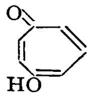
Synthetic Experiments in the cyclo*Heptatrienone Series. Part V.** *Some Derivatives of 4-Hydroxytropone.*

By R. B. Johns, A. W. Johnson, A. Langemann, and J. Murray.

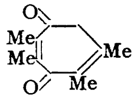
[Reprint Order No. 5782.]

Attempts are described to degrade tropone-4-carboxylic acid and its derivatives to 4-hydroxytropone. The Buchner ring-expansion of quinol dimethyl ether and subsequent oxidation by bromine lead either to 4-hydroxytropone-6-carboxylic acid or to a dibromo-4-hydroxytropone.

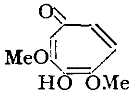
In a study of the simple 3- and 4-substituted tropones, the synthesis of 3- and 4-hydroxytropone is essential because of their obvious relation to tropolone. 3-Hydroxytropone has been prepared recently (Part IV *), and preliminary attempts to synthesise 4-hydroxytropone (I) will be discussed in the present paper. Except for 5-hydroxytropolone and certain of its substitution products which in their behaviour are essentially substituted tropolones rather than tropones, a few compounds related to (I) have been described in the literature. Duroquinone and diazomethane have been reported (Smith and Pings, *J. Org. Chem.*, 1937, **2**, 95) to give some of a compound (II) which, as its monoenol, would be 4-hydroxy-2 : 3 : 6 : 7-tetramethyltropone. In a rather similar investigation (Marini-Bettolo and Paolini, *Gazzetta*, 1954, **84**, 327) 2 : 6-dimethoxybenzoquinone with diazomethane was found to give a colourless product formulated as (III). Both of the structures (II) and (III) are open to criticism on the grounds of certain of the physical and chemical properties recorded and further study is necessary. Nozoe, Kitahara, and Abe (*Proc. Japan Acad.*, 1953, **29**, 347) were able to introduce a nuclear hydroxyl group into 2 : 4 : 7-tribromotropone by treatment with warm dilute sulphuric acid to give the compound (IV) but failed to remove the bromine atoms by hydrogenolysis without simultaneously reducing the ring. This behaviour contrasts with that of 2 : 4 : 7-tribromotropone which is an intermediate in the synthesis of tropone from *cyclo*hexenone or from *cyclo*hexanone (Dauben and Ringold, *J. Amer. Chem. Soc.*, 1951, **73**, 876; Nozoe, Kitahara, Ando, Masamune, and Abe, *Sci. Rep. Tôhoku Univ.*, 1952, **36**, 166) and with that of 2 : 5 : 7-tribromo-3-hydroxytropone, an intermediate in the synthesis of 3-hydroxytropone (Part IV). In a more detailed examination of the hydrogenolysis of 2 : 4 : 7-



(I)



(II)



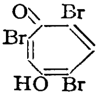
(III)

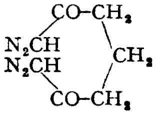
---

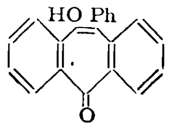
* Part IV, *J.*, 1954, 4605.

tribromotropone (Seto, *ibid.*, 1953, **37**, 377) 4-bromotropone has been isolated as a by-product (a small yield of 5-bromo-3-hydroxytropone was obtained as a by-product from the hydrogenolysis of 2 : 5 : 7-tribromo-3-hydroxytropone; Part IV) and, if this compound could be obtained in reasonable amounts, the hydrolysis to 4-hydroxytropone should present no difficulties. An attempt to convert 4-amino-7-phenyltropone into the 4-hydroxy-compound was unsuccessful (Nozoe, Mukai, and Minegishi, *Proc. Japan Acad.*, 1952, **28**, 287) and an uncharacterised yellow compound which gave no ketonic reactions and was possibly impure 4-hydroxytropone has been isolated from the reaction of 1 : 7-bisdiazoheptane-2 : 6-dione (V) with copper oxide (Rudolph and Hofmann, *Chem. Listy*, 1952, **45**, 261).

