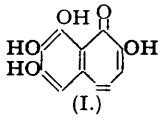
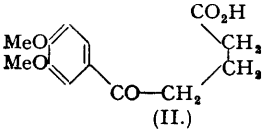
# 37. 4-*Hydroxy*-2′ : 3′-*dimethoxybenz*cyclo*heptatrien*-3-*one and Related Topics.*

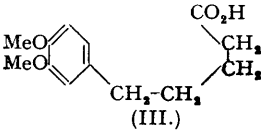
By J. A. Barltrop, A. J. Johnson, and G. D. Meakins.

Dehydrogenation of 2′ : 3′-dimethoxybenz*cyclo*heptene-3 : 4-dione (V) has been shown to give rise to the dimethoxybenztropolone (VI). Certain intermediates of potential value for the synthesis of benztropolones are described.

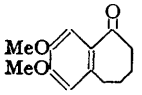
The recent publication by Caunt, Crow, Haworth, and Vodoz (*J.*, 1950, 1631), which provides synthetical proof of the correctness of the benztropolone structure (I) for purpurogallin, originally suggested by Barltrop and Nicholson (*J.*, 1948, 116), also describes the synthesis of the dimethoxybenztropolone (VI). We synthesised this compound some time ago, but withheld publication while attempts were made to extend the method to the synthesis of purpurogallin itself. In view of this communication by Haworth *et al.* it would seem desirable to submit an account of our own work in this field.

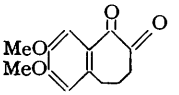

(I.)

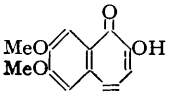

(II.)


(III.)

γ-(3 : 4-Dimethoxybenzoyl)butyric acid (II) was prepared in 83% yield by condensing glutaric anhydride with veratrole in the presence of aluminium chloride, excess of veratrole being used as solvent. This procedure constitutes an improvement on that described by Caunt, Crow, Haworth, and Vodoz (*loc. cit.*) who obtained the product in 55% yield. The reduction of (II) using Martin's modification of the Clemmensen method (*J. Amer. Chem. Soc.*, 1936, **58**, 1438) gave an almost quantitative yield of δ-(3 : 4-dimethoxyphenyl)valeric acid (III). Catalytic reduction of the keto-acid was also studied. By using freshly prepared Raney nickel catalyst under carefully controlled conditions, the reduction was effected in 82% yield. Presumably, δ-(3 : 4-dimethoxyphenyl)-δ-valerolactone (VII) is involved as an intermediate; indeed, this compound can be isolated by performing the hydrogenation over palladised charcoal at atmospheric pressure and temperature.

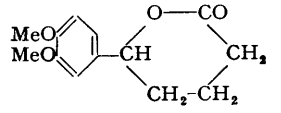

(IV.)

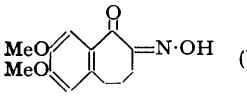

(V.)


(VI.)

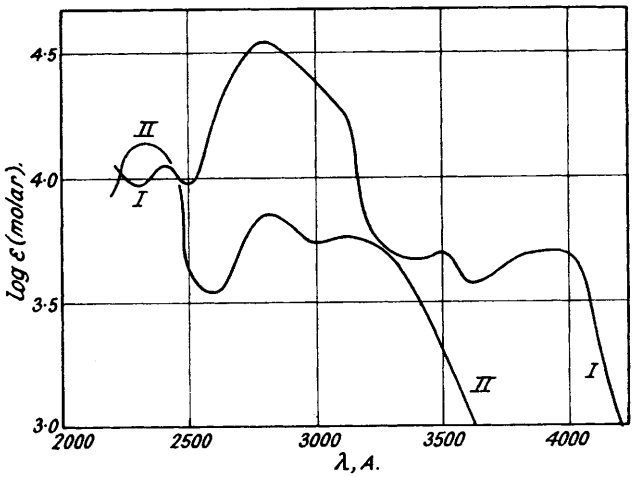
The cyclisation of δ-phenylvaleroyl chloride to benz*cyclo*heptenone by the usual methods has been reported to proceed in yields varying between 27% and 50% (Kipping and Hunter, *J.*, 1901, **79**, 602; Borsche and Roth, *Ber.*, 1921, **54**, 174; Kadesch, *J. Amer. Chem. Soc.*, 1944, **66**, 1207), but by using a high-dilution technique, Plattner (*Helv. Chim. Acta*, 1944, **27**, 801) was able to raise the yield to 87%. This last method, applied to δ-(3 : 4-dimethoxyphenyl)valeroyl chloride, effected an extremely satisfactory conversion into 2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (IV), but the procedure, involving the prolonged stirring of large quantities of boiling carbon disulphide, was clearly ill-suited to the production of (IV) in quantity. A more convenient method was found to be the cyclodehydration of the parent acid by means of phosphoric oxide in benzene solution. Distillation of (III) with zinc chloride in a high vacuum gave only small yields of a somewhat impure material.

