Hydroxybenzotropones. Part I. Synthesis of a Dimethoxybenzocyclohepta-1 : 4-diene-3 : 7-dione.

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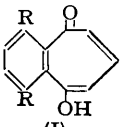
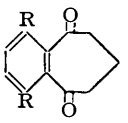
Bromination of the dienol acetate of the dione (II; R = OMe) and subsequent treatment with alkali gave the dione (XV), and not (I; R = OMe). Suppression of enolisation by *peri*-methoxyl groups has a parallel in 4 : 7-dimethoxyindane-1 : 3-dione (XVII).

The hydroxybenzotropone (I; R = H) was derived by Buchanan (*J.*, 1954, 1060) from the dione (II; R = H). As the dimethoxy-derivative (II; R = OMe) is readily accessible *via* the condensation of quinol and glutaric acid (Bruce, Sorrie, and Thomson, *J.*, 1953, 2403) it was of interest to convert it into (I; R = OMe) and compare the properties of the two hydroxybenzotropones. Some attempts to dehydrogenate the ether (II; R = OMe) by conventional methods are described first; the lack of success was accounted for later when the structure of the final product was elucidated.

Direct dehydrogenation with palladised charcoal in boiling trichlorobenzene, which was effective in the synthesis of αβ-benzotropolone (Cook and Somerville, *Nature*, 1949, **163**, 410; Cook, Gibb, Raphael, and Somerville, *J.*, 1952, 603) and purpurogallin (Caunt,

Crow, Haworth, and Vodez, *J.*, 1950, 1631), resulted only in partial demethylation of our ether (II; R = OMe). Variation of catalyst and solvent, including the incorporation of *p*-nitrotoluene (Blood and Linstead, *J.*, 1952, 2255), the use of chloranil, nitrobenzene–iodine, etc., had no effect on the diketone; sulphur dehydrogenation gave a black tar.


(I)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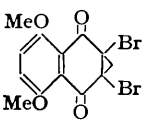
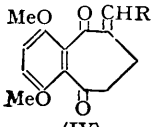

(III)

Dehydrogenation with bromine was readily effected but the brominated compounds obtained (*e.g.*, III) were not soluble in alkali. The structure of these isomeric compounds is considered in the following paper.

In another approach to the conversion of the ether (II; R = OMe) into a hydroxy-tropone we prepared the methylene derivatives (IV; R = Me and Ph) by condensation with acetaldehyde and benzaldehyde respectively, with the object of rearranging these unsaturated ketones to give the hydroxytropones (V; R = Me and Ph). After several failures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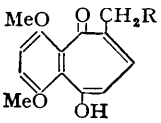
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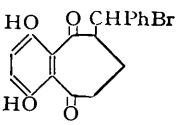
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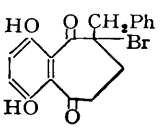
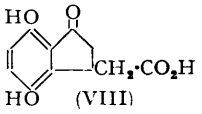
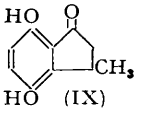
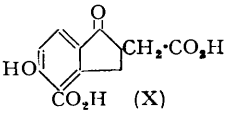
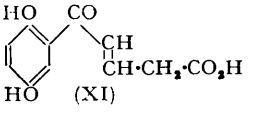

(VII)

with both basic and acidic catalysts, and also palladium–charcoal in high-boiling solvents, this method was abandoned. Leonard and Robinson later (*J. Amer. Chem. Soc.*, 1953, **75**, 2143) successfully rearranged **3** : 7-dibenzylidene*cyclo*heptane-**1** : 2-dione to **3** : 7-dibenzyltropolone and found that hydrogen bromide was a specific catalyst and the conditions were critical. We therefore returned to our benzylidene derivative and attempted rearrangement under Leonard and Robinson's conditions. This time starting material was not recovered and two isomeric bromo-compounds were isolated from the benzylidene ether. These arose by addition of hydrogen bromide to the double bond with concurrent demethylation. Remethylation with methyl sulphate and potassium carbonate in acetone also eliminated hydrogen bromide, to give the benzylidene ether (IV; R = Ph); dehydrobromination with pyridine gave the phenol (IV; OH in place of OMe). Both isomers have the same m. p. (the m. p. of a mixture is much lower) but we cannot say whether they are the compounds (VI) and (VII), or two racemic forms of (VI). We were unable to obtain a hydroxytropone from either of these substances.


