STUDIES IN MEDIUM-SIZED-RING COMPOUNDS

T H E S I S

presented to the University of Glasgow

for the degree of Doctor of Philosophy

by

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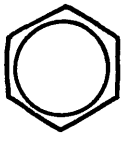
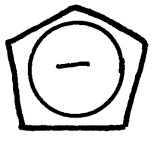
The term "aromatic" was first applied to a group of organic substances which were aromatic in that they possessed characteristic odours. It was soon recognised that these compounds were derived from benzene, and so the term "aromatic" first acquired a structural significance. The criteria of aromatic character which emerged from this classification were that the compound should have considerably less hydrogen than might have been expected on the basis of carbon analysis, but should not be noticeably unsaturated toward reagents; and that the aromatic nucleus should survive unchanged throughout a reaction in which substituent groups took part.

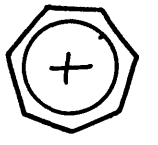
The first period of observation and classification was followed by one of rationalisation, in which the names of Claus, Dewar Armstrong, Baeyer, Thiele, and notably Kekule were prominent. Thiele's structure for benzene (I) depicts as well as possible the modern view of the structure of benzene as based on molecular orbital theory.



I



II

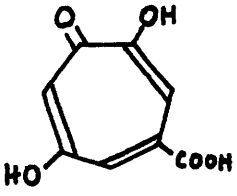


III

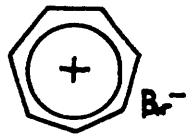
The modern period may be considered to date from the work of G.N. Lewis (1916) in which the structure of benzene was interpreted in terms of the recently-developed theory of the covalent bond, and the term "resonance" introduced. The significance of the "aromatic sextet" was recognised in 1926 by Armitt and Robinson, and Huckel[1] used molecular orbital theory to show that aromatic properties would in general be associated with those rings having $(4n + 2)$ π-electrons. It is on this basis that the aromatic nature of the cyclopentadienyl anion (II) and the cycloheptatrienyl cation (III) was anticipated. The cyclopentadienyl anion is very stable indeed, and Thiele[2] had in fact obtained its potassium salt in 1901.

The study of seven-membered ring aromatic compounds dates from 1945 when Dewar[3] invoked the now familiar 2-hydroxy-2:4:6-cyclo heptatrien-1-one structure to rationalise the known properties of stipitatic acid (IV), but there are several descriptions in the early literature of compounds which can be seen in retrospect to have been of troponoid type. Thus Merling[4] had, without realising it, obtained tropylium bromide (V) more than fifty years earlier. Our work suggests that the compound obtained by Kipping[5] in 1901 by bromination of benzosuberone was a tropone derivative (VI). The alkaloid colchicine

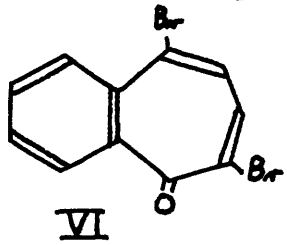
(VII), a tropolone derivative, was isolated in 1833, while its therapeutic properties were documented by Dioscorides in 78 A.D..



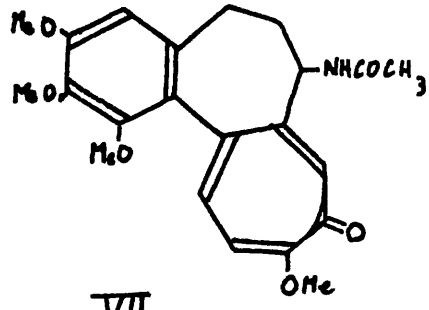
IV



V



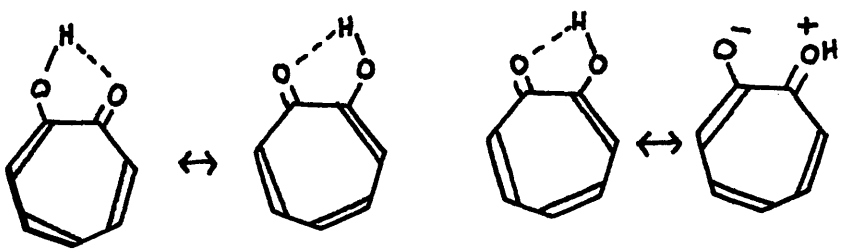
VI



VII

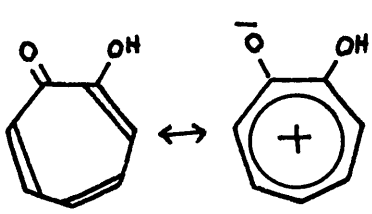
Early attempts to explain the aromatic character of tropolones in terms of the fine structure of the molecule were reviewed by Cook and Loudon[6] in 1951. Dewar's original suggestion[3] was that hydrogen-bonding was of prime importance, involving resonance forms like (VIII), but he very soon abandoned this view in favour of the suggestion that ionic forms like (IX) made the chief contribution.[7] Koch[8] supports this view on the basis of a very detailed analysis of infra-red data, but decides against the possibility of resonance degeneracy in tropolone being sufficient to make the bonds between the proton and the two oxygen atoms equivalent: he attributes the symmetry of tropolone to a very fast proton oscillation, so that the hydrogen atom is shared equally between the two oxygens on a time-average basis. All of these views,

and others which consider tropolone as a vinylogue of a carboxylic acid or of a β-diketone[9], can be used to some extent to explain the properties of tropolone; but they are all open to the criticism[6] that the 1:2 carbon-carbon bond is formulated as a "long" bond, devoid of double-bond character. This, as was conclusively shown in 1951 by the X-ray work of Robertson[10], is not the case: the tropolone ring is revealed as a flat, regular heptagon.

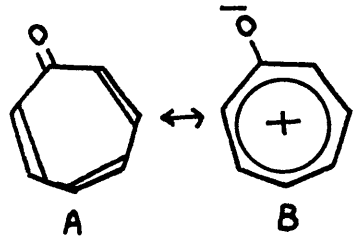


(VIII) (IX)

It is widely accepted[22,33,35,57], that the tropylium ion (III) is the fundamental aromatic unit in this series, and the more recent view is that tropolone must owe its symmetry and aromatic character in large measure to the participation of tropylium structures (XI) in the resonance hybrid. X-ray[10], dipole[11,12], and electron-diffraction[13] measurements are in good agreement with this view. As an extension of this it might be anticipated that cycloheptatrienone (tropone) (XII) should be an aromatic compound, in fact the parent of the series, to which tropolones should bear the relationship simply of hydroxyl derivatives.



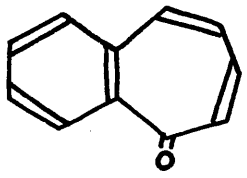
XI



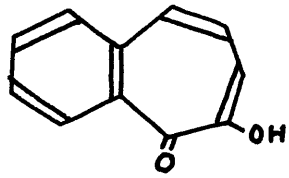
XII

This view was in fact fairly widely expressed in the literature[14-18] with little or no chemical evidence to support it.

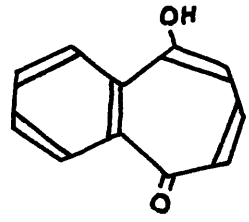
It was the aim of this work to establish, in the first place, a reliable synthetic route to a tropone, and thereafter to examine the properties and reactions of the compound for evidence of aromatic character. For this purpose the benzotropone (XIII) was selected. It was recognised that the fused benzene ring would modify the properties inherent in the tropone ring, but the benzo compound promised to be more easily handled than (XII), and offered the possibility that reactivity of the benzene and tropone rings might be compared. This choice had the added advantage that it allowed us to compare the properties of the tropone with those of its two hydroxy derivatives (XIV) and (XV) which were available to us[19,20]. In both of these compounds the presence of the benzene ring modifies, but does not extinguish, the aromatic character of the seven-membered ring.



XIII



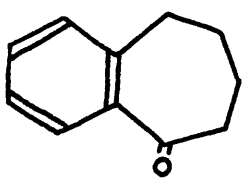
XIV



XV

2:3-Benzotropone (XIII) had previously been prepared by Eschenmoser[21] and his collaborators, but was obtained only in quantity sufficient for the measurement of some physical properties and preparation of derivatives. The route employed in their work was intrinsically not applicable to the preparation of (XIII) in quantity, involving as it does the benzoisotropolone (XV) as an intermediate; this compound is not readily accessible[21], even using the improved preparation reported by Buchanan and Sutherland[22].

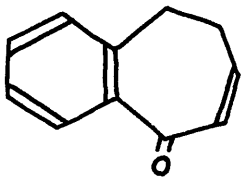
The first requirement in this work was the establishment of a method whereby a 2:3-benzotropone might be obtained in quantity. Two routes based on 2:3-benzocycloheptenone ("benzsuberone") (XVI) have been established.



(XVI)

2:3-Benzosuberone (XVI) was prepared by a modification of the method described by Cook et.al.[20]; cinnamaldehyde was condensed with malonic acid in presence of piperidine to yield cinnamilidenemalonic acid (XVII), which was hydrogenated by treatment with Raney nickel alloy in hot sodium hydroxide solution. The resulting 3-phenylpropylmalonic acid (XVIII) was decarboxylated to δ-phenylvaleric acid (XIX) by heating with copper powder. Treatment of the acid (XV) with polyphosphoric acid and working up by the method reported[20] gave about 50% of the theoretical yield of cyclic ketone: it was found that yields of up to 75% could be obtained by distilling the ketone from the reaction mixture.

The first approach to 2:3-benzotropone (XIII) which was envisaged was via 2:3-benzocyclohepta-2:3:6:7-diene-1-one (XXI).

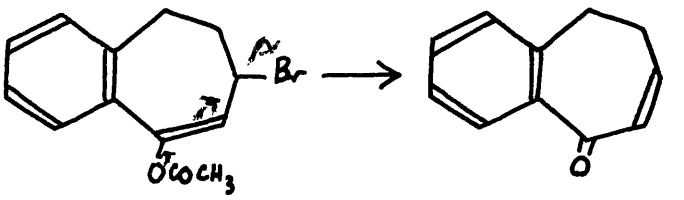


(XXl)

Treatment of 2:3-benzosuberone (XVI) with bromine in carbon tetrachloride or in acetic acid readily gave the α-bromoketone (XX) in nearly theoretical yield. Treatment of this compound with collidine yielded an oil which showed infra-red absorption at 1660 cm^{-1}, (benzosuberone, 1680 cm^{-1}), corresponding to the required αβ, α'β'-unsaturated ketone (XXl); but the product polymerised slowly at room temperature, and more rapidly on warming.

This observation was later confirmed when an account of the work of Julia[24] became available.

An alternative approach involved the enol acetate (XXll) of benzosuberone, prepared by the isopropenyl acetate technique.[25] Treatment of (XXll) with N-bromosuccinimide under the usual conditions for allylic bromination is presumed to yield (XXlll) which spontaneously eliminates acetyl bromide:

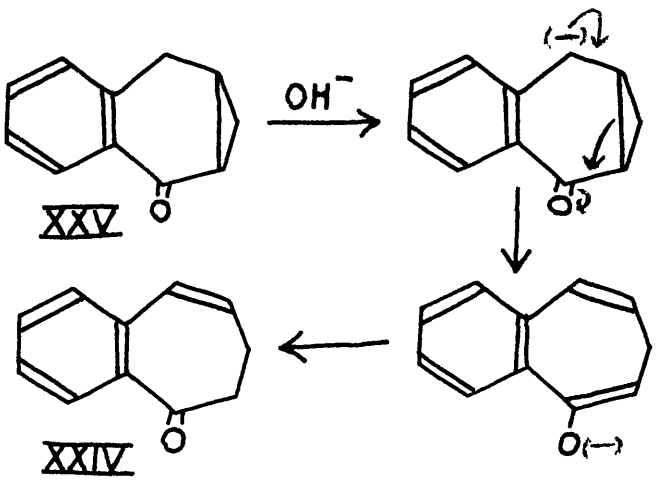


(XXIII) (XXI)

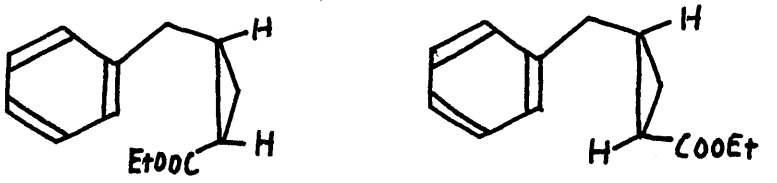
the product was an oil similar to that obtained previously, and which also polymerised.

With the failure of this route, recourse was back to the ketone (XXIV), 2:3-benzocyclohepta-2:3:4:5-diene-1-one, of which the preparation had been reported by Julia[24] from the cyclopropane ketone (XXV) obtained by Buchanan and Sutherland[22].

(a) The rearrangement of the cyclopropane ketone was repeated as described by Julia[24]; conditions considerably more forcing than those reported were used to advantage.



The preparation of the cyclopropane ketone (XXV) reported by Buchanan and Sutherland was reinvestigated. Reaction of allylbenzene and ethyl diazoacetate in presence of copper powder gave a mixture of cis and trans benzylcyclopropanecarboxylates (XXVI); better yields than those reported were obtained by using an excess of allylbenzene, which was recycled.



(XXVI)

Hydrolysis of this mixture of esters to the corresponding acids, and Friedel-Crafts cyclisation of the acid chlorides, gave the required 2:3-methylenetetralone-1 (XXV) in 40% yield.

The original workers reported[22] that the ratio of cis isomer (which alone is capable of cyclising) to trans isomer, was 10:1; this was computed on the basis of a low yield of trans acid anilide obtained from uncyclised material in one experiment. Since their yield of the cyclopropane ketone (XXV) was in no case greater than 50%, and since in our hands yields of trans acid anilide approaching 50%

have been consistently obtained, it seems probable that the ratio of isomers is in fact 1:1. There seems a priori to be no reason for preferential formation of the cis isomer. The postulated mode of action of diazoacetic ester (XXVIIa) involves decomposition (on the metal surface) to the di-radical (XXVIIb) which then attacks the electron-rich double bond of the allylbenzene. Since both reactants are

$$N\equiv\overset{+}{N} - \overset{-}{C}H - COOEt \qquad\qquad :CH - COOEt$$

(XXVIIa) (XXVIIb)

symmetrical, it is obvious that it can do this with equal facility from either side.

The possibility which remains is that the cis-form is the more stable, and that equilibration takes place during working-up; but the indications from the literature[26] are that, as might be anticipated, the trans form would in fact be the more stable.

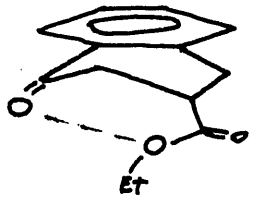
This approach to the cyclopropane ketone (XXV) had thus the inherent disadvantage that one stage had a maximum yield of 50%, so an alternative route to (XXIV) was explored. This involved the preparation of 3-hydroxymethyltetralol-1 (XXXIV).

Preparation of 3-hydroxymethyltetralol-1 (XXXIV).

Condensation of benzaldehyde and diethyl succinate gave the half-ester (XXIX) which was hydrolysed to the dicarboxylic acid (XXX). Treatment of (XXX) with Raney nickel/aluminium alloy in sodium hydroxide solution gave the saturated di-acid (XXXI), benzylsuccinic acid, which cyclised in sulphuric acid to 3-carboxytetralone (XXXII). This keto-acid gave the keto-ester (XXXIII) in surprisingly poor yield using ethereal diazoethane, and in excellent yield using the toluene azeotropone technique with sulphuric acid catalyst. The products (solid) were identical in each case, and the possibility of rearrangement of the keto-acid in presence of sulphuric acid is thus eliminated.

An attempt to prepare the ketal of (XXXIII) using ethylene glycol with p-toluenesulphonic acid catalyst, returned starting material: this is not surprising in view of the difficulties experienced in comparable cases.[27]

Reduction of the keto-ester (XXXIII) with lithium aluminium hydride in ether gave an excellent yield of the crystalline diol (XXXIV). It is noteworthy that only one stereoisomer was obtained: this might be explained by a 1:3 interaction of the type shown below:



It had been intended to carry out a selective tosylation of the diol, leading eventually to the ketone (XXXV) from which the cyclopropane ketone might have been prepared: but initial tosylation experiments were not encouraging, and when a simpler route to the dieneone (XXIV) became available this whole approach was abandoned.

Two alternative approaches to the ketone (XXIV) were investigated.

(b) 2;3-Benzocycloheptan-1:4-dione (XXXVII) was obtained as described by Buchanan and Sutherland[22], by acid hydrolysis and decarboxylation of the diester (XXXVI). As reported, the diketone (XXXVII) was found to reduce with zinc in acetic acid only as far as the mono-hydroxy compound (XXXVIII). Treatment of this 4-hydroxy-2:3-benzcycloheptan-1-one with thionyl chloride/pyridine, or (better) distillation from boric acid, effected dehydration to the required ketone (XXIV). This was in fact the first proof of the position of the double bond in (XXIV).

(c) Reaction of 2:3-benzosuberone with 1 mol. of N-bromo succinimide (in the usual conditions for allylic bromination) and treatment of the crude product with collidine also gave the required 2:3-benzocyclohepta-2:3:4:5-diene-1-one (XXIV) in fair yield.

This is the most convenient route to the ene-one (XXIV) and with this established we proceeded to investigate its oxidation to benzotropone (XIII).

Preparation of 2:3-benzotropone.

The unsaturated ketone (XXIV) obtained by these methods was readily oxidised to 2:3-benzotropone (XIII) by selenium dioxide, and the product, although contaminated with colloidal selenium, was identified by comparison of its 2:4-DNP and picrate with authentic samples.[x] The selenium could not be removed completely by any of the reported procedures, and this fact was a major drawback in this approach. However, treatment of the unsaturated ketone (XXIV) with N-bromosuccinimide gave 2:3-benzotropone directly, presumably by elimination of hydrogen bromide from the mono-bromo intermediate (XLl). This preparation thus avoids the use of selenium dioxide, and represents an acceptable route to the tropone.

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[x] We are grateful to Dr. Eschenmoser for kindly supplying samples.

We have found, however, that the method of choice for the preparation of 2:3-benzotropone is bromination (with NBS) of the α-bromoketone (XX), whereby there is obtained 4:7-dibromo-2:3-benzo cycloheptanone (XLII) which is readily dehydrobrominated by collidine to the tropone.

The radical bromination stage was found to be extremely capricious: whilst in favourable cases yields of up to 65% of tropone could be realised, in other cases under essentially identical conditions the yield of tropone was negligible or zero. This is considered to have been due to the reagent undergoing heterolytic rather than homolytic fission with resulting ionic bromination of the position α to the carbonyl group. Dehydrobromination of the resulting gem-dibromoketone would produce an αβ, α'β'-unsaturated ketone (XLIII), and it is significant that in preparations giving a low yield of 2:3-benzotropone, an unstable bromine-containing by-product was obtained with infra-red absorption at 1660 cm^{-1}.

There are many examples in the literature of N-bromosuccinimide reacting in such a manner; see, e.g. Chapman and Williams.[28]

The intermediate dibromo-ketone (XLII) could be isolated by distillation, only at the expense of great loss in yield due to charring; normally the product from the NBS reaction was treated with callidine without purification.

The dibromo compound (XLII) when obtained was a crystalline solid (m.p. 79°) and was stable for a few days at 20° or for several months at 0°C. However, on prolonged standing at room temperature, hydrogen bromide was spontaneously eliminated, and the dibromo compound was completely converted to 2:3-benzotropone hydrobromide (XLIV). Treatment of the dibromo compound (XLII) with dilute ethoxide in ethanol readily afforded 2:3-benzotropone, identified as its 2:4-DNP. Use was made of the marked basicity of 2:3-benzotropone in effecting its purification. The crude mixture from the collidine dehydrobromination stage was dissolved in chloroform, and extraction of this solution with dilute acid removed the collidine: concentrated hydrochloric acid was then used to extract the chloroform solution and a deep yellow solution of benzotropone hydrochloride obtained, from which benzotropone was regenerated on dilution with water. The pale yellow oil was separated and distilled.

This gave 2:3-benzotropone as an almost colourless liquid, b.p. 102-104°/0.003 mm.; 140-144°/0.1 mm..

2:3-Benzotropone - properties and reactions.

2:3-Benzotropone could be stored unchanged at 0°C, but darkened slowly in air at room temperature. It is very pale yellow in colour; this colour is greatly intensified when the tropone dissolves in strong acid to produce the hydroxybenzotropylium cation (XLV). This intensification of colour is reflected in the bathochromic drift of the long-wavelength absorption band (319 mμ → 404 mμ), which is observed when the tropone is dissolved in acid.

The tropone is recovered unchanged from acid solution on neutralisation or on dilution with water. Much more significantly a solution of benzotropone in concentrated sulphuric acid was heated to 280-300°C for ten minutes with little darkening of colour, and benzotropone was recovered unchanged on dilution of the cooled solution.

We were mainly interested in assessing the aromatic character of 2:3-benzotropone, and to this end its reactions were considered under three main headings,

(1) Miscellaneous reactions.

(2) Behaviour towards electrophilic reagents.

(3) Behaviour towards nucleophilic reagents.

These are considered in turn.

(1) Miscellaneous Reactions.

As reported by the Swiss workers[21], 2:3-benzotropone readily yielded a picrate, and a maleic anhydride adduct which is formulated as (LXVI). Benzotropone is not an effective dienophile; there is no reaction with butadiene under conditions in which it readily adds to maleic anhydride.

In common with other tropones but in contrast to the tropolones, 2:3-benzotropone behaves fairly normally as a ketone; it readily forms a 2:4-DNP under standard conditions, and is reduced to an alcohol with lithium aluminium hydride[21].

Unchanged starting material was recovered when attempts were made to epoxidise benzotropone with alkaline hydrogen peroxide or with perbenzoic acid.

Benzotropone gives a strong yellow colour with tetranitromethane, and rapidly decolourises aqueous potassium permanganate, and bromine water.

(2) Behaviour of Benzotropone towards Electrophilic Reagents.

(a) Bromination Experiments.

(b) Nitration Experiments.

Bromination Experiments.

When 2:3-benzotropone is treated with bromine in carbon tetrachloride or in acetic acid, there first separates an orange-red solid which cannot be purified, and which is inferred to be a complex of the kind reported by Cook et.al.[29] in the case of tropolone, and by Nozoe et.al.[30] in the use of tropone.

(Treatment of benzotropone with iodine gives a dark grey-green complex with a metallic lustre, again corresponding to the previous reports on tropolone and tropone).

The fact that complexes of this type are given by tropones as well as by tropolones suggests that the complex formation is a function of the tropone or tropylium nucleus, and would tend to discredit the suggestion by Cook et.al. that the tropolone hydroxyl group is involved. The fact that a number of polycyclic aromatic compounds[31] and even benzene[32] form complexes with halogens may be of some relevance in this connection.

On warming the benzotropone/bromine complex it redissolves, and the colour is discharged; there is no noticeable evolution of hydrogen bromide. Addition of a further quantity of bromine solution, until the bromine colour is no longer discharged, and removal of solvent,

gave a white solid. This is 4:5:6:7-tetrabromo-2:3-benzocycloheptanone (XLVII) or "benzotropone tetrabromide". The same compound was obtained by treating a solution of benzotropone with the equivalent quantity of bromine; at no time during the reaction was any hydrogen bromide evolved.

Treatment of 2:3-benzotropone with excess of liquid bromine, without temperature control, gave very readily an excellent yield of a dibromo-compound which is formulated as (XLVIII). There was copious evolution of hydrogen bromide during the reaction. The fact that the compound (XLVIII) is a tropone, follows from its analysis, I.R. spectrum (carbonyl absorption at 1634 cm^{-1}), basicity, and ability to withstand boiling concentrated sulphuric acid; the orientation of the bromine substituents in the seven-membered ring is less certain, but will be argued below.

