corresponding, more readily obtained esters. Similar conclusions were reached by Warner-Jaureg et al[12].

It had earlier been demonstrated[1] during earlier research on local anaesthetics that cyclisation of some polynuclear carboxylic acids to produce condensed aromatic, hydroaromatic or heterocyclic systems enhanced the local

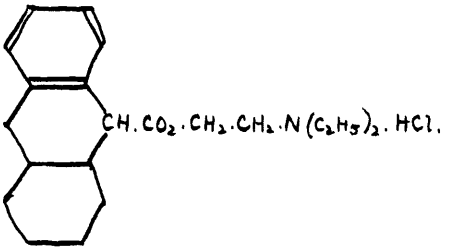
anaesthetic activity. Analogues of (VI), where the 2,2 positions in the benzene rings were joined through a single bond to form a fluorene nucleus, a methylene group to form a 9,10-dihydroanthracene, an oxygen, sulphur or imino group to form a xanthene, thioxanthene or 9,10-dihydroacridine nucleus respectively, were therefore prepared by Burtner and Cusic[13,14]. Of these, β-diethylaminoethyl fluorene-9-carboxylate hydrochloride (IX), pavatrine and β-diethylaminoethyl 9,10-dihydroanthracene-9-carboxylate hydrochloride (IX), which are pertinent to the discussion, were found to show the activity of (VI) considerably enhanced, with little increase in toxicity[15]. Lehmann and Knoefel[15] demonstrated that (VIII) was more active than (VI) against both neurotropic and musculotropic spasms though it was found to be more active neurotropically than musculotropically. (IX) was found to be a very efficient antihistamine compound, better than (VIII) in this respect[14]. Ester (IX) was, however, less active than (VIII) in abolishing spasms induced by acetylcholine or barium chloride[15].

In view of the pharmacological activities of (VI), (VII), (VIII) and (IX), a synthesis of β-diethylaminoethyl 1,2,3,4,10,11-hexahydrofluorene-9-carboxylate hydrochloride (X) and β-diethylaminoethyl 1,2,3,4,9,10,11,12-octahydroanthracene-9-carboxylate hydrochloride (XI) was desirable.

(X) embodies the carbocyclic nucleus of (VIII); (XI) has the



(X)

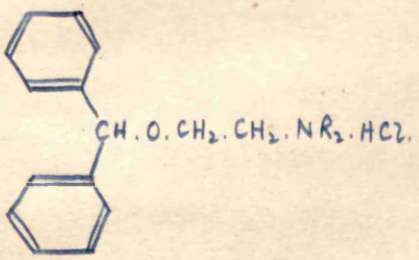


(XI)

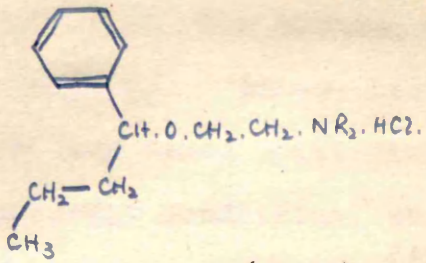
same carbocyclic nucleus as (IX) and both embody the benzene and cyclohexane nuclei of (VII), both of the features which appear to give enhanced antispasmodic properties of one type or other when compared with compounds lacking those features.

Attempts to synthesise (X) and (XI) are described later, pp. 17-29.

Apart from the amides, described above, most of the compounds prepared in the search for antispasmodic drugs based on the atropine pattern have retained two of the structural features of the parent compound, the ester group and the strongly basic tertiary nitrogen. It has recently been shown, however, that the ester group is not an essential feature in the structure of an antispasmodic. A series of basic ethers has been described[16,17] in which the ester grouping has been replaced by an ether linkage as in β-dialkylaminoethyl benzohydryl ether hydrochloride (XII) and β-dialkylaminoethyl phenylpropylmethyl



(XII)



(XIII)

ether hydrochloride (XIII).

(XII) and (XIII) it will be seen are related to trasentin (VI) and β-diethylaminoethyl phenylpropyl-acetate hydrochloride, prepared by Halpern[4,5].

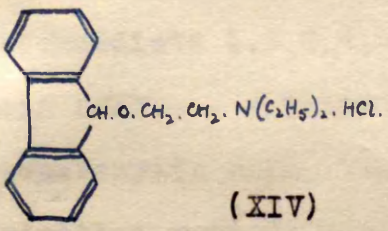
Of this series, benadryl (XII, R = CH_3) has been most extensively studied. Benadryl was found to be an extremely potent anti-histamine compound which was comparatively inactive in removing acetylcholine- or barium chloride-induced spasms[16,18]. The same properties have been noted to a more or less marked extent in the whole series of basic ethers which have been studied up to the present. Benadryl is remarkably free from undesirable side-reactions; it has little or no effect on salivary or sweat glands and its mydriatic effect, compared with that of atropine (I) is negligible[19]. (XII, R = CH_3) rivals adrenalin in alleviating spasms of asthma induced artificially by a histamine mist[21]; other antispasmodics studied had very doubtful effects against histamine-induced asthma spasm.

The most useful antispasmodic property of benadryl

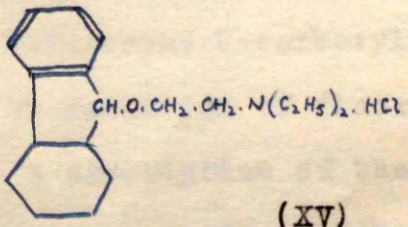
is its ability to remove the symptoms of skin rashes, where those rashes have been caused by allergy. Excess histamine, produced in the cells in the skin, may cause irritation, sores, dermatitis, etc., i.e., allergic conditions, which are speedily abolished by the administration of benadryl[22,23]. The production of symptoms of vertigo and drowsiness is the only drawback in the clinical use of benadryl[23].

As was found to be the case in the ester series[11,12], the substitution of the methochloride group for the hydrochloride group enhanced neurotropic activity, accompanied by a slight increase in toxicity and decreased musculotropic activity[24].

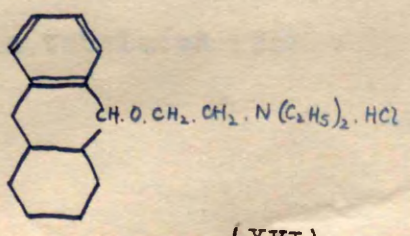
In view of the success enjoyed pharmacologically by benadryl it appeared to be of very considerable interest to produce compounds similar to benadryl with structural modifications similar to those present in the trasentin (VI) to pavatrine (VIII) series. β-diethylaminoethyl fluorenyl-9-ether hydrochloride (XIV) embodies the condensed aromatic



(XIV)



(XV)



(XVI)

system found in pavatrine (VIII) and bears the same relationship to

(VIII) as (XII, R = C_2H_5) does to trasentin (VI). β-diethylaminoethyl 1,2,3,4,10,11-hexahydrofluorenyl-9-ether hydrochloride (XV) and β-diethylaminoethyl 1,2,3,4,9,10,11,12-octahydroanthranyl-9-ether hydrochloride (XVI) embody the condensed cyclic nuclei of (VIII) and (IX) respectively as well as the cyclohexane and benzene nuclei of (VII) both of which factors were found to enhance antispasmodic activity in the ester series.

A synthesis of compounds (XIV), (XV) and (XVI) is described later, pp.29-31.

Since these compounds (XIV), (XV) and (XVI) were required for pharmacological tests in relation to a benadryl type derivative and as β-diethylaminoethanol was available from the ester series the diethylamino-derivatives (XIV), (XV) and (XVI) and not dimethylamino derivatives more strictly analogous to benadryl, were prepared and are to be compared in pharmacological tests with (XI, R = C_2H_5).

For the synthesis of (X) there was required as intermediate 1,2,3,4,10,11-hexahydrofluorene-9-carboxylic acid (XXV). A direct synthesis, by reduction of fluorene-9-carboxylic acid, was projected; a description of the reduction methods used and the various products isolated is tabulated (Table I) and described on p.17.

Table I.

	Reducing agents used	m.p. of reduced acid (sintering point in brackets)	Yield of crude acid	No. of method giving same acid	Neutral material(s) obtained
(i)	Sodium, amyl alcohol	159-160° (155°)	ca.15%	-	Yellow liquid (not purified)
(ii)	Sodium, ethanol	183-185° (179°)	ca.20%	-	Yellow liquid (not characterised)
(iii)	Sodium amalgam, sodium hydroxide	original acid recovered			9-fluorenol fluorenone
(iv)	Nickel-aluminium alloy, sodium hydroxide	182-183° (179°)	ca.65%	(v)	fluorene
(v)	Sodium, ethanol, liquid ammonia	181-183° (174°)	ca.10%	(iv)	fluorene
(vi)	Hydrogen, Adam's catalyst	original acid recovered unchanged			
(vii)	Hydrogen, palladous oxide	,,	,,		,,
(viii)	Hydrogen Raney nickel	,,	,,		,,
(ix)	As (viii) at 140-160° under 150-160 atmospheres	159° (142°)	ca.5%	-	probably mainly hexahydrofluorene

Sodium and amyl alcohol have been found useful in reducing certain aromatic acids, e.g., o-phenylbenzoic acid, o-benzylbenzoic acid, etc., to the corresponding hexahydrides, o-phenylhexahydrobenzoic acid[25] and o-benzylhexahydrobenzoic acid[26] respectively. Reduction of fluorene-9-carboxylic acid by this method yielded as well as a small quantity of acidic material, which was not obtained pure, an uncharacterised impure neutral yellow liquid.

Since the reaction conditions of method (i) may have been sufficiently vigorous to cause decarboxylation before reduction takes place, amyl alcohol was replaced by ethanol and the reduction repeated. There resulted from this reduction, as well as a somewhat larger quantity of acidic material, a neutral non-ketonic saturated liquid which was not further characterised. The acid obtained, though incompletely purified, was shown by mixed melting point to be different from that obtained by reduction method (i).

Reduction of fluorene-9-carboxylic acid with sodium amalgam in alkaline solution, another reduction using mild conditions, at room temperature or on the steam bath, resulted in most of the original acid being recovered unchanged. Neutral materials isolated proved to be fluorenone and 9-fluorenol. Isolation of these products from a reduction of fluorene-9-carboxylic acid is remarkable as an oxidation

process would appear to be involved. It appears unlikely that these neutral products are formed by a simple decarboxylation of the acid followed by air oxidation of the fluorene, so formed, since reducing conditions are present during the reaction. Wislicenus and Ruthing[27] demonstrated that alkaline solutions of fluorene-9-carboxylic acid on exposure to the atmosphere or on passing air through the solution deposited fluorenone and fluorene. In the above reduction, where an alkaline solution of the acid was stirred in a beaker for some considerable time, it may be assumed that fluorenone, deposited on the surface by air oxidation, as described by Wislicenus and Ruthing, when stirred into the solution, would be reduced by nascent hydrogen from the amalgam to -9-fluorenol. Reduction with sodium amalgam is a recognised method for reducing fluorenone to -9-fluorenol (28,29). No fluorene was detected in this reduction.

The method of reduction, found by Papa et al.[30] to be useful in reducing various groups, e.g., keto-groups to methylenes, chloro-compounds to hydrocarbons, etc.[31], has recently been found to be effective in reducing naphthalene derivatives, including naphthalene itself, to the corresponding ar-tetrahydronaphthalene derivatives[33]. Furthermore, reduction of anthracene-9-acrylic acid by this method produces a mixture of acids, some of which appear to be hydro-

genated in the aromatic nucleus[32]. When fluorene-9-carboxylic acid was reduced by this method which involves adding nickel-aluminium alloy to a hot alkaline solution of the acid, there was produced, as well as a small quantity of fluorene, an acidic material in the form of a gum. Since this gum was produced in reasonable yield (65%), several methods of separating the various possible constituents were studied.

Fractional crystallisation, from several solvents, yielded a small quantity of a pure acid which proved to be hexahydrofluorene-9-carboxylic acid. Fractional crystallisation of the potassium, sodium, ammonium, calcium and benzyl-iso-thiouronium salts met with limited success and produced the same acid, no purer and in no greater quantity than was obtained by crystallisation of the acid itself. The p-nitrobenzyl ester was too low melting to purify by fractional crystallisation. After many fractional distillations of the ethyl ester and fractional crystallisations of the regenerated acid, hexahydrofluorene-9-carboxylic acid was obtained in a state of purity though in insufficient quantity to attempt the formation of the basic ester (X). A solid acidic material, m.p. 74°, of unknown structure was also isolated. Though its melting point was not raised by crystallisation from several different solvents the possibility remains that

this substance was a mixture. Mixed melting point determinations indicated that the acids obtained by reduction methods (i) and (ii) were not hexahydrofluorene-9-carboxylic acid.

Fluorene-9-carboxylic acid on reduction with sodium and ethanol in liquid ammonia followed by treatment of the product with sodium and liquid ammonia yielded mainly a neutral material from which fluorene was the only pure product isolated. The small quantity of acidic material was mainly hexahydrofluorene-9-carboxylic acid identical with the acid obtained from method (iv). This reduction method has been used by Birch[34] to obtain from substituted aromatic compounds their tetrahydrides. Anisole and dimethylaniline, when reduced by this method, both yield cyclohexanone[34]. Reduction appears to be accompanied by hydrolysis as the dimethylamino- and methoxy-groups are replaced by a hydroxy-group; cyclohexanone is considered as tetrahydrophenol. Watt Knowles and Morgan[35] have described the reduction of 2-nitrofluorene to a mixture of 2-aminofluorene and 2-aminotetrahydrofluorene using a similar technique. In reducing fluorene-9-carboxylic acid, the quantity of sodium used was that which was required to give a hexahydride, a small quantity of which was in fact obtained. Watt et al.[35] did not treat their reduction product with

more sodium and liquid ammonia as Birch[34] did in order to complete the reduction. This probably accounts for the formation of a tetrahydride from 2-nitrofluorene and a hexahydride from fluorene-9-carboxylic acid.

