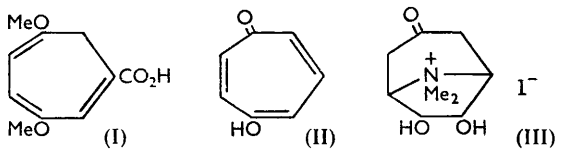
358. *Synthetic Experiments in the* cyclo*Heptatrienone Series. Part VII.**

By R. S. Coffey and A. W. Johnson.

4-Hydroxytropone has been synthesised and its physical and chemical properties compared with those of tropolone and 3-hydroxytropone.

Earlier papers in this series described a general method for the synthesis of substituted tropones which depends on the ring expansion of alkoxybenzenes with diazoacetic ester. The products, on hydrolysis, yield alkoxy*cyclo*heptatrienecarboxylic acids which can be decarboxylated and oxidised with bromine to give tropones, and syntheses of tropone-4-carboxylic acid,[1] stipitatic acid,[2,3] puberulic acid,[3] and 3-hydroxytropone [4] by this method have been described. Preliminary experiments directed towards a synthesis of 4-hydroxytropone have also been reported,[5] including the reaction of quinol dimethyl ether with diazoacetic ester which gave a bright yellow acid to which the structure 3 : 6-dimethoxy-*cyclo*heptatrienecarboxylic acid (I; arbitrary placing of double bonds) was assigned. Oxidation of this acid with bromine gave a 4-hydroxytroponecarboxylic acid which however could not be decarboxylated.

Recourse was therefore had to the method already applied in the synthesis of 3-hydroxytropone, which involved decarboxylation of the dimethoxy*cyclo*heptatrienecarboxylic acid before oxidation with bromine. 1 : 4-Dimethoxy*cyclo*heptatriene was thus obtained as a pale yellow oil which was treated with a cooled solution of bromine, to give 4-methoxy-



tropone. Demethylation by hydrogen bromide in acetic acid at 100° then gave 4-hydroxytropone [6] (II) together with a monobromo-substitution product, m. p. 215°, which was easily separated by virtue of its solubility in dilute acid. The yield of 4-hydroxytropone by this method is low and the lack of material has prevented a full investigation of its properties.

Nozoe and his colleagues [7] described the synthesis of 4-hydroxytropone from 4-bromotropone, a by-product from the preparation of 2 : 4 : 7-tribromotropone from *cyclo*heptanone.[7,8] The physical properties of 4-hydroxytropone prepared by the present method agree closely with those quoted by the Japanese authors. More recently, Meinwald and Chapman [9] have described a third synthesis of 4-hydroxytropone, which involves the action of a weak base on teloidinone methiodide (III), although the conditions for the decomposition appear to be critical. The properties of 4-hydroxytropone, like those of tropolone, are modified considerably by the presence of a fused benzene ring as in (IV).[10]

A comparison of the physical properties of the 2-, 3-, and 4-hydroxytropones (Table 1) emphasises the modification of the properties of 2-hyroxytropone (tropolone) caused by hydrogen bonding, *e.g.*, increased volatility, decreased melting point, ferric reaction,

* Part VI, *J.*, 1955, 1841.

[1] Bartels-Keith, Johnson, and Langemann, *J.*, 1952, 4461.
[2] Bartels-Keith, Johnson, and Taylor, *J.*, 1951, 337.
[3] Johns, Johnson, and Murray, *J.*, 1954, 198.
[4] Johns, Johnson, and Tisler, *ibid.*, p. 4604.
[5] Johns, Johnson, Langemann, and Murray, *J.*, 1955, 309.
[6] Coffey, Johns, and Johnson, *Chem. and Ind.*, 1955, 658.
[7] Nozoe, Mukai, Ikegami, and Toda, *ibid.*, p. 66.
[8] Seto, *Sci. Rep. Tôhoku Univ.*, 1953, **37**, 377.
[9] Meinwald and Chapman, *J. Amer. Chem. Soc.*, 1956, **78**, 4816.
[10] Buchanan, *J.*, 1954, 1060.

decreased acid strength, solubility in non-polar solvents, and the lower position (1615 cm.$^{-1}$) of the carbonyl band in the infrared spectrum. The physical properties of 4-hydroxytropone are rather closer to those of tropolone than are those of 3-hydroxytropone, *e.g.*, the marked bathochromic shift observed in the ultraviolet spectra of 2- and 4-hydroxytropone on formation of the anions, which is not shown by 3-hydroxytropone.