Our own preliminary experiments suggested that the 2′ : 3′-dimethoxybenz*cyclo*hepten-3-one could be neither oxidised smoothly with selenium dioxide to the diketone (V), nor readily nitrosated with *iso*amyl nitrite and sodium ethoxide. However, it was found that nitrosation under carefully controlled conditions in the presence of hydrogen chloride afforded the 4-oximino-2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (VIII) in virtually quantitative yield.

(VII.) 


(VIII.)

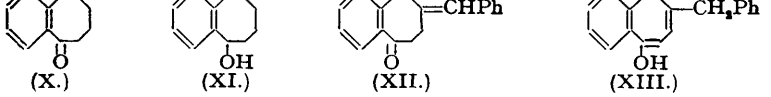
Although the oximino-ketone could be transformed into the diketone (V) by prolonged warming with nitrous acid, subsequent experiments revealed that hydrolysis by dilute hydrochloric acid in the presence of formaldehyde was much better. Haworth *et al.* (*loc. cit.*) encountered difficulty in effecting this hydrolysis and obtained the dione as an oil. We find the compound to be a highly crystalline solid, m. p. 104°.




*I.* 4-*Hydroxy*-2′ : 3′-*dimethoxybenz*cyclo*heptatrien*-3-*one*.
*II.* 2′ : 3′-*Dimethoxybenz*cyclo*heptene*-3 : 4-*dione*.

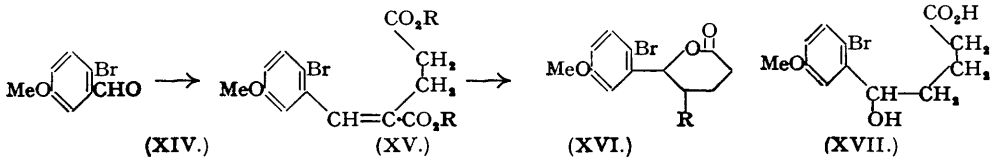
Dehydrogenation of the dione over palladised charcoal in boiling trichlorobenzene (cf. Cook and Somerville, *Nature*, 1949, **163**, 410) gave the dimethoxybenztropolone (VI) in 8% yield. The substance appears to be identical with that described by Haworth *et al.*; it resembles all other known tropolones in forming no ketonic derivatives.

Some preliminary experiments have been made to devise syntheses of tropolones avoiding the unsatisfactory dehydrogenation stage, which is a feature of all methods hitherto described. Benz*cyclo*heptene-3 : 7-dione (X), prepared by a modification of Dieckmann's method (*Ber.*, 1899, **32**, 2227), on hydrogenation, afforded a small quantity of 7-hydroxybenz*cyclo*hepten-3-one (XI), isolated as its semicarbazone. The dione (X) readily afforded a monobenzylidene derivative (XII), which from its large melting point range is presumably a mixture of geometrical isomers. Attempts to isomerise it to (XIII) have been unsuccessful.


(X.) (XI.) (XII.) (XIII.)

A related approach involves the preparation of compounds of the general type (XI) from δ-(*o*-bromophenyl)valerolactones (XVI; R = H) by an intramolecular Grignard reaction. No

lactones of the type contemplated are known and their preparation by the following scheme was attempted :



(XIV.) (XV.) (XVI.) (XVII.)