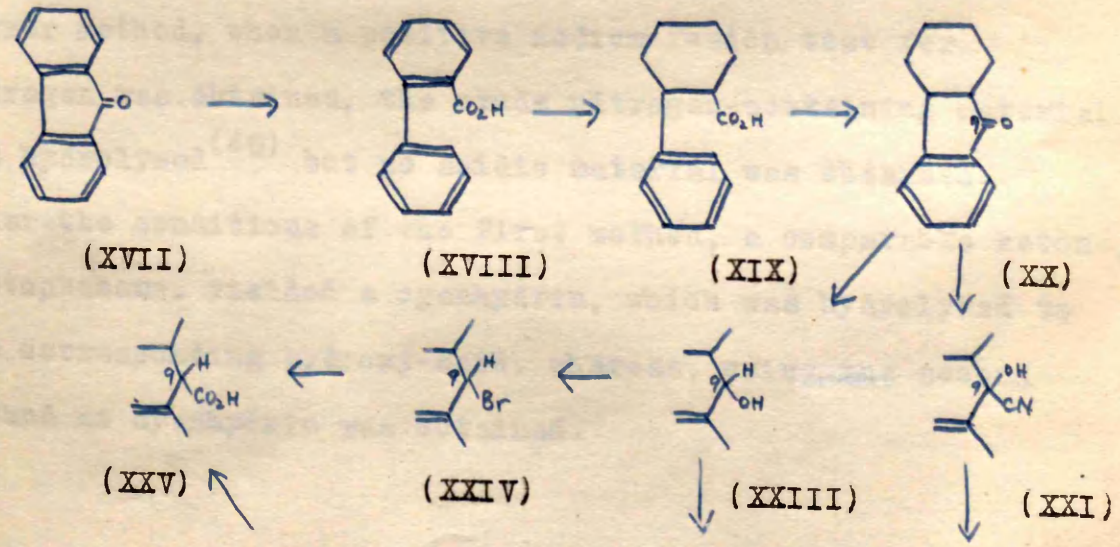
Catalytic reduction at ordinary temperatures and pressures using specially purified fluorene-9-carboxylic acid was without success though several different catalysts were tried. (See table, methods (vi), (vii), (viii)).

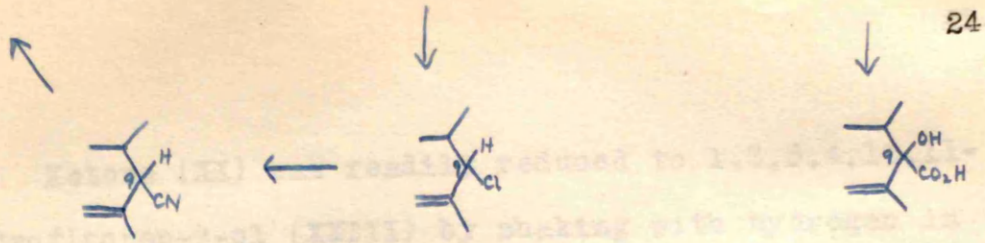
When Raney nickel, prepared by Adkins and Pavlic's method[36], was used as catalyst at elevated temperatures and pressures to reduce fluorene-9-carboxylic acid there was obtained only a small quantity of acidic material which, when partially purified by fractional crystallisation, was in insufficient quantity to compare, by mixed melting point, with the acids obtained by other reduction methods. The main bulk of the product was a neutral, saturated non-ketonic yellow liquid, whose boiling point, 125-126°/14 mm., indicated that it was 1,2,3,4,10,11-hexahydrofluorene. (Cook and Hewett[37] state that hexahydrofluorene has b.p. 127°/15 mm.). Dehydrogenation over sulphur yielded fluorene, showing the retention of the fluorene nucleus. Analysis indicated that the liquid contained an oxygenated derivative which was not removed either by several fractional distillations or by passing through a column of alumina. It is

suggested that the liquid is mainly hexahydrofluorene contaminated by an oxygenated fluorene derivative.

It seems certain that the poor yields of acidic material produced in the above series of reductions is due to the apparent ease of decarboxylation of fluorene-9-carboxylic acid in alkaline solution, coupled in some cases with a tendency of alkaline solutions of the acid to be oxidised by atmospheric oxygen to fluorene and fluorenone[27]. The fluorene and fluorenone, so formed, would be converted, according to the reducing conditions present in the reaction to 9-fluorenol or di-, tetra-, hexa-, etc. hydrides of fluorene or the corresponding 9-hydroxy derivatives.

Since none of the above reduction methods gave an easily purified yield of hexahydrofluorene-9-carboxylic acid (XXV) an alternative route, a synthesis from hexahydrofluorenone (XX) as outlined below, was now investigated





(XXVII) (XXVI) (XXII)

Fluorenone (XVII) was converted to o-phenylbenzoic acid (XVIII) by stirring with fused potassium hydroxide in p-cymene as diluent. (Huntress and Siekel[38] describe the use of diphenyl ether as diluent.) o-phenylhexahydrobenzoic acid (XIX), obtained from (XVIII) by sodium and amyl alcohol reduction[25,39], was readily converted to hexahydrofluorenone (XX) via the acid chloride in presence of aluminium chloride, as described by Cook and Hewett[37].

Attempts to prepare the cyanhydrin (XXI) of the ketone (XX) by the methods described by Mackenzie and Wood[40] for acetophenone and by Weissberger and Glass[41] for iso-durylaldehyde were unsuccessful. In one run, using the former method, when a positive sodium fusion test for nitrogen was obtained, the crude nitrogen-containing material was hydrolysed[40] but no acidic material was obtained. Under the conditions of the first method, a comparable ketone, acetophenone, yielded a cyanhydrin, which was hydrolysed to the corresponding hydroxy-acid, whereas, using the second method no cyanhydrin was obtained.

Ketone (XX) was readily reduced to 1,2,3,4,10,11-hexahydrofluoren-9-ol (XXIII) by shaking with hydrogen in presence of Raney nickel[36] as catalyst at ordinary temperatures and pressures. Though stereoisomerism is possible there was no evidence of the production of more than one stereoisomer. 9-Fluorenol was produced in like manner from fluorenone[42].

The bromo- and chloro-compounds (XXIV) and (XXVI) respectively, prepared by treatment of (XXIII) with the corresponding dry hydrogen halide (cf. Bachmann[43]), could not be isolated in a pure state, as, on standing, the corresponding hydrogen halide was evolved. The decomposition product, obtained by allowing the halogeno-derivative to stand for some time, or by boiling with pyridine, was an unsaturated yellow liquid† which gave fluorene on dehydrogenation. Attempted formation of a dibromide of the yellow liquid yielded a brown oily material which could not be induced to crystallise by the usual methods. Distillation of the brown oil gave a pale yellow liquid which contained no bromine. The unsaturated yellow oil†, assumed to be a tetrahydrofluorene contaminated by an oxygenated fluorene derivative (analysis demonstrated the presence of oxygen), was not obtained pure after several fractional distillations.

The crude bromo-compound (XXIV) reacted with magnesium to form the Grignard complex, from which, however, no acidic material was obtained after treatment of the complex with carbon dioxide. The product, part of which appeared to be identical with the unsaturated liquid† described above, was mainly a crystalline material, which was not homogeneous. Several fractional crystallisations of this material yielded no pure homogeneous material. Molecular weight determination of a partially purified specimen indicated that it was a bifluorenyl derivative.

The crude chloro-compound*, after treatment with potassium cyanide, yielded a liquid which, before distillation, appeared to contain some nitrogenated compound. Distillation yielded an unsaturated, nitrogen-free liquid†, probably identical with that obtained above. No pure nitrogenated material was obtained.

Attempts to hydrolyse the crude nitrogen-containing liquid yielded an unsaturated liquid† probably identical with

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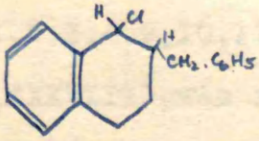
†Since no solid derivative of the unsaturated liquid was obtained, it was identified at each stage of the synthesis by its ability to decolourise bromine water in the cold and by its dehydrogenation product, fluorene.

*There is no real evidence that the material described as 'the crude chloro-compound' was not mainly the decomposition product, probably tetrahydrofluorene.

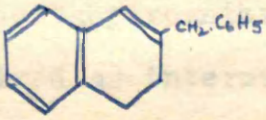
that described above. No acidic material was obtained by alkaline hydrolysis. Acid hydrolysis gave a non-crystalline acidic material which was insoluble in organic solvents, water and acids, and did not melt below 340°.

At this stage attempted synthesis of (XXV) was discontinued.

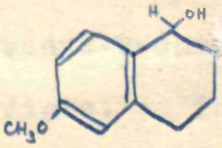
The instability of these halogeno-derivatives is remarkable though it is not confined to the fluorene nucleus. Carruthers[44] encountered the same difficulty in a similar series of reactions in which 1-chloro-2-benzyl-1,2,3,4-tetrahydronaphthalene (XXVIII) was required as intermediate. Though Carruthers was able to isolate the chloro-compound



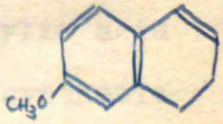
(XXVIII)



(XXIX)



(XXX)



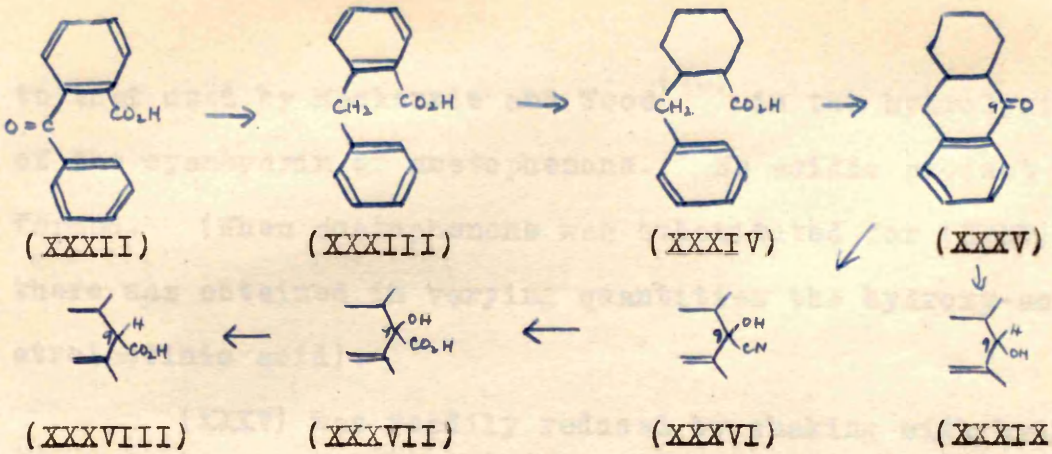
(XXXI)

(XXVIII) in a state of purity, on one occasion the most usual product was the unsaturated compound, 2-benzyl-3,4-dihydronaphthalene (XXIX).

The similarity of the compounds (XXVI) and (XXVIII), where a chlorine atom attached to a secondary carbon atom is directly adjacent to a hydrogen atom attached to a tertiary carbon atom, indicates that the reason for the instability of these halogeno-compounds is steric. Long and Burger[45] report, however, that attempts to convert

1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (XXX) to the corresponding halide yielded only 6-methoxy-3,4-dihydronaphthalene (XXXI) as product. This is unlikely to be a steric effect similar to that suggested for (XXVI) and (XXVIII). On the other hand α-phenylethyl chloride and 1-chloro-1,2,3,4-tetrahydronaphthalene, substances comparable with the chloride which Long and Burger failed to isolate, are reasonably stable. Instability may possibly be an effect of the p-methoxy-group in Long and Burger's product. It would, however, on these data, be unwise to attempt to draw further conclusions.

In order to synthesise the basic ester (XI), 1,2,3,4,9,10,11,12-octahydroanthracene-9-carboxylic acid (XXXVIII) was required as intermediate. The synthetic route outlined (XXXII) to (XXXVIII) was projected as a method of obtaining (XXXVIII). No attempt was made to reach (XXXVIII) through a 9-halogeno-derivative prepared from 9-hydroxy-trans-as-octahydroanthracene (XXXIX) in view of the difficulties encountered in the analogous hexahydrofluorene series. It was preferred that (XXXIX) be used in the synthesis of the basic ether (XVI).



(XXXII) (XXXIII) (XXXIV) (XXXV)

(XXXVIII) (XXXVII) (XXXVI) (XXXIX)

o-Benzoylbenzoic acid (XXXII), prepared from phthalic anhydride and benzene in a Friedel and Crafts reaction[48], was converted to o-benzylhexahydrobenzoic acid (XXXIV) in a two stage reduction. Zinc and ammonia were used to convert (XXXII) to o-benzylbenzoic acid (XXXIII)[49], which yielded (XXXIV) on reduction with sodium and amyl alcohol[26]. (XXXIV) was converted to trans-as-hexahydroanthrone using sulphuric acid as described by Cook, Hewett and Lawrence[26].

An attempt to prepare the cyanhydrin (XXXVI) of ketone (XXXV) by the method which Plattner, Fürst and Studer[50] used to prepare the cyanhydrin of indanone, failed, the ketone (XXXV) being recovered largely unchanged. As it was possible that the cyanhydrin (XXXVI) was unstable under the conditions used in attempting to isolate it, the hydrolysing agent was added before attempted isolation of the cyanhydrin and the resultant treated in a manner similar

to that used by Mackenzie and Wood[40] in the hydrolysis of the cyanhydrin of acetophenone. No acidic product was formed. (When acetophenone was substituted for (XXXV) there was obtained in varying quantities the hydroxy-acid, atrolactinic acid).

(XXXV) was readily reduced by shaking with hydrogen in presence of Raney nickel[36] as catalyst at ordinary temperatures and pressures. The product (XXXIX) was identical with that obtained by Cook, McGinnis and Mitchell[51] using Adam's catalyst. No evidence of any other stereo-isomer being formed was noted.

The alcohols, 9-fluorenol, hexahydrofluoren-9-ol (XXIII) and 9-hydroxy-trans-as-octahydroanthracene (XXXIX) were converted to the basic ethers β-diethylaminoethyl fluorenyl-9-ether (XIV), β-diethylaminoethyl 1,2,3,4,10,11-hexahydrofluorenyl-9-ether (XV) and β-diethylaminoethyl trans-as-octahydroanthranyl-9-ether respectively by condensing the corresponding sodio-derivatives of the alcohols with β-diethylaminoethyl chloride in a Williamson ether synthesis as described by Martin et al.[16] cf.(17,52). The alternative method of synthesis, where sodium β-diethylamino-ethoxide is condensed with the chloro-hydrocarbon, was not used here due to the instability of 9-chloro-hexahydrofluorene. The basic ether (XII, R = C_2H_5) was also prepared, by

condensation of sodium benzohydroxide with β-diethylaminoethyl chloride as described by Martin et al.[16], as it was required for the purpose of comparison with ethers (XIV), (XV) and (XVI) in pharmacological tests.

The ether (XII, R = C_2H_5) readily formed a crystalline hydrochloride and acid oxalate (XVI) formed a crystalline picrate and acid oxalate but no salt suitable for testing on living tissue was obtained in a crystalline form. (XIV) and (XV) readily formed crystalline oxalates but no other salt of a wide series studied could be induced to crystallise.