(VIII)


(IX)


(X)

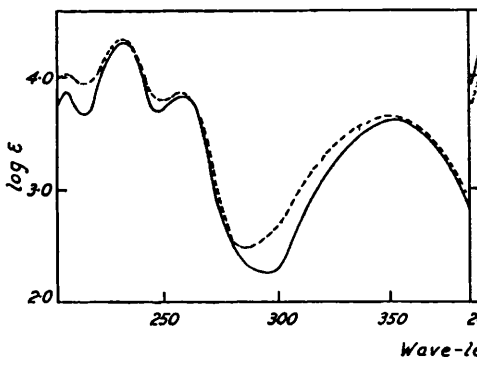

(XI)

In view of the difficulty encountered in dehydrogenating our ether (II; R = OMe) the possibility of avoiding this step was considered. This *might* be achieved in small yield in the first stage of the synthesis by condensing quinol, not with glutaric acid, but with α-chloroglutaric or glutaconic acid, directly to the hydroxytropone (I; R = OH). A trial with glutaconic acid gave the indanone (VIII), which was not surprising. This ketone formed a diacetate and a *p*-nitrophenylhydrazone, and was very similar to **4** : 7-dihydroxy-**3**-methylindan-**1**-one (IX). The ultraviolet absorption curves of the two indanones are shown in Fig. **1**. A curious feature of the acid (VIII) is its remarkable resistance to decarboxylation. The oxoindanylacetic acid (X) is similar; the benzenoid carboxyl group is readily eliminated but that in the side-chain is not affected by copper chromite in quinoline (Pasternack, Conover, *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 1928). The formation of the acid (VIII) clearly proceeds *via* the intermediate (XI) and the reaction is thus analogous to the cyclisation of β-aroylacrylic acids (Baddeley, Holt, and Makar, *J.*,1952,

3289; Baddeley, Holt, Makar, and Ivinson, *ibid.*, p. 3605) and the formation of indanones by the condensation of naphthalene with maleic anhydride (Lambert and Martin, *Bull. Soc. chim. belges*, 1952, **61**, 132) and of quinol with γ-butyrolactone (Bruce, Sorrie, and Thomson, *loc. cit.*).

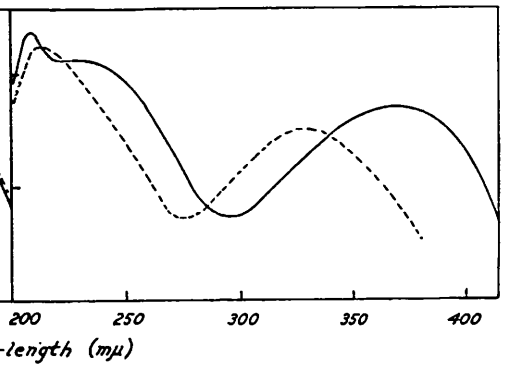
Finally we made use of Buchanan's method (*loc. cit.*) to obtain the hydroxybenzotropone (I; R = OMe). (We are indebted to Dr. Buchanan for information prior to publication.) Reaction of the ether (II; R = OMe) with *iso*propenyl acetate gave a mono- (XII) and a di-enol acetate (XIII). Both of these were converted by bromination with *N*-bromosuccinimide and treatment of the oily product with warm methanolic potassium hydroxide into the same compound, regarded initially as the hydroxytropolone (I; R = OMe). When the bromination product (from both mono- and di-enol acetates) was dissolved in pyridine

FIG. 1.



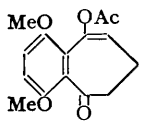
—— 4 : 7-Dihydroxy-3-methylindan-1-one.
– – – 4 : 7-Dihydroxy-3-oxo-1-indanylacetic acid.
Solvent : ethanol.

FIG. 2.

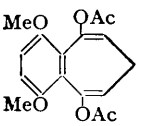


—— 1′ : 4′-Dimethoxy-1 : 2-benzo*cyclo*hepta-1 : 4-diene-3 : 7-dione.
– – – 1′ : 4′-Dimethoxy-1 : 2-benzo*cyclo*heptene-3 : 7-dione.
Solvent : ethanol.

and subsequently poured into dilute hydrobromic acid a pale yellow bromo-derivative, m. p. 125°, $C_{15}H_{15}O_5Br$, was isolated. It became black on storage. Further treatment of this with aqueous or alcoholic alkali gave the same final product in very low yield.