4-Hydroxytropone possesses the expected basic properties, forming a hydrochloride, m. p. 183° (decomp.), and on methylation with diazomethane it is converted into 4-methoxytropone, an oil (or low-melting solid [7]) which was characterised as its picrate. 4-Methoxytropone, which is a vinylogous ester, is hydrolysed to the 4-hydroxy-compound by either acid or alkali. Nozoe *et al.*[7] prepared the benzoate of 4-hydroxytropone and also referred to the formation of a crystalline product with 2 : 4-dinitrophenylhydrazine but

TABLE 1. *The physical properties of* 2-, 3-, *and* 4-*hydroxytropone.*

	2-Hydroxytropone [11] (tropolone)	3-Hydroxytropone [4]	4-Hydroxytropone
M. p.	49°	179—180°	212°
pK_a	6·7	5·4	5·65
Volatility	Sublimes at 100°/150 mm.	Sublimes slowly at 130°/0·1 mm.	Sublimes slowly at 130°/0·1 mm.
Ferric reaction	Green	—	—
Solubility in non-polar solvents	Sol.	Insol.	Insol.
Max. (mμ) in ultraviolet spectrum of 95% EtOH soln.	351, 320, 303 (infl.), 237, 228	309, 298, 255, 247	333, 226—227
Max. (mμ) in ultraviolet spectrum of 0·1N-NaOH soln.	393, 330, 234	304, 295, 267, 257	360, 227—228
Principal max. in infrared spectrum (1650—1150 cm.$^{-1}$)	1615, 1553, 1475, 1440, 1255	1647, 1587, 1550, 1515, 1477, 1443, 1258, 1230, 1196	1645, 1600, 1529, 1439, 1282, 1212

TABLE 2. *Ultraviolet absorption spectra of the bromine substitution products of tropone and* 4-*hydroxytropone.*

Compound	Ref.	Ultraviolet max. (mμ) of solutions in 95% EtOH (except where otherwise stated)
Tropone	14	225, 297, 310 (*iso*octane)
2-Bromotropone	15	246, 315 (*cyclo*hexane)
2 : 7-Dibromotropone	15	262, 335—349 (*cyclo*hexane)
2 : 4 : 7-Tribromotropone	16	272, 340—352
4-Hydroxytropone	This paper	227—228, 333
4-Bromo-5-hydroxytropone	,,	223, 351
2 : 4-Dibromo-5-hydroxytropone	,,	246—250, 370
2 : 4 : 7-Tribromo-5-hydroxytropone	,,	262, 396

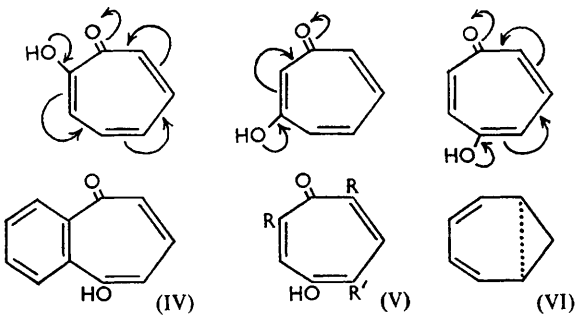
we have been unable to confirm the preparation of the latter derivative and in fact Nozoe [12] has since stated that 4-hydroxytropone is indifferent to ketonic reagents.