The ethers (XIV), (XV) and (XVI) were prepared for pharmacological testing by purification of the acid oxalates and distillation of the regenerated free bases. These tests are at present being carried out.

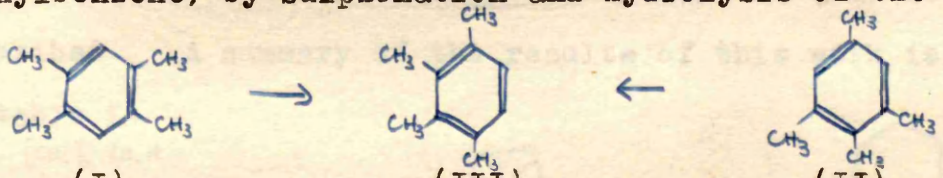
Part II. Isomerisation reactions.

Reactions involving intermolecular or intramolecular migrations or elimination of alkyl groups in polyalkylbenzenes have long been recognised and have redeived considerable study. These types of reaction may be brought about by heat alone, though it is more usual for a catalyst to be employed, since much milder conditions may then be used. Many different substances have been used to catalyse this type of reaction, e.g., aluminium halides, zinc chloride, ferric chloride, boron trifluoride, sulphuric acid, etc.[58]. Of these aluminium chloride (for review see Nightingale[59]) and sulphuric acid[60] have been extensively studied.

Aluminium chloride, it has been found, can, when heated with polyalkylbenzenes, cause these substances to rearrange with or without loss of alkyl groups. For instance, hexamethylbenzene and pentamethylbenzene, on treatment with aluminium chloride under varying conditions give durene (1,2,4,5-tetramethylbenzene) (I) and isodurene (1,2,3,5-tetramethylbenzene) (II) in varying proportions accompanied by lower methylated benzenes[61]. Though there is no generally accepted mechanism for these rearrangements with aluminium chloride it seems almost certain that the mechanism is connected with complexes, which are undoubtedly

formed, several of which have, in fact, been isolated[62,63].

In the Jacobsen reaction[60], where sulphuric acid is used as the isomerising agent, the role of the acid in bringing about isomerisation is known.[64] It has been shown that migration of alkyl groups takes place only after sulphonation of the hydrocarbon. Durene (I) and isodurene (II) may be converted to prehnitene (III) (1,2,3,4-tetramethylbenzene) by sulphonation and hydrolysis of the



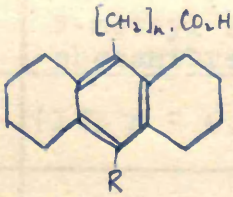
(I) (III) (II)

sulphonic acid so formed[65,66].

The Jacobsen reaction, which is limited in application to tetra- and penta-alkylbenzenes, usually gives rise to products in which the alkyl groups occupy vicinal positions. The Jacobsen reaction is, in fact, the only method available for the preparation of prehnitene (III).

More recently, hydrofluoric acid has been shown to bring about disproportionation involving alkyl groups in alkylbenzenes at elevated temperatures and pressures, a process finding increasing importance in industry. Under these conditions toluene has been converted to a mixture of benzene and xylenes[67].

A new type of isomerisation in the s-octahydroanthracene nucleus, where isomerisation is accompanied by cyclisation under the influence of hydrogen fluoride has recently been described[68,69]. The conversion of β-(9-s-octahydroanthranyl)propionic acid (IV, n = 2, R = H) to 1'-keto-9,10-cyclopenteno-s-octahydrophenanthrene (V) and of γ-(9-s-octahydroanthranyl)butyric acid (IV, n = 3, R = H) to keto-dodecahydrotriphenylene (VI) has been described. A summary of the results of this work is given in table I.



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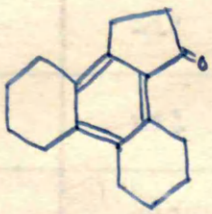

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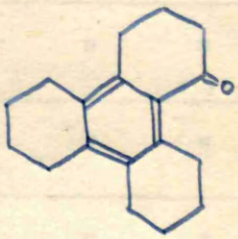
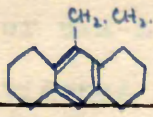


(VI)

The tabulated results indicate that under certain conditions the s-octahydroanthracene nucleus can be converted to the s-octahydrophenanthrene nucleus using hydrogen fluoride at room temperature. The conditions required for rearrangement of the original nucleus appear to be 1) the presence of a side chain in the 9-position, which, on cyclisation at the ortho-position, would give a stable, i.e. five- or six-membered ring and 2) the presence on that side chain of an appropriately located, i.e., β- or γ-carboxylic acid group.

Table I.

	Compound treated	% Isomerisation	Result
(i)	s-octahydroanthracene	nil	unchanged starting material
(ii)	9-methyl s-octahydroanthracene	nil	" " "
(iii)	9-ethyl s-octahydroanthracene	nil	" " "
(iv)	s-octahydrophenanthrene	nil	" " "
(v)	9-methyl-s-octahydrophenanthrene	nil	" " "
(vi)	(IV, n = 0, R = H)	nil	" " "
(vii)	(IV, n = 1, R = H)	nil	" " "
(viii)	(IV, n = 2, R = H)	100%	(V)
(ix)	(IV, n = 3, R = H)	100%	(VI)
(x)	(IV, n = 2, R = CH_3)	100%	mixture of ketonic products
(xi)	4-(9-s-octahydrophenanthryl)butene-1 	nil	original starting material

As regards condition 1), the presence of a normal propionic or butyric acid side chain in the 9-position of the s-octahydroanthracene nucleus, compounds (viii) to (x) (Table I), appears to be essential, these being side chains capable of giving on ring closure on the ortho-position a five- or six-membered ring. Other 9-substituted s-octahydroanthracene derivatives, compounds (i) to (iii), (vi) and (vii) (Table I) showed no tendency to give rearranged products even when a carboxylic acid group was present in the side chain. Furthermore, s-octahydrophenanthrene derivatives, compounds (iv) and (v) (Table I), were not rearranged. These results are in accordance with those of Calcott, Tinker and Weinmeyer[70] who found that in alkylations of benzene using hydrogen fluoride as catalyst at room temperature, there was no evidence for the migration of alkyl groups during alkylation (s-octahydroanthracene may be regarded as a 1,2,4,5-tetraalkylbenzene).

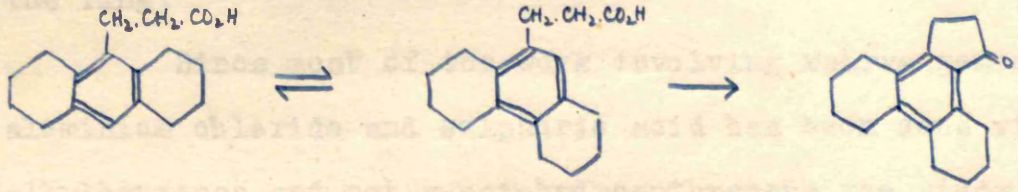
As regards condition 2), the presence of a suitably located carboxylic acid group as opposed to any other group normally capable of reacting at the ortho-position to yield a five- or six-membered ring, e.g., alkene, halogeno-, etc., little evidence is at present available, only the butene side chain, compound (xi) (Table I) having been studied. It is noteworthy, however, that in alkylations of benzene

with hydrogen fluoride unsaturated substances similar to butene-1 have been used to produce alkylbenzenes[70] as have cyclisations been brought about by the use of unsaturated side chains[74].

Isomerisation of the s-octahydroanthracene nucleus is not in itself a new reaction though rearrangement has not previously been described under such mild conditions. Schroeter[71] observed that when s-octahydroanthracene was heated to 80° in presence of aluminium chloride there was obtained a mixture from which both s-octahydroanthracene and s-octahydrophenanthrene were isolated in approximately equimolecular proportions. The same mixture was obtained when s-octahydrophenanthrene was similarly treated. Again, under the conditions of the Jacobsen reaction[72], there was isolated from s-octahydroanthracene, s-octahydrophenanthrene-9-sulphonic acid in almost theoretical yield. This reaction is not reversible, s-octahydrophenanthrene does not yield s-octahydroanthracene-9-sulphonic acid under similar conditions.

The new cyclisation-isomerisation reaction seems to differ from the previously described rearrangements in that it is more restricted; no rearrangement occurs unless both conditions 1) and 2) are satisfied, whereas in rearrangements with aluminium chloride or sulphuric acid isomerisation of

the s-octahydroanthracene nucleus occurs in all cases. If reaction proceeds via the formation of an equilibrium mixture of (VII) and (VIII) followed by cyclisation to form (V)



(VII) (VIII) (V)

then the driving force for the isomerisation is not merely reaction of the s-octahydroanthracene nucleus with the catalyst to form (VIII) but involves the propionic acid side chain as well. If the mechanism involved only the s-octahydroanthracene nucleus and the isomerising agent, hydrogen fluoride, as it must do in the aluminium chloride rearrangement, we would expect isomerisation to occur in all cases. No evidence of this (Table I, (i) to (vii)) was noted though the possibility of an equilibrium mixture being present, where the s-octahydroanthracene nucleus is much more in evidence than that of s-octahydrophenanthrene must not be overlooked. This state of affairs is however unlikely as compounds (viii) to (x) (Table I) are speedily converted to the corresponding ketones in exceptionally high yields. It seems more likely that the driving force of the isomerisation is the tendency

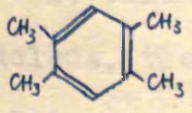
of the propionic or butyric acid side chain to cyclise at the ortho-position, under the influence of hydrogen fluoride, causing the group present to migrate to a vacant position on the ring.

Since most of the work involving rearrangements with aluminium chloride and sulphuric acid has been done with polyalkylbenzenes and not s-octahydroanthracene the study of the new cyclisation-isomerisation reaction has been extended to durene and pentamethylbenzene derivatives. The results of this study are tabulated (Table II) and described below.

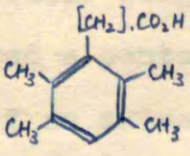
Table II

	Compound treated	% starting material recovered	Product	% pure product obtained
(i)	(I)	84	unchanged starting material	
(ii)	(IX, n = 0)	90	"	" "
(iii)	(IX, n = 1)	92	"	" "
(iv)	(IX, n = 2)	70	(XI)	ca. 4%
			(XII)	ca. 5%
(v)	(IX), n = 3)	36	(XIII)	ca. 44%
(vi)	(X, n = 2)	37	(XII)	ca. 26%
(vii)	(X, n = 3)	92	unchanged starting material.	

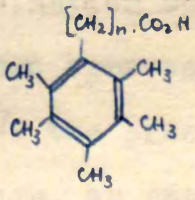
Durene (I), durylcarboxylic acid (IX, n = 0) and durylacetic acid (IX, n = 1) on treatment with hydrogen fluoride were recovered largely unchanged. β-durylpropionic acid (IX, n = 2) though recovered largely unchanged, yielded a mixture of two ketones, probably 4,5,7-trimethylindan-1-one (XI) and 5,6,7,8-tetramethylindan-1-one (XII). γ-durylbutyric acid (IX, n = 3) gave a considerably larger quantity of a ketone, probably 5,6,7,8-tetramethyl-1,2,3,4-tetrahydronaphthalen-1-one (XIII) as well as some unchanged starting material. β-pentamethylphenylpropionic acid (X, n = 2) yielded, as well as some unchanged starting material, a ketonic product from which (XII) was isolated. γ-pentamethylphenylbutyric acid (X, n = 3) yielded a trace of ketonic material insufficient for the material to be identified, the major part of the original acid being recovered unchanged.



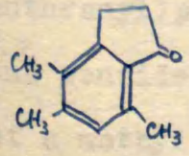
(I)



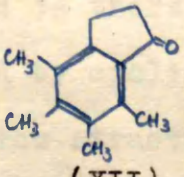
(IX)



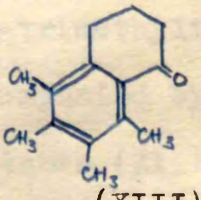
(X)



(XI

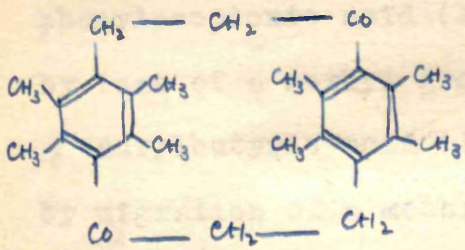


(XII)

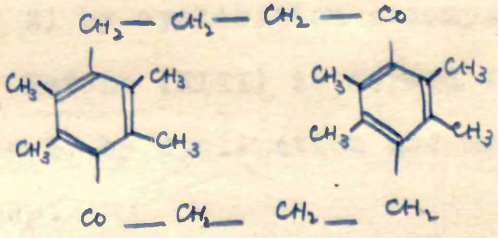


(XIII)

The ketones (XI), (XII) and (XIII), which had not been previously described, were characterised as oximes and the structures established by analysis, molecular weight determination and dilute nitric acid oxidation. Molecular weight determination indicated that the ketones were not bimolecular structures of the types (XIV) and (XV).



(XIV)



(XV)

Oxidation of ketone (XI) gave benzenepentacarboxylic acid demonstrating that five substituents were present on the benzene ring. Analysis indicated that ketone (XI) had formula $(C_{12}H_{14}O)_n$, molecular weight determination showed n = 1, oxidation indicated a pentasubstituted benzene nucleus, the formation of an oxime indicated the presence of a keto-group. The most reasonable structure, by analogy with similar experiments (above) with β-(9-s-octahydroanthranyl)propionic acid is therefore 4,5,7-trimethylindan-1-one considered as formed by cyclisation accompanied by loss of a methyl group*. The structures of ketones (XII) and

* It is assumed that the methyl groups in (XI) occupy positions 5,6 and 7 as shown, since there is no evidence to date of any group apart from the ortho-group to the propionic acid side chain being displaced in this type of cyclisation-isomerisation reaction.

(XIII), in accordance with their respective analyses, molecular weights and oxidation products, mellitic acid in both cases, were similarly inferred.

Ketone (XII) may be considered as being formed from β-durylpropionic acid (IX, n = 2) by simultaneous cyclisation and migration of a methyl group and from β-pentamethylphenylpropionic acid (X, n = 2) by cyclisation accompanied by loss of a methyl group. Ketone (XIII) is formed from γ-durylbutyric acid (IX, n = 3) by cyclisation accompanied by migration of a methyl group.

An independent synthesis of the ketones (XI), (XII) and (XIII) was not attempted as one stage of that synthesis would involve ring closure of a polymethylbenzene derivative using as catalyst a reagent previously known to bring about migration of methyl groups.