2-Bromo-5-methoxybenzaldehyde (XIV), prepared in improved yield by a modification of Pschorr's method (*Annalen*, 1912, **391**, 23), would not condense with ethyl glutarate in the presence of either sodium, or sodium ethoxide. Potassium *tert.*-butoxide appeared to promote satisfactory reaction between (XIV) and ethyl glutarate but subsequent hydrolysis, decarboxylation, and lactonisation under the conditions used by Johnson (*J. Amer. Chem. Soc.*, 1945, **67**, 1357) in analogous condensations with ethyl succinate gave only a small amount of neutral material which was hydrolysed to δ-(2-bromo-5-methoxyphenyl)-δ-hydroxyvaleric acid (XVII). The low yield may be due to differences between the ease of formation of γ- and δ-lactones.

Fittig (*Annalen*, 1882, **216**, 99; 1889, **255**, 293) showed that substituted benzaldehydes, sodium succinate, and acetic anhydride condense to give phenylparaconic acids and phenyl*iso*crotonic acids, and that the paraconic acids may be transformed into the *iso*crotonic acids by pyrolysis. Condensation between (XIV) and sodium glutarate under similar conditions gave α-(2-bromo-5-methoxybenzylidene)glutaric acid (XV; R = H), a type of product finding no analogy in Fittig's work. The benzylidene-glutaric acid was expected to decarboxylate readily, but it was unaffected by pyrolysis, and copper-containing catalysts caused debromination. Mineral acids isomerised the acid (XV; R = H) to the lactone (XVI; R = $CO_2H$). Efforts to effect a decarboxylation and rearrangement of the lactone, analogous to the paraconic acid–*iso*crotonic acid transformation, have been unsuccessful.

## Experimental.

γ-(3 : 4-*Dimethoxybenzoyl*)*butyric Acid.*—To a stirred, ice-cold solution of glutaric anhydride (10 g.) in veratrole (100 c.c.), finely pulverised aluminium chloride (26 g.) was added all at once and the stirring continued for one hour at 0°. After 15 hours at room temperature, the mixture was added to concentrated hydrochloric acid (100 c.c.) and ice and then extracted with chloroform. The organic layer was extracted with sodium carbonate solution and this on acidification precipitated γ-(3 : 4-dimethoxybenzoyl)butyric acid (18·5 g., 83%), m. p. 141—144°. After two recrystallisations from ethanol, the acid was obtained as colourless rhombs, m. p. 145—146° (Caunt, Crow, Haworth, and Vodoz, *loc. cit.*, give m. p. 140—145°) (Found : C, 61·6; H, 6·4. Calc. for $C_{13}H_{16}O_5$ : C, 61·9; H, 6·4%).

δ-(3 : 4-*Dimethoxyphenyl*)*valeric Acid.*—(*a*) Concentrated hydrochloric acid (125 c.c.) was added to a boiling mixture of γ-(3 : 4-dimethoxybenzoyl)butyric acid (30 g.), amalgamated zinc (70 g.), water (60 c.c.), and toluene (100 c.c.) after 0, 6, and 18 hours. After being boiled for 36 hours, the reaction mixture was worked up in the usual manner. δ-(3 : 4-Dimethoxyphenyl)valeric acid (27·8 g., 97%) was obtained as a colourless solid, m. p. 72—74°.

(*b*) A solution of the keto-acid (5 g.) in ethanol (100 c.c.) was hydrogenated over freshly prepared Raney nickel catalyst at 80° and 50 atmospheres. After removal of the catalyst from the solution, and evaporation, trituration of the residue with light petroleum (b. p. 40—60°) gave the valeric acid (4 g., 82%), m. p. 71—74°.