From the ethyl acetate mother-liquors from which this dibromo-compound (XLVIII) had been crystallised, there was obtained a small quantity of a tribromocompound which was not a tropone, and which is formulated as (X), 4:5:7-tribromo-2:3-benzocyclohepta-2:3:6:7-diene-1-one.

It was found that when either the tetrabromo-compound (XLVII) or the tribromo-compound (X) was heated above its melting-point, it lost

hydrogen bromide: in each case the product was shown to be the dibromo-benzotropone (XLVIII) obtained by treatment of benzotropone with liquid bromine. Similarly, in both cases the dibromotropone was obtained on treatment with collidine or with alkali. Sodium bicarbonate solution and a weakly basic resin, both removed 2HBr from the tetrabromide; but using exactly 1 mol. of decinormal sodium hydroxide in presence of a little methanol, the tribromo-compound (X) could be isolated.

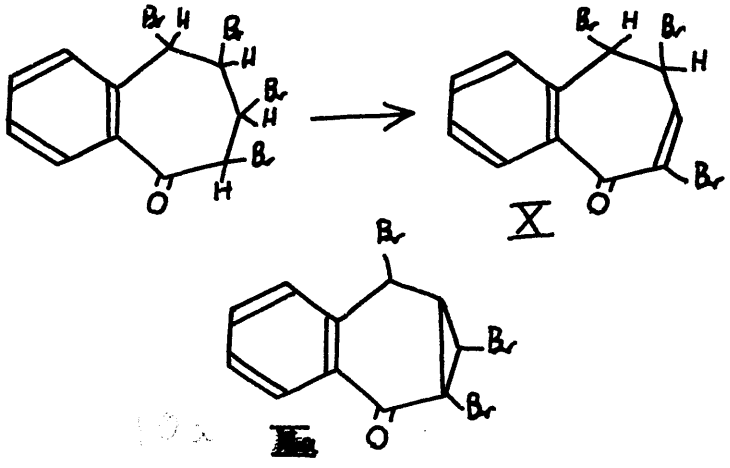
It has been known for some time[5] that 2:3-benzosuberone (XVI) yields a solid product when treated with bromine. We have re-examined this reaction, and obtained the solid product, to which we assign the tropone structure (VI) i.e. (L). The fact that the compound is a tropone follows from its analysis, spectra, (see appendix) and the practically diagnostic stability in boiling sulphuric acid. This dibromobenzotropone is different from that obtained by bromination of benzotropone; but the same compound as that obtained from benzotropone, was found to be obtained also when Julia's ketone (XXIV) was treated with liquid bromine.

Both of the dibromobenzotropones, and the tribromo-compound, were oxidised to phthalic acid, eliminating the possibility that substitution had occurred in the benzene ring; none of these compounds could be made to yield a 2:4-DNP.

The results of these bromination experiments may be rationalised as follows:-

The structure of the tetrabromide (XLVII) is definitely established on the basis of its analysis and the fact that exactly 2 mols of bromine were consumed in its formation, with no trace of hydrogen bromide evolved.

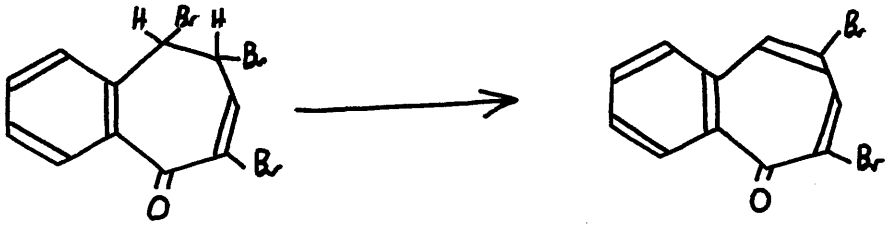
[While there are four asymmetric centres in this molecule, the number of isomers possible must be controlled by steric factors].



X

Removal of one molecule of hydrogen bromide from this molecule would obviously be most facile if the hydrogen in the position α to the carbonyl were involved: that the product obtained is in fact the α,β-unsaturated ketone (X) and not a cyclopropane compound such as (Xa), follows from the carbonyl absorption of the product (1665 cm^{-1}), and from the fact that only phthalic acid could be isolated on oxidation.

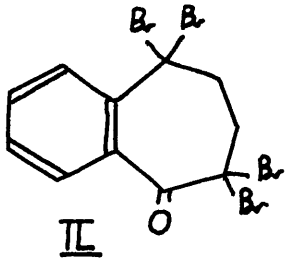
A cyclopropyl phenyl ketone of this type would be expected[22] to absorb at 1680 cm^{-1}, and it has been shown[22] that such compounds are resistant to oxidation.



XLVIII

The appearance of the 6:7-double bond would be expected to make the hydrogen atom in the 5-position the more labile of the two still able to eliminate, and on this basis the product expected is that formulated as (XLVIII).

The fact that a different dibromobenzotropone is obtained by bromination of benzosuberone, can also be taken into account. It is very probable, both on mechanistic grounds and by analogy with the bromination of cycloheptanone, that the intermediate in the formation of the tropone inferred to be (VI) is the tetrabromo-compound (IL) formed by di-bromination α to the carbonyl group, and in the benzylic position; there is in this case only one possible dehydrobromination product. Thus, there is in each case good reason to believe that one bromine



II

substituent is in the 7-position, α- to the carbonyl group: further weight is given to this by the fact that in common with known α-bromo tropones[55] neither of the dibromotropones can be made to form a 2:4-DNP, which benzotropone itself does readily. The position of the second bromine atom is not definitely established in either case, but there is considerable evidence to support the structure assigned.

Several attempts were made to effect a tropolone-type ring contraction of the dibromobenzotropones, by treatment with base. In some experiments a resinous acid product was obtained which could not be purified, but in general the dibromotropone was either recovered or destroyed depending on the severity of the conditions.

The results of these attempts are summarised in Table I.

Table I.

Compound	Reagent	Temp.	Result
5:7-dibromo ( )	10 N NaOH	100°	Acidic resin
"	10 N NaOH under N_2	100	"
"	KOH in ethylene glycol	140	"
"	KOH/methanol	70	tar
"	2 mol. MeONa/16 hrs.	20	starting material
"	1 mol. MeONa/16 hrs.	20	"
"	sodamide/NH_3		resin
"	liq. NH_3		starting material
"	liq. NH_3/methanol		"
"	sulphuric acid	300	"
"	hydrochloric acid/ ethanol	80	"
4:7-dibromo ( )	10 N KOH	100	"
"	10 N KOH + ethanol	100	resin
"	KOH	200	"
"	KOH/ethylene glycol	120-140	"
"	sulphuric acid	300	starting material

The rearrangement to benzenoid compounds in alkaline or sometimes in acid media[55] is general for tropolones and α-halotropones, but there are several instances of compounds failing to ring-contract which have an additional hydroxyl or halogen substituent in the ring.[55] The case of dibromobenzotropones may well be a further example of this.

(b) Nitration of benzotropone.

The remarkable stability of 2:3-benzotropone in sulphuric and hydrochloric acids has been noted. In marked contrast to this, the tropone was found to be readily attacked by "nitrating mixture", nitric acid, 50% aqueous nitric acid, or nitric acid in carbon tetrachloride, to give in each case a good yield of a nitro derivative which is formulated as the dinitrobenzotropone (LIII).

When a few milligrams of nitric acid were added to excess of benzotropone, a white crystalline material separated. This was too unstable to be analysed, but from the fact that benzotropone was regenerated on addition of water, and from the infra-red spectrum (NO_3^- absorption at 1385 cm^{-1}) it is probably the nitrate (LI) of benzotropone.

Dinitrobenzotropone (LIII) was produced in the course of a few hours when benzotropone was treated with nitric acid. The

appearance of the nitro-compound was accompanied by the evolution of oxides of nitrogen from the mixture. Since benzotropone exists in solution in strong acid as the positively-charged hydroxybenzotropylium ion (XLV), it was considered unlikely that the nitration was accomplished by the normal mechanism of electrophilic attack of NO_2^+. From the fact that nitrogen oxides were always observed in the reaction, and the observation that better yields were obtained with nitric acid alone than with nitrating mixture, the possibility was considered that this was an addition/elimination reaction of N_2O_4, the latter produced by a mutual oxidation/reduction of benzotropone and nitric acid.

That this was indeed the case was confirmed by treating benzotropone with dinitrogen tetroxide. A stream of the gas in dry nitrogen was bubbled into a solution in carbon disulphide of benzotropone. A globule of dark oil collected, and at the end of the reaction was obtained as a pasty solid on removing solvent under vacuum at $0^{\circ}C$. Even at this temperature the solid was visibly losing "brown fumes"; and in the course of a few minutes the evolution of nitrogen oxides ceased. The product - now yellow - was found to be identical with the dinitro-compound obtained previously. The yield of dinitro-compound was in this case almost theoretical.

The structure (LIII) is postulated on mechanistic grounds and by analogy with comparable reaction of benzotropone with bromine.

Dinitrobenzotropone

This appears to be the first nitro-tropone to have been prepared and so its properties are of some interest. That the compound is a tropone follows from its analysis and spectra (see later), its reversible solubility in sulphuric acid and its oxidation to phthalic acid. This degradation proves that the nitro substituents are located in the seven-membered ring. That it is indeed a nitro compound and not a nitrite is indicated by the presence of the characteristic $C = C^{NO_2}$ absorption at 1525 and 1332 cm^{-1} in the infra-red spectrum[50], and by the failure of the sulphuric acid-diphenylamine colour reaction.[34]

The dinitrotropone dissolves readily in aqueous alkali, and even in dilute bicarbonate or ammonia solution: the ultra-violet absorption of the alkaline solution is quite different from that of the solution in ethanol. No identifiable product was obtained on acidification of the alkaline solution. This solubility in alkali must be ascribed to hydration of the nitrotropone; the solubility in alkali of nitroparaffins is well known.[35] Acidification might then be expected to produce a retro-aldol reaction, destroying the seven-membered ring.

The behaviour of the dinitrotropone towards catalytic hydrogenation was quite typical of nitro-alkenes.[36] In neutral solution absorption of hydrogen ceased after uptake of only 3-4 mols, but in acid solution the theoretical amount (9 mols.) was smoothly and rapidly absorbed. The product of the neutral reduction was 2:3-benzosuberone (XVl), the isolation of which incidentally proves that the seven-membered ring system had remained intact during the nitration. The low uptake of hydrogen under these conditions may indicate that the first step in the reaction is hydrogenation of the diene system, followed by elimination of nitrous acid from the product, and finally reduction of the resulting benzotropone.

The product of the hydrogenation in acid would be expected to be the diaminoalcohol (LIV), and in agreement with this the hydrogenation product is more soluble in water than in organic solvents. The aqueous solution consumed periodate, but the product could not be further characterised.

It is seen that benzotropone does not behave as an aromatic compound toward reagents which effect electrophilic substitution in benzene: this is indeed what was expected, having regard to the electron-deficiency of the tropone ring. On this basis also it might

be expected that if benzotropone is to show aromatic character, this would be demonstrated by the behaviour with nucleophilic reagents. Several attempts were made to bring about nucleophilic substitution using sodamide, hydrazine, and aqueous and alcoholic alkali. In each case the tropone was either recovered or destroyed depending on the severity of the conditions. (See Table II).

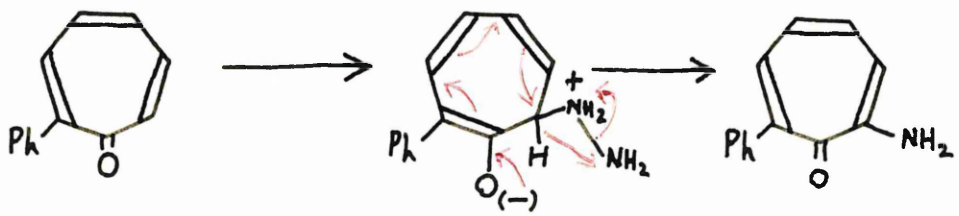
Table II.

Attempted nucleophilic substitution of benzotropone

Reagent	Temp.	Result
2N NaOH	100°	starting material
NaOMe	70	"
KOH/ethylene glycol	120-130	resin
KOH	100-180	charred
$NaNH_2$/liq.NH_3	-30	resin
MeOH/liq.NH_3	-30	starting material
$H_2N.NH_2$/EtOH	80	"
$H_2N.OH$/liq.NH_3	-30	"

There are reports of alkali-catalysed ring-contraction of tropones, such as tropone-4-carboxylic acid (LVI)[37] and 2-phenyltropone (LVII)[38],

and it is postulated that these rearrangements are normal tropolone-type ring-contractions, following on hydroxylation of the tropone in the α-position. However, Nozoe has been unable to bring about a similar reaction with tropone itself.[30] While there does not appear to be an example in the literature of the isolation of a tropolone formed by hydroxylation of a tropone, there are examples of amination of tropones being effected by hydrazine or hydroxylamine. Thus, the phenyltropone[38] (LVII) gives the 2-amino-derivative (LVIII): this reaction has been interpreted[38] as a nucleophilic substitution, the mechanism of which is seen to involve a hydride transfer step (LXII).



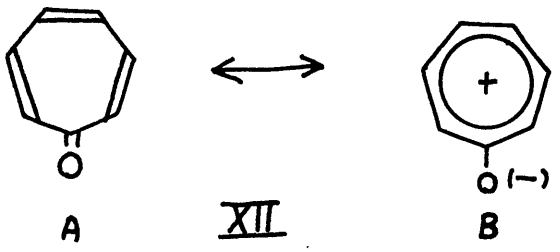
LVII LXII LVIII

This in fact appears to be the only type of case in which tropones undergo substitution in a manner which might be considered indicative of aromatic character, and (with the exception of the purely negative

evidence that we were unable to epoxidise benzotropone) indeed the only piece of chemical evidence pointing to aromatic character is tropones. It will be argued below that an alternative mechanism (LXlll) which does not presuppose aromatic character, is equally valid.

There can be no doubt that tropones are aromatic when physical criteria of aromaticity are applied. Tropone is indeed "a cyclic compound with a large resonance energy where all the annular atoms take part in a single conjugated system", a description which Dewar[52] considers as defining an aromatic compound.

The occurrence of aromatic character in tropone is a result of the canonical form (XllB) making a significant contribution to the "resonance hybrid". All of the physical properties of tropones are in agreement with this suggestion. Possibly most remarkable is the fact that tropone itself is readily soluble in water; the



A XII B

implication of this is that the molecule in the ground state is of a highly polar nature, as in (B). This is reflected very convincingly in the high dipole moment of tropone (4.17D) as measured by Nozoe et.al.[39]. Comparison of this value with the figure of 3.D calculated for cycloheptatrienone[40] would indicate on the simplest approximation that the contributions of the canonical forms (A) and (B) to the resonance hybrid are in the ratio (A):(B) = 1:4. The polarisation of the carbonyl group is reflected also in the very low value for molecular polarisability (9.61 eV) as measured by Nozoe et.al.[41] This contrasts with 9.91 eV measured for cyclohexanone. Electron diffraction studies by Kubo[42] have shown that the carbon-carbon bond lengths in tropone vapour are approximately equal, again indicating that the π-electrons of the triene system are significantly delocalised.

Theoretical approaches to the structure of tropones also point to aromatic character. Thus, following on the preparation of tropone[43,44] in 1951 R.D. Brown[45] using the L.C.A.O. molecular-orbital

approach went so far as to predict that tropone would be an aromatic compound in which diene character would be so reduced that it probably would not react with maleic anhydride, and that it would be sufficiently aromatic to undergo electrophilic substitution in the 2-position. (This latter prognostication received some support soon afterwards when Nozoe[46] reported that bromination of tropone afforded a 2:7-dibromo compound by substitution).

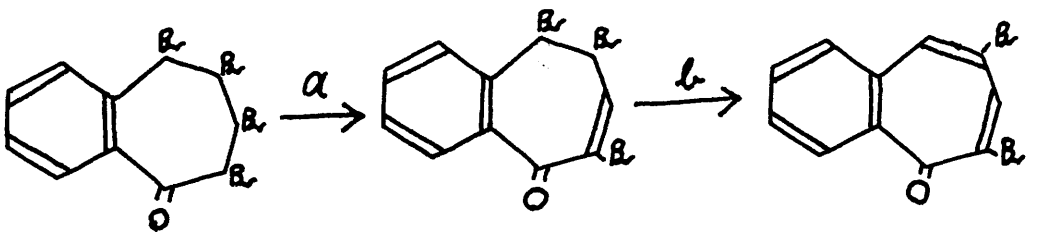
Rather surprisingly there is no reference in the literature to a direct determination of the resonance energy of a tropone from heat of combustion or heat of hydrogenation data, but Hubbard[47] has arrived at a value of 16-24 K.cal/mole by a process of inference based on the measured value (36 K.cal/mole) for tropolone. These figures compare with a value of 6.7 K.cals/mole measured for cycloheptatriene.[48]

The infra-red absorption of tropones gives further evidence for the polarisation of the carbon-oxygen bond. In the case of 2:3-benzotropone there are three bands in the carbonyl region, at 1642, 1612, and 1590 cm^{-1}. While it is not possible to allocate the carbonyl stretching frequency with certainty[11], even 1642 $cm.^{-1}$ is a low value. This may be compared with the value of 1637 cm^{-1} reported by D.H. Reid[49] in the case of perinaphthenone (LXl), in which the carbonyl group is known to be highly polar.

Tropones thus fulfil the physical requirements for aromaticity very adequately. But a further requirement of an aromatic compound is what Sir Robert Robinson has called "reduced unsaturation", and Wilson Baker's[50] definition of an aromatic compound takes account of this:-

"A molecule may be said to be of aromatic type if it is a cyclic unsaturated compound containing at least two double bonds in the ring when represented by conventional symbols, and in which the bonds interact to a greater or lesser extent, thus bringing about a certain stabilisation of the molecule by resonance, which will in consequence be more saturated than if the double bonds were fixed and purely olefinic in character."

Our experiments have shown that 2:3-benzotropone displays little or no "reduced unsaturation". Bromine - the classical reagent for unsaturation - is rapidly absorbed by benzotropone, and it has been shown to <u>add</u> to the double bonds of the tropone ring. The benzotropone tetrabromide does lose hydrogen bromide fairly readily to produce a dibromotropone, and it may be that the attainment of the tropone structure represents a driving force in this reaction: but the crowding of the four bromine atoms and the labilising effect of the carbonyl group are probably more important. It is very significant in this connection that it is possible to dehydrobrominate the tetrabromide (XLVII) <u>stepwise</u> using one equivalent of base (a) when under the conditions of the reaction



XLVII X XLVIII

but with excess base the dehydrobromination goes to completion (b).

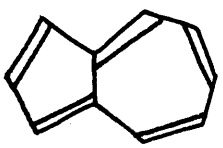
[The early report by Nozoe[46] that bromine reacts with tropone by a substitution mechanism has recently been corrected[51]: it is found that in this case too the dibromotropone (LIX) finally obtained is the result of elimination of hydrogen bromide from an intermediate tetrabromo addition product (LX)].

The remarkable stability of benzotropone and substituted benzotropones in boiling sulphuric acid has been noted, and while this stability is indicative of aromatic character, it is not that of benzotropone but of the hydroxybenzotropylium ion, in which form benzotropone exists in sulphuric acid of strength greater than about 50%. While benzotropone does react with nitric acid, this has been shown to be not substitution by NO_2^+ or NO_3^-, but addition of N_2O_4 followed by elimination of HNO_2.

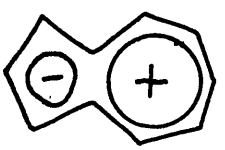
Tropone[30] and benzotropone[11] are readily hydrogenated, in marked contrast to the corresponding tropolones, which require forcing conditions. The relative ease with which tropolones are obtained by hydrogenolysis of bromotropolones may also be contrasted with the difficulty experienced by Nozoe et.al.[30] in preparing tropone from bromotropone, when carefully poisoned catalyst had to be employed.

Surprisingly, we were unable to effect <u>any</u> nucleophilic substitutions of benzotropone. Reference has been made to the fact that amination reactions of the type reported by Nozoe[38] may be interpreted in terms of a nucleophilic substitution mechanism, and that this represents the only chemical evidence of aromatic character in tropones. In view of the demonstrated dienone character of tropones, an addition/elimination mechanism such as (LXII) might be equally valid. While there is little to choose between these alternative explanations of the amination of phenyltropone, the addition/elimination hypothesis would accommodate more convincingly than the nucleophilic substitution mechanism, the amination of the bromotropone (LIII), producing (LV), in which the bromine atom <u>resists</u> nucleophilic displacement.[54]

The picture of benzotropone which emerges from this work is that of an unsaturated ketone rather than an aromatic compound, and the same would seem to be very largely true of the parent tropone. Both compounds give derivatives with reagents which effect electrophilic substitution in the aromatic nucleus, but the course of the reaction has been shown in each case to involve an addition/elimination mechanism. It has not been found possible to effect nucleophilic substitution in benzotropone, and the few cases cited for tropone derivatives are susceptible of more than one explanation. There is in fact no convincing chemical evidence at all for aromaticity in tropones. This is at variance with the physical picture of the molecule; but since physical measurements are concerned with the ground electronic and energetic state, and chemical reactions with excited states, there is no real incompatibility in the two positions. It is interesting to contrast the case of tropones in this connection with that of azulenes[54] which are shown by physical methods to consist largely of (1XL) rather than (XL) in the ground state, but which have the reactions of an aromatic compound.

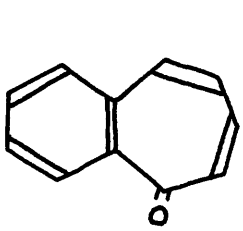


1XL

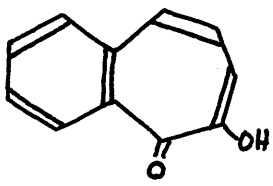


XL

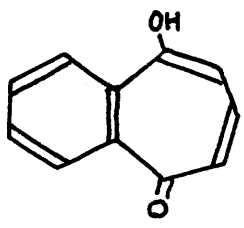
Finally comparison may be made of the properties of benzotropone (XIII), benzotropolone (XIV) and benzoisotropolone (XV).



XIII



XIV



XV

Benzotropolone(XIV) is a fairly typical tropolone. It is an aromatic compound in that it is readily substituted in the seven-membered ring by electrophilic reagents. The isotropolone (XV) is similarly aromatic in its reactions; while the tropone (XIII) has been shown to be a fairly normal unsaturated ketone.

Thus the presence of a hydroxyl group somewhere in the tropone ring is seen to be a prerequisite of aromatic character: the juxtaposition of the carbonyl group and this hydroxyl is important, but

not all-important. Tropones may be formally the most fundamental compounds of the series, as Nozoe claims; but their chemical properties bear no resemblance to those of their hydroxy derivatives, and particularly of their 2-hydroxy derivatives, the tropolones.

The Stobbe Condensation of diethyl succinate and benzyl methyl ketone.

The first requirement in this work had been the establishment of a convenient route to a 2:3-benzotropone, and with the initial failure of the scheme based on 2:3-benzosuberone (p. 9 , this thesis), recourse was had to the method reported by Dice and Allen[58] for the synthesis of 2:3-benzo-5-methylcyclohepta-2:5-diene-1-one (LXVII) from which a substituted benzotropone might readily have been obtained.