(XII)



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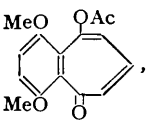
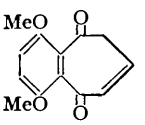
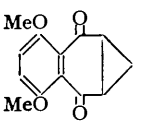


(XIV)



(XV)

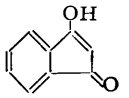


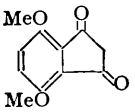
(XVI)

From this it seems that the intermediate bromo-compound is either (XIV), which is improbable, or the bromoacetate of (I; R = OMe). If the acetate groups are partially brominated by reaction with *N*-bromosuccinimide it would account for the low overall yield in the synthesis of the benzotropones (I; R = H and OMe).

The final product was a yellow, crystalline solid, m. p. 163—164°, forming a pale yellow solution in hot aqueous sodium carbonate and warm aqueous sodium hydroxide. It dissolved in concentrated hydrochloric acid, as does the ether (II; R = OMe), and gave no ferric colour or picrate. Attempts to isolate a hydrochloride led to decomposition. No hydroxyl derivatives could be obtained under standard conditions and no pure monocarbonyl derivatives could be isolated, but a dioxime was readily obtained. The compound is thus very different from the hydroxybenzotropone (I; R = H) and is formulated as (XV). This is supported by the results of catalytic hydrogenation [uptake of one mol. of hydrogen regenerated the original dione (II; R = OMe)], the ultraviolet spectrum [compared with that of (II; R = OMe) in (Fig. 2)], and the infrared spectrum which shows a broad carbonyl band at 1678 cm.$^{-1}$ (it could not be resolved) and no hydroxyl band in

the 3-μ region. Most of these results also support structure (XVI) equally, but it is difficult to see how (XVI) could arise from (XIII) and since the compound dissolves in, and can be recovered from, alkali, structure (XVI) seems to be excluded. Infrared bands at 1047 and 990 cm.$^{-1}$ cannot be ascribed to a *cyclo*propane ring (as in XVI), since the ether

(XVII) 

 (XVIII)

(II; R = OMe) absorbs in the same region having a weak band at 990 and stronger bands at 1016, 1045, and 1060 cm.$^{-1}$. Treatment with hydrobromic acid in acetic acid does not yield a naphthazarin derivative which would be expected from (XVI) (see the following paper). The formation of the diketone (XV) rather than the tropolone analogue (I; R = OMe) indicates the absence of aromatic character in this type of ring system; the parent compound (I; R = H) behaves largely as an enol ketone.

The effect on the seven-membered ring brought about by the introduction of two *peri*-methoxyl groups into (I; R = H) has a parallel in the indanedione series. The enol form of indane-1 : 3-dione (XVII) is a vinylogue of the hydroxybenzotropone (I; R = H). Similarly 4 : 7-dimethoxyindane-1 : 3-dione (XVIII) (Hayes and Thomson, unpublished work) corresponds to (XV). The hydroxy-ketone (XVII), like (I; R = H), is soluble in cold aqueous sodium hydrogen carbonate but the ether (XVIII), like (XV), enolises with difficulty and is insoluble in cold alkalis, dissolving only in hot aqueous sodium hydroxide.

Experimental

4 : 7-*Dihydroxy*-3-*oxo*-1-*indanylacetic Acid* (VIII).—A finely powdered mixture of glutaconic acid (6·4 g.) and quinol (6 g.) was added with stirring to a molten mixture of anhydrous aluminium chloride (90 g.) and sodium chloride (20 g.), at 180—195°. After the addition the mixture was stirred for a further 10 min., cooled, and decomposed with 12% hydrochloric acid (750 ml.). After filtration both precipitate and filtrate were extracted with ether and the combined extracts shaken with aqueous sodium hydrogen carbonate solution. This was acidified and extracted with ether to give, after evaporation, an oil which was washed with a little ethyl acetate, crystallised from ethyl acetate–light petroleum (b. p. 80—90°), and sublimed *in vacuo* as pale yellow crystals, m. p. 208° (0·5 g., 4%) (Found : C, 59·3; H, 4·8. $C_{11}H_{10}O_5$ requires C, 59·45; H, 4·5%). This *acid* gives a green ferric chloride colour. Light absorption : Max. at 206, 232, 256, and 348 mμ (log ε 4·05, 4·32, 3·83, and 3·64 respectively) in MeOH. The orange p-*nitrophenylhydrazone* crystallised from aqueous alcohol as the monohydrate, m. p. 224° (decomp.) (Found : C, 54·3; H, 4·45; H, 10·7. $C_{17}H_{15}O_6N_3,H_2O$ requires C, 54·4; H, 4·55; N, 11·2%). The *diacetate*, crystallised from aqueous methanol, had m. p. 181° (Found : C, 59·1; H, 4·9. $C_{15}H_{14}O_7$ requires C, 58·8; H, 4·6%).