Bromination of 4-hydroxytropone with excess of bromine under forcing conditions caused the formation of 2 : 4 : 7-tribromo-5-hydroxytropone (V; R = R′ = R″ = Br), the structure of which has been proved beyond doubt.[13] A monobromo-4-hydroxytropone was obtained as a by-product from the preparation of 4-hydroxytropone (see above) and what appears to be the same compound (ultraviolet spectrum) was obtained in very small yield from a bromination (1 mol. of bromine) of 4-hydroxytropone. The main product from all brominations at room temperature of 4-hydroxytropone has been a dibromo-derivative, m. p. 190°, which was also obtained by further bromination of the monobromo-compound. The action of excess of bromine in hot acetic acid on dibromo-4-hydroxytropone gave 2 : 4 : 7-tribromo-5-hydroxytropone. Thus if it is assumed that the bromine

[11] Doering and Knox, *J. Amer. Chem. Soc.*, 1951, **73**, 828; Koch, *J.*, 1951, 513.
[12] Nozoe, *Fortschr. Chemie org. Naturstoffe*, 1956, **13**, 232.
[13] Nozoe, Kitahara, and Abe, *Proc. Japan Acad.*, 1953, **29**, 347.
[14] Doering and Detert, *J. Amer. Chem. Soc.*, 1951, **73**, 876.
[15] Seto, *Sci. Rep. Tôhoku Univ.*, 1953, **37**, 275.
[16] Nozoe, Kitahara, Ando, and Masamune, *Proc. Japan Acad.*, 1951, **27**, 415.

atoms do not rearrange, the monobromo-compound must be the 2-, 5-, or 7-bromo-derivative and, from its ultraviolet spectrum (Table 2), 2- and 7-substitution, which causes a marked bathochromic shift of the lower wave-length band in the spectrum, can be eliminated.

Thus the monobromo-substitution product is 4-bromo-5-hydroxytropone (V; R = R″ = H, R′ = Br) and the dibromo-compound contains bromine in either the 2 : 5- (V; R = R′ = Br, R″ = H) or the 5 : 7-positions (V; R = H, R′ = R″ = Br) of 4-hydroxy-tropone, of which the latter is favoured for steric and electronic reasons. It is of interest



(IV) (V) (VI)

that the most easily obtainable bromine substitution product of tropolone is the 3 : 5 : 7-tribromo-derivative, with 3-hydroxytropone [4] it is the 2-monobromo-derivative, and with 4-hydroxytropone the 5 : 7-dibromo-compound. In each case these positions are those of high electron density caused by the combined directive effects of the two oxygen atoms.

Qualitative coupling tests showed that 4-hydroxytropone, 4-bromo-5-hydroxytropone, and 5-hydroxytropone-3-carboxylic acid all gave red dyes with diazotised sulphanilic acid, whereas 2 : 4-dibromo-5-hydroxytropone did not. Thus whereas 4-hydroxytropone couples primarily at position 5,[12] it can also couple at position 7 but not 2. This accords with the bromination experiments where substitution occurs preferentially at positions 5 and 7, and only at 2 under forcing conditions.

Re-examination of the product from quinol dimethyl ether and diazoacetic ester has revealed that there are at least three isomeric 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acids present. The first, m. p. 158—160°, is identical with the product described earlier [5] (where the m. p. was given as 153—154°). The second, isolated in rather greater quantity, has m. p. 138—140°, and the third, m. p. 134—136°, has been obtained only in small quantity. Mixing any two of the acids caused a depression of the melting point. The last was the least stable and the most soluble in organic solvents, and the first was the least soluble. These acids are double-bond isomers of 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acid (*e.g.*, I) as all three have the same ultraviolet absorption; after oxidation with bromine and hydrolysis with hydrogen bromide, all gave 5-hydroxytropone-3-carboxylic acid. It is of interest that Doering *et al.*[17] recently assigned structures to all four of the double-bond isomers of *cyclo*heptatrienecarboxylic acid (the Buchner acids) by use of nuclear magnetic resonance and identification of the products of thermal decomposition of the Diels–Alder adducts with diethyl acetylenedicarboxylate, and they present evidence to suggest that the acids are derivatives of tropilidene (VI) which has a planar ψ-aromatic structure in contrast to *cyclo*heptatriene.