The Dice and Allen synthesis involved a Stobbe condensation of diethyl succinate and benzyl methyl ketone, and cyclisation of the resulting half-ester (LXIV) to the keto-ester (LXVI), which was hydrolysed and decarboxylated to the required unsaturated ketone (LXVII).

This preparation was of particular interest to us in that it appears to be the only example in the literature of the direct formation of a seven-membered ring ketone by Friedel-Crafts type cyclisation.

Very variable yields were reported in the cyclisation reaction, which is not surprising in view of our findings; but the fact that the original workers reported a yield of 75% of ketone on occasion, infers that the stereochemistry of the half-ester produced in the Stobbe reaction was as in (LXIV) and not as in (LXV) where cyclisation to a seven-membered ring is precluded.

There is a priori no apparent reason for the predominance of the favourable isomer of the half-ester; and while the production of geometrically isomeric half-esters from unsymmetrical ketones in the Stobbe reaction is well known[59], the possibility of this seems to have been ignored by the original workers.

The occurrence of such geometrical isomers in the product from the condensation of benzyl methyl ketone and diethyl succinate has been demonstrated; the crude product has in fact been completely separated into four crystalline components.

Benzyl methyl ketone reacted with diethyl succinate in presence of potassium tert. butoxide under dry nitrogen, to give after acidification a yield corresponding to 90% of the half-ester (LXIV). The condensation was carried out exactly according to the procedure described by Dice and Allen[58], but in each of five preparations the bulk of the product distilled at 220-225°C/11 mm., in contrast to the reported 140-144°C/7-8 mm.[58].

Alkaline hydrolysis of the crude oil followed by acidification gave the dicarboxylic acid (LXVIII), m.p. 178°, as reported by Dice and Allen, and hydrolysis and decarboxylation with hydrobromic acid gave

a low yield of the acid which Dice and Allen formulate as (LXX).

Repeated attempts to cyclise the acid (LXX) with polyphosphoric acid, and to cyclise its acid chloride with stannic chloride or aluminium chloride yielded no ketonic material.

With the failure of this cyclisation a more detailed examination of the original product was undertaken.

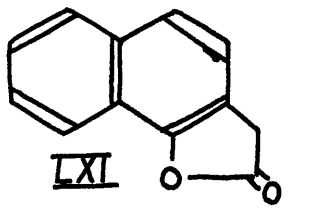
The oil obtained by distilling the crude product from the Stobbe reaction deposited some crystals on standing. Trituration with ethyl acetate accelerated this process, and the non-acidic compound thus obtained was inferred to be an unsaturated lactone from its infra-red spectrum ($_{C=O}$ at 1787 cm^{-1})......"Lactone A" m.p. 165-166°
The residual gum was completely separated by a combination of trituration and fractional crystallisation into three further components,

A dicarboxylic acid half-ester ..... "Half-ester B" m.p. 138-140°

and two dicarboxylic acids ..... "Dicarboxylic acid C" m.p. 160-161°

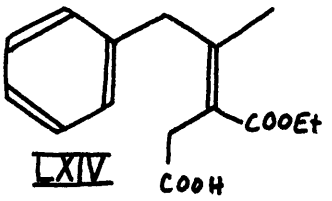
"Dicarboxylic acid D" m.p. 179-180° .

The structures of these compounds have been shown to be,



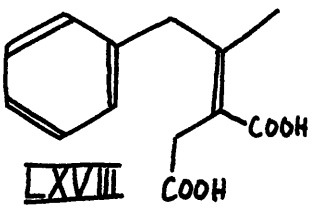
LXI

LACTONE A, m.p. 166°



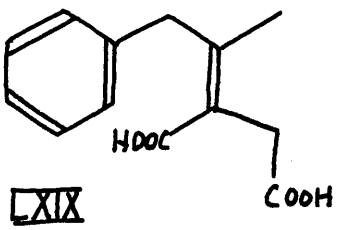
LXIV

HALF-ESTER B, m.p. 133°



LXVIII

DI-ACID C, m.p. 178°



LXIX

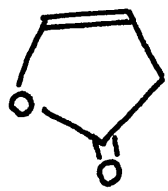
DI-ACID D, m.p. 161°

Proof of structures of compounds A, B, C, D.

Lactone A (LXI).

The lactone m.p. 178° analysed for $C_{12}H_{10}O_2$, whereby the elimination of two molecules of water from the corresponding dicarboxylic acid was inferred: a Rast molecular weight determination confirmed that the compound was monomeric, and hence that the elimination of H_2O was intramolecular.

The infra-red spectrum of the lactone showed a strong absorption in the carbonyl region at 1787 cm^{-1}, which corresponds[56] to a β:γ-unsaturated γ-lactone, i.e. of the type



The ultra-violet absorption spectrum in ethanol is illustrated (fig.). The sharp absorption peak near 324 mμ is characteristic of the naphthalene system. (Cf. α-naphthyl acetate).

When this work had been completed an unambiguous synthesis of this naphthalene lactone was published[60], and a mixed melting point determination verified the structure assigned.

There are several examples in the literature of the cyclisation of a γ-phenylcrotonic acid to a naphthalene derivative during distillation. See, e.g., Hugh and Kon[61] and Marion[62].

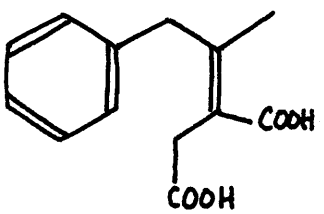
The half-ester B (LXIV).

The analysis of this material is in agreement with the required formula, $C_{15}H_{18}O_4$; the neutralisation equivalent indicates the presence of one acid function per molecule. The relative positions of the acid and ester functions follows from the known mechanism

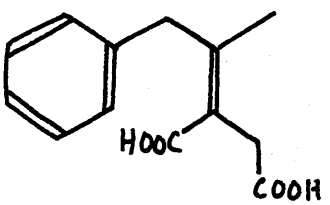
of the Stobbe reaction, and the position of the double bond from ozonolysis to benzyl methyl ketone, identified as its 2:4-dinitrophenyl-hydrazone.

The stereochemistry at the double bond is inferred from the hydrolysis of this half-ester to the dicarboxylic acid ("C") m.p. 178°, first obtained by Dice and Allen.

The Dicarboxylic acids C and D.

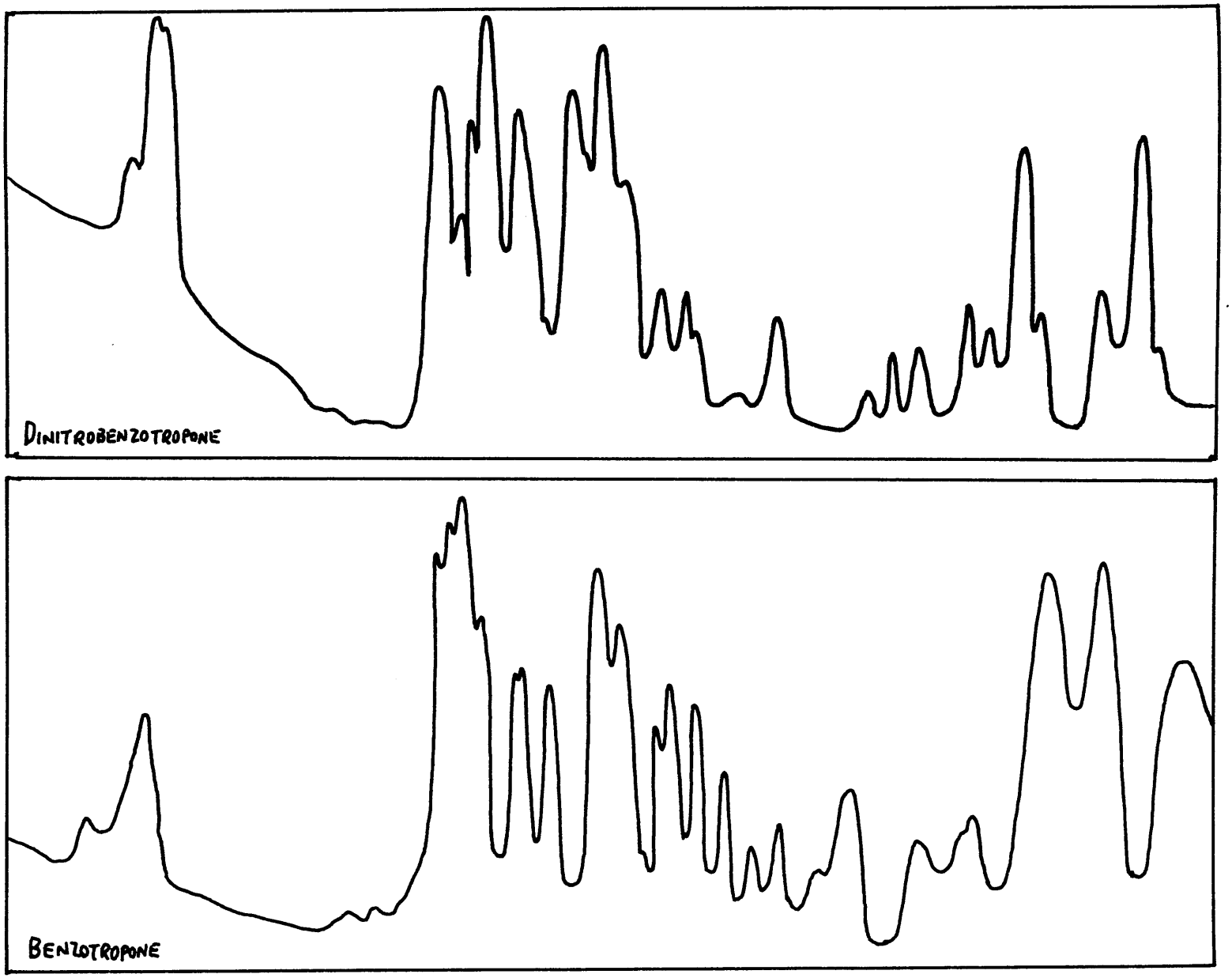


C m.p. 178°



D m.p. 161°

These isomeric di-acids depress each others' melting points. In both cases the position of the double bond follows from ozonolysis to benzyl methyl ketone.


DINITROBENZOTROPONE
BENZOTROPONE

CARBONYL ABSORPTION OF BENZOSUBERONE DERIVATIVES

1680 ; 1603 cm^{-1}.

1684 ; 1603 cm^{-1}.

1665 ; 1603 cm^{-1}.

1708 ; 1603 cm^{-1}.

1675 ; 1603 cm^{-1}.

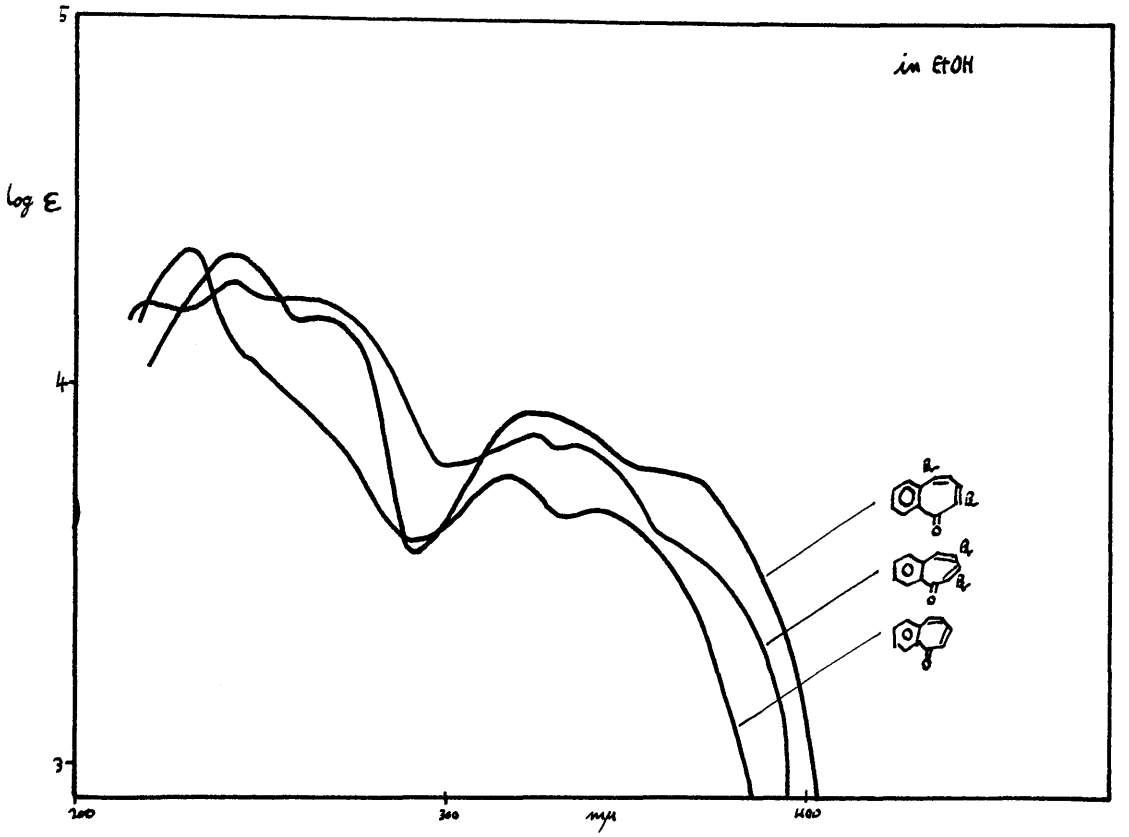
1665 ; 1603 cm^{-1}.

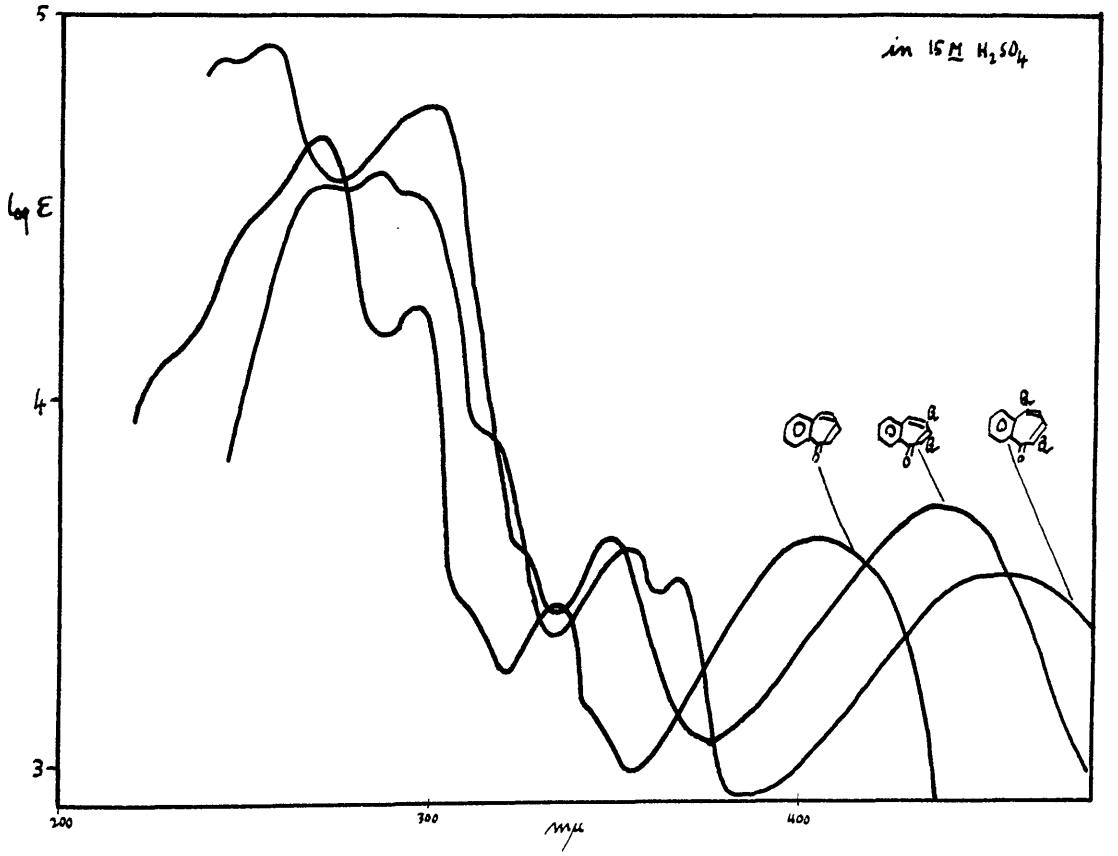
1680 ; 1603 cm^{-1}.

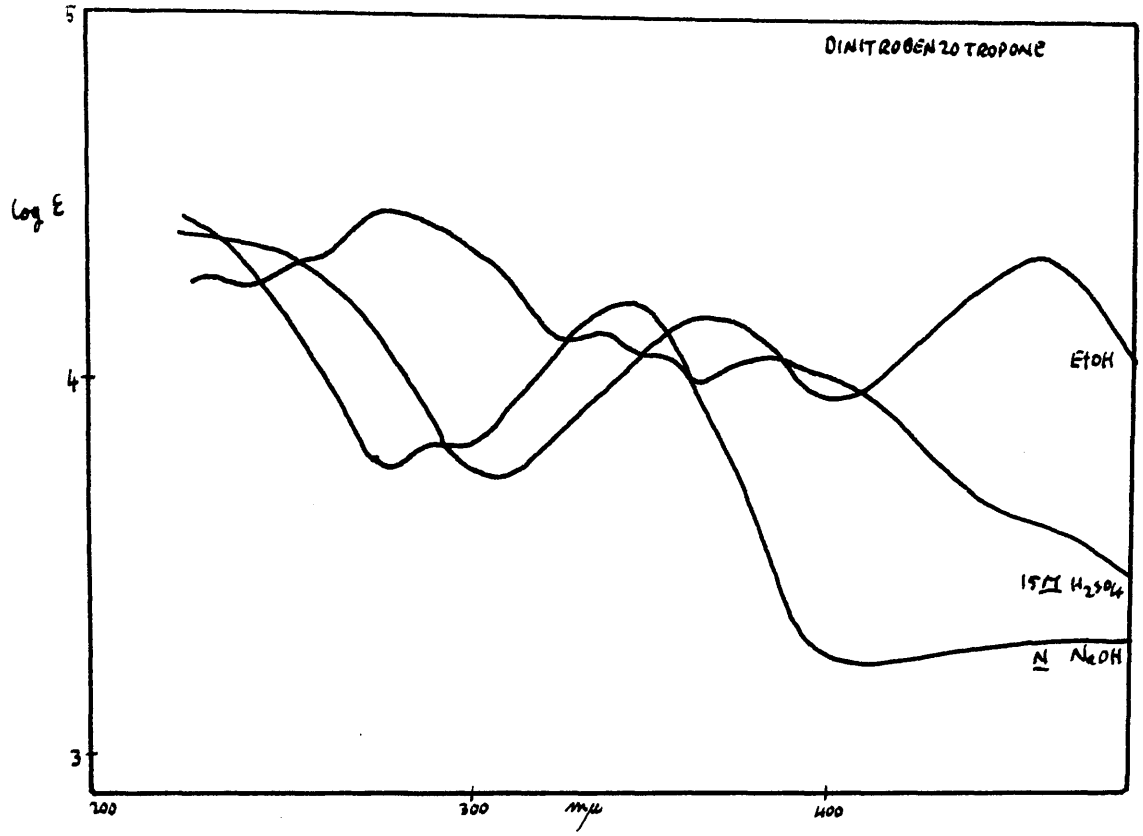
1634 ; 1603 cm^{-1}.

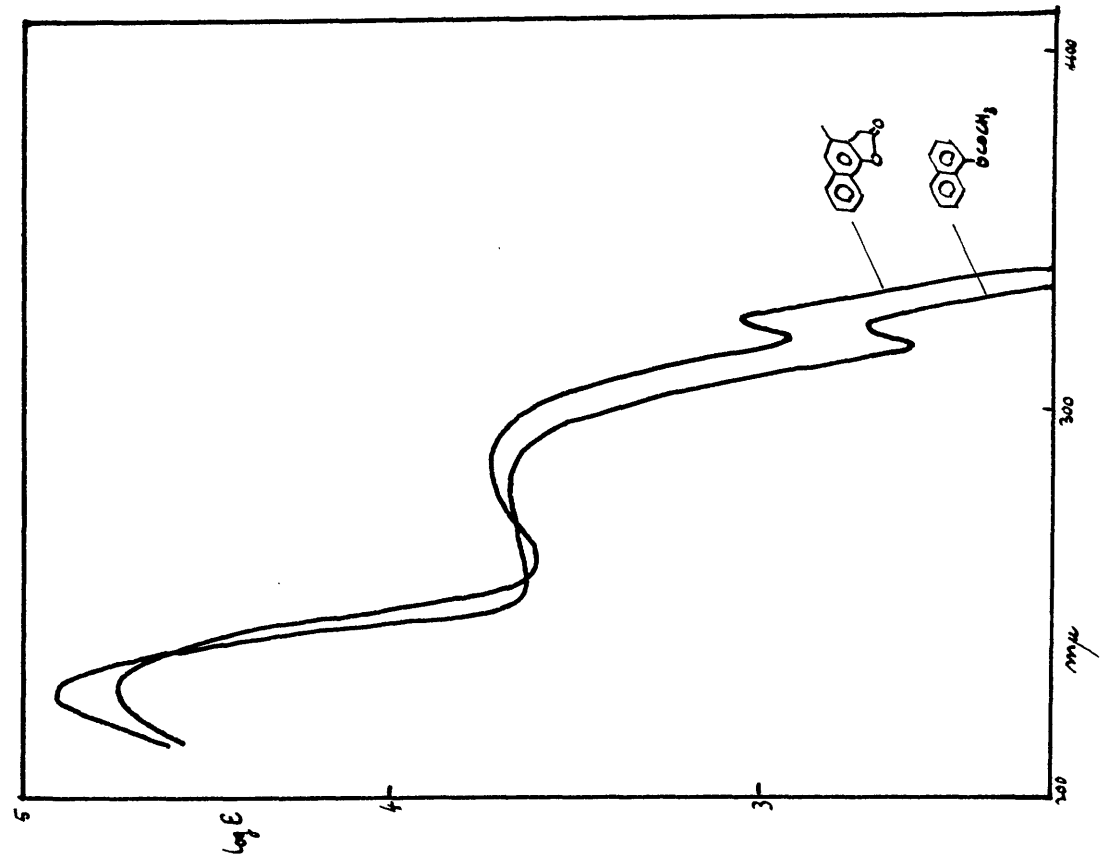
1642 ; 1612 ; 1588 cm^{-1}.

1634 ; 1588 cm^{-1}.