δ-(3 : 4-*Dimethoxyphenyl*)-δ-*valerolactone.*—A solution of γ-(3 : 4-dimethoxybenzoyl)butyric acid (0·5 g.) in aqueous sodium hydroxide was hydrogenated for 16 hours over palladised-charcoal catalyst at room temperature and pressure. After removal of the catalyst, acidification, and isolation with ethyl acetate, δ-(3 : 4-*dimethoxyphenyl*)-δ-*valerolactone* was obtained as a clear glass, which, on being triturated with ether–light petroleum, gave colourless crystals, m. p. 156—159°. Two recrystallisations from ether–light petroleum furnished colourless prisms, m. p. 158—159° (Found : C, 65·7; H, 6·9. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

2′ : 3′-*Dimethoxybenz*cyclo*hepten*-3-*one.*—(*a*) Phosphorus pentachloride (2·4 g.) was added to a solution of δ-(3 : 4-dimethoxyphenyl)valeric acid (1·9 g.) in carbon disulphide (50 c.c.), and the mixture was refluxed for 30 minutes and then diluted with carbon disulphide (300 c.c.). The mixture was added dropwise during 30 hours to a vigorously stirred, gently boiling solution of stannic chloride (2·5 c.c.) in carbon disulphide (300 c.c.). After a further 5 hours, the solvent was distilled off, the complex decomposed with hydrochloric acid, and the product extracted with ether. The organic layer was washed with sodium carbonate solution, dried, and distilled. 2′ : 3′-Dimethoxybenz*cyclo*hepten-3-one (1·4 g., 80%) was collected as an almost colourless oil, b. p. 160—165° (bath temp.)/0·07 mm. It crystallised from ether–light petroleum in colourless needles, m. p. 63—64° (Found : C, 71·2; H, 7·4. Calc. for $C_{13}H_{16}O_3$ : C, 70·9; H, 7·3%); dinitrophenylhydrazone, deep red-plates (glacial acetic acid), m. p. 226—227° (Found : C, 56·8; H, 4·9; N, 14·2. Calc. for $C_{18}H_{20}O_6N_4$ : C, 57·0; H, 5·0; N, 14·0%). Haworth *et al.* (*loc. cit.*) obtained orange prisms, m. p. 234—236°. The semicarbazone formed prisms (from ethanol)

m. p. 205—206° (Found : C, 60·2; H, 6·8. Calc. for $C_{14}H_{19}O_3N_3$ : C, 60·6; H, 6·9%) (Haworth *et al.* obtained needles, m. p. 190—192°).

(*b*) The acid was cyclised by means of phosphoric oxide in benzene solution with results similar to those described by Caunt, Crow, Haworth, and Vodoz.

4-*Benzylidene*-2′ : 3′-*dimethoxybenz*cyclo*hepten*-3-*one*.—A small quantity of sodium ethoxide dissolved in ethanol was added to a solution of 2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (0·38 g.) and benzaldehyde (0·19 g.) in absolute ethanol. After 24 hours, 4-*benzylidene*-2′ : 3′-*dimethoxybenz*cyclo*hepten*-3-*one* (0·46 g., 90%), m. p. 154—156°, was collected. It separated from ethanol in pale-yellow needles, m. p. 157—158° (Found : C, 78·0; H, 6·4. $C_{20}H_{20}O_3$ requires C, 77·9; H, 6·5%).

2′ : 3′-*Dimethoxy*-4-*oximinobenz*cyclo*hepten*-3-*one*.—*iso*Amyl nitrite (5 g.) in dry ether (50 c.c.) was added dropwise during 2 hours to an ice-cold, stirred solution of 2′ : 3′-dimethoxybenz*cyclo*hepten-3-one (5 g.) in dry ether. Dry hydrogen chloride was passed into the mixture simultaneously. Stirring and the flow of hydrogen chloride were continued for a further ½ hour. Next morning the oximino-ketone hydrochloride (6·1 g., 95%) was collected; it formed a bright red solid. A solution of this in boiling water was neutralised and cooled. The oximino-ketone formed pale-yellow needles, m. p. 173° (Found : C, C, 62·6; H, 6·0. Calc. for $C_{13}H_{15}O_4N$ : C, 62·6; H, 6·0%). Rapid cooling of the hot aqueous solution produced colourless crystals, m. p. 163—165°. The 2 : 4-*dinitrophenylhydrazone* crystallised from benzene in brick-red needles, m. p. 168—172° (decomp.) (Found : C, 53·6; H, 4·7. $C_{19}H_{19}O_7N_5$ requires C, 53·2; H, 4·4%).