Experimental

Ultraviolet spectra were determined for 95% EtOH solutions, and infrared spectra for Nujol mulls except where otherwise stated.

3 : 6-*Dimethoxy*cyclo*heptatrienecarboxylic Acid* (cf. Johns, Johnson, Langemann, and

[17] Doering, Laber, Vonderwahl, Chamberlain, and Williams, *Proc. Japan Acad.*, 1956, **78**, 5448.

Murray [5]).—The crude acid (5 g.), prepared in the manner already described, was fractionally crystallised from benzene–light petroleum (b. p. 60—80°), the following isomers being obtained: Acid A (0·45 g.), m. p. 158—160°, identical with the acid obtained previously; [5] the infrared spectrum showed main maxima at 1670, 1618, 1532, 1472, 1423, 1378, 1357, 1287, 1257, 1221, 1205, 1167, and 1133 cm.$^{-1}$. *Acid B* (0·52 g.), m. p. 138—140° (Found: C, 61·3; H, 6·6. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%); the infrared spectrum showed main maxima at 1690, 1657, 1617, 1553, 1465, 1443, 1369, 1336, 1287, 1255, 1201, 1182, and 1152 cm.$^{-1}$. Acid C (30 mg.), m. p. 134—136°; the infrared spectrum showed main maxima at 1689, 1620, 1563, 1471, 1432, 1366, 1333, 1282, 1215, 1180, and 1167 cm.$^{-1}$.

5-Hydroxytropone-3-carboxylic Acid.—Each of the above acids A, B, and C was dissolved separately in the minimum quantity of chloroform, and the solutions were treated with bromine (1 mol.) in chloroform at 0°. The mixtures were warmed on the water-bath for 10 min. and the solvent was then removed under reduced pressure. The resulting gums were heated at 100° with 48% aqueous hydrobromic acid for 1 hr., the solvent was again removed under reduced pressure, and the residues crystallised from water (charcoal) to give 5-hydroxytropone-3-carboxylic acid as pale yellow needles, m. p. 240° (decomp.); in each case the physical properties, particularly the ultraviolet and infrared spectra, were identical with those recorded earlier.[5]

4-Hydroxytropone.—A mixture of 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acid (2 g.) and copper bronze (40 g.) was divided into four portions and each heated rapidly in a soda-glass tube, and the distillate collected in a receiver cooled below 0°. The combined distillates were dissolved in ether (60 c.c.) and extracted with 10% aqueous sodium carbonate solution (3 × 20 c.c.), the ethereal solution dried, and the solvent removed. The residual dark viscous oil (0·14 g.) was distilled, to give crude 1 : 4-dimethoxy*cyclo*heptatriene as a pale yellow oil (0·1 g.), b. p. 95—110°/0·2 mm.

This product was dissolved in chloroform (5 c.c.), cooled to 0°, and then treated with a solution of bromine (1 mol.) in chloroform. After 10 min., the solvent was removed at atmospheric pressure on the water-bath, hydrogen bromide being evolved. The residue was hydrolysed by heating it for 1 hr. with 20% hydrobromic acid (6 c.c.), after which the solvent was removed under reduced pressure. The residue was dissolved in hot water, and the solution kept overnight; a yellow solid (51 mg.), m. p. 198°, was obtained. This was crude 4-bromo-5-hydroxytropone and its further purification is described below. The filtrate obtained after separation of the bromo-compound was evaporated to dryness and the residual brown gum digested with acetone. The colourless solid (36 mg.) which separated was the hydrobromide of 4-hydroxytropone. It was soluble in water and the solution gave an immediate precipitate with silver bromide. It was sublimed at 120°/2 × 10^{-4} mm., giving pale yellow 4-hydroxytropone (21 mg.), m. p. 212° (Nozoe *et al.*[7] give m. p. 212°) (Found: C, 68·7; H, 5·0. Calc. for $C_7H_6O_2$: C, 68·85; H, 4·95%). Light absorption: (i) max. at 333 and 226—227 mμ (log ε 4·14 and 4·28), min. at 268 mμ (log ε 2·72); (ii) in 0·1N-NaOH, max. at 360 and 227 mμ (log ε 4·34 and 4·30), min. at 284 mμ (log ε 2·77). The infrared spectrum showed main max. at 2440 (broad), 1645, 1621, 1600, 1529, 1439, 1399, 1282, and 1212 cm.$^{-1}$.