5
log ε
4
3
200
300
mμ
400
in EtOH

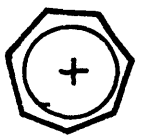

5
log ε
4
3
200
300
mμ
400
in 15 M H2SO4


DINITROBENZOTROPONE
Log ε
5
4
3
200
300
400
mμ
EtOH
15% H2SO4
N NaOH


log ε
5
4
3
200
300
400
mμ
OCOCH3

I

II



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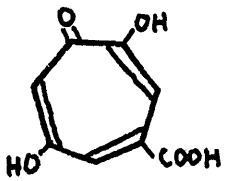
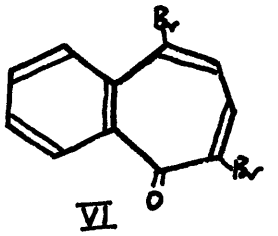


IV

V



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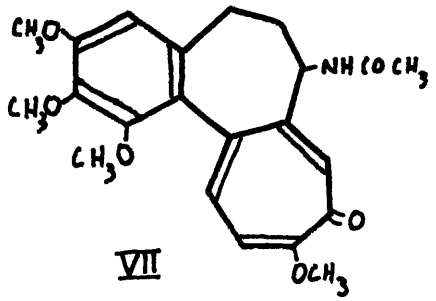

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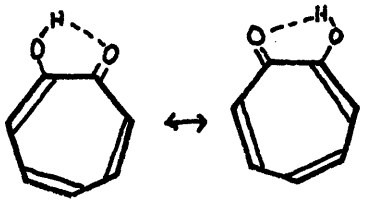

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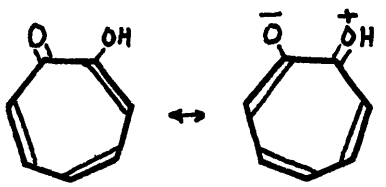

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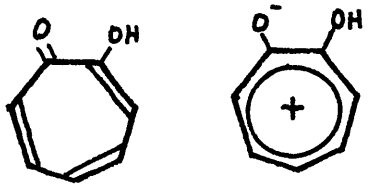
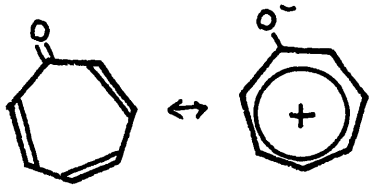


XI



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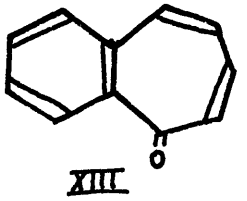

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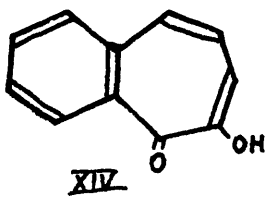

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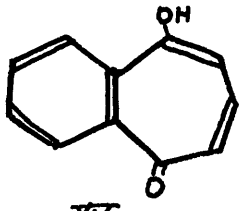

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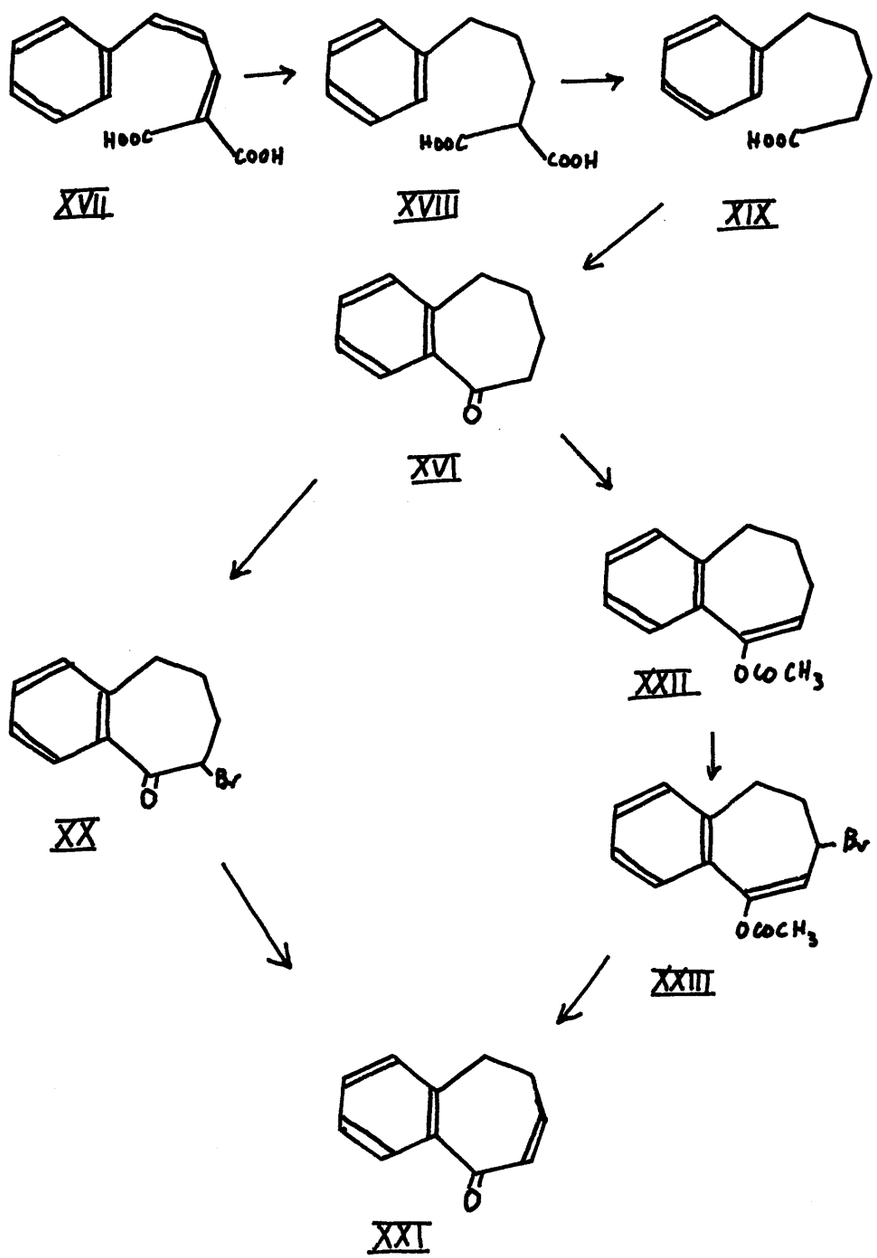
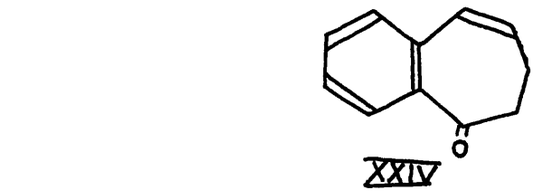
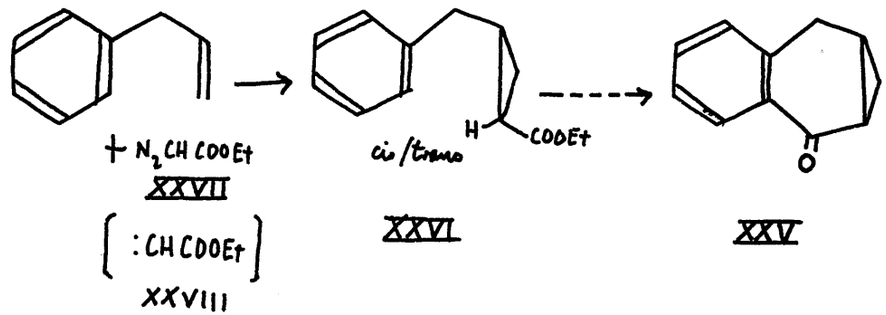
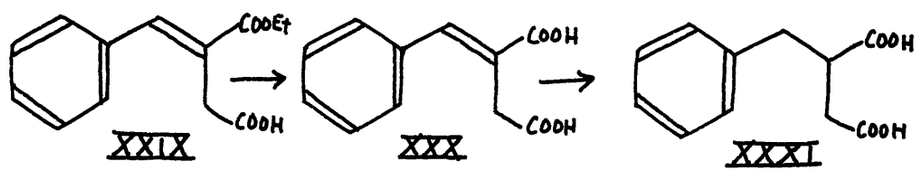
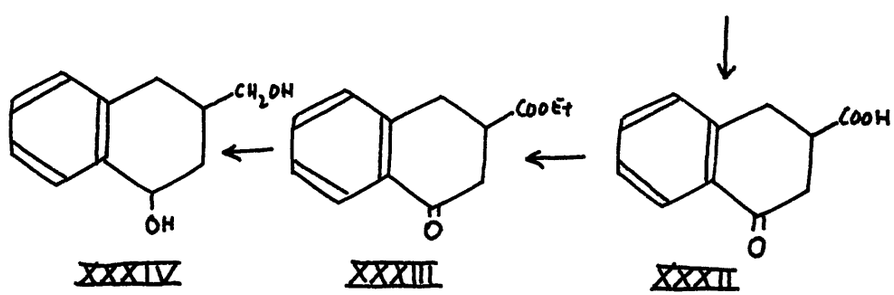

HOOC
COOH
XVII
HOOC
COOH
XVIII
HOOC
XIX
O
XVI
OCOCH3
XXII
Br
O
XX
Br
OCOCH3
XXIII
O
XXI

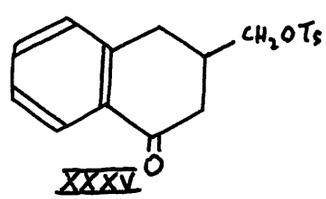

O

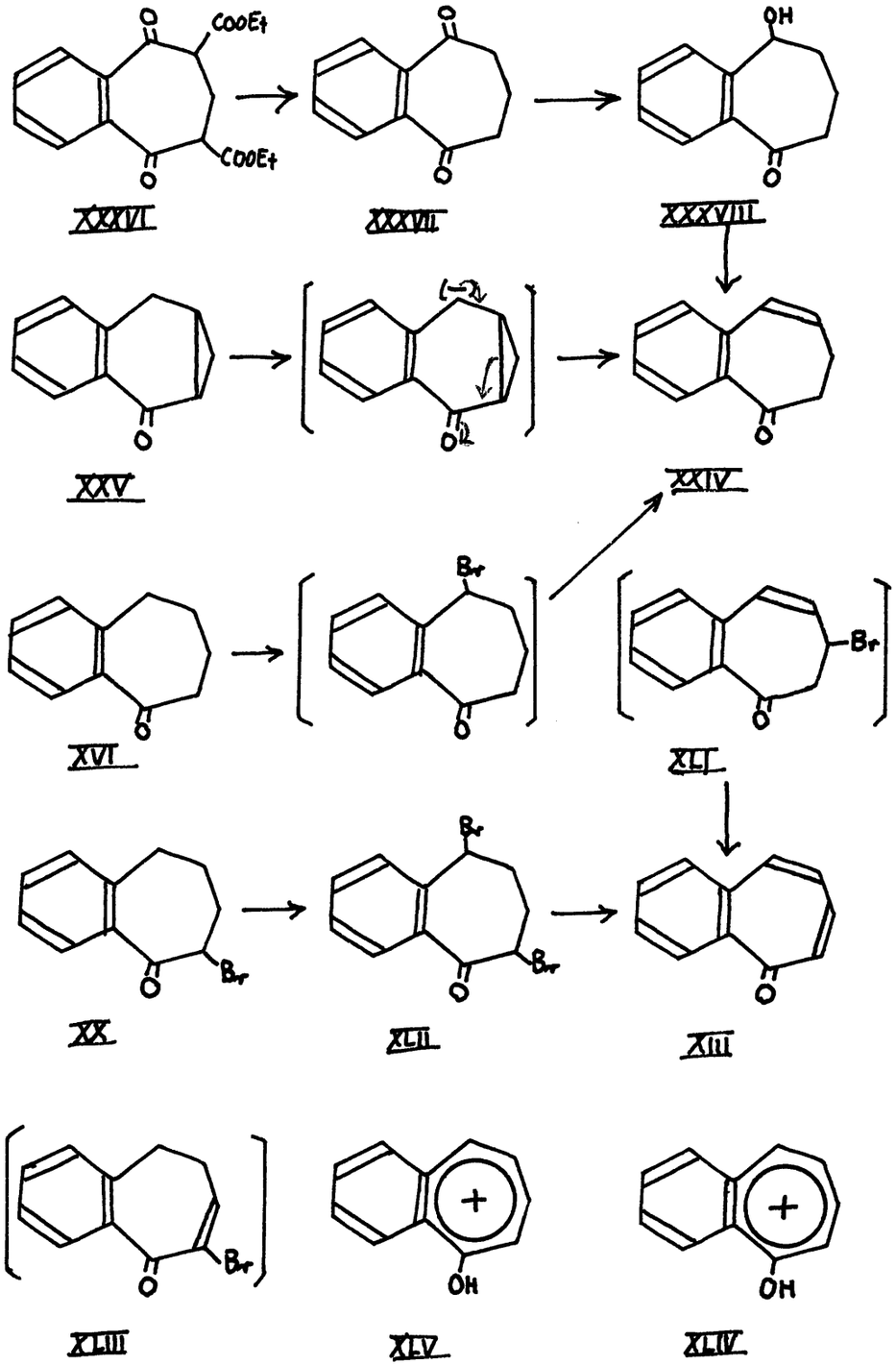
XXIV

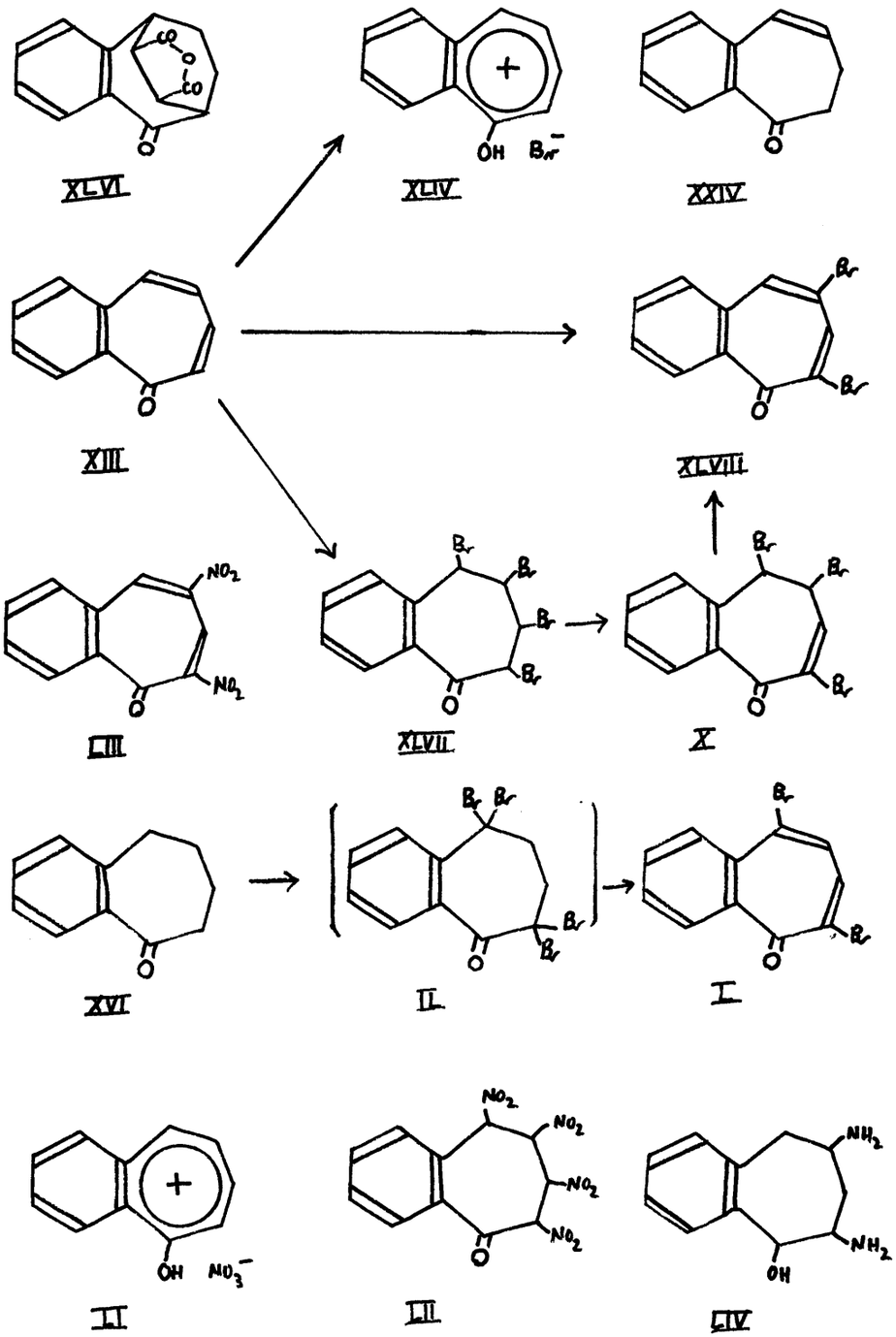

+ N2CH COOEt
XXVII
[:CH COOEt]
XXVIII
cis/trans
H
COOEt
XXVI
O
XXV


COOEt
COOH
XXIX
COOH
COOH
XXX
COOH
COOH
XXXI

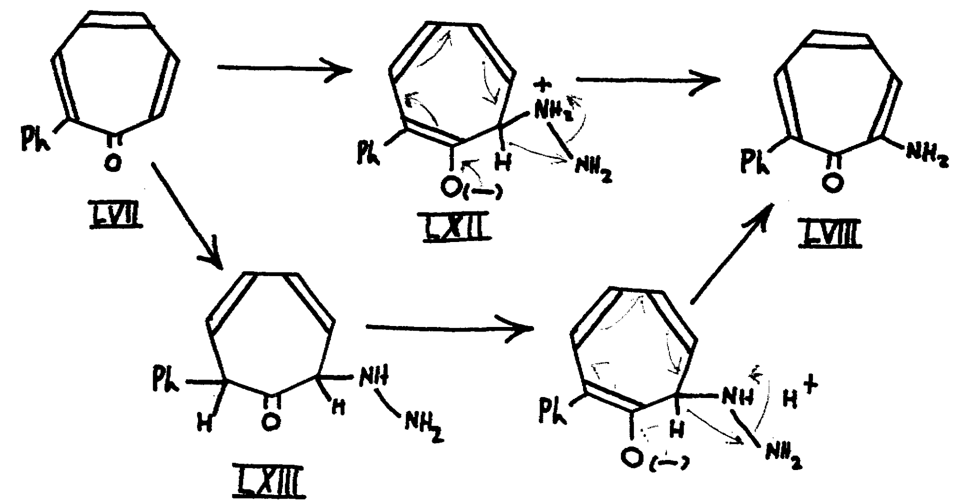

COOH
O
XXXII
COOEt
O
XXXIII
CH2OH
OH
XXXIV

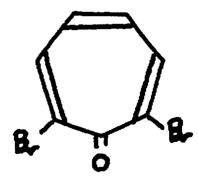

CH2OTs
O
XXXV


COOEt
COOEt
OH
XXXVI
XXXVII
XXXVIII
XXV
XXIV
XVI
Br
Br
XLI
XX
Br
Br
XLII
XIII
Br
XLIII
OH
XLV
OH
XLIV

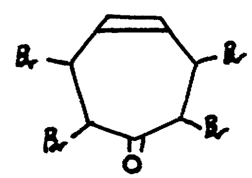

XLVI
XLIV
XXIV
XIII
XLVIII
LIII
XLVII
X
XVI
II
I
LI
LII
LIV

SHEET 6

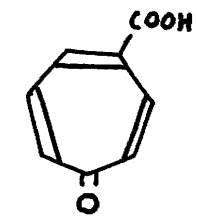




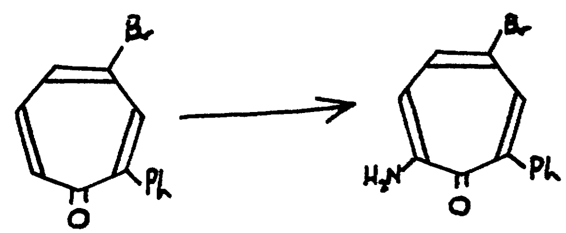
LIX



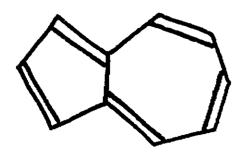
LX

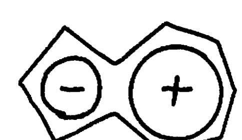


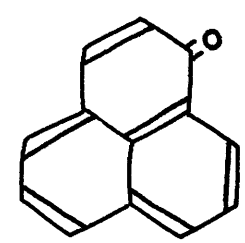
LVI

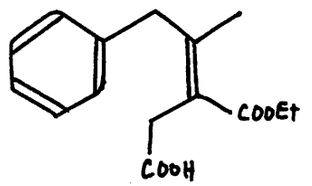


LIIIa LV


IXL


XL


LXI



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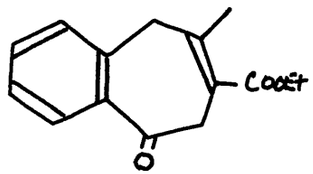
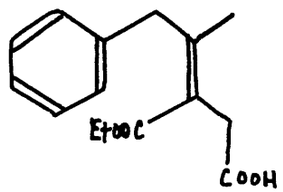


LXVI



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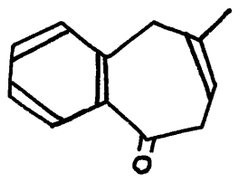

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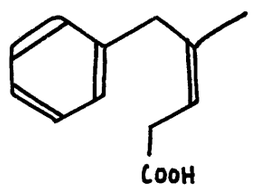
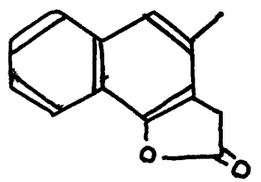


LX



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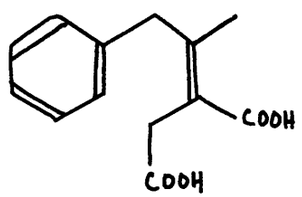

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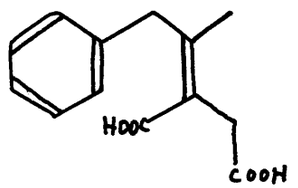

LXIX

EXPERIMENTAL.

The statement ..... "X was worked up in the usual manner...." implies that X was extracted from aqueous solution or suspension with several portions of ether; the ether solution was then washed with water and dried over sodium sulphate; finally ether was removed under vacuum on the steam bath.

The "standard conditions" for preparation of 2:4-dinitrophenyl hydrazones were as follows:- 2:4-dinitrophenylhydrazine (50-100 mg.) was warmed with 4-5 ml. of methanol, and 1-2 drops of hydrochloric acid were added to give a clear solution, to which the carbonyl compound was added.

Melting-points are uncorrected.

2:3-Benzosuberone (2:3-benzocyclohepta-2:3-ene-1-one).

δ-Phenylvaleric acid (XIX)[20] (50 g., 0.28M) was added to polyphosphoric acid prepared from phosphorus pentoxide (300 g.) and phosphoric acid (S.G. 1.75, 150 ml.).* The mixture was stirred at 100° for two hours, then 2:3-benzosuberone was distilled off under vacuum (150-180°/18 mm.) as a yellow oil; yield 33 g., 74%. Redistillation gave 2:3-benzosuberone as a colourless oil b.p. 142°/14 mm..

7-Bromo-2:3-benzosuberone (XX).

2:3-Benzosuberone (16 g., 0.1 M) in carbon tetrachloride (50 ml.) was stirred while a solution of bromine (16 g., 1 mol.) in carbon tetrachloride was added over 15 minutes. Hydrogen bromide was evolved continuously and the bromine colour discharged. The solution was heated under reflux for 30 minutes, then solvent was removed under vacuum. The product was distilled through a 6" vacuum-jacketed Vigreux column at 106-108°/0.05 mm.; yield 22.9 g., 96%. n_D^{20} 1.5981. Found: Bromine, 33.51%; $C_{11}H_{11}OBr$ requires 33.65%.

Under standard conditions an orange 2:4-DNP was obtained, m.p. 231°.

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* Use of commercially available polyphosphoric acid resulted in lower yields.

Dehydrobromination of 7-bromo-2:3-benzosuberone (XX).

7-Bromo-2:3-benzosuberone (2.4 g., 0.01M) was heated with collidine (15 ml.) at 170° for an hour; crystals of collidine hydrobromide separated. Hydrochloric acid (6N, 50 ml.) was added to the cooled mixture, and working up in the usual manner afforded a pale yellow oil, $\nu_{max.}$ (film) 1660 cm.$^{-1}$. The product polymerised on standing for an hour at room temperature or on attempting to distil.