2′ : 3′-*Dimethoxybenz*cyclo*heptene*-3 : 4-*dione*.—(*a*) A mixture of the oximino-ketone (2 g.), formaldehyde (10 c.c.; 40% aqueous solution), and 2N-hydrochloric acid (2 c.c.) was heated on the steam-bath for ten minutes. The deep-yellow solution, after being diluted with water (30 c.c.) and cooled, deposited 2′ : 3′-dimethoxybenz*cyclo*heptene-3 : 4-dione (1·65 g., 85%), which, recrystallised from boiling water, formed yellow leaflets, m. p. 104—105° (Found : C, 66·9; H, 6·0. Calc. for $C_{13}H_{14}O_4$ : C, 66·7; H, 6·0%). It gave mono-2 : 4-dinitrophenylhydrazone, orange plates (from benzene), m. p. 247° (decomp.) (Found : C, 54·7; H, 4·0; N, 13·4. Calc. for $C_{19}H_{18}O_7N_4$ : C, 55·1; H, 4·3; N, 13·5%) (Haworth *et al.*, *loc. cit.*, obtained yellow needles, m. p. 253°), and a *semicarbazone*, plates (from ethanol), m. p. 225—226° (Found : N, 14·1. $C_{14}H_{17}O_4N_3$ requires N, 14·4%). The diketone gave a deep-brown colour with ferric chloride and red solutions with alkali.

(*b*) The oximino-ketone (0·45 g.) was heated in a pressure bottle for 36 hours at 35—40° with sodium nitrite (1·2 g.), aqueous ethanol (100 c.c.; 50%), and concentrated sulphuric acid (1·2 c.c.). The solution was neutralised with sodium carbonate solution, concentrated under reduced pressure at 60°, filtered from the brown oil which separated first, and allowed to cool. The dione separated as yellow crystals (0·15 g., 37%), m. p. 95—97° raised to 104—105° by recrystallisation from water.

4-*Hydroxy*-2′ : 3′-*benz*cyclo*heptatrien*-3-*one*.—The dione (0·9 g.), 35% palladised charcoal (1·2 g.), and *s*-trichlorobenzene (15 c.c.) were refluxed in a stream of nitrogen for four hours. After being diluted with benzene, filtered from catalyst, and washed with sodium carbonate solution, the mixture was extracted with 2N-sodium hydroxide solution. Acidification precipitated the product which was isolated with chloroform and crystallised from water. The tropolone (0·06 g., 8%) was obtained as yellow needles, m. p. 145—146° (Found : C, 67·0; H, 5·1. Calc. for $C_{13}H_{12}O_4$ : C, 67·2; H, 5·2%). It formed no ketonic derivatives, and dissolved in concentrated hydrochloric acid to a bright yellow solution from which it was precipitated unchanged by dilution.

*Benz*cyclo*heptene*-3 : 7-*dione*.—Ethyl phthalate (84 g.), ethyl glutarate (70·4 g.), and sodium wire (17·5 g.) were heated together in an oil-bath at 120—130° for four hours. The product was boiled for 36 hours with concentrated sulphuric acid (144 c.c.) and water (600 c.c.), and extracted with ethyl acetate. The organic layer was washed with sodium hydroxide solution, and distilled. Benz*cyclo*heptene-3 : 7-dione (19 g.) was collected at 173—176°/10 mm. The product slowly set to prisms, m. p. 45—46°.

7-*Hydroxybenz*cyclo*hepten*-3-*one*.—The 3 : 7-dione (0·5 g.) dissolved in ethanol was hydrogenated over palladised charcoal and a small proportion of Adams's catalyst at room temperature and pressure until one molar proportion of hydrogen had been absorbed. The solution after filtration and concentration gave a small yield of 7-hydroxybenz*cyclo*hepten-3-one, isolated as the *semicarbazone*, which separated from aqueous ethanol in prisms, m. p. 186—188° (Found : C, 61·3; H, 6·5. $C_{12}H_{15}O_2N_3$ requires C, 61·8; H, 6·4%).