1′ : 4′-*Dihydroxy*-1 : 2-*benzo*cyclo*heptene*-3 : 7-*dione* (II; R = OH).—The procedure of Bruce, Sorrie, and Thomson (*loc. cit.*) was modified to give an increased yield. A mixture of glutaric acid (13·2 g.) and quinol (11 g.) was added slowly with stirring to a molten mixture of anhydrous aluminium chloride (150 g.) and sodium chloride (50 g.); the temperature was maintained at 180—200° throughout the addition (20—30 min.). The cooled mass was then decomposed with water (1 l.) and concentrated hydrochloric acid (500 ml.), and the mixture warmed to 80°. The precipitate crystallised from light petroleum (b. p. 100—120°) as bright red needles of the dione, m. p. 149° (9 g., 43%). It gave a dark green ferric chloride colour and dissolved in aqueous sodium carbonate. Light absorption : Max. at 216, 260, and 410 mμ (log ε 4·25, 3·9 and 3·92 respectively) in *cyclo*hexane. The dimethyl ether had max. at 214 and 330 mμ (log ε 4·29 and 3·55 respectively) in MeOH. The *oxime* of the dimethyl ether had m. p. 175° (from light petroleum) (Found : C, 62·3; H, 6·0; N, 5·35. $C_{13}H_{15}O_4N$ requires C, 62·6; H, 6·0; N, 5·6%).

Attempted Dehydrogenation of the Ether (II; R = OMe).—The dimethoxy-dione (2 g.) was refluxed in 1 : 2 : 4-trichlorobenzene (20 ml.) with palladised charcoal (2 g., 10%) for 11 hr. under nitrogen. The material soluble in aqueous sodium hydroxide (10%) crystallised from light petroleum (b. p. 100—120°) to give starting material, and, after concentration of the mother-liquor, the yellow *monomethyl ether*. The latter, separated from light petroleum (b. p.

80—90°), had m. p. 86° (Found: C, 65·0; H, 5·3; OMe, 13·35. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·45; OMe, 14·1%).

*4-Ethylidene-1′ : 4′-dimethoxy-1 : 2-benzo*cyclo*heptene-3 : 7-dione* (IV; R = Me).—To 1′ : 4′-dimethoxy-1 : 2-benzo*cyclo*heptene-3 : 7-dione (1 g.), dissolved in concentrated hydrochloric acid (60 ml.), was added acetaldehyde (0·3 g.). After 3 days, the orange precipitate was collected (0·7 g., 63%). Crystallisation from benzene–light petroleum (b. p. 100—120°) gave the dull yellow *ethylidene derivative*, m. p. 228° (Found: C, 69·1; H, 6·0. $C_{15}H_{16}O_4$ requires C, 69·25; H, 6·15%).

*4-Benzylidene-1′ : 4′-dimethoxy-1 : 2-benzo*cyclo*heptene-3 : 7-dione* (IV; R = Ph).—Freshly distilled benzaldehyde (0·4 g.) was added to the dimethoxy-dione (1 g.) in concentrated hydrochloric acid (60 ml.). Next day the yellow precipitate was collected and crystallised from glacial acetic acid (charcoal); the *product* was obtained as lemon-yellow needles, m. p. 204° (0·8 g., 58%) (Found: C, 74·35; H, 5·9. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%).

4-Bromobenzyl(?)*-1′ : 4′-dihydroxy-1 : 2-benzo*cyclo*heptene-3 : 7-dione* (VI).—To a solution of glacial acetic acid (35 ml.) saturated with anhydrous hydrogen bromide was added the benzylidene-dione (0·5 g.). The mixture was warmed at 60° for 11 hr., after which it was poured into water. The dull yellow precipitate was collected and crystallised from light petroleum (b.p. 100—120°) (charcoal) in yellow needles, m. p. 157° (100 mg.) (Found: C, 57·8; H, 3·9; Br, 20·3. $C_{18}H_{15}O_4Br$ requires C, 57·6; H, 4·0; Br, 21·3%). The mother liquor gradually deposited a second crop of yellow needles. Recrystallisation from light petroleum (b. p. 100—120°) gave lemon-yellow needles of an *isomer* (?) (70 mg.), m. p. 157° depressed on admixture with the previous compound (Found: C, 57·5; H, 3·9%). The first bromo-compound with methyl sulphate–potassium carbonate in boiling acetone gave 4-benzylidene-1′ : 4′-dimethoxy-1 : 2-benzo*cyclo*heptene-3 : 7-dione, m. p. and mixed m. p. 204°.