These results, it will be seen, confirm the hypothesis that isomerisation occurs only when accompanied by cyclisation on the ortho-position with formation of a stable five- or six-membered ring, cf. condition 1).

In the cyclisation of the acid (IX, n = 2) by this hypothesis, one would expect that, on ring closure, the displaced methyl group from one or other of the ortho-positions would either be lost yielding (XI) or would appear in the vacant para position to yield (XII). Of these two possi-

bilities the latter, i.e. migration, seems to be favoured to a slight extent. The corresponding pentamethylbenzene derivative (X, n = 2) can, of course, on ring closure yield only one product (XII) with loss of a methyl group.

In the case of the acid (IX, n = 3) only the ketone (XIII) formed by migration of the liberated methyl group was isolated. No evidence of a trimethyltetralone, analogous to (XI) was noted. The remarkable result obtained with the acid (X, n = 3), where no ketonic product was formed is difficult to explain, and, in fact, it would be unwise to attempt to do so until further information regarding the cyclisation of γ-pentasubstituted phenylbutyric acids has been acquired.

In the case of the s-octahydroanthracene derivatives only one product would be expected where isomerisation takes place since if the carbocyclic ring were broken through ring closure of the 9-substituent in the ortho-position, the alkene chain so formed would be held in the meta-position until cyclisation on the para-position, which is vacant, can take place. In the case of the corresponding durene compounds the chances of the liberated methyl group reacting at the para-position are somewhat less than in the case of the corresponding s-octahydroanthracene series so that there is the possibility of the formation of two separate products

which in fact are isolated in the case of β-durylpropionic acid (IX, n = 2).

These results confirm the hypothesis that there exists a considerable difference between this new type of isomerisation and isomerisations of hydrocarbons under the influence of aluminium chloride and sulphuric acid. In general it may be stated that, when durene (I) is produced under the influence of aluminium chloride, it is generally accompanied by isodurene (II), which substance is present in greater quantity[59,61,73]. No evidence of the formation of prehnitene (III) in reactions using aluminium chloride has yet been found. Durene itself with aluminium chloride at elevated temperatures gives a mixture of lower homologues. The Jacobsen reaction with durene, as stated above, yields prehnitene (III) accompanied by pseudocumene (1,2,4-trimethylbenzene) and pentamethylbenzene.

In the durene and pentamethylbenzene as well as the s-octahydroanthracene series it appears likely that in the new isomerisation-cyclisation reaction the driving force is the tendency for a suitable side chain to cyclise on the ortho-position under the influence of the isomerising reagent, thereby releasing from that position an alkyl group which is then free to assume a vacant position on the benzene ring. Only that alkyl group, i.e., the ortho group, appears to be affected in this type of isomerisation, whereas in

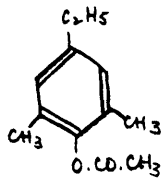
previously described (aluminium chloride and sulphuric acid) rearrangements more general lability of alkyl groups appears to exist. This is almost certainly due to the fact that the conditions of reaction in the new cyclisation isomerisation reaction are much milder (ca. 15°) than those of previously described isomerisations (80-160°).

The fact that the lower homologues of durylpropionic acid and durene itself are unaffected by treatment with hydrogen fluoride confirms the belief that isomerisation is not of the general type present when using aluminium chloride at elevated temperatures.

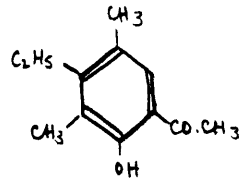
Baddeley[95] has indicated that migrations of alkyl groups in benzene homologues, phenols, arylketones and hydroxyarylketones, in presence of aluminium chloride, are related to each other and to the Jacobsen reaction. It seems likely that hydrogen fluoride isomerisations are also related to these types of isomerisation. Baddeley, moreover, suggests that the steric effect of a bulky group ortho to an alkyl group provides the impetus for the migration of that alkyl group. In the new isomerisation-cyclisation reaction, where much milder conditions of temperature exist than in the rearrangements described by Baddeley, the impetus of the carboxylic- and carboxymethyl-groups in compounds (ii) and (iii) (Table II) is insufficient to cause displacement

of an ortho methyl-group. The impetus provided by the bulkier β-carboxyethyl- and γ-carboxypropyl groups in compounds (iv), (v) and (vi) (Table II) accompanied by the impetus provided by the ability of the bulky group to cyclise in the ortho position under the influence of the catalyst is sufficient to cause migration of the ortho-methyl group.

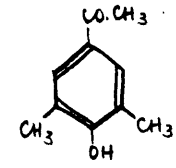
The closest analogy to the new isomerisation-cyclisation reaction is to be found in the Fries rearrangement of alkylated phenol acetates described by Auwers and Mauss[75] and rearrangements in acylations described by Hennion and McLeose[76]. In the Fries rearrangement, an acyl group, in presence of aluminium chloride under mild conditions (40°) was found to cause displacement of an alkyl group generally in the ortho- or para-position. The displaced alkyl group was then either lost or took up a vacant position in the benzene nucleus. In this reaction, however, further migrations, comparable with the aluminium migrations described above with hydrocarbons, took place. For instance the acetate of 2,6-dimethyl-4-ethylphenol (XIV) on treatment with aluminium chloride at 40° yielded a mixture of 2,4-dimethyl-3-ethyl-6-acetylphenol (XV) and 2,6-dimethyl-4-acetylphenol (XVI).[75] (XVI) is formed by loss of an alkyl group whose place is taken by an acetyl-



(XIV)



(XV)



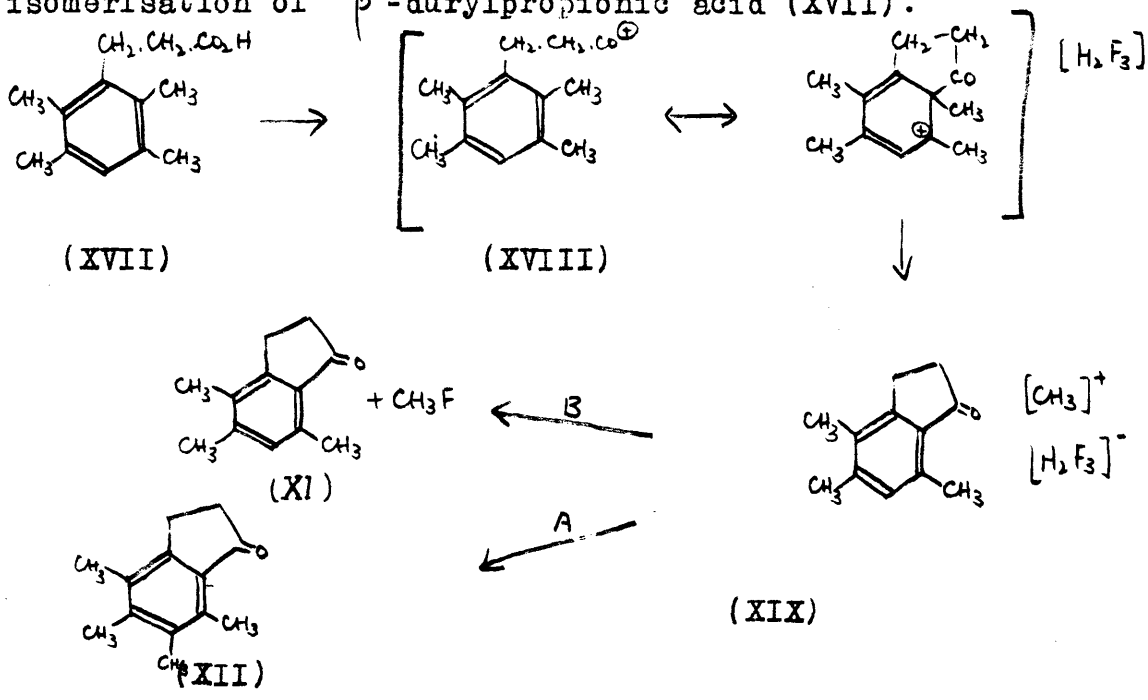
(XVI)

group, c.f., formation of ketone (XI); (XV) is formed by rearrangement similar to the formation of ketones (XII) and (XIII) followed by a further rearrangement involving a methyl- and ethyl-group, probably of the 'general type' of hydrocarbons described above.

It should be noted, moreover, that the isomerisation of β-(9-s-octahydroanthranyl)propionic acid (IV, n = 2) can be achieved *via* the acid chloride under mild conditions[69]. The product (V) is identical with that obtained by treating the acid (IV, n = 2) with hydrogen fluoride.

These data suggest a possible mechanism for hydrogen fluoride cyclisations, a subject as yet largely unstudied. In acylations and cyclisations involving aluminium chloride the formation of the complex ions $[R.CO]^+$ and $[AlCl_4]^-$ is postulated. The analogous ions formed with hydrogen fluoride would be $[R.CO]^+$ and $[H_2F_2Cl]^-$ using an acyl chloride, and $[R.CO]^+$ and $[H_2F_2OH]^-$ using the free acid. The latter ion in presence of excess hydrogen fluoride would almost certainly become $[H_2F_3]^-$ so that the

following series of intermediates (XVII) to (XI) and (XII) may be considered as possibilities in the cyclisation—isomerisation of β-durylpropionic acid (XVII).



(XVII) follows both routes A and B almost equally in extent whereas the butyric acid (IX, n = 3) tends to follow route A exclusively, complete remethylation taking place. In the pentamethylbenzene series the propionic acid (X, n = 2) can yield only one ketone (XII) the displaced methyl ion being lost.*

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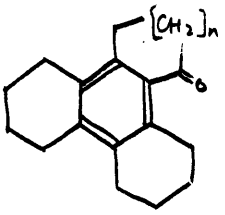
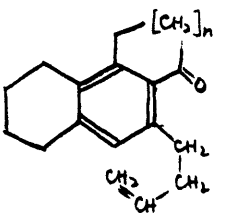
*Little work has been done on the by-products of isomerisation reactions as regards the loss of alkyl groups though it is generally assumed that the displaced group reacts with the isomerising agent, hydrogen, another displaced group or loses hydrogen to form an alkyl chloride, an alkane, a dialkane or an alkene respectively.

This mechanism would also explain the reactions in the s-octahydroanthracene series where at least two products are possible, i.e. (XX) and (XXI). (XXI) would readily be converted to (XX) by the same mechanism which provides alkylation and cyclisation in the benzene nucleus using hydrogen fluoride[70,74].



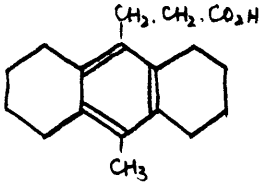
(XX)



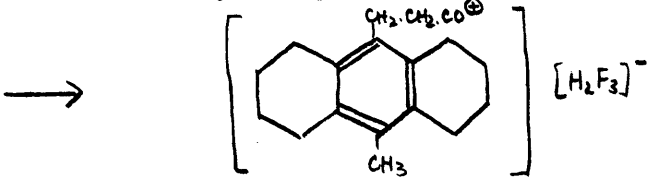
(XXI)

This mechanism offers no explanation of the lack of ketonic product from the acid (X, n = 3). As indicated above further study is required on the action of hydrogen fluoride on pentasubstituted phenylbutyric acids.

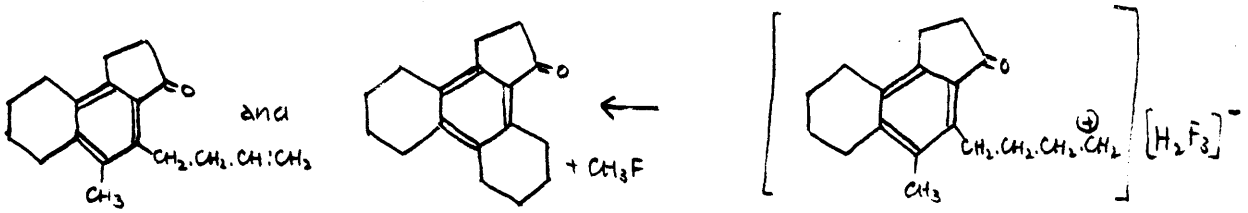
A possible explanation of the mixture of ketonic products[69] obtained from β-(10-methyl-s-octahydroanthranyl) propionic acid (XXII) is offered by this mechanism in the series of intermediates (XXI) to (XXV) and (V) below. The inseparable mixture isolated by Badger, Carruthers and



(XXII)



(XXIII)



(XXV) (V) (XXIV)

Cook[69] may be a mixture of ketones (V) and (XXV). It would, however, be advisable to study the possibilities of isomerisation in compounds with butene or propene side chains where ortho-methyl substituents are present before drawing further conclusions. This is especially true in view of the fact that 4-(9-s-octahydroanthranyl) butene-1 (xi, Table I) is unaffected by hydrogen fluoride, whilst it has been shown that cyclisation accompanied by isomerisation occurs more readily and more completely in the s-octahydroanthracene series than in the polymethylbenzene series.

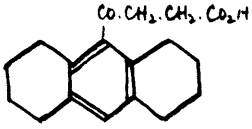
Durene was obtained by bischloromethylation of xylene followed by reduction as described by von Braun and Nelles[78]. However, since reduction as described by these workers using zinc, sodium hydroxide and benzene was unsatisfactory, alternative methods were investigated. Catalytic methods, using palladium, were found to give pure products in excellent yield in small scale (2 g.) runs. In larger scale runs, however, the time required for reduction was tediously long and incompletely reduced products were

obtained. Reduction, using zinc and alcohol by the method of Hewett[79] yielded non-homogeneous oils probably bimolecular products comparable with those obtained from bischloromethylnaphthalene by Badger, Cook and Crosbie[80]. Reduction was most readily achieved using zinc, previously treated with copper sulphate solution and sodium hydroxide solution with bischloromethylxylene dissolved in toluene in a layer on top. Methods involving the use of methyl chloride in a Friedel and Crafts reaction[81] were not used as the reaction appears to be difficult to control and the products difficult to separate.

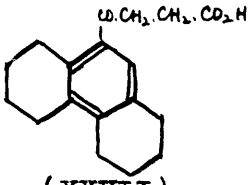
Durylcarboxylic acid was obtained from bromodurene[82] via the Grignard reagent[83]. By a modification of Nauta and Dienske's method[84] for the chloromethylation of mesitylene, there was obtained from durene, chloromethyldurene (cf. 85) accompanied by a small quantity of bischloromethyldurene. Durylacetic acid was prepared from chloromethyldurene via durylacetonitrile by normal procedures.