Under standard conditions there was obtained a red 2:4-DNP, which, chromatographed in benzene on 4" alumina and recrystallised from glacial acetic acid had m.p. 218°. Found: C, 58.14%; H, 4.10%; N, 15.77%; $C_{17}H_{14}O_5N_4$ requires C, 57.81%; H, 3.98%; N, 15.82%.

Mattox-Kendall reaction of 7-bromo-2:3-benzosuberone.

7-Bromo-2:3-benzosuberone (XX) (2.4 g., 0.01M) was treated with a hot solution of 2:4-dinitrophenylhydrazine (2 g.) in glacial acetic acid (20 ml.) containing a little hydrochloric acid. The solution was heated under reflux for five minutes, then solvent was removed under vacuum. The residue, chromatographed in benzene on 4" alumina, gave a low yield of the 2:4-DNP of 2:3-benzocyclohepta-2:3:6:7-diene-1-one, m.p. 218°, obtained above.

2:3-Benzosuberone enol acetate (XXll).

2:3-Benzosuberone (10 g., 0.062M) and isopropenyl acetate (50 g.) were heated in presence of p-toluenesulphonic acid at such a rate that acetone distilled slowly from a 6" vacuum-jacketed fractionating column. After two hours, 6.3 ml. of distillate had been collected (theoretical 4.02 ml.). To the cooled solution were added benzene (50 ml.) and sodium carbonate solution (2N, 30 ml.). The organic layer was separated, washed with water, and dried over sodium sulphate. Removal of solvent and isopropenyl acetate under vacuum gave an oil which distilled at 90-92°/0.1 mm., and solidified in the receiver. 2:3-Benzosuberone enol acetate had m.p. (cryst. 40-60° petrol) 59°. Found: C, 77.11%; H, 6.81%. $C_{13}H_{14}O_2$ requires: C, 77.20%; H, 6.94%.

Reaction of 2:3-benzosuberone enol acetate (XXll) with N-bromosuccinimide.

The enol acetate (XXll) (1.51 g., 0.0075M) in chloroform (10 ml.) plus carbon tetrachloride (10 ml.) was heated under reflux for an hour with N-bromosuccinimide (1.37 g., 1.05 mol.). The cooled solution was washed with 3 x 20 ml. portions of water, and the organic layer removed and dried over sodium sulphate. Removal of solvent under vacuum gave an oil which had carbonyl absorption, $\nu_{max.}$ 1660 cm^{-1}, and which under standard conditions gave the 2:4-DNP of 2:3-benzocyclo hepta-2:3:6:7-diene-1-one obtained previously.

Ethyl 2-benzylcyclopropanecarboxylates (XXVl).

To refluxing allylbenzene (150 ml.) containing copper powder (0.5 g.) diazoacetic ester (57 g., 0.5 M) was added over a period of two hours. Heating was continued for a further three hours, then the mixture was cooled and the copper powder filtered off. Excess allylbenzene was removed by steam-distillation, and worked up in the usual manner from the distillate, for re-cycling.

The cis/trans ethyl 2-benzylcyclopropanecarboxylates distilled at 273-276°/760 mm.; yield 41 g., 44% (calculated on diazoacetic ester).

2-Benzylcyclopropanecarboxylic acids.

The mixed esters (XXVl) (35 g., 0.17 M) were heated for an hour under reflux with sodium hydroxide (35 g.) in water (120 ml.) containing methanol (30 ml.). The cooled alkaline solution was washed with 2 x 50 ml. portions of ether, then acidified with hydrochloric acid. The mixed cyclopropanecarboxylic acids were worked up in the usual manner, and obtained on distillation at 184-186°/17 mm., as a colourless oil. Yield, 24 g., 86%, of mixed acids.

2:3-Methylenetetralone-1; cyclisation of ethyl 2-benzylcyclopropane-cis-carboxylic acid.

The cis/trans cyclopropanecarboxylic acids (19 g., 0.11M) were heated under reflux for 15 minutes with thionyl chloride (30 ml.). Excess thionyl chloride was removed under vacuum, and the mixture of acid chlorides was added to a suspension of aluminium chloride (16 g.) in dry ethylene chloride (150 ml.). There was copious evolution of hydrogen chloride. The mixture was left at 20° for three hours, then poured carefully on to ice (300 g.) and hydrochloric acid (100 ml.). The aqueous layer was separated and washed with 3 x 50 ml. portions of ethylene dichloride: the organic layers were combined, and extracted with 3 x 30 ml. portions of 5N sodium hydroxide solution. The alkaline washings were retained - solution "A".

The ethylene dichloride solution was washed with water and dried over sodium sulphate. Removal of solvent gave an oil which distilled at 140-145°/35 mm., to yield 7 g. (41%) of 2:3-methylene-tetralone-1, which yielded a 2:4-DNP identical with an authentic sample.

The alkaline washings from the cyclisation (solution "A" above) were acidified with hydrochloric acid. Working up in the usual manner yielded 8 g. (42%) of 2-benzylcyclopropane-trans-carboxylic acid as a white solid which crystallised from pentane at -30° as white prisms m.p. 43°.

Phenylitaconic acid (XXX).

Sodium (69 g., 3M) was dissolved in dry ethanol (1.5 litres). Benzaldehyde (130 g., 1.25M) and diethyl succinate (234 g., 1.35 M) were

added together to the refluxing ethoxide over a period of minutes. The solution was refluxed with stirring for a further two hours, then 750 ml. of ethanol was distilled off. The solution was allowed to cool and 600 ml. of water was added; a further 750 ml. of solvent was distilled off, and the aqueous solution heated under reflux for a further two hours. After addition of water (1 litre) to the cooled solution, it was acidified to pH 4 with hydrochloric acid; the precipitated phenylitaconic acid was filtered off, and had m.p. (recryst. $MeOH/H_2O$) 183°. Yield 101 g., 39%.

Benzylsuccinic Acid (XXXI).

1.5 litres of 10% sodium hydroxide solution was stirred in a 5-litre beaker, and heated at 95-100° by a steam coil. Phenylitaconic acid (52 g., 0.25 M) was dissolved in this solution, and Raney nickel/aluminium alloy (150 g.) was added portionwise over an hour. Stirring and heating were continued for a further hour, then the nickel was removed by filtration. The alkaline solution was added while still hot to excess of 6N sulphuric acid; the precipitated benzylsuccinic acid floated to the surface as an oil which solidified into a cake on cooling, and could be removed. Yield 47 g., 86%.

3-Carboxytetralone-1 (XXXll).

Benzylsuccinic acid (XXXl) (45 g., 0.45 M) was dissolved in sulphuric acid and the solution maintained at 20° for sixteen hours, then added to 2Kg. of crushed ice. The precipitated pale yellow solid was filtered off, washed with water and dried in air. Yield 43 g., 58%. A sample crystallised from aqueous methanol, m.p. 147°.

Ethyl 1-tetralone-3-carboxylate.

(a) Using diazoethane.

3-Carboxytetralone-1 (XXXll) (6 g.) dissolved in methanol (100 ml.) was added to a solution of diazoethane (from 35 g. N-nitroso-ethylurea, 10 mols.). The solution was left for 16 hours, then solvent and excess diazoethane were removed under vacuum. The residual oil was distilled to yield the required 3-carboxytetralone-1 ethyl ester, b.p. 198°/19 mm., yield 4 g., 61%, and 1.8 g. of material boiling at 240-250°/19 mm., which was shown to be unchanged keto-acid.

The keto-ester (XXXlll) solidified in the receiver, and had m.p. (cryst. aqueous EtOH) 40°. It readily yielded a 2:4-DNP, m.p. (cryst. HOAc) 203° under standard conditions, and a semicarbazone m.p. (cryst. EtOH) 151°. Found: C, 60.96%; H, 5.96%; N, 15.02%. $C_{14}H_{17}N_3O_3$ requires C, 61.09%; H, 6.19%; N, 15.28%.

(b) Using ethanol and sulphuric acid.

3-Carboxytetralone-1 (XXXII) (24 g., 0.125 M), ethanol (160 ml.) toluene (80 ml.) and sulphuric acid (0.5 ml.) were heated to gentle reflux under a Soxhelet extractor, the thimble of which contained 30 g. of anhydrous potassium carbonate. Heating was continued for ten hours, then solvents were removed under vacuum. The product distilled at 198-199°/21 mm.. Yield 22.8 g. (84%) of ethyl 1-tetralone-3-carboxylate, identical with material obtained in (a) above.

Treatment of 3-carbethoxytetralone-1 (XXXIII) with ethyl orthoformate.

The keto-ester (XXXIII) (3 g.) was heated under reflux in ethyl orthoformate (20 g.) containing p-toluenesulphonic acid (0.3 g.) for 90 minutes. Excess ethyl orthoformate was removed under vacuum, and dry sodium carbonate (1 g.) was added. The product, worked up in the usual manner, distilled at 112-114°/0.12 mm., and had infra-red absorption identical with that of the starting keto-ester (XXXIII).

Treatment of 3-carbethoxytetralone-1 with ethylene glycol.

The keto-ester (XXXIII) (4 g.) and ethylene glycol (2 g., 2 mol) was heated under reflux in dry benzene containing p-toluenesulphonic acid (0.5 g.) in an apparatus fitted with a water-separator. After

four hours 1.1 ml. of water had collected and heating was stopped. Sodium carbonate (1 g.) was added, and the product worked up in the usual manner was shown to be unchanged keto-ester, as in the experiment above.

3-Hydroxymethyl-tetralol-1 (XXXIV).

The keto-ester (XXXIII) (4 g.) in dry ether (30 ml.) was added over 40 minutes to a vigorously stirred suspension of lithium aluminium hydride (1.1 g., 2 mol) in dry ether (30 ml.). The mixture thus obtained was heated under reflux with stirring for four hours, then allowed to stand at 20° for 16 hours. After addition of ether saturated with water, and dilute sulphuric acid, the product was worked up in the usual manner and distilled at 150-155°/15 mm.. The infra-red spectrum of the product showed no absorption between 1600 cm^{-1} and 1800 cm^{-1}, and had a strong absorption near 3500 cm^{-1}.

Trituration with pentane caused solidification, and crystallisation from benzene afforded large rhombs of 3-hydroxymethyl-1-tetralol, m.p. 110°. Yield, 2.7 g. (82%). (Found: C, 74.28%; H, 7.86%; $C_{11}H_{14}O_2$ requires: C, 74.16%; H, 7.97%.

2:3-Benzocyclohepta-2:3:4:5-diene-1-one (XXIV). [x]

Rearrangement of 2:3-methylenetetralone-1 (XXV).

Sodium wire (4 g.) was heated under reflux for sixteen hours with dry tert. amyl alcohol (10 ml.) and dry benzene (90 ml.).

The cyclopropane ketone (XXV) (2 g., 0.012 M) was heated for six hours under reflux with 20 ml. of the solution of sodium tert. amyloxide obtained above. On cooling, dilute hydrochloric acid was added. Working up in the usual manner gave an oil which distilled at 146-150°/15 mm., yield 1.2 g., (60%). The product had infrared and ultraviolet characteristics similar to those reported by Julia. This ketone, 2:3-benzocyclohepta-2:3:4:5-diene-1-one, gave, under standard conditions, a red 2:4-DNP which was chromatographed in benzene on 4" alumina, and had m.p. (cryst. HOAc) 217°. This corresponds to 222° (corrected); Julia reports 224° (corrected).

2:3-Benzocycloheptane-1:4-dione (XXXVII).

2:3-Benzo-5:7-dicarbethoxycycloheptane-1:4-dione (XXXVI) (17 g., 0.053 M) was added to water (250 ml.) containing dioxan (30 ml.) and sulphuric acid (7 ml.). The mixture was heated under reflux for

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x We are grateful to Dr. Sylvestre Julia for supplying information in advance of publication.

48 hours. The cooled mixture was extracted with 3 x 100 ml. portions of ethyl acetate; this extract was dried with sodium sulphate and solvent removed under vacuum, to yield 2:3-benzocycloheptane-1:4-dione which distilled at 160-162°/8mm.. Yield 7 g., 75%.

4-Hydroxy-2:3-benzosuberone (XXXVIII).

The diketone (XXXVII) (1 g.) was heated under reflux for two hours with zinc dust (5 g.) in glacial acetic acid (30 ml.). The cooled solution was made alkaline with 5N sodium hydroxide solution, and the product worked up in the usual manner. 360 Mg. was obtained of an oil distilling at 190-250°(bath)/15 mm.. The infra-red spectrum of this oil showed absorption at 1680 cm^{-1} (Ar - CO - R) and at 3600 cm^{-1} (-OH). Under standard conditions there was obtained a 2:4-DNP which had m.p. 195° and was identical with an authentic sample.

Dehydration of the ketal (XXXVIII).

(a) Using thionyl chloride/pyridine.

The ketol (XXXVIII) (75 mg.) was dissolved in AR pyridine (2 ml.) and thionyl chloride (300 mg.) was added. The solution was left for 16 hours and acidified with hydrochloric acid, then the product was worked up in the usual manner. A small quantity of brown oil was obtained which yielded under standard conditions a 2:4-DNP, m.p. 215°,

which did not depress the m.p. of the DNP of an authentic sample of Julia's ketone (XXIV).

(b) Using boric acid.

The ketol (XXXVIII) (750 mg.) was heated with boric acid (1 g.) at 160° for 30 minutes, then product was distilled off at 200° (bath)/15 mm., and identified as 2:3-benzocyclohepta-2:3:4:5-diene-1-one (XXIV) by comparison of infra-red spectra, and by preparation of a 2:4-DNP identical to that obtained in (a) above.

Reaction of 2:3-benzosuberone (XVI) with N-bromosuccinimide.

2:3-Benzosuberone (XVI) (20 g., 0.125M) in dry AR carbon tetrachloride (100 ml.) was treated with N-bromosuccinimide (25 g., 0.14 M) and dibenzoyl peroxide (200 mg.). The mixture was heated under reflux over a 100 Watt lamp for an hour. At the end of this time no NBS remained; there was white solid presumed to be succinimide, floating on the surface. The mixture was washed with water (3 x 100 ml.), and CCl_4 was distilled off. The product was heated with collidine (50 ml.) at 100° for two hours; collidine hydrobromide was filtered off, and chloroform (50 ml.) added; the chloroform solution was extracted with 6N hydrochloric acid till washings were acid. The collidine-free chloroform solution was washed with water and dried over sodium sulphate,

then chloroform was removed under vacuum. The product distilled at 146°/15 mm., and was identified as 2:3-benzocyclohepta-2:3:4:5-diene-1-one (XXIV) by identity of its infra-red spectrum with that of an authentic sample. Yield 6.8 g., 30%.

2:3-Benzotropone (~~XLV~~ XIII).

(a) From 2:3-benzocyclohepta-2:3:4:5-diene-1-one (XXIV), with selenium dioxide.

The ketone (XXIV) (1.06 g.) and selenium dioxide (800 mg.) were heated under reflux with tert. butyl alcohol (20 ml.) and acetic acid (3 ml.) for three hours. Filtration of the cooled reaction mixture removed some of the precipitated selenium; the filtrate was added to 50 ml. of ether. This solution was extracted with hydrochloric acid (5 ml.), and the dark yellow aqueous solution of 2:3-benzo-1-hydroxy tropylium hydrochloride was separated. Water (10 ml.) was added and the emulsion thus produced was extracted with chloroform (3 x 10 ml. portions); the solution was dried with sodium sulphate, and solvent removed under vacuum. Distillation (complicated by the continued presence of colloidal selenium) yielded 300 mg. of an oil which had infra-red and ultra-violet characteristics identical with those of an authentic sample of 2:3-benzotropone. Prolonged boiling with

2:4-dinitrophenylhydrazine hydrochloride in methanol gave a magenta-coloured 2:4-DNP.

(b) From (XXIV) with N-bromosuccinimide.

The ketone (XXIV) (1.56 g., 0.01M) was dissolved in dry AR carbon tetrachloride (15 ml.) and there was added dry N-bromosuccinimide (1.7 g., 0.01M) and a few mg. of dibenzoyl peroxide. The mixture was heated under reflux over a 100 Watt lamp for two hours; hydrogen bromide was evolved continuously. At the end of this period no NBS remained; the carbon tetrachloride solution was washed with water and dried over sodium sulphate. Removal of solvent under vacuum yielded an oil which was on the basis of its infra-red spectrum very largely 2:3-benzotropone, but which still contained a little bromine (Lassaigne test). The oil was treated with collidine (5 g.) at 100° for an hour, and yielded 2:3-benzotropone (1.02 g., 66%) purified as above via its hydrochloride.

2:3-Benzotropone.

(c) From 7-bromo-2:3-benzosuberone (XX).*

The α-bromoketone (XX) (13.6 g., 0.057 M), redistilled three times and used immediately, was treated with dry N-bromosuccinimide

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* Despite elaborate attempts to standardise conditions, this reaction was extremely capricious; yields varied from zero to that quoted in apparently identical experiments.

(11 g., 1.1 mol) (which had been recrystallised from water and pumped at 0.1 mm. for 8 hours) in dry carbon tetrachloride (100 ml.) containing ca. 50 mg. of dibenzoyl peroxide. The mixture was heated under reflux for three hours over a 100 Watt lamp, and on cooling was washed with 3 x 100 ml. portions of water. The solution was dried over sodium sulphate and solvent was removed to yield crude 4:7-dibromo-2:3-benzo suberone, (XLll). This crude dibromo compound (XLll) was heated with collidine (150 ml.) at 100° for three hours, then briefly to the boiling point of collidine. Collidine hydrobromide was filtered from the cooled mixture, and collidine was removed, and the product worked up and purified via its hydrochloride as described above. Yield of 2:3-benzotropone, b.p. 140°/0.1 mm., 5.6 g. (63%).

4:7-Dibromo-2:3-benzosuberone (XLll).

The dibromo compound (XLll) could be obtained by distillation of the crude material ("B" above) only at the expense of great loss in yield. Thus, the crude material ("B") was heated at 0.003 mm.; a small quantity of an oil distilled at 135-145° (both 250°). Trituration of this oil with carbon tetrachloride afforded 4:7-dibromo-2:3-benzosuberone (XLll) as a white solid, m.p. (cryst. EtOAc) 80°. Found: C, 41.36%; H, 3.32%; Br, 50.42%. $C_{11}H_{10}OBr_2$ requires: C, 41.52%; H, 3.14%; Br, 50.32%.

2:3-Benzotropone hydrobromide (XLIV).

(a) A sample of 4:7-dibromo-2:3-benzosuberone (XLII) was stable when kept in a refrigerator for three months; a similar sample which was left at room temperature lost hydrogen bromide spontaneously. The product had m.p. (recryst. EtOAc) 89°, and dissolved in water to give benzotropone; under standard conditions it yielded a 2:4-DNP identical with an authentic sample of benzotropone 2:4-DNP. Found: C, 51.38%; H, 4.31%; Br, 31.48%. $C_{11}H_9OBr$ requires: C, 51.76%; H, 4.31%; Br, 31.21%.

(b) 2:3-Benzotropone (200 mg.) in carbon tetrachloride (3 ml.) was exposed to hydrogen bromide gas. A white solid precipitated, which was found to be identical with the 2:3-benzotropone hydrobromide obtained in (a) above.

4:7-Dibromo-2:3-benzotropone (L).

(a) 2:3-Benzosuberone (XVI) (1 g.) was treated with liquid bromine, dropwise, till the bromine colour persisted: a further 3 g. of bromine was added, and the mixture left for three days. Hydrogen bromide was evolved on gentle warming and trituration of the gummy product with methanol gave a small quantity (120 mg., 5%) of a crystalline solid which is inferred to be 4:7-dibromo-2:3-benzotropone (L). Recrystallisation from acetic acid gave pale yellow crystals m.p. 220°. The compound (L)

dissolved in concentrated sulphuric acid, from which solution (L) could be recovered unchanged even after boiling for 15 minutes. It had infra-red and ultraviolet spectra similar to that of 2:3-benzotropone. Found: C, 41.79%; H, 2.34%; Br, 50.64%. $C_{11}H_6OBr_2$ requires: C, 41.98%; H, 1.92%; Br, 50.94%.

(b) The same compound (L) was obtained when benzosuberone (XVI) (0.8 g., 0.005 M) was treated with bromine (1.6 g., 0.01 equiv.) in carbon tetrachloride; the bromine was rapidly absorbed. The crude bromination product was heated in chloroform under reflux with N-bromosuccinimide (2 g.), for eight hours. Throughout this time the solution was irradiated with ultra-violet light. The chloroform solution was washed with water, dried over sodium sulphate, and chloroform was removed; the product was heated with collidine at 170° for 15 minutes. Chloroform was added, and collidine extracted with dilute hydrochloric acid; then sulphuric acid (5 ml.) was added to the chloroform solution; the dibromo-compound (L) (28 mg.) precipitated from the sulphuric acid on dilution.

Bromination of 2:3-benzotropone (~~XIV~~ XIII) with liquid bromine.

2:3-Benzotropone (~~XIV~~ XIII) (100 mg.) was treated with bromine (5 drops) without temperature control; hydrogen bromide was evolved

copiously. Excess bromine was removed under vacuum. The gummy product remained solid on trituration with methanol, and gave fine needles m.p. 169° from ethyl acetate. This compound has physical properties like 4:7-dibromo-2:3-benzotropone (L) (see above), and is inferred to be 5:7-dibromo-2:3-benzotropone (XLVIII). Found: C, 41.97%; H, 2.29%. $C_{11}H_6OBr_2$ requires: C, 41.98%; H, 1.92%.

From the mother-liquors there was obtained on concentration a tribromo compound, m.p. 156° d., which is inferred to be 4:5:7-tribromo-2:3-benzocyclohepta-2:3:6:7-diene-1-one (X); carbonyl absorption $\nu_{max.}$ (nujol) 1660 cm^{-1}. Found: C, 33.31%; H, 1.65%. $C_{11}H_7OBr_3$ requires: C, 33.22%; H, 1.77%.

When heated to its melting point this tribromo compound (X) lost hydrogen bromide. The solid product of dehydrobromination had m.p. (cryst. EtOAc) 165°, and was shown to be identical with an authentic sample of 5:7-dibromo-2:3-benzotropone (XLVIII).

4:5:6:7-Tetrabromo-2:3-benzocyclohept-2:3-eneone ("benzotropone tetrabromide") (XLVII).

2:3-Benzotropone (XLV) (600 mg., 0.0038 M) in dry AR carbon tetrachloride (1 ml.) was treated with a solution of bromine (1.25 g., 4 mol) in carbon tetrachloride (12 ml.). On the addition of the

bromine solution, and up to the addition of 8-9 ml. of the bromine solution, a red crystalline solid separated; this redissolved after a time when the remainder of the bromine solution had been added, or on warming. At no time was any hydrogen bromide evolved.

(The red complex dissolved in methanol with disappearance of the red colour, and the 2:4-DNP of 2:3-benzotropone was obtained from this solution).

Carbon tetrachloride was removed under vacuum, with the temperature kept below 30°C. Trituration with methanol/ether of the gum thus obtained afforded white crystals; recrystallisation from ethyl acetate/pentane at -30°C afforded 4:5:6:7-tetrabromo-2:3-benzocyclohept-2:3-eneone (XLVll) as small white prisms m.p. 123° d. Found: C, 28.12%; H, 1.55%; Br, 66.95%. $C_{11}H_8OBr_4$ requires C, 27.87%; H, 1.68%; Br, 67.13%.