*4-Benzylidene-1′ : 4′-dihydroxy-1 : 2-benzo*cyclo*heptene-3 : 7-dione*—This was obtained from each of the above isomers, by dissolution in warm pyridine and, next day, pouring into dilute hydrobromic acid. The orange-yellow *product* was isolated by chloroform extraction and, crystallised from light petroleum (b. p. 100—120°), had m. p. 99° (Found: C, 73·7; H, 4·8. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·75%). Methylation gave the dimethyl ether, m. p. and mixed m. p. 204°.

*3-Acetoxy-1′ : 4′-dimethoxy-1 : 2-benzo*cyclo*hepta-1 : 3-diene-7-one.*—1′ : 4′-Dimethoxy-1 : 2-benzo*cyclo*heptene-3 : 7-dione (1 g.), *iso*propenyl acetate (2 ml.), and concentrated sulphuric acid (1 drop) were refluxed for 2 hr. Potassium acetate was added to neutralise the acid catalyst, and the mixture evaporated to dryness *in vacuo*. The solid residual *monoacetate* was washed with alcohol and crystallised from light petroleum (b. p. 100—120°) as feathery needles, m. p. 120° (1 g., 84%) (Found: C, 64·9; H, 5·85. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%). The *dienol acetate* was obtained by refluxing the monoacetate (1 g.) for 3·5 hr. with *iso*propenyl acetate (5 ml.) and concentrated sulphuric acid (1 drop), the acetone formed being allowed to distil off. It crystallised from light petroleum (b. p. 100—120°) in long needles, m. p. 151° (0·7 g., 60%) (Found: C, 64·1; H, 5·6. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·65%). This can also be obtained directly from the dimethoxy-dione (I; R = OMe) in 30% yield.

*1′ : 4′-Dimethoxy-1 : 2-benzo*cyclo*hepta-1 : 4-diene-3 : 7-dione.*—This was prepared from each of the above enol acetates by the same procedure. The acetate (2 g.) was dissolved in dry carbon tetrachloride (75 ml.) and *N*-bromosuccinimide (1 mol.) added. After refluxing about 2 hr., when a blue or violet colour developed, the mixture was cooled and the insoluble succinimide filtered off (the colour does not appear during the bromination of the monoenol acetate). Distillation of the solvent under reduced pressure left a dull yellow oil which was treated in one of two ways. (*a*) Addition of pyridine to dissolve the oil gave a deep red solution. After 12 hr., this mixture was poured into dilute hydrobromic acid, and the precipitate collected and crystallised from light petroleum (b. p. 80—90°), pale yellow crystals, m. p. 125°, being obtained (Found: C, 51·4; H, 4·1; Br, 22·2. $C_{15}H_{15}O_5Br$ requires C, 50·75; H, 4·2; Br, 22·5%). Subsequent treatment of this compound as in (*b*) gave the final product in low yield. (*b*) The oil from the bromination was dissolved in methanolic potassium hydroxide (25 ml.; 5%) and warmed gently on the steam-bath for 30 min. The mixture was then cooled, poured into water, and acidified with dilute hydrochloric acid, and the resulting suspension extracted with chloroform and dried ($MgSO_4$). Hot light petroleum (b. p. 100—120°) was then added to the chloroform solution, and most of the latter solvent boiled off. When the solution had cooled it was decanted from a little sticky naterial and then concentrated to turbidity. On cooling, the *diketone* separated in clusters of orange crystals. Recrystallisation from light petroleum gave yellow material, m. p. 163—164° (37% from the dienol acetate, 17% from the monoenol acetate)

(Found : C, 67·0; H, 5·25. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·15%). Light absorption : Max. at 208, 225 (inflection), and 370 mμ (log ε 4·38, 4·13, and 3·72 respectively) in MeOH. The *dioxime* decomposed at *ca.* 300—310° (crystals from dimethylformamide) (Found : C, 59·4; H, 5·5; N, 10·4. $C_{13}H_{14}O_4N_2$ requires C, 59·5; H, 5·4; N, 10·7%). The diketone (0·1 g.) was hydrogenated over Adams catalyst in glacial acetic acid (5 ml.). Hydrogen (1 mol.) was absorbed in 10 min. and the reaction was then stopped. The solvent was removed *in vacuo* and the residue crystallised from light petroleum (b. p. 100—120°) to give 1′:4′-dimethoxy-1 : 2-benz*ocyclo*heptene-3 : 7-dione as colourless prisms, m. p. and mixed m. p. 149°.

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