4-*Benzylidenebenz*cyclo*heptene*-3 : 7-*dione*.—Benz*cyclo*heptene-3 : 7-dione (1·2 g.) and benzaldehyde (0·76 g.) were stirred at 0° for three hours with a solution of sodium hydroxide (0·36 g.) in water (10 c.c.) and ethanol (15 c.c.). After 12 hours, the solid was collected, washed with water, and dried. Two recrystallisations from ether–light petroleum gave 4-*benzylidenebenz*cyclo*heptene*-3 : 7-*dione* as a pale-yellow solid, m. p. 190—216° (Found : C, 82·1; H, 5·6. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3%). The benzylidene compound, when heated with alkali under varying conditions, gave traces of alkali-soluble material which could not be purified.

2-*Bromo*-5-*methoxybenzaldehyde*.—A mixture of 2-bromo-5-hydroxybenzaldehyde (50 g.), potassium carbonate (40 g.), methyl iodide (40 c.c.), and dry acetone (300 c.c.) was heated under reflux for eight hours, more methyl iodide (20 c.c.) being added after four hours. The mixture was filtered and the insoluble solids twice washed with boiling acetone. The combined filtrates were evaporated to dryness and the product (43 g., 80%) isolated with ether. It separated from methanol in crystals, m. p. 72—73°.

*Condensation of Ethyl Glutarate with* 2-*Bromo*-5-*methoxybenzaldehyde*.—A solution of potassium (2 g.) in *tert.*-butanol (50 c.c.) was refluxed in a nitrogen atmosphere with the aldehyde (10 g.) and ethyl glutarate (16·4 c.c.). After 40 minutes, concentrated hydrochloric acid (9·5 c.c.) in water (46 c.c.) and salt were added, and the butanol layer was separated off and concentrated under reduced pressure. The product, a dark liquid, was dissolved in ether and extracted with 5% potassium carbonate solution. The

aqueous layer was acidified and then extracted with ether, the extract being washed with water and brine, dried, and evaporated to a clear brown syrup (9 g.). This was refluxed for 4½ hours with a mixture of acetic acid (33 c.c.), hydrobromic acid of constant b. p. (22·5 c.c.), and water (13 c.c.), carbon dioxide being evolved. After evaporation under reduced pressure, the residue, in ether, was washed with 5% potassium carbonate solution; the ethereal layer yielded a brown resin, which was hydrolysed by being heated for 30 minutes at 100° with 2% sodium hydroxide solution. After being washed with ether, the aqueous layer was treated with charcoal and acidified, and the precipitate isolated with ether and distilled. δ-(2-*Bromo-5-methoxyphenyl*)-δ-*hydroxyvaleric acid*, b. p. 125—130° (bath temp.)/0·05 mm., set to pale-yellow needles (Found : C, 47·9; H, 5·0. $C_{12}H_{15}O_4Br$ requires C, 47·5; H, 5·0%).

α-(2-*Bromo-5-methoxybenzylidene*)*glutaric Acid.*—Sodium glutarate (13·5 g.), 2-bromo-5-methoxybenzaldehyde (16 g.), and acetic anhydride (110 c.c.) were heated for ten hours at 130—140°. Boiling water (300 c.c.) was added and then sufficient acetic acid to dissolve everything except a small amount of residual oil. The supernatant liquid was decanted and on cooling yielded the *benzylideneglutaric acid* (7·8 g.). The mother-liquors gave a further quantity (4·4 g.) of the acid. It separated from aqueous acetic acid in pale-yellow needles, m. p. 188—189° (Found : C, 47·1; H, 3·7. $C_{13}H_{13}O_5Br$ requires C, 47·4; H, 3·9%), $\lambda_{max.}$ 2750, 3300 A., $\varepsilon_{max.}$ 10,600, 2200 (in methanol). The substance rapidly decolorised permanganate solution.

δ-(2-*Bromo-5-methoxyphenyl*)-γ-*carboxy*-δ-*valerolactone.*—A solution of the above acid (0·5 g.) in 2N-sodium carbonate solution was acidified with an excess of dilute hydrochloric acid. After 6 days at room temperature, the *lactone* (0·4 g.) was collected. It crystallised from aqueous ethanol in colourless needles, m. p. 231—233° (Found : C, 47·0; H, 3·7. $C_{13}H_{13}O_5Br$ requires C, 47·4; H, 3·9%). The substance did not decolorise potassium permanganate solution.

Absorption spectra are by Dr. F. B. Strauss.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, August 4th*, 1950.