Condensation of chloromethyldurene with ethyl malonate in the usual fashion yielded ethyl β-durylmethyl malonate, which on hydrolysis to the corresponding acid followed by decarboxylation yielded β-durylpropionic acid. Chain lengthening by the Arndt and Eistert procedure, via γ-durylbutyramide yielded γ-durylbutyric acid.

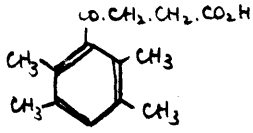
Since it had been shown[69] that the interaction of s-octahydroanthracene with succinic anhydride under the influence of aluminium chloride at 15° in carbon disulphide yielded an isomerised product β-(9-s-octahydrophenanthroyl) propionic acid (XXVII), the analogous reaction with durene was investigated. When condensation of durene and succinic anhydride was carried out in carbon disulphide there was obtained in poor yield a mixture of two acids which were separated by fractional crystallisation of their sodium salts.



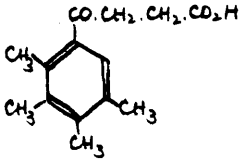
(XXVI)



(XXVII)



(XXVIII)



(XXIX)

The structure of the acid present in larger quantity (77%) was established by heating with hydrochloric acid[86] when durene was obtained. When reduced by the Clemmensen procedure (see below), some γ-durylbutyric acid, identical with that prepared by the Arndt and Eistert procedure from β-durylpropionic acid, was obtained indicating that this acid was β-duroylpropionic acid (XXVIII). The acid present in smaller quantity on oxidation with sodium hypobromite yielded prehnitylcarboxylic acid, characterised as the amide, showing that the unknown acid was β-prehnitoyl-

propionic acid (XXIX). No evidence, apart from the melting point of the crude acid mixture (117-128°) was obtained of the formation of an acid, m.p. 118°, claimed by Muhr[86] to be β-duroylpropionic acid. It seemed likely that the acid obtained by Muhr was the mixture described above.

In tetrachloroethane condensation of durene and succinic anhydride in presence of aluminium chloride yielded (XXVIII) (93% of crude acidic material obtained) in much better yield. No acidic impurity was isolated. In tetrachloroethane s-octahydroanthracene under identical conditions yielded a mixture of (XXXVII) and β-(9-s-octahydroanthranoyl) propionic acid (XXVI)[69].

These results are comparable in that when carbon disulphide was used as solvent a greater degree of isomerisation was noted in both cases than when tetrachloroethane was present. The results are also noteworthy in that whereas isomerisation is considerable in both solvents in the s-octahydroanthracene series only slight isomerisation takes place in the durene series, a result comparable with the results in hydrogen fluoride isomerisations above. In the cyclisation-isomerisation reaction with hydrogen fluoride, rearrangement, when it takes place in the s-octahydroanthracene series, is almost complete (no acid is recovered), whereas in the durene series only partial rearrangement occurs (a considerable

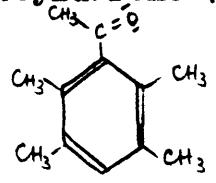
quantity of unchanged acid is recovered (see Tables I and II).

Badger, Carruthers and Cook[69] demonstrated that in the s-octahydroanthracene series the isomerisation is not reversible, i.e., s-octahydrophenanthrene when condensed with succinic anhydride gave only (XXVII). Thus it would appear that this isomerisation differs from the high temperature aluminium chloride rearrangements where a mixture is obtained from either s-octahydroanthracene or s-octahydrophenanthrene.

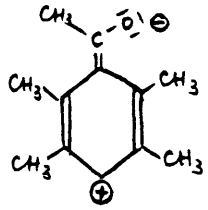
This migration bears a striking resemblance to the Jacobsen reaction whose relation to aluminium chloride catalysed rearrangements was pointed out by Baddeley[95]. In both the Jacobsen reaction and this rearrangement, migration of a methyl group is brought about by substitution in the benzene nucleus, by sulphuric acid in the Jacobsen reaction and by succinic acid here. Moreover, both yield prehnitene derivatives and both, at least in the s-octahydroanthracene series, are irreversible. It is likely, then, that the mechanisms of both reactions are similar and as indicated by Baddeley[95] are connected with the steric effect of the entering group. (See below for steric hindrance effect in β-duroylpropionic acid).

Reduction of β-duroylpropionic acid to γ-durylbutyric acid by the Huang-Minlon modification of the Kischner Wolff reduction[87] method was without success, only unchanged

starting material was recovered. Reduction by the Clemmensen procedure yielded the required acid, γ-durylbutyric acid, only in small quantities, the major part of the product being unchanged (XXVIII). These results are probably due to steric hindrance, a contingency not unexpected in a substituted durene derivative. The smaller acetyl radical in acetyldurene (XXX) is a classical example of the "steric inhibition of resonance" effect. (XXX) has, in fact, a dipole moment comparable with that of aliphatic ketones and considerably less than that acetophenone[93]. This is due to the very small resonance contribution from the resonance form (XXXI) which cannot exist to any great extent due to steric hindrance.



(XXX)



(XXXI)

The steric effect, similar to that which prevents esterification of 2,6-dimethylbenzoic acid by the Fischer Speier method[94] is almost certainly the cause of failure to reduce (XXVIII) by the Kischner Wolff method where the bulky hydrazide group is almost certainly added on as intermediate, a process which would be considerably hindered sterically. The Clemmensen method, which was found to give some of the required acid, would probably have provided complete reduction though this would have required a tediously

long time and large quantities of reagents.

Pentamethylbenzene was obtained from two sources. Chloromethyldurene readily yielded the required product in excellent yield on shaking with hydrogen and palladium. On a larger scale pentamethylbenzene was obtained from mesitylene via bischloromethylmesitylene[84]. Reduction of the latter compound proved troublesome. Except on a small scale (2 g.) reduction using catalytic methods was slow and incomplete. More vigorous chemical methods[30,79] yielded oils and only small quantities of the desired product. The modification of von Braun and Nelles'[78] method for reduction of bischloromethylxylene (see above for preparation of durene) was most effective though even here a poor yield of the required product was obtained.

Chloromethylpentamethylbenzene was obtained by chloromethylation of pentamethylbenzene by Nauta and Dienske's method for mesitylene[84]. This compound, accompanied with unchanged starting material, was also obtained when hexamethylbenzene was heated with phosphorus pentachloride. Jacobsen[88] claims to have prepared by this method a substance, m.p. 99°, which he assumed to be chloromethylpentamethylbenzene (no analysis). It seems likely that this substance was a mixture of the product and starting material since the chloromethylpentamethylbenzene obtained in this work had melting point 82-84°.

Condensation of the chloromethyl-compound with ethyl malonate in the usual fashion gave ethyl pentamethylbenzylmalonate, which, after hydrolysis and decarboxylation, yielded β-pentamethylphenylpropionic acid. This acid was also obtained from β-durylpropionic acid. β-(p-chloromethylduryl)propionic acid, obtained by chloromethylation of β-durylpropionic acid, on catalytic reduction gave the required acid. On one occasion on which acetic acid was used as solvent during chloromethylation β-(p-acetoxymethylduryl)-propionic acid was obtained, mixed with another acid, which on hydrolysis gave an acid, $C_{14}H_{20}O_3$, (not β-(p-hydroxymethylduryl)propionic acid) which was not further investigated as it was obtained in poor yield and the conditions for its production could not be duplicated.

β-(p-hydroxymethylduryl)propionic acid was obtained by alkaline hydrolysis of both β-(p-chloromethylduryl)-propionic acid and β-(p-acetoxymethylduryl)propionic acid.

γ-pentamethylphenylbutyric acid was prepared by the Arndt and Eistert procedure from its lower homologue the propionic acid via γ-pentamethylphenylbutyramide.

Experimental, Part I.

Fluorene-9-carboxylic acid - Fluorene-9-carboxylic acid was obtained by the action of aluminium chloride on benzilic acid[53] and benzene[54].

Reduction of fluorene-9-carboxylic acid.

(i) Sodium and amyl alcohol. - Sodium (8 g.) was added over a period of 3 hours to a refluxing solution of fluorene-9-carboxylic acid (2 g.) in amyl alcohol (130 c.c.). The cooled solution was added to water and steam distilled. The amyl alcohol distillate was separated, dried over anhydrous calcium oxide and fractionally distilled. The liquid residue, which still contained some amyl alcohol, was not further investigated. The alkaline aqueous residue from steam distillation was filtered and acidified. The precipitated acid (ca. 0.3 g.) after crystallisation from hexane, cyclohexane and benzene had m.p. 159-160° (155°)*.

(ii) Sodium and ethanol. - Sodium (8 g.) was added over a period of 2 hours to a refluxing solution of fluorene-9-carboxylic acid (2 g.) in ethanol (100 c.c.). Most of the ethanol was then removed on the water bath, water was added and the residue extracted with ether. The acidified aqueous

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* Figures in brackets after melting points here and from here may be taken to indicate the temperature at which sintering commenced when the substance was heated.

layer yielded an acid (ca. 0.4 g.) which formed needles, m.p. 183-185° (179°) and mixed m.p. with acid from reduction (i) 160-171°, from hexane, cyclohexane and light petroleum. The ether extract yielded a yellow liquid which did not decolourise bromine water and gave no precipitate with 2,4-dinitrophenylhydrazine solution.

(iii) Sodium amalgam and sodium hydroxide solution. - Fluorene-9-carboxylic acid (5 g.) in sodium hydroxide solution (200 c.c., 6N) was stirred at room temperature with sodium amalgam (412 g., 4%)[55]. After 16 hours, a yellow solid, which had separated out on the surface, was removed by filtration, the filtrate then being stirred with the incompletely decomposed amalgam at 100° for 8 hours. The yellow solid was sublimed, 140°/3.5 mm., and crystallised from alcohol (twice) to give white needles, m.p. and mixed m.p. with authentic specimen of 9-fluorenol 152-154°. An ethanolic solution of the crude yellow solid, with 2,4-dinitrophenylhydrazine solution, yielded a red precipitate which formed red needles, m.p. and mixed m.p. with authentic specimen of fluorenone 2,4-dinitrophenylhydrazone 282.5°, from ethyl acetate.

The alkaline filtrate above was stirred at 100° for a further 4 hours, cooled and filtered. The residue on the paper proved to be mainly 9-fluorenol. The acidified

filtrate yielded fluorene-9-carboxylic acid, m.p. and mixed m.p. with original acid 221-223° after crystallisation from benzene (once).

(iv) Nickel-aluminium alloy and sodium hydroxide solution.- cf.(30). To a stirred solution of fluorene-9-carboxylic acid (3.5 g.) in sodium hydroxide solution (450 c.c., 10%), heated to 90° was added nickel-aluminium alloy (27 g. in 1-2g. lots). The mixture was then stirred for 1 hour longer, at 90° then filtered hot. The filtrate, acidified by pouring into excess concentrated hydrochloric acid, yielded an acid (ca. 2 g.) in the form of sticky masses. After crystallisation from alcohol, sublimation, 135°/1 m.m., recrystallisation from benzene, light petroleum (twice), hexane and cyclohexane there was obtained hexahydrofluorene-9-carboxylic acid (ca. 15 mg.) in the form of needles, m.p. 182-183° (179°). (Found: C, 77.2; H, 7.2. $C_{14}H_{16}O_2$ requires C, 77.7; H, 7.5%). Mixed m.p. with acid from reduction (i) was 154-173° and from reduction (ii) was 151-169°.

A second run where the mixture was heated under reflux yielded (from the reflux condenser) a neutral product which formed white needles, m.p. and mixed m.p. with authentic specimen of fluorene 113-114°, from hexane.

Ammonium salt. - The ammonium salt, prepared by evaporating a solution of the crude acid, m.p. 122-144°, in ammonia to dryness, was dissolved in water to form a saturated solution and the solution evaporated to half bulk and filtered. The filtrate on acidification yielded a resinous product; the residue on the paper on like treatment gave a white powder, m.p. 117-173°.

Calcium salt. - The calcium salt, prepared by mixing aqueous solutions of the ammonium salt and calcium chloride, filtering the precipitated salt and drying, was insoluble in both hot and cold water.

Potassium salt. - A saturated solution of potassium hydroxide in ethanol was added to a solution of the crude acid, m.p.122-144°, in ether till just alkaline to phenolphthalein. The potassium salt, so precipitated, was washed with ether and crystallised from water. The white needles so formed, on acidification yielded a powder, m.p. 144-151° (106°).

Sodium salt. - The sodium salt, prepared in a manner analogous to the potassium salt when treated in like fashion, yielded an acid m.p. 139-164° (121°).

Benzyl-iso-thiouronium salt. - This salt was prepared by mixing an aqueous solution of the potassium salt with an ethanolic solution of benzyl-iso-thiouronium chloride. The salt, which precipitated, formed needles, m.p. 144-148° (119°) from water. Some nine crystallisations of the salt from

benzene and water merely caused the melting point to fluctuate. Acidification of an aqueous solution of the salt yielded an acid, m.p. 120-132°.

p-Nitrobenzyl ester. - The ester, prepared in the usual fashion from the sodium salt was liquid at room temperature.

Ethyl ester. - Dry hydrogen chloride gas was passed through a solution of the crude acid (32.5 g.) in ethanol (500 c.c.) for 1 hour and the resultant solution refluxed for 4 hours. The residue, after removal of ethanol by distillation, dissolved in ether, was twice extracted with sodium carbonate solution, dried over anhydrous sodium sulphate and fractionally distilled through a column (1.5 in.) of glass beads. Three fractions 1), 2) and 3) were obtained. Fractions 1) and 2) were redistilled to give fractions 1A), 1B), 1C), 2A), 2B), 2C) and 2D) as listed below.

Fraction 1) b.p. 142-148°/2 mm. (7.25 g.).

1A) b.p. 125-132°/0.7 m.m. (2.8 g.)

1B) b.p. 133°/0.7 m.m. (3.4 g.)

1C) b.p. 134°/upwards/0.7 m.m. (1 g.)

Fraction 2) b.p. 149°/2 m.m. (18.8 g.)

2A) b.p. 134-136°/0.5 m.m. (12.4 g.)

2B) b.p. 136-138°/0.5 m.m. (2.4 g.)

2C) b.p. 138-140°/0.5 m.m. (2 g.)

2D) residue in flask (2 g.)

Fraction 3) b.p. 150-152°/2 m.m. (3.0 g.).

Hydrolysis of the ester fractions. - Hydrolysis of fraction 3) using aqueous ethanolic potassium hydroxide gave as product a dark coloured gum which was induced to crystallise only with difficulty. Hydrolysis by the method below for fraction 2D) was employed for all other fractions as a less darkly coloured product was obtained in better yield.