4-Hydroxytropone was soluble in water, alcohols, acetone, dioxan, and acetic acid. It was almost insoluble in benzene, chloroform, and light petroleum. Its aqueous solution was acidic to litmus and its p*K* in water at 20° was 5·65. Alkaline solutions were pale greenish-yellow. It gave no ferric reaction and did not react with 2 : 4-dinitrophenylhydrazine. The hydrochloride, m. p. 183°, was formed by bubbling dry hydrogen chloride through a solution in glacial acetic acid. It decomposed at 140°/0·2 mm., 4-hydroxytropone being re-formed and obtained as a sublimate. The picrate crystallised from aqueous methanol as yellow needles, m. p. 85—87° (lit.,[7] 90°) (rapid heating; the picrate decomposed below its m. p. to 4-hydroxytropone and picric acid) (Found: C, 43·95; H, 2·95; N, 12·05. Calc. for $C_{13}H_9O_9N_3$: C, 44·45; H, 2·6; N, 12·0%). 4-Hydroxytropone was regenerated from its picrate when the ethanolic solution was shaken with a slight excess of Dowex 2 resin in the hydroxide form.

4-Methoxytropone.—A methanolic solution (5 c.c.) of 4-hydroxytropone (35 mg.) was treated with excess of ethereal diazomethane. After 30 min. the solvent was removed under reduced pressure and the residual brown gum sublimed at 60—70°/0·5 mm., to give a colourless oil which rapidly resinified in air. Light absorption max. at 324—325 and 222 mμ (log ε 3·80 and 4·11), min. at 265 mμ (log ε 2·75). The picrate formed yellow needles, m. p. 131° (lit.,[7] 132—133°) (Found: C, 46·7; H, 3·05; N, 11·4. Calc. for $C_{14}H_{11}O_9N_3$: C, 46·0; H, 3·0; N, 11·4%).

The picrate was reconverted into the free base by Dowex 2 resin as in the case of 4-hydroxytropone, and 4-methoxytropone was converted into 4-hydroxytropone by 20% hydrobromic acid at room temperature.

4-Bromo-5-hydroxytropone.—(i) *From* 3 : 6-*dimethoxy*cyclo*heptatrienecarboxylic acid.* The crude product, m. p. 198°, described above as a by-product in the preparation of 4-hydroxytropone, was sublimed at 140°/0·2 mm. and then crystallised from aqueous ethanol, to give pale yellow needles, m. p. 215° (Found: C, 41·9; H, 2·6. $C_7H_5O_2Br$ requires C, 41·8; H, 2·5%). Light absorption max. at 351 and 222—223 mμ (log ε 4·09 and 4·23), min. at 276—277 mμ (log ε 3·05), and an inflection at 234—236 mμ (log ε 4·18). The infrared spectrum showed max. at 1639, 1587, 1541, 1449, 1383, 1313, 1277, 1259, 1214, 1117, 931, 857, 822, 788, 768, 740, and 712 cm.$^{-1}$. The pK in water at 20° was 4·9.