The compound lost hydrogen bromide at its melting point. A small sample was heated at 130° for five minutes, and the cooled product crystallised from ethyl acetate to yield pale yellow leaflets, m.p. 166° which were identified as 5:7-dibromo-2:3-benzotropone by comparison with an authentic sample.

Dehydrobromination of benzotropone tetrabromide (XLVll).

The tetrabromide (XLVll) (20 mg.) in methanol (2 ml.) was treated with 5N sodium hydroxide solution (5 drops). As the alkali entered the solution a yellow colour developed and yellow leaflets separated. The crystals were filtered off, and were identified as 5:7-dibromo-2:3-benzotropone (XLVlll) by comparison with an authentic sample.

The same dibromotropone (XLVlll) was obtained on treating (XLVll) with sodium bicarbonate solution, and with Amberlite IRA-400 (OH) resin.

Partial dehydrobromination of (XLVll).

The tetrabromide (XLVll) (472 mg., 0.001 M) was treated with sodium hydroxide solution (0.1 N, 10 ml.) (1 mol) in presence of methanol (2 ml.) on the steam bath for an hour. The crystals which separated had m.p. (EtOAc) 152° d., and were identical with the compound identified as 4:5:7-tribromo-2:3-benzocyclohepta-2:3:6:7-diene-1-one (X), obtained as a by-product in the bromination of benzotropone with liquid bromine.

Bromination of 2:3-benzocyclohepta-2:3:4:5-diene-1-one (XXIV).

The unsaturated ketone (XXIV) (100 mg.) was treated with liquid bromine (5 g.) and left at room temperature for 28 days. Excess bromine was removed under vacuum to leave a pasty gum, which was heated at 100° for 8 hours, after which a small quantity of solid was obtained by triturating with ethyl acetate. Recrystallisation from glacial acetic acid afforded 5:7-dibromo-2:3-benzotropone identical with an authentic sample.

Treatment of 2:3-benzotropone with alkali.

2:3-Benzotropone (100 mg.) was heated under reflux with 2N sodium hydroxide solution (10 ml.) for 30 minutes. On cooling and working up in the usual manner, 2:3-benzotropone was recovered unchanged.

2:3-Benzotropone (60 mg.) was heated with potassium hydroxide (500 mg.) moistened with water (2 drops) at 160-180° for ten minutes. The mixture charred and only intractable materials were obtained.

2:3-Benzotropone (60 mg.) was heated with potassium hydroxide (0.5 g.) in ethylene glycol (2 ml.) at 120-130° for ten minutes. An alkali-soluble brown intractable resin was obtained on acidification.

Sodium (50 mg.) was dissolved in methanol (2 ml.) and to this solution was added 2:3-benzotropone (80 mg.). The solution was heated under reflux for 24 hours, at the end of which time working up in the

usual manner afforded 2:3-benzotropone, identified as its 2:4-DNP.

To liquid ammonia (30 ml.) was added ferric nitrate (100 mg.) followed by a few mg. of sodium, then a further 200 mg. of sodium. When the blue colour had disappeared, 2:3-benzotropone (180 mg.) was added; ammonia was allowed to evaporate through a cellophane membrane. Ether (10 ml.) was added when little ammonia remained. Water (1 ml.) was added carefully, followed by hydrochloric acid until the mixture was acid. Filtration yielded an alkali-soluble, intractable resin.

To 10 ml. of methanol cooled in CO_2/acetone was added 10 ml. of liquid ammonia, and benzotropone (120 mg.). The solution was allowed to stand for 20 hours while ammonia evaporated; on removal of methanol, 2:3-benzotropone was recovered.

Treatment of 2:3-benzotropone with hydrazine hydrate.

2:3-Benzotropone (100 mg.) and hydrazine hydrate (100 mg.) were heated under reflux in ethanol (5 ml.) for an hour. A red colour developed, but the product obtained on removing solvent was found to be unchanged 2:3-benzotropone.

Treatment of 2:3-benzotropone with hydroxylamine hydrochloride.

2:3-Benzotropone (156 mg.) was treated with hydroxylamine hydrochloride (200 mg.) in liquid ammonia (5 ml.). After 1 hour

the ammonia had evaporated, and the product, extracted into ether, was found to be 2:3-benzotropone.

Treatment of 2:3-benzotropone with alkaline hydrogen peroxide.

2:3-Benzotropone (300 mg.) was left for ten days in ethanol (3 ml.) containing 5N sodium hydroxide solution (1 ml.) and 30% hydrogen peroxide (2 ml.). Acidification and working up in the usual manner gave unchanged 2:3-benzotropone.

Treatment of 2:3-benzotropone with perbenzoic acid.

2:3-Benzotropone (156 mg.) was treated with perbenzoic acid (400 mg., 3 mol) in chloroform (10 ml.) at 20° for 24 hours. Washing with 10% sodium bicarbonate solution (10 ml.) and working up in the usual manner gave unchanged 2:3-benzotropone.

Oxidation of substituted benzotropones.

(a) The isomeric 4:7- and 5:7-dibromobenzotropones (XLVIII) and (L).

In each case, the dibromo-compound (XLVIII) (L) (100 mg.) was treated with potassium permanganate (1 g.) in water (10 ml.) containing potassium hydroxide (0.5 g.). The mixture was heated at 100° for three hours, sodium bisulphite was added, and the solution filtered. The filtrate was acidified with hydrochloric acid, and working up in the

usual manner yielded a few mg. of crystals plus oil. This was treated with one drop of acetic anhydride at 100° for ten minutes, then the solution was evaporated to dryness at 100°/15 mm.. The product sublimed at 140-160° (bath)/15 mm., and was obtained as fine needles m.p. 130° which were identical with an authentic sample of phthalic anhydride.

(b) Dinitrobenzotropone (Llll).

The dinitro-compound (Llll) (45 mg.) was heated with 6N nitric acid (3 ml.) at 100° for two hours, and the mixture filtered to remove unchanged starting-material. Nitric acid was removed from the filtrate under vacuum, leaving a small solid residue which sublimed to yield needles of phthalic anhydride m.p. 130° and mixed m.p.

Attempted rearrangement of 5:7-dibromo-2:3-benzotropone (XLVlll).

(a) The dibromo-compound (XLVlll) (100 mg.) was heated with 10 N sodium hydroxide solution (2 ml.) and ethanol (0.1 ml.) at 100° for an hour. A dark colour appeared in the solution, and was discharged on acidification, when a brown resinous precipitate was obtained which could not be characterised.

(b) The experiment was repeated in an atmosphere of nitrogen, with the same result.

(c) The dibromo-compound (XLVIII) (200 mg.) was treated with potassium hydroxide (0.5 g.) in ethylene glycol (2 ml.). The dibromo-compound, insoluble at 20°, dissolved at 40° with the appearance of a dark brown colour. On acidification a brown intractable resin was obtained.

(d) To potassium hydroxide (2 g.), water (0.2 ml.) and methanol (10 ml.) was added the dibromo-compound (100 mg.). Warming on the steam bath produced a dark colour within a few minutes. Filtration, and acidification of the filtrate gave a brown intractable tar.

(e) The dibromo-compound (160 mg.) was treated with 2 ml. of a solution of sodium methoxide containing 11.5 mg. of sodium (2 mol) at 20° for sixteen hours; the solution was deep brown coloured, but filtration returned 130 mg. of starting material.

(f) The dibromo-compound (160 mg.) was treated with 1 ml. of a solution of sodium methoxide containing 11.5 mg. sodium (1 mol) at 20° for sixteen hours; filtration returned 140 mg. of starting material.

(g) To sodamide (from 800 mg. sodium) in 100 ml. liquid ammonia was added the dibromo-compound (100 mg.), and left for 16 hours while the ammonia evaporated through a cellophane membrane. Addition of ether, water, and acid gave a brown intractable resin.

(h) To 20 ml. of liquid ammonia was added 200 mg. of the dibromo-compound (XLVIII). It was recovered unchanged after 24 hours when the

ammonia had evaporated.

(i) To 10 ml. of methanol at -30° was added liquid ammonia (10 ml.) and the dibromo-compound (200 mg.). The mixture was allowed to stand for 72 hours at 20°, while ammonia evaporated; the starting material was recovered unchanged.

(j) The dibromo-compound (XLVIII) (100 mg.) was dissolved in sulphuric acid (2 ml.). The solution was boiled for 5 minutes, cooled, and poured into water (10 ml.). The dibromo-compound was precipitated unchanged.

(k) The dibromo-compound (XLVIII) (100 mg.) was heated for an hour under reflux with ethanol (1 ml.) and hydrochloric acid (1 ml.). The starting material was recovered unchanged.

Attempted rearrangement of 4:7-dibromo-2:3-benzotropone (L).

(a) The dibromo-compound (L) (50 mg.) was heated at 100° with 10 N potassium hydroxide solution (5 ml.); the bromo-compound was completely insoluble. Ethanol (1 ml.) was added and heating was continued for two hours. A brown solution resulted, from which a brown intractable resin was obtained on acidification.

(b) The dibromo-compound (L) (100 mg.) was heated with potassium hydroxide (3 g.) moistened with water (0.1 ml.) at 200° for 20 minutes. Addition of water and hydrochloric acid afforded an intractable brown

amorphous solid.

(c) Treatment with potassium hydroxide in ethylene glycol at 120-140° gave a similar brown resin on acidification.

(d) The dibromo-compound (L) (20 mg.) was dissolved in sulphuric acid (2 ml.). The yellow solution was boiled for ten minutes, cooled, and poured into water, when starting material was recovered unchanged.

Nitration of 2:3-benzotropone.

(a) To a mixture of sulphuric acid (4 ml.) and nitric acid (1 ml.) was added 2:3-benzotropone (130 mg.). A yellow colour developed, which in the course of a few seconds became red and after ten minutes, deep magenta; oxides of nitrogen were evolved. The mixture was allowed to stand at 20° for 24 hours, by which time it was once more yellow, then poured on to ice. A yellow solid separated, which was washed with water, and crystallised from acetic acid in needles, m.p. 165°. This is inferred to be 5:7-dinitro-2:3-benzotrop-1-one. Yield 120 mg., 60%. Found: C, 53.51%; H, 2.57%; N, 11.21%. $C_{11}H_6O_5N_2$ requires: C, 53.69%; N, 2.44%; N, 11.38%.

(b) To AR nitric acid (15 ml.) was added 2:3-benzotropone (500 mg.); crystals appeared slowly, accompanied by the evolution of oxides of nitrogen, over 4-5 hours. Filtration yielded long needles m.p. 165° identical with the material obtained in (a) above, yield 650 mg., 88%.

The same dinitro-compound was obtained using 50% aqueous nitric acid, or nitric acid in acetic acid. In each case the appearance of the dinitro compound was accompanied by the appearance of "brown fumes".

2:3-Benzotropone nitrate.

On adding a drop of AR nitric acid to 200 mg. of 2:3-benzotropone there was obtained a pale yellow solid which was completely insoluble in non-polar solvents, and from which 2:3-benzotropone was regenerated in polar solvents. The compound gave a strong positive test with diphenylamine/sulphuric acid, and had infra-red absorption at 1385 cm^{-1}(vs) and 1826 cm^{-7}(m) characteristic of the NO_3^- anion.

The compound is inferred to be 1-hydroxy-2:3-benzotropylium nitrate.

Treatment of 2:3-benzotropone with dinitrogen tetroxide.

In a stream of dry nitrogen, dinitrogen tetroxide prepared by heating a 4:1 mixture of silver sand and lead nitrate, was passed through

a solution of 2:3-benzotropone (100 mg.) in 15 ml. of dry carbon disulphide. The solution became deep yellow, then brown; a globule of brown oil separated. Carbon disulphide was removed under vacuum at a temperature below 30°, when the brown oil solidified, and was found to weigh 270 mg.. It rapidly evolved brown fumes even at 20°, and after fifteen minutes there remained a yellow solid m.p. 149°, which recrystallised from ethyl acetate, m.p. 164°, and was identical with a previously obtained sample of 5:7-dinitro-2:3-benzotropone (L111). Yield, 212 mg., 96%.

Hydrogenation of 5:7-dinitro-2:3-benzotropone (L111).

(a) Under neutral conditions.

The dinitro-compound (L111) (100 mg.) was treated with hydrogen/platinum oxide (100 mg.) in ethyl acetate (25 ml.). After an hour 20 ml. H_2 (catalyst) plus 30 ml. (corresponding to $3H_2$) had been absorbed; no further absorption took place. Catalyst and solvent were removed to yield a pale yellow oil which was identified by comparison of I.R. spectra and identity of 2:4-DNP's, as 2:3-benzosuberone. Yield 53 mg., 85%.

(b) Under acid conditions.

The dinitro-compound (100 mg.) dissolved in acetic acid (30 ml.) containing sulphuric acid (2 ml.) and platinum from 110 mg. platinum oxide,

was shaken with hydrogen. After an hour absorption of hydrogen had practically ceased, and 92 ml. (corresponding to 9 H_2) had been consumed. Catalyst was removed, water (60 ml.) was added, and the solution basified with 2N sodium hydroxide solution. The product, which remained in the aqueous layer on washing with ether, consumed periodate but was not further characterised.

Experiments on diene and dieneophile properties of benzotropone and derivatives.

(a) Benzotropone/maleic anhydride.

2:3-Benzotropone (100 mg.) and maleic anhydride (20 mg.) were heated at 200° for 30 minutes. The cooled product was extracted with benzene, from which addition of cyclohexane precipitated the adduct, m.p. (recryst. benzene) 229°.

(b) Bromobenzotropones/maleic anhydride.

To samples of 200 mg. each of 4:7- and 5:7-dibromo-2:3-benzotropones (XLVlll), (L) dissolved in xylene was added maleic anhydride (200 mg.). The solutions, heated under reflux for eight hours, deposited crystals of starting-materials on cooling.

Similar results were obtained on attempting to carry out the reaction in refluxing nitrobenzene.

(c) Benzotropone/butadiene.

2:3-Benzotropone (154 mg.) was treated with a solution in benzene (50 ml.) of butadiene (0.5 g., 10 mol) at 20° for 20 hours. On removal of solvent and butadiene starting material was recovered.

(d) Dinitrobenzotropone/butadiene.

A similar experiment with dinitrobenzotropone (L111) (173 mg., 0.6 mM) and butadiene (0.5 g., 10 mol) also returned starting material.

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PART II

Synthetic Approaches to Colchicine

INTRODUCTION

The alkaloid colchicine (I) which occurs in the Autumn Crocus (Colchicum Autumnale) has been used medicinally for thousands of years, yet it is only within the last ten years that the structure of the molecule has been established beyond reasonable doubt. Dewar[1] in 1945 pointed out that the properties of colchicine could be rationalised in terms of a tropolone structure, and the work principally of Cook[2,3,4], Rapoport[5,6,7], Lowenthal[8] and their respective collaborators has confirmed that this is the case. The nature of tropolone methyl ethers is however such that chemical methods do not in general allow one to distinguish between the alternative possibilities III and IV, and to date the assignment of the relative positions of carbonyl and methoxyl functions in ring C rests solely on X-ray evidence[15].

It might be anticipated that a synthesis of colchicine would be a reasonably simple matter, at least relative to the problems which faced the workers on steroids or strychnine: the fact is that, despite the vast amount of effort and great diversity of approaches which have been applied to the problem, the most which has been achieved is the isolation by Nozoe[9] of a minute quantity of material which behaved like colchiceine (II) on a paper chromatogram.

The great majority of attempts at synthesis of colchicine or colchicine analogues are comprised in three general approaches:-

(1) Starting from an A - B fused system, an attempt is made to elaborate ring C[10] (V).

(2) Starting with a molecule containing suitably-substituted rings A and C, an attempt is made to form ring B[11] (VI).

(3) Starting with rings A and C joined by a 3-carbon fragment, an attempt is made to effect ring-closure[12] (VII).

While the formation and aromatisation of ring C might be expected to be the most difficult part of the synthesis, and this consideration would tend to favour approaches (2) and (3), most of the synthetic work has in fact been on the lines of approach (1). This can no doubt be attributed to accessibility of starting-materials.

Attempts to synthesise the carbon skeleton of colchicine are of interest - for not even the molecule lacking methoxyl groups in ring A has been made - but the electronic and steric consequences of the methoxyl groups in colchicine make the results of such work of limited applicability to the alkaloid itself. Thus, the steric hindrance of the *peri* methoxyl group is very marked; a compound such as VIII has been shown[13] to have very little carbonyl reactivity - it does not for

example undergo the Reformatski reaction. The corresponding unmethoxylated compound (IX) we have found to be very reactive indeed.

That this deactivating effect of the methoxyl group is not confined only to the reactions of a carbonyl group in ring B has been shown by Sutherland[14], who was unable to alkylate the ketone (X) despite the use of a wide variety of conditions.

An obvious means of circumventing this difficulty is to obtain an A - B fused compound with the hindered position 1 of ring B already substituted.

The present work had two main aims,

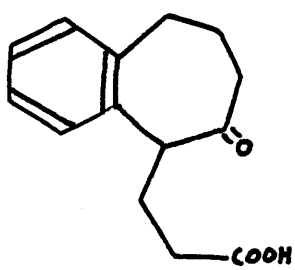
(I) To investigate approaches to colchicine aimed at the synthesis of a system with rings A and B fused, ring B having a suitable carbon fragment in the 1 - position; and in particular to evaluate the usefulness of the natural product ELEMICIN (3:4:5-trimethoxyallylbenzene) (XI) as a starting-material for colchicine synthesis.

(II) To study on an unmethoxylated compound the projected later stages in formation of ring C.

DISCUSSION

Cyclopentadiene is known[16] to react with phenol to give a mixture of o- and p- cyclopentenylphenols (XII) and (XIII) in good yield. Initial experiments were aimed at effecting this substitution in methoxylated compounds, in particular methyl trimethoxybenzoate; concomitantly, the elaboration of the side-chain was investigated.

A cyclopentenyl substituent promised to be particularly useful, for it was anticipated that oxidation would yield a compound of the type (XIV) from which the required A - B fused system (XV) might have been obtained



XV

The reaction of phenol and cyclopentadiene was repeated as described by Bader[16], but this could not be duplicated in any methoxylated compound, despite the employment of a large variety of conditions. (See Table I).

Table I

Cyclopentadiene was treated with the following:-

Compound	Catalyst	Solvent	Temp.
Anisole (1 mol)	H_3PO_4	toluene	30°
Anisole (2 mol)	H_3PO_4	toluene	30
Gallic acid	H_3PO_4	toluene	30
Gallic acid	H_3PO_4	dioxan	50
Gallic acid	H_3PO_4	cyclopentadiene	40
Methyl trimethoxy-benzoate	H_3PO_4	toluene	120
Methyl trimethoxy-benzoate	CH_3SO_3H	ether	0
Methyl trimethoxy-benzoate	CH_3SO_3H	ether	20
Methyl trimethoxy-benzoate	CH_3SO_3H	ether	40

In each case there was obtained only cyclopentadiene polymer and starting material.

An Arndt-Eistert reaction was found to offer an acceptable method for the homologation of trimethoxybenzoic acid. The acid was converted to the acid chloride, which on treatment with diazomethane gave the crystalline diazoketone (XVl); treatment of a methanolic

solution of the diazoketone with silver benzoate/triethylamine according to Newman[17] gave a 70% yield of methyl trimethoxyphenylacetate, from which β-trimethoxyphenylethanol (XVll) was obtained on $LiAlH_4$ reduction.

β-Phenylethanol was used as a model compound to investigate conditions for a further elaboration of the carbon chain.

β-Phenylethyl iodide was obtained ether by treatment of the alcohol with phosphorus and iodine, or by treating the p-toluene sulphonate of the alcohol with potassium iodide in acetone; the relative reactivities of the iodide and tosylate with formamido- and acetamido malonic esters, were compared. The yields of condensed product in four experiments carried out under identical conditions are indicated in Table II.

Table II

Reactants			Yield
Acetamidomalonate	+	iodide	48%
Acetamidomalonate	+	tosylate	22%
Formamidomalonate	+	iodide	41%
Formamidomalonate	+	tosylate	11%

It is seen that the iodide is significantly better than the tosylate, and the acetyl derivative marginally better than the formyl. The generally low yields are accounted for by the appearance of styrene

(identified as its dibromide) in the product, formed by base-catalysed elimination of HI or HOTs from the starting-material. This represented a rather serious drawback to this reaction-sequence.

The acylaminomalonic esters (XVlll, XIX) were hydrolysed and decarboxylated in acid to the known α-aminoacid, benzylalanine (XX). This, on treatment with acetic anhydride/pyridine, readily underwent the Dakin-West reaction[18] to yield the acetamidoketone (XXl) identified as its 2:4-DNP.

While not particularly elegant this method of building on the side chain could have been used if justified by other results; but at this stage it became obvious that attempts to introduce a cyclopentanyl residue into the trimethoxybenzene ring were doomed and this approach was abandoned.

Another related approach had as its starting-material the lactone (XXll) prepared[19] by reaction of bromotrimethoxybenzoic acid and resorcinol. It was anticipated that it might be possible to hydrogenate this molecule selectively, as was found possible by Walker[20] in a corresponding case; the resulting β-diketone (XXlla) would have been convertible to the glutaric acid system (XIV) which was our objective. Unfortunately, (XXll) was found to be resistant to hydrogenation under a variety of conditions.

ELEMICIN

With the failure of these approaches we turned our attention to the material ELEMICIN (3:4:5-trimethoxyallylbenzene) (XI). Elemicin is one of the very few fairly readily available natural products containing the trimethoxybenzene ring of colchicine, with a substantial carbon fragment in the 1-position, and is of obvious potential value as a starting-material for colchicine synthesis.

Elemicin is a colourless oil, b.p. $148^{\circ}/10$ mm., which takes its name from Elemi oil in which it occurs with Elemol; another rich source is the Australian plant Backhousia Myrtifolia.

Elemicin was synthesised by Claisen rearrangement of 1:3-dimethoxy-2-allyloxybenzene (XXIV), and methylation of the product. The trimethoxy compound thus obtained was found to be identical in I.R. spectrum with a sample of natural elemicin.* A sample of "elemicin" from a different source had a spurious absorption band at 970 cm^{-1}, inferred to be a trans C=C vibration. This was confirmed when isoelemicin (XXV) was obtained and found to absorb strongly at this frequency.

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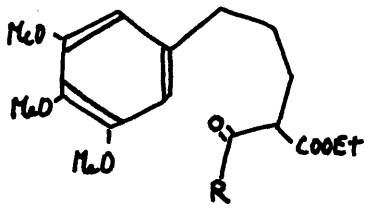
* We are grateful to the Director of Research, Dragoco, Holzminden, and to the Director, The Museum of Applied Arts and Sciences, Sydney, for generous samples of elemicin.

There are reports[21] of the occurrence in plants of propenyl compounds along with the corresponding substituted allylbenzenes, but the rearranged material was present in such quantity (20 - 30%) in this sample that it was almost certainly an artifact.

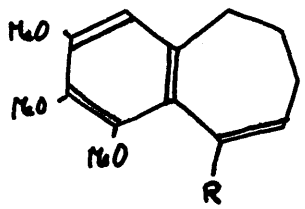
Isoelemicin was obtained, homogeneous to V.P.C., when this mixture of isomers was refluxed with aqueous/alcoholic potassium hydroxide.

It was anticipated that reactions would be possible at the allylic carbon atom of isoelemicin, and various attempts were made to substitute it in this position. N-bromosuccinimide certainly reacted with isoelemicin, to give an oil which analysed approximately for (XXVI), but could not be purified. It failed to give an S-alkylthiourea derivative.