A mixture of fraction 2D), concentrated hydrochloric acid (3 c.c.) and glacial acetic acid (5 c.c.) was heated to 100° for 3 hours. The residue, added to water, was extracted with ether and washed with water. The ether extract, purified by extraction with sodium carbonate followed by acidification yielded a brown gum (ca. 1.6 g.) which readily gave crystals from light petroleum.

A list of the results of hydrolysis is given below. In each case the product was crystallised from light petroleum.

Fraction 1A) on hydrolysis yielded an acid m.p. 75° (68°)

" 1B) " " " " " " 173° (68°)

" 1C) " " " " " " 178° (158°)

" 2A) " " " " " " 78° (72°) designated $2A_1$)

" 168° (64°) designated $2A_2$)

" 2B) " " " " " " 162° (75°) designated $2B_1$)

182° (161°) designated $2B_2$)

Fraction 2C) on hydrolysis yielded an acid m.p. 178° (174°)

" 2D) " " " " " " " 180° (171°)

" 3) " " " " " " " 73° (66°).

The acids from fraction 2A), i.e., $2A_1$) and $2A_2$) were readily separated. When a mixture of the two acids was added to hexane, boiled for 1 minute and filtered immediately, the residue on the paper was mainly $2A_2$); $2A_1$) crystallised from the filtrate on cooling. Acids $2B_1$) and $2B_2$) were similarly separated.

Since the acids 1A), $2A_1$) and 3) had similar melting points and since a mixture of any one acid with any other showed no depression of the melting point, they were combined. There was obtained from the combined specimen an acid, which formed large colourless prisms after charcoaling, m.p. 74° (68°), after crystallisation from light petroleum (twice) and hexane (4 times). (Found; C, 76.3; H, 6.8%).

As the acids 1C), $2B_2$), 2C) and 2D) had similar melting points and as a mixture of any one acid with any other showed no depression of the melting point, they were combined. The combined specimens gave hexahydrofluorene-9-carboxylic acid, m.p. 182-183° (172°) from benzene, light petroleum (4 times), cyclohexane and hexane (twice). (Found: C, 78.0; H, 7.4. $C_{14}H_{16}O_2$ requires C, 77.7; H, 7.5%)

Acids $2B_1$), 1B) and $2A_2$) were combined, ground in a

mortar, boiled with hexane for 30 seconds and filtered immediately. The insoluble part was combined with the group of high-melting acids above whilst the crystals which formed in the filtrate were added to the low-melting group.

(v) Sodium, ethanol and liquid ammonia. - cf. (34). To a solution of fluorene-9-carboxylic acid (2 g.) and ethanol (15 c.c.) in liquid ammonia (50 c.c.) was added, whilst stirring, sodium (2 g.) in small pieces. After standing overnight, further quantities of sodium (2 g.) and liquid ammonia (50 c.c.) were added and left for 6 hours when excess ammonia was permitted to evaporate. The residue, with water added, was extracted with ether. The dried ether extract yielded a neutral material which after sublimation, 130°/2 m.m., crystallisation from alcohol, benzene and light petroleum (twice) formed needles, m.p. and mixed m.p. with authentic specimen of fluorene 113-114°. The aqueous residue, above, on acidification yielded an acid (ca. 0.2 g.) which formed needles, m.p. and mixed m.p. with hexahydro-fluorene-9-carboxylic acid 179-182° (174°) from benzene, light petroleum and cyclohexane.

(vi), (vii), (viii) Catalytic methods. - The acid used here was purified by crystallisation from acetic acid (analar). No absorption of gas was noted when fluorene-9-carboxylic acid in glacial acetic acid was shaken with hydrogen in

presence of Adam's catalyst or reduced palladous oxide at ordinary temperatures and pressures. Likewise, no absorption of gas was noted when an ethanolic solution of the acid was shaken with hydrogen in presence of Raney nickel catalyst, prepared by Adkins and Pavlic's method[36].

(ix) Hydrogen and Raney nickel at elevated temperatures and pressures. - A mixture of fluorene-9-carboxylic acid (5 g.), ethanol (350 c.c.) and Raney nickel (2 g.) was stirred with hydrogen at 140-160° under a pressure of 150-160 atmospheres for 5.5 hours. The product, after removal of the catalyst and solvent by filtration and distillation, was a yellow liquid. This liquid was dissolved in ether and extracted with sodium carbonate solution. The alkaline extract, on acidification, yielded an acid (0.25 g.) which formed needles, m.p. 159° (142°) from benzene alcohol and hexane. The neutral material, from the ether extract, was distilled, b.p. 125-126°/14 m.m.; 265°/755 m.m., to give a pale yellow liquid which did not decolourise bromine water and gave no precipitate with 2,4-dinitrophenylhydrazine solution. (Found: C, 86.2; H, 9.5%). Heating the liquid with palladium black at 260° for 2 hours yielded a resin. Heating with sulphur at 220° for 4 hours gave fluorene, m.p. and mixed m.p. with authentic specimen 113-114°. When a solution of the liquid in benzene was passed through a column of

alumina there was obtained a pale yellow liquid, b.p. 129-130°/15 m.m., which darkened on standing. (Found: C, 84.3; H, 10.5%).

o-Phenylbenzoic acid.- Fluorenone was converted to the required acid by stirring with potassium hydroxide in p-cymene at 175° for 30 minutes (cf. (38)). Average yield was 89%, m.p. 110°.

o-Phenylhexahydrobenzoic acid. - The required acid was obtained by reduction of o-phenylbenzoic acid using sodium and amyl alcohol as described by Gutsche and Johnson[39]. Average yield was 68%, m.p. 104-105°.

Hexahydrofluorenone.- This ketone was obtained from o-phenylhexahydrobenzoic acid as described by Cook and Hewett[37]. Average yield was 60%, b.p. 130°/1 m.m., m.p. 43°.

Attempts to prepare 9-cyano-9-hydroxy-hexahydrofluorene.- 1) (cf. Mackenzie and Wood[40]). To a mixture of potassium cyanide (5 g. analar), water (0.5 c.c.) and hexahydrofluorenone (1 g.) was added, dropwise, with vigorous stirring over a period of 1 hour, concentrated hydrochloric acid (7 c.c.). The mixture was kept at 15° for the first 30 minutes of addition of acid, then cooled to 0°. After standing at 0° for a further 30 minutes ether was added. The dried separated ether extract yielded a liquid residue, which gave a positive test for nitrogen (sodium fusion). The

liquid residue, after standing overnight with concentrated hydrochloric acid was extracted with ether which was extracted with sodium carbonate solution. The acidified alkaline extract was extracted with ether which left no residue on distillation. The first ether extract yielded a neutral product which formed a 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. with authentic specumen of hexahydrofluorenone 2,4-dinitrophenylhydrazone 188°.

When acetophenone (1 g.) was substituted for hexahydrofluorenone in the above experiment atrolactinic acid (0.1 g.) was obtained.

2). (cf. Weissberger and Glass[41]). A solution of hexahydrofluorenone (1 g.) in light petroleum (10 c.c.) was shaken for 30 minutes in a tightly stoppered flask with a solution of potassium cyanide (5 g. analar) and ammonium chloride (5 g.) in water (25 c.c.). The separated, dried organic layer left on distillation a residue which gave a negative test for nitrogen (sodium fusion). This residue formed a 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. with authentic specimen of hexahydrofluorenone 2,4-dinitrophenylhydrazone 188°. Acetophenone when treated by this method gave a negative test for nitrogen (sodium fusion) at the cyanhydrin stage.

Hexahydrofluorenol. - Hexahydrofluorenone (6.7 g.) in ethanol

(150 c.c.) was shaken with hydrogen and Raney nickel (5 g.) at ordinary temperatures and pressures for 25 minutes. The product, 1,2,3,4,10,11-hexahydrofluoren-9-ol (5 g.) formed colourless needles, m.p. 130°, from hexane. (Found: C, 83.0; H, 8.5. $C_{13}H_{16}O$ requires C, 83.2; H, 8.5%).

Fluorenol. - (cf. (42)). Fluorenone (6 g.) in alcohol (200 c.c.) was reduced to fluorenol (4.7 g.), m.p. 153°, by shaking with hydrogen for 15 minutes at ordinary temperatures and pressures in presence of Raney nickel (5 g.) as catalyst.

Raney nickel catalyst used in these reductions was prepared by Adkins and Pavlic's method[36].

Attempts to prepare hexahydrofluorene-9-carboxylic acid. 1). (cf. Bachmann[43]). A mixture of hexahydrofluorenol (5 g.), dry benzene (150 c.c.) and anhydrous calcium chloride was stirred for 90 minutes whilst a rapid stream of dry hydrogen bromide gas was passed through the suspension. The suspension was stirred for 60 minutes longer, then filtered. The filtrate was divided into 2 equal parts. The first part was dried over anhydrous potassium carbonate for several days. The second part was evaporated to dryness in a stream of dry air.

The residue, a brown liquid, which could not be induced to solidify and which appeared to be evolving

hydrogen bromide gas was distilled, b.p. 128-132°/1.5 m.m. An inconclusive test was obtained for bromine after sodium fusion. Dehydrogenation of the distilled product at 240° for 1 hour with palladium black yielded fluorene, m.p. and mixed m.p. with authentic specimen 114-115°. The distillate, above, was boiled with pyridine for 1 hour and the resultant on fractional distillation yielded pyridine and a yellow liquid b.p. 130°/1.5 m.m., which gave a negative sodium fusion test for bromine, decolourised bromine water in the cold, and gave no precipitate with 2,4-dinitrophenylhydrazine solution. Dehydrogenation, as above, again yielded fluorene.

The first part of benzene extract was evaporated to dryness in a stream of dry air. The residue (3 g.) in dry ether (100 c.c.) was added to magnesium (0.3 g.) to form the Grignard complex. Most of the magnesium was converted to a white precipitate. After refluxing for 1 hour, dry carbon dioxide gas was passed through the suspension for 2 hours. After standing for 1 hour longer, the residue was stirred with ice and dilute hydrochloric acid. The ether layer was separated and extracted with sodium carbonate, which was acidified and extracted with ether. This latter ether extract on distillation left no residue. The former ether extract, dried over anhydrous calcium chloride yielded an oil, b.p. 130-160°/2 m.m., which decolourised bromine

water in the cold and on dehydrogenation gave fluorene, and a residue which did not distil below 200°/1 m.m. This residue formed plates, m.p. 134-135°, from acetone, ethyl acetate, hexane (twice), cyclohexane (thrice) after sublimation, 130°/5.4 x 10^{-4}m.m. (Found M, 291 (Rast)).

To the unsaturated compound from pyridine treatment, in ice cold carbon tetrachloride, was added bromine until the colour of the bromine was not immediately discharged on addition. The residue, from evaporation of the carbon tetrachloride in a stream of dry air at room temperature, a brown liquid, which could not be induced to solidify or crystallise was distilled, b.p. 130-150°/2 m.m. The distillate, a yellow liquid, gave a negative test (sodium fusion) for bromine.

2). Hexahydrofluorenol (2 g.) was treated with dry hydrogen chloride gas as described above for hydrogen bromide. The product, a yellow liquid, which appeared to be evolving hydrogen chloride gas, was distilled, b.p. 131-135°/1.5 m.m. The distillate, a pale yellow liquid, gave a negative sodium fusion test for chlorine, decolourised bromine water immediately in the cold and on dehydrogenation (palladium, 220°, 1 hour) yielded fluorene, m.p. and mixed m.p. with authentic specimen 113-115°.

Freshly prepared, undistilled liquid (0.5 g.), which

gave a positive sodium fusion test for chlorine, in ethanol (50 c.c. 70%) was refluxed with potassium cyanide (2 g.) for 4 hours. The product, from distillation of the ethanol, after washing thrice with water (20 c.c.) was a yellow liquid which gave a positive sodium fusion test for nitrogen. Distillation of this product, b.p. 123-151°/1 m.m., yielded a liquid which decolourised bromine water immediately in the cold, gave a negative sodium fusion test for nitrogen, and on dehydrogenation as described above yielded fluorene.

A solution of nitrogenated product (above) (1 g.) in water (5 c.c.), glacial acetic acid (15 c.c.) and concentrated sulphuric acid (5 c.c.) was refluxed for 3 hours. The cooled residue was poured into water and extracted with ether, which was then extracted with sodium hydroxide solution. Acidification of the alkaline extract yielded a brown amorphous powder which was insoluble in water, benzene, alcohol, acetone and pyridine. This brown solid did not melt below 350° and did not sublime below 250°/0.5 m.m. The ether extract yielded a yellow oil, b.p. 128-137°/1.5 m.m., which rapidly decolourised bromine water in the cold, gave a negative sodium fusion test for nitrogen and on dehydrogenation as described above yielded fluorene.

A mixture of nitrogenated product (above) (0.5 g.) sodium hydroxide (4 g.) and water (8 c.c.) was refluxed for 24 hours. The cooled mixture was extracted with ether. The dried ether extract yielded a yellow liquid, b.p. 132-151°/2 m.m., which rapidly decolourised bromine water in the cold and on dehydrogenation, as described above, yielded fluorene. The alkaline extract, on acidification, yielded a gelatinous precipitate which was filtered. The white material was silica (microcosmic bead test) which on boiling with benzene for 2 hours, filtering and evaporating to dryness gave no residue.

o-Benzoylbenzoic acid. - The required acid was obtained by the Friedel and Crafts procedure from benzene and phthalic anhydride[48]. Average yield was 72%, m.p. 126-127°.

o-Benzylbenzoic acid. - o-Benzoylbenzoic acid was reduced to the required acid using zinc and ammonia as described by Barnett, Cook and Nixon[49]. Average yield was 88%, m.p. 115-117°.

o-Benzylhexahydrobenzoic acid. - (cf. Cook, Hewett and Lawrence[26]). Sodium (110 g.) was added in slices to a gently refluxing, stirred solution of o-benzylbenzoic acid (20 g.) in amyl alcohol (1300 c.c.). When solution of the sodium was complete (ca. 2.5 hours) the amyl alcohol was removed in steam and the partially acidified residue filtered through a charcoal pad. The acidified filtrate yielded

the required acid (17.5 g.), which was crystallised from cyclohexane then light petroleum. The yield of pure acid, m.p. 133-134°, was 11.5 g.

trans-as-hexahydroanthrone. - (cf. Cook, Hewett and Lawrence[26]) The required ketone was obtained by dissolving the above acid in concentrated sulphuric acid in the cold. Average yield was 68%, m.p. 109°.