(ii) *From 4-hydroxytropone.* A slightly impure preparation of the monobromo-compound was isolated as a by-product from the bromination of 4-hydroxytropone with 1 mol. of bromine (see below). Removal of the solvent from the alcoholic extract gave a gum (20 mg.) from which a pale yellow solid (8 mg.), m. p. 164—166°, was obtained after sublimation. The m. p. was raised to 194—196° (not depressed when mixed with an authentic specimen of 4-bromo-5-hydroxytropone), on re-sublimation at 130°/0·05 mm. (Found: C, 41·3; H, 2·7%).

2 : 4-*Dibromo-5-hydroxytropone.*—(i) *From 4-hydroxytropone.* A stirred solution of 4-hydroxytropone (100 mg.) in glacial acetic acid (12 c.c.) at 10° was treated slowly with a solution of bromine (1 mol.) in acetic acid. Then the solution was kept for 20 min. and next heated on the steam-bath for 10 min. After a further 3 hr. at room temperature a yellow solid had separated which was removed by filtration and crystallised from aqueous methanol, to give 2 : 4-*dibromo-5-hydroxytropone* as pale yellow needles (96 mg.), m. p. 192° (Found: C, 30·2; H, 1·8. $C_7H_4O_2Br_2$ requires C, 30·0; H, 1·4%), $\lambda_{max.}$ 368—369 and 240—246 mμ (log ε 4·12 and 4·23), $\lambda_{min.}$ 284 and 212 mμ (log ε 3·1 and 4·03), $\nu_{max.}$ 1623, 1546, 1471, 1439, 1348, 1295, 1274, 1250, 1153, 990, 920, 845, 802, and 778 cm.$^{-1}$.

The acetic acid solution was evaporated under reduced pressure and the residue extracted with chloroform (4 × 10 c.c.). The insoluble residue (21 mg.) was sublimed at 140°/0·2 mm., to give unchanged 4-hydroxytropone. The chloroform extract was evaporated and the solid so obtained crystallised from aqueous methanol, to give brown needles which were further purified by sublimation at 140°/0·2 mm., a bright yellow solid, m. p. 218°, being obtained. This was a mixture of di- and tri-bromotropones (Found: C, 26·6; H, 1·3%), $\lambda_{max.}$ 387 and 251—259 mμ. The methanolic solution was treated as described in the previous experiment and yielded 4-bromo-5-hydroxytropone.

In another experiment 4-hydroxytropone (70 mg.) in acetic acid at 10° was treated with bromine (3 mol.) also in acetic acid. The mixture was kept for 20 min. at room temperature, then heated at 100° for 10 min. as before, and on cooling 2 : 4-dibromo-5-hydroxytropone (115 mg.) crystallised. A further quantity (11 mg.; total yield 75%) was obtained by concentration of the filtrate. The product was identical with that obtained in the previous experiment.

(ii) *From 4-bromo-5-hydroxytropone.* The monobromo-compound (16 mg.) was dissolved in acetic acid (5 c.c.) and treated with a solution of bromine (1 mol.) in acetic acid at room temperature. After the addition, the solution was concentrated, and diluted with water, yellow 2 : 4-dibromo-5-hydroxytropone (21 mg.) being precipitated. After crystallisation from aqueous methanol, this had m. p. 192°, undepressed on admixture with the sample prepared directly from 4-hydroxytropone. The ultraviolet and infrared spectra also corresponded with those of the previous product.

2 : 4 : 7-*Tribromo-5-hydroxytropone.*—A solution of 4-hydroxytropone (14 mg.) in acetic acid (3 c.c.) at 100° was treated with a solution of bromine (5 mol.) in acetic acid. When the mixture was kept overnight at room temperature, yellow needles (25 mg.), m. p. 231° raised to 236° (lit.,[13] 239°) on crystallisation from ethanol, were obtained (Found: C, 23·75; H, 0·7. Calc. for $C_7H_3O_2Br_3$: C, 23·4; H, 0·8%). Light absorption max. were at 396 and 262 mμ (log ε 4·31 and 4·34), min. at 298 and 232 mμ (log ε 3·18 and 4·06). The same product was obtained from a similar bromination of 2 : 4-dibromo-5-hydroxytropone.

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