Many attempts were made to use the crude bromo-compound to alkylate ethyl acetonedicarboxylate and ethyl β-ketoadipate, and model experiments as well were carried out with cinnamyl bromide; however no useful results were achieved. It had been hoped that compounds of the type (XXVII) would be obtained which might have been hydrogenated and cyclised to be required structure (XXVIII).



XXVII



XXVIII

Two potential sources of difficulty in these experiments are the possibility of abnormal reaction of the bromo-compound[22] and of O- rather than C-alkylation of the β-ketoester.[23]

Isoelemicin on oxidation with selenium dioxide readily yields the expected 3:4:5-trimethoxycinnamaldehyde (XXIII), but this is contaminated with selenium. An attempt to carry out the same reaction using sodium dichromate/acetic acid[25] gave only trimethoxy benzaldehyde. Mercuric acetate has been successfully used to oxidise allylic methylene groups[28]; whilst there was some indication (spectroscopic, and appearance of mercury in the reaction mixture) that the reaction was working, the yield was negligible.

Treatment of elemicin and isoelemicin with formaldehyde/HCl in an attempt to chloromethylate, resulted in polymer formation: the tendency of styrenes to polymerise is of course well-known.

No homogeneous material could be obtained by bromination of elemicin, but isoelemicin readily gave the known dibromide (XXIX), and

on treatment with excess bromine gave a previously unreported tetrabromo-compound which is inferred to be (XXX). Surprisingly, a tribromo-compound could not be obtained: treatment of isoelemicin with 1 mol of bromine gave a mixture of the tetrabromo-compound (XXX) and starting-material.

Reaction of elemicin and maleic anhydride.

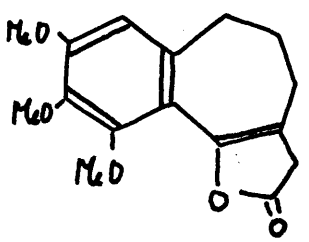
Attention was now focussed on the "conjugative addition" reaction[24] known to occur between allylbenzenes and maleic anhydride. Allylbenzene itself readily gives the anhydride XXXl, and it was hoped that the corresponding trimethoxy-compound XXXll would also be readily obtained.

Attempts were made to carry out the reaction between elemicin and maleic anhydride under a wide variety of conditions of time, temperature, and concentrations; with equimolecular proportions of reagents and with large excess of elemicin. Bromomaleic anhydride, which has been reported to be more reactive[33] was also employed; but in no case was a useful yield of XXXll obtained.

Distillation of the reaction mixture after removal of solvent invariably gave a non-crystallisable glass, which was largely soluble in hot sodium carbonate solution. A small quantity was

obtained of carbonate-insoluble solid, which analysed for an isomer of the anhydride (XXXll) ($C_{16}H_{18}O_3$), and which on the basis of its I.R. spectrum was probably a lactone.

In one experiment, acidification of the carbonate extract gave a small quantity of a gum, the infra-red spectrum and neutralisation equivalent of which were compatible with its formulation as the required dicarboxylic acid (XXXlll). This material was hydrogenated and the crude product treated with polyphosphoric acid, when there was obtained a low yield of the enol lactone (XXXIV) previously described by Horton[26].



XXXIV

There was an indication in the literature[27] that the addition of maleic anhydride might be facilitated by the presence in the benzene ring of a free hydroxyl group, and accordingly an attempt was made to react maleic anhydride and 3:5-dimethoxy-4-hydroxyallylbenzene; the results were no more promising than with elemicin itself.

Thus it is seen that the conjugated addition reaction can be accomplished with elemicin; but while a formal synthesis of the enol lactone (XXXIV) has been achieved it is hardly a practicable route.

Synthesis of the carbon skeleton of colchicine: a novel cyclisation reaction.

Reference has already been made[24] to the very facile reaction of maleic anhydride and allylbenzene. The unsaturated anhydride (XXXI) obtained by this reaction was hydrogenated to yield the saturated compound (XXXV).

The reported[29] cyclisation of (XXXV) to the keto-acid (XXXVI), using aluminium chloride in nitrobenzene, gave in our hands non-reproducible results and low yields. Attempts to carry out the cyclisation in polyphosphoric acid or liquid hydrogen fluoride were also unsuccessful, but it was found that yields of over 90% could readily be obtained using aluminium chloride in ethylene dichloride with careful temperature control. The methyl ester (IX) was readily prepared from (XXXVI) by treatment with ethereal diazomethane.

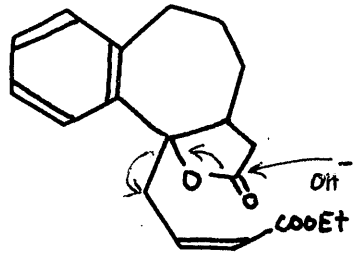
The Reformatski reaction of (IX) and ethyl bromoacetate has been reported by Schofield[30]; we were interested in carrying out this reaction with ethyl γ-bromocrotonate in place of ethyl bromoacetate.

The normal solvents[31] in the Reformatski reaction are ether, benzene, and mixtures of these. Attempts to react the ketoester (IX) with zinc and ethyl bromocrotonate were not promising, since the complex

was a tenacious gum which occluded the surface of the zinc. However, the complex was found to be dissolved by tetrahydrofuran; and when this solvent was substituted for ether/benzene, the reaction was violent, even in the cold.

Working-up in the usual manner, by addition of dilute acid, ether extraction, and distillation, gave an oil which deposited crystals on standing. The analysis of the solid material and its infra-red spectrum were compatible with the structure (XXXVII); lactonisation was also observed by Schofield[30]. The spectra of the oil and solid were very similar, from which it was inferred that the product was a mixture of stereoisomeric lactones.

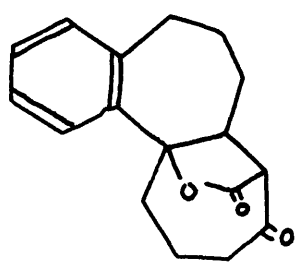
Treatment of (XXXVII) with base in an attempt to hydrolyse it resulted only in the production of keto-acid (XXXVI) and crotonic acid. This is presumed to be a disproportionation reaction of the type described by Johnson[32], which might follow a mechanism such as (IXL),



IXL

Hydrogenation of the lactone-ester (XXXVll) readily gave the solid saturated lactone (XXXVlll). This has the correct number of carbon atoms for formation of a seven-membered-ring ketone, and it was originally intended to obtain from (XXXVlll) the diester (XLl) and carry out a Dieckmann cyclisation. However, this would have introduced problems of stereoisomerism, and it occurred to us that there was no obvious reason why a Dieckmann-type cyclisation should not be able to be carried out on the lactone (XXXVlll) itself, which is different from (XLl) only in that one of the ester functions is cyclic.

In fact it was found that not only did the lactone (XXXVlll) ring-close under the conditions of the Dieckmann reaction, but that acid treatment of the product (presumed to be XLll) hydrolysed the lactone

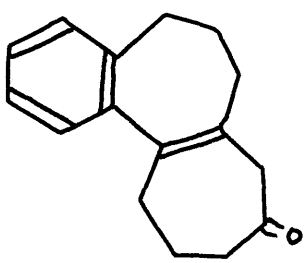


XLII

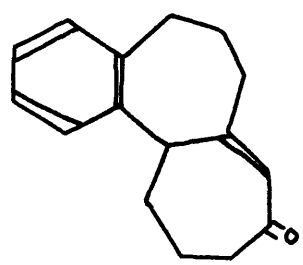
and decarboxylated and dehydrated the product in one step. A yield of 2:4-DNP derivative corresponding to 38% of the tricyclic ketone was obtained.

The ketone itself could be obtained (by treating the product from acid hydrolysis with Girard's reagent T) as an oil with I.R. absorption at ca. 1695 cm^{-1}, and a U.V. absorption maximum at 243 mμ (log ε = 4.13).

Whilst the expected product is the styrene (XLlll) the spectroscopic characteristics of the ketone and in particular of its 2:4-DNP (long-wavelength absorption at 390 mμ) would favour its formulation as (XLIV) in which the double bond has shifted into conjugation with the carbonyl group. This it might reasonably be expected to do under the conditions of acid hydrolysis.



XLIII



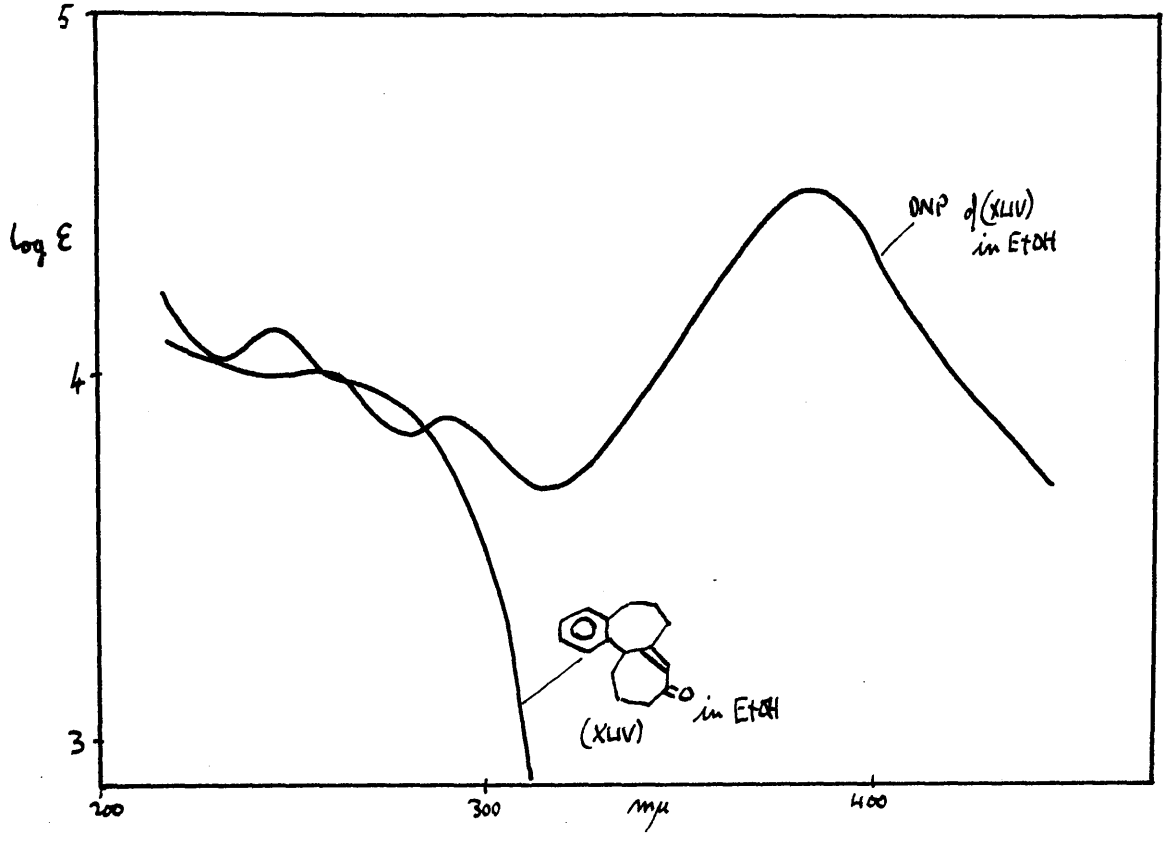
XLIV

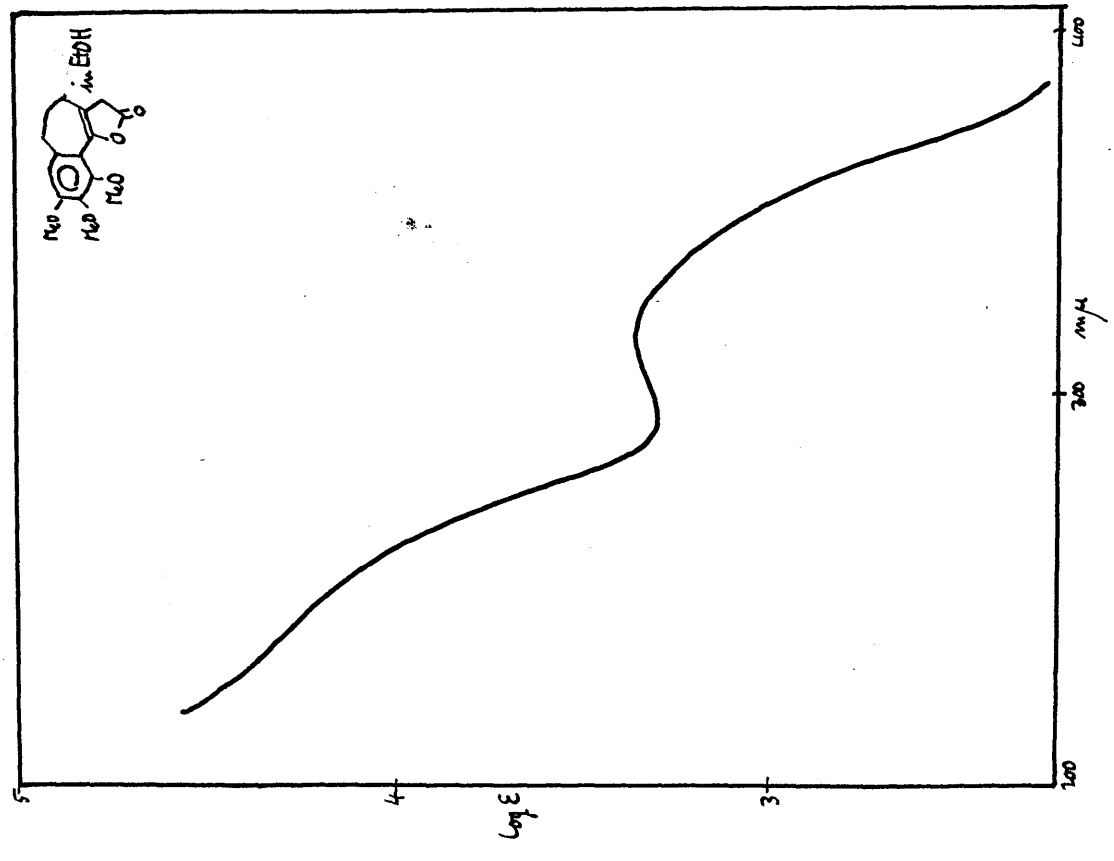
It has thus been found possible to obtain the tricyclic carbon skeleton in only three steps (including a hydrogenation) from the readily-available keto-ester IX, and the yields are such that it should be possible to obtain substantial quantities of (XLlll) or (XLIV).

Other work in the Department has as its aim the synthesis, by a completely different route, of a methoxylated compound corresponding to (XLIII) or (XLIV), and if this is obtained the unmethoxylated ketone would be useful for model experiments on the tropolonisation of ring C.

While it was not envisaged that the reaction-sequence used in this work would be applicable to a synthesis of colchicine itself - because of the previously noted failure of the methoxylated keto-ester (VIII) in the Reformatski reaction - the ease with which the tricyclic ketone is obtained (with the carbonyl in the correct position for formation of a tropolone) would make an approach via the trimethoxy compound corresponding to (XXXVIII) seem very attractive; this would give the methoxylated ketone (XL), which has been obtained by Rapoport[34] by degradation of colchicine, and which could thus serve as a relay.

The possibility remains that a reagent - possibly an acetylene derivative - might be found, which would be able to overcome the steric hindrance of the methoxyl group in VIII.


5
log ε
4
3
200
300
mμ
400
DNP d(XLIV)
in EtOH
(XLIV)
in EtOH


in EtOH
MeO
MeO
MeO
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log ε
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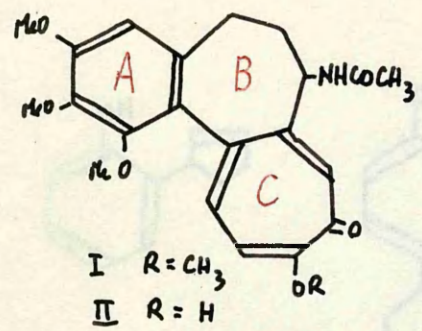
300
200
mμ



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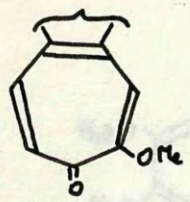
II R = H



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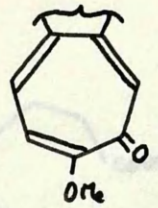

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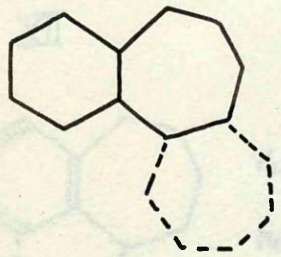

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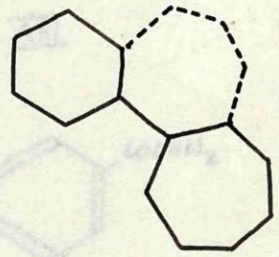

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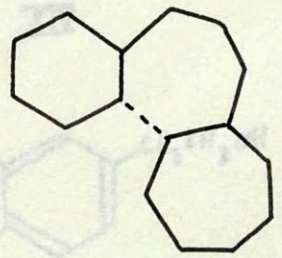

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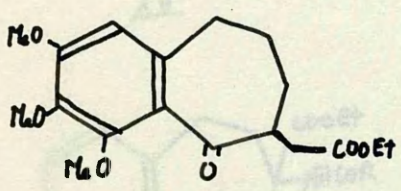

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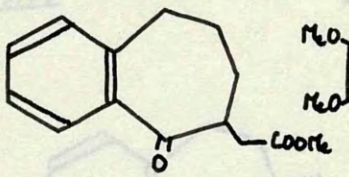

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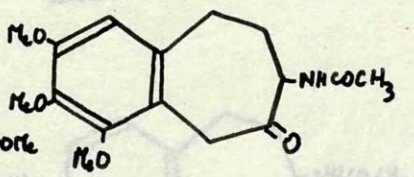

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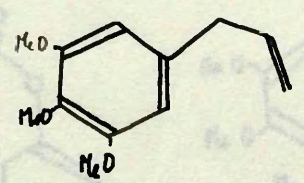

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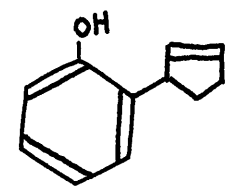

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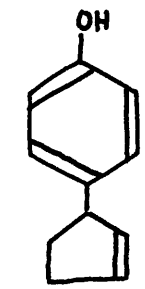

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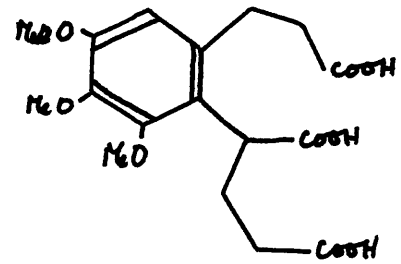

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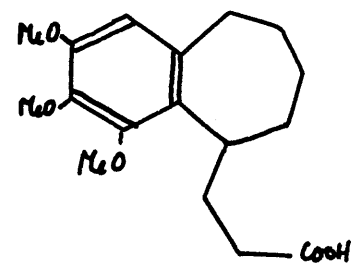

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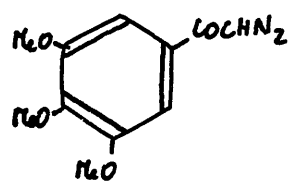

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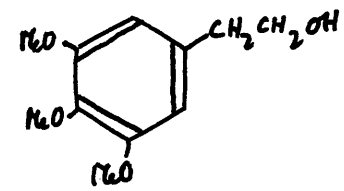

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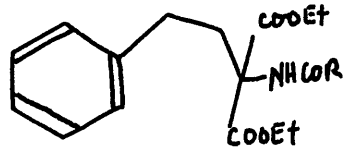
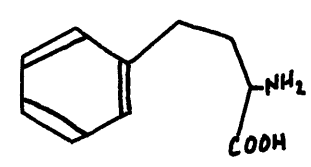


XVIII R = CH_3

XIX R = H



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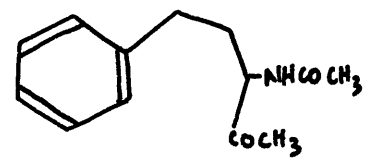

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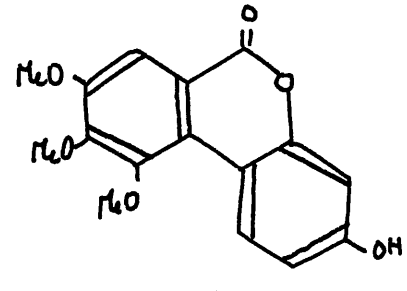

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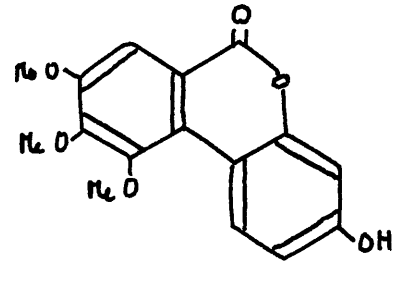

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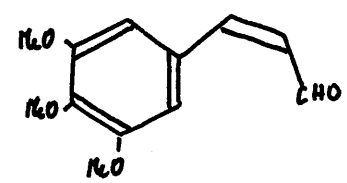

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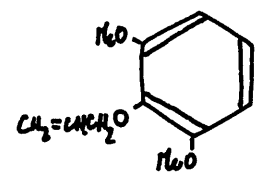

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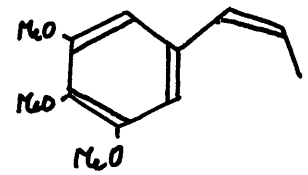

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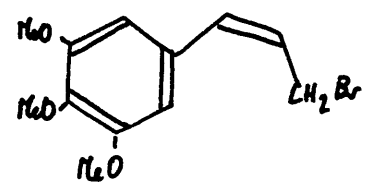

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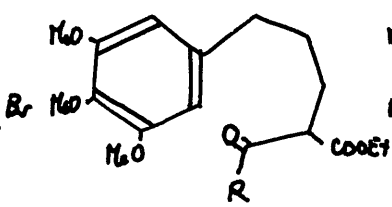

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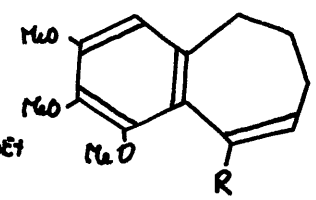

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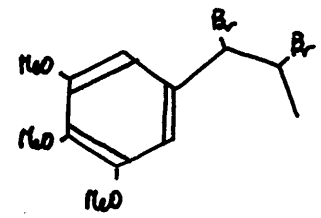

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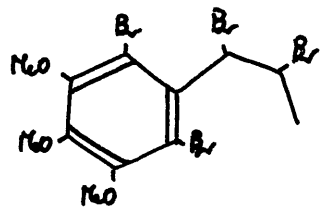

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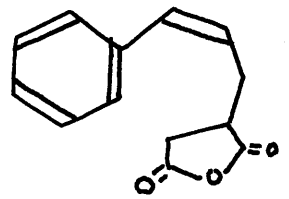

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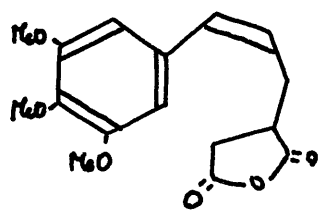

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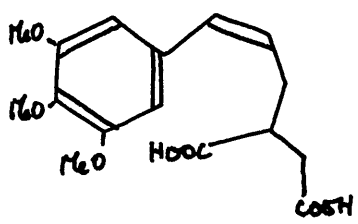

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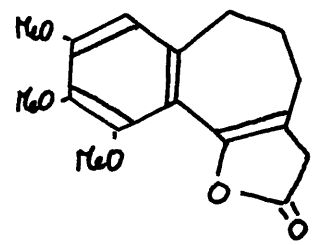

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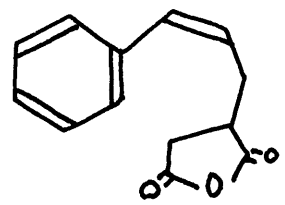

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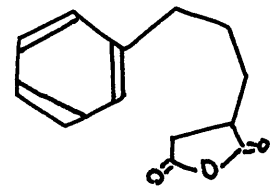

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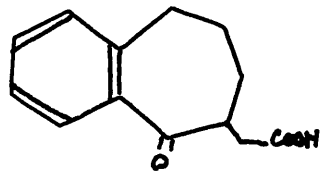

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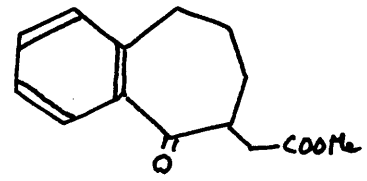

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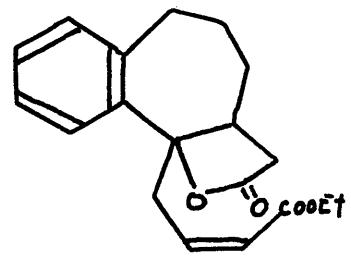

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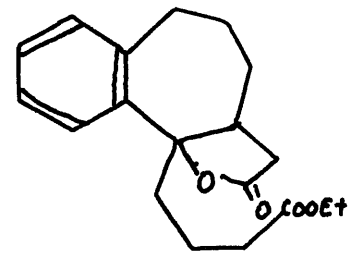

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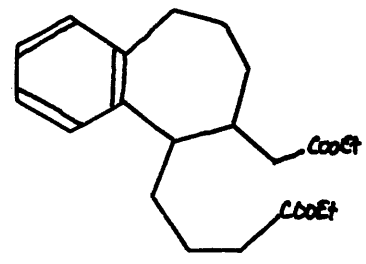

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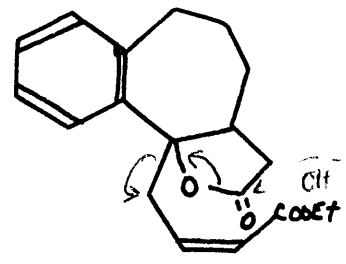

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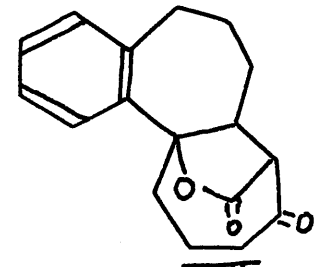

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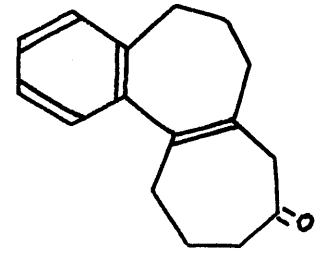

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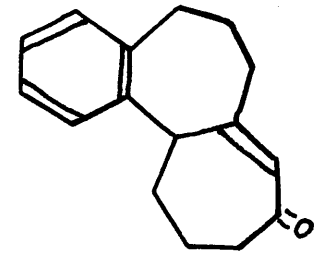

XLIV

Attempted condensation of cyclopentadiene and anisole.