Attempted preparation of 9-hydroxy-9-cyano-trans-as-octahydroanthracene. - (cf. Plattner, Fürst and Studer[50]). To a stirred mixture of trans-as-hexahydroanthrone (2 g.) in ether (20 c.c.) and potassium cyanide (8 g. analar) in water (12 c.c.), cooled to -5°, was added, dropwise, concentrated hydrochloric acid (9.2 c.c.), over a period of 2 hours. After stirring at -5° for a further 4 hours, the tightly stoppered flask and contents were kept at 0° for 2 days. The separated ether layer, washed 4 times with ice water (10 c.c.) was dried over anhydrous sodium sulphate and evaporated to dryness in a stream of dry air at 0°. The residue formed white needles, m.p. and mixed m.p. with specimen of original ketone 109-110°, from methanol.

In a second run concentrated hydrochloric acid (50 c.c.) was added before removal of the ether in a stream of dry air. The mixture obtained was left overnight then mechanically shaken for 1 hour, when it was made alkaline

and extracted with ether. The ether extract yielded trans-as-hexahydroanthrone, m.p. and mixed m.p. with original ketone, 108-109°. The alkaline extract was acidified and extracted with ether which was dried over anhydrous sodium sulphate. No residue was obtained when this extract was distilled.

When acetophenone (1 g.) was substituted for trans-as-hexahydroanthrone there was obtained, as residue, at this stage atrolactinic acid (0.17 g.).

9-Hydroxy-trans-as-octahydroanthracene. - (cf. Cook, McGinnis and Mitchell[51]). trans-as-hexahydroanthrone (1 g.) in ethanol (40 c.c.) was reduced with hydrogen at ordinary temperatures and pressures using Raney nickel as catalyst in 195 minutes. The product, the required alcohol (0.66 g.) formed needles, m.p. and mixed m.p. with Cook et al's[51] product, 135-136°.

Benzohydrol. - Benzophenone (10 g.) in alcohol (300 c.c.) was shaken with hydrogen for 4 hours at ordinary temperatures and pressures in presence of Raney nickel as catalyst. Benzohydrol (7.4 g.), m.p. 66° was obtained.

β-Diethylaminoethanol. - Ethylene chlorohydrin and diethylamine were condensed as described in Organic Syntheses[56] to yield the desired product. Average yields were ca. 75%, b.p. 67-70°/20 m.m.

β-Diethylaminoethyl chloride. - The required chloride was obtained from β-diethylaminoethanol by refluxing with thionyl chloride as described by Slotta and Behnisch[57]. Average yields were ca. 50%, b.p. 148°/750 m.m.

β-Diethylaminoethyl benzohydryl ether. - (cf. Martin et al[16]). A mixture of benzohydrol (3 g.), sodium (0.37 g. atomised) and xylene was refluxed for 10 minutes. To the cooled residue was added β-diethylaminoethyl chloride (1.9 g.) in xylene (30 c.c.) and the resultant refluxed for a further 10 hours. The cooled residue was diluted with ether and extracted with hydrochloric acid. The acid extract, made alkaline with sodium hydroxide solution, was extracted with ether, which was dried over anhydrous potassium carbonate, and fractionally distilled. The required basic ether (2.4 g.) was obtained as a colourless oil from the fraction b.p. 154°/1 m.m. The hydrochloride, formed by passing dry hydrogen chloride gas through a solution of the base in dry ether formed white needles, m.p. 142-143° from ether, isopropanol. (Found: C, 71.3; H, 8.0; N, 4.4. Calculated for $C_{19}H_{26}ONCl$: C, 71.3; H, 8.2; N, 4.4%). The acid oxalate, made by mixing solutions of the base and anhydrous oxalic acid in dry ether, formed white needles, m.p. 92°, from ether, isopropanol. (Found: C, 67.6; H, 7.6; N, 3.9. $C_{21}H_{27}O_5N$ requires C, 67.4; H, 7.3; N, 3.8%).

β-diethylaminoethyl fluorenyl-9-ether. - When 9-fluorenol was substituted for benzohydrol in the above condensation there was obtained β-diethylaminoethyl fluorenyl-9-ether (2.0 g.) as a pale yellow oil, b.p. 125-130°/0.07 m.m., which darkened in colour on standing. (Found: C, 80.8; H, 8.1; N, 5.0. $C_{19}H_{23}ON$ requires C, 81.1; H, 8.2; N, 5.0%). The acid oxalate, prepared as described above, formed white needle clusters, m.p. 122°, from ether, isopropanol. (Found: C, 68.0; H, 6.9; N, 4.0. $C_{21}H_{25}O_5N$ requires C, 67.9; H, 6.8; N, 3.8%). Attempts to prepare the tartrate, citrate, picrate, etc. by similar methods resulted in the formation of oils which could not be induced to crystallise or, if they did, only unchanged acid was obtained.

β-diethylaminoethyl hexahydrofluorenyl-9-ether. - When hexahydrofluorenol was substituted for benzohydrol there was obtained β-diethylaminoethyl 1,2,3,4,10,11-hexahydrofluorenyl-9-ether (1.7 g.) as a pale yellow oil, b.p. 120-123°/0.05 m.m., isolated as the acid oxalate, which formed white needle clusters, m.p. 135-138° from ether, isopropanol. (Found: C, 66.6; H, 8.3; N, 3.7. $C_{21}H_{31}O_5N$ requires C, 66.8; H, 8.3; N, 3.7%). As above, no other salt could be isolated in a crystalline form.

β-diethylaminoethyl trans-as-octahydroanthranyl-9-ether. - When 9-hydroxy-trans-as-octahydroanthracene was substituted

for benzohydrol there was obtained β-diethylaminoethyl trans-as-octahydroanthranyl-9-ether (2.1 g.) as a pale yellow oil, b.p. 137°/0.07 m.m., isolated as the acid oxalate, which formed white needle clusters, m.p. 134°, from ether, isopropanol. (Found: C, 67.4; H, 8.5; N, 3.8. $C_{22}H_{33}O_5N$ requires C, 67.5; H, 8.5; N, 3.6%). The picrate formed small yellow needles, m.p. 107-108°, from ether, isopropanol. (Found: C, 58.7; H, 6.7; N, 10.3. $C_{26}H_{34}O_8N_4$ requires C, 58.8; H, 6.5; N, 10.6%). The hydrochloride was a deliquescent solid. The citrate and tartarate were oils which could not be induced to solidify.

Experimental, Part II.

Durene. - Durene was prepared by bischloromethylation of technical xylene followed by reduction of the bischloromethylxylene with zinc and sodium hydroxide solution as described by von Braun and Nelles[78]. Toluene is preferable to benzene as solvent in the reduction, zinc should be treated with copper sulphate solution before adding to sodium hydroxide solution. Average yields were 25-30%, m.p. 78-80°, b.p. 210°/750 m.m.

Durylcarboxylic acid. - Bromodurene, prepared by direct bromination of durene as described by Gissmann[82] was converted to the desired product through the Grignard reagent as described by Fuson and Kelton[83]. Durylcarboxylic acid (35%) formed needles, m.p. 179°, from light petroleum.

Chloromethyldurene. - A mixture of durene (22 g.), glacial acetic acid (50 c.c.), concentrated hydrochloric acid (110°) and formaldehyde (10.7 g., 40%) was stirred at 70° for 6 hours whilst a rapid stream of hydrogen chloride gas was bubbled through the mixture. A further quantity of formaldehyde (4.4 g., 40%) was added after 3 hours. After cooling and decantation of the aqueous layer, the residue in benzene, washed with water and dilute sodium carbonate solution, was dried over anhydrous potassium carbonate. Chloromethyldurene (22 g.) was distilled, b.p. 139-141°/

15 m.m., and formed needles, m.p. 65-66°, from methanol. (Fuson and Sperati[85] record b.p. 143-144°/18 m.m., and m.p. 67°.) The residue in the flask, after sublimation, 160°/15 m.m., yielded bischloromethyldurene, which formed needles, m.p. 193-194° from light petroleum. (Found: C, 62.0; H, 6.8; Cl, 30.5. $C_{12}H_{16}Cl_2$ requires C, 62.3; H, 7.0; Cl, 30.7%).

Durylacetic acid. - A mixture of chloromethyldurene (2 g.) in ethanol (25 c.c.) and potassium cyanide (5 g., analar) in water (9 c.c.) was refluxed for 2 hours. The cooled mixture was added to water filtered and dried. Durylacetonitrile (1.8 g.), so produced, after distillation, b.p. 168°/20 m.m., formed needles, m.p. 84-85° from aqueous methanol. (Found: C, 83.3; H, 8.5; N, 8.3. $C_{12}H_{15}N$ requires C, 83.2; H, 8.7; N, 8.1%).

Durylacetonitrile (0.75 g.) was heated to 150° under reflux for 10 hours with a mixture of water, concentrated sulphuric acid and glacial acetic acid (15 c.c., 1:1:1). The cooled residue was poured into water and filtered. Durylacetic acid (0.32 g.), further purified by reprecipitation from sodium carbonate solution, formed needles, m.p. 198-199°, from benzene. (Found: C, 75.2; H, 8.1. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%).

Ethyl β-durylmethylmalonate. - A mixture of sodium (3.5 g., atomised), benzene (75 c.c.) and ethyl malonate (24.2 g.) was heated under reflux for 3 hours. While still warm, chloromethyldurene (25.2 g.) in benzene (40 c.c.) was added and the resultant mixture refluxed for a further 2 hours. The cooled mixture was added to water and the separated organic layer dried over anhydrous sodium sulphate. Fractional distillation yielded chloromethyl durene, ethyl malonate and ethyl β-durylmethylmalonate (31 g.), b.p. 158-160°/0.5 mm., which formed prisms, m.p. 58-59°, from light petroleum. (Found: C, 70.5; H, 8.6. $C_{18}H_{20}O_4$ requires C, 70.6; H, 8.6%).

β-durylmethylmalonic acid. - The above ester (30 g.) in ethanol (75 c.c.) was refluxed for 3 hours with potassium hydroxide (21 g.) in water (30 c.c.). The resultant mixture was added to water and the partially acidified solution filtered through a pad of charcoal. The acidified filtrate yielded β-durylmethylmalonic acid (22.4 g.) which formed plates, m.p. 176° (with evolution of carbon dioxide) with a nacreous lustre, from water. (Found: C, 67.4; H, 6.9. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2%).

β-durylpropionic acid. - The above acid (20 g.) was heated to 180° until the evolution of carbon dioxide had ceased. β-durylpropionic acid (15 g.) formed needles, m.p. 170°, from

benzene. (Found: C, 75.6; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%). β-durylpropionamide prepared from the acid via the acid chloride, formed needles, m.p. 201-202°, from ethanol. (Found: C, 76.2; H, 9.0; N, 7.0. $C_{13}H_{19}ON$ requires C, 76.1; H, 9.3; N, 6.8%).

β-duroylpropionic acid. - 1) To a stirred, ice-cold suspension of anhydrous aluminium chloride (10 g.) in dry carbon disulphide (25 c.c.) was added over a period of 30 minutes, a solution of durene (3.3 g.) and succinic anhydride (2.5 g.) in carbon disulphide (50 c.c.). The resultant mixture, after stirring for a further 4 hours at 0°, was left at room temperature overnight. Carbon disulphide was then decanted and the viscous residue, decomposed with ice and concentrated hydrochloric acid, was then filtered. The acid (2.7 g.), m.p. 117-128° so obtained, was converted to its sodium salt by warming with hot dilute sodium carbonate solution. On cooling the sodium salt formed needles which were again crystallised from water. Regeneration of the acid from these needles yielded β-duroylpropionic acid (2.2 g.) which formed needles, m.p. 160-161°, from ethanol. (Found: C, 71.6; H, 8.0. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%). p-nitrobenzyl β-duroylpropionate formed white needles, m.p. 120-121°, from methanol. (Found: C, 68.3; H, 6.4; N, 3.5. $C_{21}H_{23}O_5N$ requires C, 68.3; H, 6.3; N, 3.8%).

When the acid (0.12 g.) was heated with concentrated hydrochloric acid (1 c.c.) in a sealed tube to 150° for 5 hours, there was obtained durene (0.07 g.), m.p. and mixed m.p. with authentic specimen 77-80°.

The mother liquors from crystallisation of the sodium salt above, on acidification, yielded β-prehnitoylpropionic acid (0.29 g.) which formed needles, m.p. 107-108°, from benzene, hexane. (Found; C, 71.6; H, 7.7. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%). β-prehnitoylpropionic acid (0.1 g.) was added to ice-cold sodium hypobromite solution (10 c.c., 10%) and the resultant mixture gradually heated to 100°, at which temperature it was maintained for 3 hours, with occasional shaking. The mixture was then filtered and the filtrate acidified. The dried, filtered, precipitated acid formed needles, m.p. 165-166°, from ligroin. (Prehnitylcarboxylic acid has m.p. 168-169°[91]). The amide of this acid, prepared *via* the acid chloride, formed plates, m.p. 200°, from water. (Prehnitylcarboxylamide has m.p. 222°[92]).

2). A sludge of succinic anhydride (2.5 g.) in tetrachloroethane (30 c.c.) was added to a stirred ice cold suspension of anhydrous aluminium chloride (10 g.) and durene (3.35 g.) in tetrachloroethane (60 c.c.) over a period of 30 minutes. After stirring at 0° for 4 hours more and standing overnight

at room temperature the residue was decomposed with ice and concentrated hydrochloric acid and the tetrachloroethane removed in steam. The filtered residue yielded β-duroylpropionic acid (4.1 g.), m.p. 157-159°, which was purified via the sodium salt as described above and gave needles, m.p. and mixed m.p. with acid from carbon disulphide method 160-161° (3.1 g.). Mother liquors yielded only a further quantity (0.7 g.) of β-duroylpropionic acid.

γ-durylbutyric acid. - 1). A mixture of β-durylpropionic acid (2 g.), thionyl chloride (2.5 c.c.), benzene (15 c.c., dry) and pyridine (1 drop) was heated under reflux for 2 hours. Excess thionyl chloride was removed in vacuo and the residue washed with benzene (10 c.c. thrice) which was also removed in vacuo. The residue in benzene (15 c.c.) was added dropwise with shaking to an ice cold solution of diazomethane (from 7 g. nitroso-methylurea) in ether (100 c.c.) and left at room temperature for 4 hours, when the ether was removed in a stream of dry air. A mixture of the residue, dioxan (20 c.c.), ammonia solution (15 c.c., 20%) and silver nitrate solution (3 c.c., 10%) was then heated on the water bath for 2.5 hours and filtered hot, the residue on the paper being washed with hot dioxan (15 c.c.). The cooled combined filtrates were added to water and filtered. γ-durylbutyramide (1.05 g.) so obtained formed plates,

m.p. 171-172°, from ethanol. (Found: C, 76.8; H, 9.5; N, 6.1. $C_{14}H_{21}ON$ requires C, 76.7; H, 9.7; N, 6.4%). The amide (1.05 g.), potassium hydroxide (5 g.) and ethanol (50 c.c.) were heated under reflux for 12 hours. The resulting solution, after distillation of excess ethanol, on acidification yielded γ-durylbutyric acid (0.78 g.) which formed plates, m.p. 139-140°, from cyclohexane. (Found: C, 76.2; H, 9.0. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.1%).