(a) Anisole (45 g., 0.4 mol) was mixed with syrupy phosphoric acid (12 g.) and shaken while a solution of cyclopentadiene (14 g., 0.2 mol) in toluene (20 ml.) was added portionwise. The mixture was shaken for four hours while the temperature was not allowed to exceed 30°C. Sodium carbonate (7 g.) was added, and the mixture was filtered; distillation of the organic material afforded only solvent, anisole, and cyclopentadiene polymer.

(b) The experiment was repeated as above, using anisole (22.5 g., 0.2 mol), phosphoric acid (12 g.) and cyclopentadiene (14 g., 0.2 mol). Only starting-materials and polymer were obtained on working-up.

Attempted condensation of cyclopentadiene and gallic acid.

(a) Gallic acid (34 g., 0.2 mol) with syrupy phosphoric acid (12 g.) was shaken with 50 ml. of toluene. Cyclopentadiene (14 g., 0.2 mol) was added and the mixture shaken for eight hours. Filtration returned 33 g. (97%) of gallic acid.

(b) Gallic acid (42 g., 0.25 mol) dissolved in dioxan (120 ml.) was stirred with phosphoric acid (20 g.) while cyclopentadiene (18 g.) was added. The mixture was stirred at 50°C for six hours; addition of petroleum ether gave 39 g. of unchanged gallic acid.

(c) Gallic acid (34 g., 0.2 mol) mixed with phosphoric acid (20 ml.) was placed in the thimble of a Soxhelet apparatus in which 150 g. of cyclopentadiene monomer was heated under reflux. The experiment had to be abandoned after an hour by which time the cyclopentadiene had polymerised.

Attempted condensation of methyl 3:4:5-trimethoxybenzoate and cyclo pentadiene.

(a) The trimethoxy-ester (4.6 g., 0.02 mol) was dissolved in toluene (120 ml.) containing phosphoric acid (1 g.). Cyclopentadiene (1.5 g.) was added, and the mixture was stirred under reflux for four hours. The toluene solution was decanted; removal of solvent gave 4.2 g. of unchanged starting material.

(b) The trimethoxy-ester (2.3 g., 0.01 mol) was dissolved in ether (10 ml.) to which was added methanesulphonic acid (1 g.). The solution was cooled to $0^{\circ}C$, and 1 g. of cyclopentadiene was added, dropwise. The mixture was maintained at $0^{\circ}C$. for 30 minutes then passed over Amberlite IRA-400 (OH) to remove the acid. Removal of ether from the organic material gave only unchanged ester.

The above procedure was repeated twice with the temperature at 20° and 40° respectively. As before, starting material was recovered unchanged in each case.

Methyl 3:4:5-trimethoxybenzoate.

Dimethyl sulphate (400 g., 3.2 mol) was added portionwise to a stirred refluxing solution of gallic acid (100 g., 0.6 mol) in acetone (3 litres), containing potassium carbonate (750 g., 5.4 mol). After the addition was complete (ca. 2 hours) heating and stirring were continued for a further 18 hours. The cooled mixture was filtered, and the acetone solution concentrated to 1 litre. Addition of 1 litre of water caused precipitation of the required ester, which was collected by filtration. Yield 96 g., 77%. A sample crystallised from methanol had m.p. 82°.

3:4:5-Trimethoxybenzoic acid.

Methyl 3:4:5-trimethoxybenzoate (100 g., 0.44 mol) was heated under reflux for two hours in water (100 ml.) containing sodium hydroxide (20 g.). Acidification of the cooled solution gave 87 g. (93%) of the acid. A sample crystallised from water had m.p. 168°.

3:4:5-Trimethoxybenzoyl chloride.

Trimethoxybenzoic acid (100 g.) was heated under reflux for four hours with 50 ml. of thionyl chloride in dry benzene (100 ml.). Thionyl chloride and solvent were removed under vacuum at 100°C. The product solidified on cooling, and crystallisation from benzene/petrol gave 96 g., (84%) of the acid chloride, m.p. 76°.

Methyl 3:4:5-trimethoxyphenylacetate.

Trimethoxybenzoyl chloride (5.8 g.) was dissolved in 70 ml. of ether. To this solution was added slowly a solution of diazomethane (3 g.) in ether (150 ml.). Removal of solvent after twelve hours gave 4.1 g. (70%) of the bright yellow diazoketone (XVl), m.p. 98-100°C (decomp.).

The diazoketone (4.0 g., 0.017 mol) was dissolved in methanol (100 ml.), and placed in a flask connected to a nitrometer. Silver benzoate (500 mg.) in triethylamine (5 ml.) was added to the diazoketone solution; a black precipitate appeared, and nitrogen was evolved. The mixture was warmed to 60°; after 15 minutes 350 ml. (92%) of nitrogen had been evolved. Filtration of the cooled mixture and removal of solvent gave an oil which on distillation afforded 2.84 g. (68%) of the required ester, b.p. 154-156°/2.0 mm..

3:4:5-Trimethoxyphenylethanol (XVll).

Methyl trimethoxyphenylacetate (12.0 g., 0.05 mol) was dissolved in dry tetrahydrofuran (70 ml.), and this solution was added dropwise over an hour to a stirred, refluxing solution of lithium aluminium hydride (2 g.) in tetrahydrofuran (100 ml.). Stirring and refluxing were continued for a further three hours, then the cooled solution was treated with saturated sodium sulphate solution. Filtration, and removal of

solvents under vacuum, gave an oil which was distilled to yield 8.2 g. (84%) of the required alcohol (XVll), b.p. 144-148°/0.4 mm.. Treatment with p-nitrobenzoyl chloride/pyridine gave a p-nitrobenzoate, m.p. (cryst. MeOH) 99°.

β-Phenylethyl p-toluenesulphonate.

β-Phenylethanol (12.7 g., 0.1 mol) in pyridine (50 ml.) was cooled in ice. p-Toluenesulphonyl chloride (19 g., 0.1 mol) was added, and the mixture allowed to stand at 20° for 16 hours, then poured into water (200 ml.). The oil which separated was cooled in ether to -30° when the required tosylate was obtained crystalline. Yield 20 g. (80%); m.p. 36°.

3:4:5-Trimethoxyphenylethyl p-toluenesulphonate.

The alcohol (XVll) (1.2 g., 0.005 mol) was cooled to 0°C in pyridine (5 ml.). Treatment with p-toluenesulphonyl chloride as above gave an oil which crystallised on standing. 3:4:5-Trimethoxyphenylethyl tosylate had m.p. (cryst. MeOH) 95°. (Found: C, 59.08; H, 6.02; S, 8.74%. $C_{18}H_{22}O_6S$ requires: C, 58.88; H, 5.80; S, 8.47%).

β-Phenylethyl iodide.

(a) β-Phenylethyl tosylate (2.76 g., 0.01 mol) was refluxed for 3 hours in A.R. acetone (50 ml.) with sodium iodide (1.5 g., 0.01 mol). Removal of solvent and distillation of the residual oil gave 2.0 g. (87%)

of β-phenylethyl iodide.

(b) β-Phenylethyl alcohol (146 g.) and red phosphorus (8.27 g.) were mixed in a 250 ml. flask equipped with a Soxhlet extractor containing 127 g. of iodine. After refluxing for 12 hours the organic material was decanted and washed with sodium thiosulphate and water. Removal of solvent after drying (Na_2SO_4) gave 194 g. (84%) of β-phenylethyl iodide, identical in I.R. spectrum with the sample obtained in (a) above.

3:4:5-Trimethoxyphenylethyl iodide.

The p-toluenesulphonate (1.4 g., 0.0038 M) was refluxed for two hours in A.R. acetone with sodium iodide (0.6 g., 0.004 M). Removal of solvent and distillation of the residual oil gave 790 mg. (65%) of the iodide, b.p. 180° (bath)/0.2 mm..

Condensation of β-phenylethyliodide and β-phenylethyl p-toluenesulphonate with acetamido- and formamidomalonic esters.

In each of four flasks, sodium hydride (1.2 g., 0.05M) was dissolved in dimethylformamide (80 ml.).

To flask I was added acetamidomalonic ester (10.8 g., 0.05M) followed by β-phenylethyl iodide (11.6 g., 0.05M).

To flask II was added acetamidomalonic ester (10.8 g., 0.05M) followed by β-phenylethyl p-toluenesulphonate (13.8 g., 0.05M).

To flask III was added formamidomalonic ester (10.2 g., 0.05M) followed by β-phenylethyl iodide (11.6 g., 0.05M).

To flask IV was added formamidomalonic ester (10.2 g., 0.05M) followed by β-phenylethyl β-toluenesulphonate (13.8 g., 0.05M). The mixtures were heated under reflux for 4 hours, then solvent was removed under vacuum, and water (100 ml.) was added to each. The contents of each flask were then extracted with 2 x 50 ml. portions of ethyl acetate; the dried solvent was removed, and the products distilled separately to yield in each case a small quantity of an oil b.p. 48-50°/0.5 mm., (which was identified as styrene via its infra-red spectrum and the preparation of the dibromide, m.p. 73°) and quantities of oils which distilled at 150° (bath)/0.5 mm., as detailed below:

I	acetamido + iodide	7.8 g. (48%)
II	acetamido + tosylate	3.5 g. (22%)
III	formamido + iodide	6.3 g. (41%)
IV	formamido + tosylate	1.7 g. (11%)

The crude phenylethylacylaminomalonic esters (XVlll),(XIX) had infra-red absorption in the carbonyl region at 1735 cm^{-1} and 1655 cm^{-1}.

Benzylalanine (XX).

The acetamidomalonic ester (XVlll) (6.1 g., 0.02M) was heated at 100° for 4 hours with 6N hydrochloric acid (70 ml.). Addition of ammonia to the cooled solution gave a solid precipitate of benzylalanine (XX), m.p. 288° decomp.. Yield 2.8 g., 77%.

Hydrolysis of the formamidoester (XIX) (2 g., 0.006M) similarly, gave 640 mg. (61%) of the same aminoacid (XX).

3-Acetamido-5-phenylpentan-2-one (XXl).

The aminoacid (XX) (1.8 g., 0.01M) was heated at 100° for 8 hours with acetic anhydride (20 ml.) and pyridine (10 ml.). Removal of solvents and distillation gave 970 mg. (46%) of 3-acetamido-5-phenyl propan-2-one, b.p. 260°/1 mm., which yielded a yellow 2:4 DNP, m.p. (cryst. MeOH) 176°. (Found: C, 57.24; H, 5.14; N, 17.46%. $C_{19}H_{22}O_5N_5$ requires: C, 57.22; H, 5.27; N, 17.46%).

Attempted hydrogenation of 2-(2':4'-dihydroxyphenyl)-3:4:5-trimethoxy benzoic acid δ-lactone (XXll).[19]

The lactone (XXll) (2.2 g., 0.008M) in water (100 ml.) containing sodium hydroxide (0.8 g., 0.02M) was shaken at 100° for 6 hours with 10% palladium/charcoal (3 g.) under hydrogen at 6 atmospheric pressure. No hydrogen was absorbed.

The experiment was repeated with platinum oxide (500 mg.) replacing the palladium. Only sufficient hydrogen was absorbed to reduce the PtO_2.

Starting-material was recovered in each case on acidification.

Reaction of elemicin and maleic anhydride.

Elemicin (XI) (10.4 g., 0.05M) and maleic anhydride (1 g., 0.01M) were heated in refluxing xylene (50 ml.) for 18 hours. Xylene and excess elemicin were removed by distillation; the residue cooled to give a non-crystalline glass. This was added to hot sodium carbonate solution when most of it dissolved; a small quantity of solid was left undissolved, which had m.p. (cryst. MeOH) 184°. This material had I.R. carbonyl absorption at 1780-1800 cm^{-1}, and neutralisation equivalent = 160. (Found: C, 63.06; H, 5.84. $C_{16}H_{18}O_6$ requires C, 62.81; H, 5.89%).

Acidification of the carbonate solution (above) afforded 1.5 g. of a gum which absorbed 70 ml. of hydrogen in 20 hrs. when shaken with platinum (100 mg.).

The crude hydrogenation product (1.5 g.) was heated at 100° for 4 hours with polyphosphoric acid (30 g.). The cooled mixture was treated with water, and organic material extracted into ether; the ether was washed with sodium carbonate solution, then dried (Na_2SO_4). Removal of solvent gave a gum which crystallised on standing; recrystallisation from ethyl acetate/pentane gave 62 mg. (2.1%) of 7-carboxymethyl-2:3-trimethoxybenzocycloheptenone enol lactone (XXXIV) m.p. 123°, identical

with an authentic sample. (Found: C, 66.16; H, 6.08%. Calc. for $C_{16}H_{17}O_5$. C, 66.46; H, 5.89%).

Isoelemicin (XXV).

Elemicin (XI) (10.4 g., 0.05M) in ethanol (50 ml.) containing potassium hydroxide (20 g.) in water (7 ml.) was heated under reflux for 14 hours. Ethanol was removed under vacuum, and ether (200 ml.) added; the ether extract was washed with ester and dried; removal of solvent gave 10.2 g. (98%) of isoelemicin, b.p. 111°/0.1 mm..

Isoelemicin dibromide (XXIX).

Isoelemicin (2.08 g., 0.01M) in carbon tetrachloride (20 ml.) was treated dropwise with bromine (1.6 g., 0.01 mol) in carbon tetrachloride (16 ml.). Removal of solvent gave 3.5 g. (95%) of isoelemicin dibromide, m.p. (cryst. 60-80° petrol) 89°.

Treatment of isoelemicin dibromide (2.87 g., 0.01M) with liquid bromine for 48 hours yielded 3.2 g. (72%) of 1-(2:3-dibromopropyl)-2:6-dibromo-3:4:5-trimethoxybenzene (XXX) m.p. (cryst. MeOH) 86°. (Found: C, 27.24; H, 2.47%. $C_{12}H_{14}O_3Br_4$ requires: C, 27.34; H, 2.66%).

Trimethoxycinnamyl bromide (XXVI).

Isoelemicin (2.08 g., 0.01M), N-bromosuccinimide (1.8 g.) and dibenzoyl peroxide (50 mg.) were heated under reflux for 2 hours in 20 ml. of dry carbon tetrachloride. Succinimide was filtered from the cooled

solution, which was then washed with water. Removal of solvent and distillation gave 2.7 g. (94%) of the crude bromo-compound (XXVI).

Trimethoxycinnamaldehyde (XXIII).

Isoelemicin (4.16 g., 0.02M) in glacial acetic acid (40 ml.) was heated with selenium dioxide (2.3 g., 0.02IM) under reflux for 6 hours. Removal of solvent and distillation from glass wool after shaking with mercury gave 2.1 g. of a red oil, containing colloidal selenium. This oil rapidly gave a 2:4-DNP under standard conditions, but this also could not be freed from selenium.

Trimethoxybenzaldehyde.

Isoelemicin (2.08 g., 0.01M) and sodium dichromate (2.0 g.) were heated at 100° for 3 hours in glacial acetic acid (30 ml.). Washing with water, adding ether, drying and removing solvent gave an oil from which by chromatography in benzene on 4" alumina there was obtained 0.9 g. (40%) of 3:4:5-trimethoxybenzaldehyde, identical with an authentic sample.

Treatment of isoelemicin with mercuric acetate.

Isoelemicin (2.08 g., 0.01M) was heated with mercuric acetate (3.2 g.) for 22 hours at 150°. The cooled mixture was extracted with ether; removal of solvent and distillation gave 1.8g. of starting material, and a very small quantity of a higher boiling material with infra-red

absorption at 1730 cm^{-1}.

Cinnamylsuccinic anhydride (XXXI).

Allylbenzene (190 g.) was refluxed with maleic anhydride (159 g.) and o-dichlorobenzene (200 ml.) for 24 hours. Distillation yielded 140 g. of the required anhydride, b.p. 190-200°/0.5 mm., which solidified in the receiver and had m.p. (cryst. benzene/petrol) 100°.

3-Phenylpropylsuccinic anhydride (XXXV).

The unsaturated anhydride (XXXI) (54 g., 0.25M) in ethyl acetate (150 ml.) was shaken with hydrogen at 6 atmospheric pressure in presence of 1 g., 10% palladium/charcoal till absorption ceased. Filtration and removal of solvent gave (XXXV) in quantitative yield.

This reduction failed completely when acetic anhydride was used as solvent.

7-Carboxymethyl-2:3-benzocycloheptenone (XXXVI)

To aluminium chloride (13.2 g.) in ethylene dichloride (100 ml.) (dried by distillation from $AlCl_3$) was added dropwise the anhydride (22 g., 0.1M) in dry ethylene dichloride (100 ml.), while the mixture was vigorously stirred and maintained at -5° - -10°C. (Drikold/acetone).

The mixture was left at 20° for five days, then added to ca. 200 g. of ice; conc. hydrochloric acid was added till all of the precipitated aluminium hydroxide was dissolved. The ethylene dichloride layer was

separated, and the aqueous layer washed with 2 x 100 ml. portions of ethylene dichloride. The combined organic layers were dried; removal of solvent and distillation yielded 9.1 g. (90%) of the required keto-acid, m.p. 129°. Recrystallisation was not necessary.

The methyl ester (IX) was obtained in theoretical yield when the acid (XXXVI) was added to ethereal diazomethane.

1-(3-Carbethoxyprop-2-enyl)-2:3-benzocycloheptan-1-ol-7-acetic acid lactone (XXXVII).

The keto-ester (IX) (2.32 g., 0.01M) and zinc wool (700 mg., 0.011M) were added to tetrahydrofuran (20 ml.). Ethyl bromocrotonate (27 g., 0.015M) was added dropwise; considerable heat was evolved. The rate of addition of the bromo-ester was adjusted to keep the solution refluxing gently. When all of the bromocrotonate was added the mixture was heated under reflux for 4 hours by which time all of the zinc had dissolved. Solvent was removed under vacuum, water (50 ml.) was added, followed by dilute sulphuric acid. Finally organic materials were were extracted into ether, which was dried (Na_2SO_4) and removed. Distillation afforded an oil b.p. 168-174°/0.4 mm., which deposited crystals on standing. Yield 2.7 g., 73%. The I.R. spectra of the solid and of the oil were identical, with carbonyl absorption at ca. 1780 and ca. 1740 cm^{-1}. The solid 1-(3-carbethoxyprop-2-enyl)-2:3-

benzocycloheptan-1-ol-7-acetic acid had m.p. (cryst. Et_2O) 107°. (Found: C, 72.54; H, 7.20%. $C_{19}H_{22}O_4$ requires: C, 72.61; H, 7.00%).

1-(3-Carbethoxypropyl)-2:3-benzocycloheptan-1-ol-7-acetic acid lactone (XXXVIII).

The crude ester-lactone (XXXVII) (500 mg.) and platinum oxide (250 mg.) were shaken with hydrogen. In two hours, 130 ml. had been absorbed. Removal of solvent from refiltered solution gave an oil which crystallised on trituration with ether. A sample recrystallised from ether/pentane at -30° had m.p. 132°; the I.R. spectrum differed from that of (XXXVII) in that it lacked the C=C vibration at 1630 cm^{-1} and the C=C trans vibration at 945 cm^{-1}. (Found: C, 71.66; H, 8.21%. $C_{19}H_{24}O_4$ requires: C, 72.1; H, 7.6%).

2:3-Benzo-9-oxobicyclo(5,5,0)dodec-7-ene (XLIII).

The lactone-ester (500 mg., 1.6 m.Mole) in dry xylene (20 ml.) was stirred under reflux with sodium hydride (100 mg., 4 m.Mole) for 6 hours. Glacial acetic acid (2 ml.) was added; solvents were removed under vacuum from the filtered solution. Distillation gave an oil with I.R. absorption at ca. 1700 cm^{-1} as well as having ester and lactone bands. Under standard conditions there was obtained a red 2:4-DNP, which was chromatographed in benzene on 4" alumina to yield 260 mg. (38%) of material which had m.p. (recryst. chloroform/methanol) 190-191°.

(Found: C, 64.75; H, 5.11; N, 14.00%. $C_{22}H_{22}O_4N_4$ requires C, 64.98; H, 5.41; N, 13.80%). The U.V. absorption spectrum showed a strong maximum at 390 mμ. (See appendix).

The crude ketone (XLIII or XLIV) was obtained when the product from the cyclisation was warmed with dilute acid and extracted with reagent T. The oily ketone had I.R. absorption at ca. 1695 cm^{-1}; the U.V. absorption spectrum is illustrated. (See appendix).

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