2). A mixture of β-duroylpropionic acid (1.7 g.), potassium hydroxide (0.46 g.), hydrazine hydrate (0.61 g., 90%) and diethyleneglycol was heated in the fashion described by Huang-Minlon[87]. The resultant acid was unchanged β-duroylpropionic acid, m.p. and mixed melting point with original acid 158-160°.

2a). A mixture of β-duroylpropionic acid (1.5 g.), amalgamated zinc (10 g.), concentrated hydrochloric acid (75 c.c.), glacial acetic acid (10 c.c.) and toluene (15 c.c.) was refluxed for 36 hours. Further quantities of zinc (5 g.) and concentrated hydrochloric acid (15 c.c.) were added after 15 hours. When cold, ether was added and the ether layer extracted with potassium carbonate solution, which on acidification yielded an acid (1.2 g.), m.p. 120-125°. This acid, dissolved in hot sodium carbonate solution, yielded

crystals on cooling. The crystalline sodium salt, on shaking with dilute hydrochloric acid, yielded unchanged β-duroylpropionic acid (0.85 g.), m.p. and mixed m.p. with original acid 157-159°. The sodium salt mother liquors, on acidification, yielded, γ-durylbutyric acid (0.21 g.), m.p. and mixed m.p. with specimen from Arndt and Eistert method, 137-140°.

Pentamethylbenzene. - 1). Bischloromethylmesitylene, obtained from mesitylene as described by Nauta and Dienske[84], was most readily reduced by the method described above for bischloromethylxylene. A mixture of bischloromethylmesitylene (75 g.) in toluene (350 c.c.), zinc (150 g. previously treated with copper sulphate solution) and sodium hydroxide solution (300 g. in 3000 c.c.) was stirred whilst heated to 90°. Pentamethylbenzene (25 g.) was obtained by fractional distillation, b.p. 231°, m.p. 53°, of the organic layer.
2). Chloromethyldurene (10 g.) in acetone (150 c.c.) was shaken with hydrogen at ordinary temperatures and pressures in presence of palladium on asbestos (5 g., 6%) as catalyst for 100 minutes. Pentamethylbenzene (8 g.) was obtained.

Chloromethylpentamethylbenzene. - 1). A mixture of pentamethylbenzene (15 g.), concentrated hydrochloric acid (75 c.c) and formaldehyde (7.2 g. and 3 g., 40%) was treated as described above for the preparation of chloromethyldurene. Distilla-

tion, b.p. 148°/14 m.m., yielded chloromethylpentamethylbenzene (12 g.) which formed prisms, m.p. 82-84°, from light petroleum. (Found: C, 73.1; H, 8.8; Cl, 17.9. $C_{12}H_{17}Cl$ requires C, 73.3; H, 8.7; Cl, 18.0%).

2). When hexamethylbenzene (4 g.) and phosphorus pentachloride (5 g.) were heated together at 140° there was obtained as residue a black viscous mass, which, after washing with water and sodium carbonate solution, on distillation, b.p. 170°/20 m.m., yielded chloromethylpentamethylbenzene (0.12 g.), m.p. and mixed m.p. with authentic specimen 82-83°, and hexamethylbenzene (0.31 g.), m.p. and mixed m.p. with authentic specimen 164-168°. The main bulk was a black oily material which did not distil.

Ethyl pentamethylbenzylmalonate. - Chloromethylpentamethylbenzene (12 g.), treated as described above for chloromethyldurene, yielded ethyl pentamethylbenzylmalonate (14.5 g.), b.p. 177-180°/1.5 m.m., which formed needles, m.p. 71-73°, from ethanol. (Found: C, 71.2; H, 8.9. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.8%).

Pentamethylbenzylmalonic acid. - The above ester (14.5 g.) hydrolysed as described above for ethyl β-durylmethylmalonate yielded pentamethylbenzylmalonic acid (9.4 g.) which formed plates, m.p. 191.5° (with evolution of carbon dioxide) from aqueous ethanol. (Found: C, 68.4; H, 7.4.

$C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%).

β-pentamethylphenylpropionic acid. - 1). The above acid (9.4 g.) was heated to 195° until the evolution of carbon dioxide had ceased. β-pentamethylphenylpropionic acid (6.4 g.) so formed, crystallised from benzene in needles, m.p. 175-176°. (Found: C, 76.2; H, 9.3. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.2%).

2). A mixture of β-durylpropionic acid (2 g.), concentrated hydrochloric acid (15 c.c.) and formaldehyde (1.5 c.c., 40%) was stirred at 60° for 6 hours while a stream of dry hydrogen chloride gas was passed through the suspension. After 3 hours a further quantity (1 c.c., 40%) of formaldehyde was added. The resultant suspension, whilst still hot, was poured into water and filtered. β-(p-chloromethyldaryl)propionic acid (1.9 g.) so obtained formed needles, m.p. 216-218°, from dioxan (twice). (Found: C, 66.2; H, 7.5; Cl, 14.1. $C_{14}H_{19}O_2Cl$ requires C, 66.0; H, 7.5; Cl, 13.9%). β-(p-acetoxymethyldaryl)propionic acid, obtained by treatment of the above acid with sodium acetate, formed long fine needles, m.p. 203-204°, from aqueous acetic acid. (Found: C, 69.0; H, 8.0. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%). β-(p-hydroxymethyldaryl)propionic acid, formed by sodium carbonate hydrolysis of either of the two acids above, crystallised from ethyl acetate in short firm

needles, m.p. 212-214°. (Found: C, 71.4; H, 8.4. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%). In one run of the chloromethylation where acetic acid was present as solvent, there was obtained β-(p-acetoxymethylduryl)propionic acid, m.p. and mixed m.p. with specimen prepared above 201-203°; which on hydrolysis yielded β-(p-hydroxymethylduryl)propionic acid, m.p. and mixed m.p. with authentic specimen, 211-213°. Mother liquors from crystallisation of the acetylated acid, obtained directly, yielded an acid which on sodium carbonate hydrolysis gave an acid, which formed micro-needles, m.p. 100-102°, from benzene (thrice). (Found: C, 71.3; H, 8.4. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%).

β-(p-chloromethylduryl)propionic acid (0.3 g.) in acetone (15 c.c.) was shaken with hydrogen and palladium black (0.03 g.) at ordinary temperatures and pressures for 60 minutes. The product, β-pentamethylphenylpropionic acid (0.21 g.), formed needles, m.p. and mixed m.p. with acid obtained by method 1) 173-174°, from benzene.

γ-pentamethylphenylbutyric acid. - β-pentamethylphenylpropionic acid (2.4 g.) by the Arndt and Eistert procedure as described for β-durylpropionic acid above, yielded γ-pentamethylphenylbutyramide (1.15 g.) which formed micro-niddles, m.p. 184-186° from benzene. (Found: C, 77.4; H, 10.2; N, 6.4. $C_{15}H_{23}ON$ requires C, 77.2; H, 9.9;

N, 6.0%). The amide on hydrolysis by the procedure used for γ-durylbutyramide above, yielded γ-pentamethylphenylbutyric acid (0.7 g.) which formed plates, m.p. 157-158°, from benzene. (Found: C, 76.8; H, 9.4. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.5%).

Isomerisations and cyclisations with anhydrous hydrogen fluoride. - The substance to be investigated (1 g.) was left in contact with anhydrous hydrogen fluoride (25-30 c.c.) for 36-48 hours. The residue, poured on ice, was extracted with ether which was then extracted with sodium carbonate solution. The ether extract was dried over anhydrous sodium sulphate whilst the alkaline extract was boiled with animal charcoal for 1 hour, filtered and the filtrate acidified.

1). Durene. - No acidic material was obtained from the alkaline extract. The ether extract yielded durene (0.96 g.) m.p. 75-78°, which, on crystallisation from aqueous alcohol, gave a pure product (0.84 g.), m.p. and mixed m.p. with authentic specimen of durene 78-79°.

2). Durylcarboxylic acid. - The carbonate extract yielded an acid (0.90 g.) which formed needles, m.p. and mixed m.p. with authentic specimen of durylcarboxylic acid 177-178°, from light petroleum. The ether extract, on distillation, left no residue.

3). Durylacetic acid. - The carbonate extract yielded an acid (0.92 g.) which formed needles m.p. and mixed m.p. with authentic specimen of durylacetic acid 195-197°, from benzene. The ether extract left no residue on distillation.

4). β-durylpropionic acid. - The carbonate extract yielded unchanged β-durylpropionic acid (0.7 g.) which crystallised from benzene in needles, m.p. and mixed m.p. with authentic specimen 167-169°. The ether extract yielded a brown gum (0.25 g.) which solidified on standing. The solid material, dissolved in benzene, was passed through a column of alumina (2 cm. x 1.5 cm.), which had previously been heated to 250° in vacuo for 2 hours. No evidence of the formation of bands was noted. Distillation of the eluted benzene yielded a pale yellow solid which crystallised from light petroleum in white needle clusters (Ketone A) and large yellow prisms (Ketone B) which were mechanically separated.

Ketone A formed a red 2,4-dinitrophenylhydrazone which decomposed above 250° without melting. A, i.e., 4,5,7-trimethylindan-1-one (ca. 0.04 g.) formed long fine needles, m.p. 104-105°, from light petroleum (thrice). (Found: C, 82.5; H, 8.0%; M, 199 (Rast). $C_{12}H_{14}O$ requires C, 82.7; H, 8.1%; M, 174). Any yellow prisms, which separated during purification of A, were removed by hand. The oxime, made in the usual fashion in presence of

sodium hydroxide, formed needles, m.p. 223-224°, from benzene, light petroleum. (Found: C, 76.3; H, 7.8; N, 7.6. $C_{12}H_{15}ON$ requires C, 76.2; H, 8.0; N, 7.4%). The oxime (0.03 g.) was refluxed for 2.5 hours with dilute hydrochloric acid (2 c.c.) and a little ethanol. The product formed needles, m.p. and mixed m.p. with original ketone 103-104° from light petroleum.

Ketone A (0.15 g.) was heated in a sealed tube to 175° for 6 hours with nitric acid (1 c.c., sp.gr. 1.42) and water (2 c.c.). The resulting solution was evaporated to dryness and the residue in dry ether esterified using diazomethane (from 4 g. nitrosomethylurea). The product formed needles, m.p. and mixed m.p. with specimen of methyl benzenepentacarboxylate prepared by oxidation and esterification from pentamethylbenzene 144-146°, from methanol (twice). (Cf. (89,90)).

Ketone B formed an orange 2,4-dinitrophenylhydrazone which decomposed without melting above 260°. B, i.e., 4,5,6,7-tetramethylindan-1-one (ca. 0.05 g.) formed colourless plates, m.p. 150-151°, from light petroleum (thrice). (Found: C, 82.8; H, 8.6%; M, 172 (Rast). $C_{13}H_{16}O$ requires C, 82.9; H, 8.6%; M, 188). Traces of trimethylindanone were best removed by crystallisation from hexane; trimethylindanone crystallised out first and was removed by filtration.

Evaporation of the filtrate yielded ketone B which was then purified by crystallisation from light petroleum. The oxime formed needles, m.p. 211-213°, from ethanol. (Found: C, 77.0; H, 8.4; N, 7.2. $C_{13}H_{17}ON$ requires C, 76.8; H, 8.4; N, 6.9%). The oxime, hydrolysed as described above for trimethylindanone oxime, yielded tetramethylindanone which formed plates, m.p. and mixed m.p. with original ketone 149-150°, from light petroleum. Oxidation of ketone B with dilute nitric acid as described above for trimethylindanone followed by esterification, yielded methyl mellitate which formed plates, m.p. and mixed m.p. with authentic specimen 187°, from methanol (twice).

γ-durylbutyric acid. - The carbonate extract yielded unchanged γ-durylbutyric acid (0.36 g.), m.p. and mixed m.p. with original acid 138-139°, after crystallisation (once) from cyclohexane. The ether extract yielded a brown solid (0.5 g.) which after charcoaling, crystallised from ethanol (thrice) in white needles, m.p. 106-107°, of 5,6,7,8-tetramethyl-1,2,3,4-tetrahydronaphthalen-1-one. (Found: C, 83.4; H, 9.0%; M, 200 (Rast). $C_{14}H_{18}O$ requires C, 83.1; H, 9.0%; M, 202). The oxime formed small needles, m.p. 186-187°, from ethanol. (Found: C, 77.2; H, 8.8; N, 6.6. $C_{14}H_{19}ON$ requires C, 77.4; H, 8.8; N, 6.5%). Hydrolysis of the oxime as described for trimethylindanone oxime, yielded,

after crystallisation from ethanol, needles, m.p. and mixed m.p. with tetramethyltetralone 105-106°.

Oxidation and esterification of the ketone as described above for trimethylindanone gave after crystallisation (twice) from methanol, methyl mellitate, m.p. and mixed m.p. with authentic specimen 185-186°.

6). β-pentamethylphenylpropionic acid. - The carbonate extract yielded unchanged acid (0.37 g.), m.p. and mixed m.p. with authentic specimen of β-pentamethylphenylpropionic acid 175-177°, after crystallisation from benzene. The ether extract yielded a yellow gum (0.54 g.) which, dissolved in benzene, was passed through a column of alumina (2 cm. x 1.5 cm.). The eluted benzene solution yielded a yellow solid which formed colourless plates, m.p. and mixed m.p. with a specimen of tetramethylindanone prepared from β-duryl-propionic acid 150-152°, from light petroleum (twice). (Found: M, 197 (Rast). $C_{13}H_{16}O$ requires M, 188). The oxime formed needles, m.p. and mixed m.p. with specimen prepared above from β-durylpropionic acid 213-214°, from ethanol. Oxidation and esterification, as described above for trimethylindanone, of this ketone yielded methyl mellitate, m.p. and mixed m.p. with authentic specimen 187-188°, after crystallisation (twice) from methanol.

7). γ-pentamethylphenylbutyric acid. - The carbonate extract

gave unchanged acid (0.92 g.), m.p. and mixed m.p. with authentic specimen 155-156°, after crystallisation from benzene. The ether extract on distillation gave only a trace of neutral product.

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