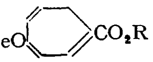
The synthesis of 4-hydroxy-2 : 3-benzotropone has been reported recently (Buchanan, *J.*, 1954, 1060; see also Barltrop, Johnson, and Meakins, *J.*, 1951, 181) and 4-hydroxy-5-phenyl-2 : 3 : 6 : 7-dibenzotropone (VI) is also known (Cook, *J.*, 1928, 58; Buchanan, *Chem. and Ind.*, 1952, 855) but, as in the tropolone series, the fused benzenoid rings doubtless will exert a considerable effect on the behaviour of the hydroxytropone.

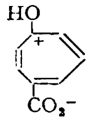

(IV)

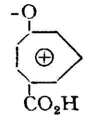

(V)


(VI)

An attractive possibility for the synthesis of 4-hydroxtyropone seemed to be the substitution of a hydroxyl for the carboxy-group in tropone-4-carboxylic acid. As has been shown (Bartels-Keith, Johnson, and Langemann, *J.*, 1952, 4461) this acid may be prepared conveniently by reaction of anisole and ethyl diazoacetate and, after hydrolysis of the product so obtained, phenoxyacetic acid and 4-methoxy*cyclo*hepta-1 : 3 : 5-trienecarboxylic acid (VII; R = H) have been isolated. The latter acid can then be oxidised to tropone-4-carboxylic acid with bromine. Later experiments have shown that the yield of the ester (VII; R = Et) is increased materially (to 58% calculated on ethyl diazoacetate) if the condensation is carried out in a glass-lined autoclave in an atmosphere of oxygen-free nitrogen (25 atm.) as recommended by Grundmann and Ottmann (*Annalen*, 1953, **582**, 163) for the similar reaction with benzene.


(VII)

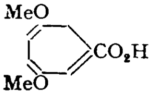

(VIII)


(IX)

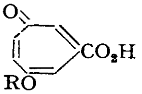
Tropone-4-carboxylic acid, which has pK_a 3·2 at 24° was formerly believed to have the zwitterion structure (VIII) but an examination of the infra-red spectrum of its silver salt showed that the carbonyl frequency of the free acid at 1709 cm.$^{-1}$ had been replaced by a new band at 1555 cm.$^{-1}$ ascribed to the carboxylate ion. The carbonyl band at 1629 cm.$^{-1}$, corresponding to the tropone-carbonyl group, was unchanged. In methyl tropone-4-carboxylate, the ester-carbonyl band is at 1715 cm.$^{-1}$ and the tropone-carbonyl band at 1634 cm.$^{-1}$. The structure of the acid has therefore been amended to (IX), *i.e.*, that of a normal substituted tropone.

A number of attempts to degrade the carboxyl of (IX) to a hydroxyl, bromo-, or amino-group, had no success, including the Schmidt reaction on the free acid, the Curtius reaction on the acid chloride, and the action of bromine on the silver salt and on the free acid. The action of silver trifluoroacetate and bromine on the acid (VII; R = H) (cf. Rottenberg, *Helv. Chim. Acta*, 1953, **36**, 1115) and the Hofmann reaction on its amide gave tropone-4-carboxylic acid as the sole recognisable product. This approach has therefore been temporarily abandoned. In the course of the work several new derivatives of 4-methoxy*cyclo*hepta-1 : 3 : 5-trienecarboxylic acid and of tropone-4-carboxylic acid were prepared but in general attempts to prepare derivatives of the acid (IX) from the corresponding derivatives of (VII ; R = H) were unsuccessful and led to the production of tropone-4-carboxylic acid itself. With excess of bromine the acid (IX) gave a dibromo-substitution product and, in a further structural proof, the acid has been treated with hydroxylamine (cf. Nozoe, Kitahara, Ando, Masamune, and Abe, *loc. cit.*) to give 2-aminotropone-5-carboxylic acid, which by reaction with alkali gave the known tropolone-5-carboxylic acid (Cook, Raphael, and Scott, *J.*, 1952, 4416).

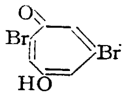
We therefore turned to the possibility of obtaining 4-hydroxytropone from quinol dimethyl ether by methods analogous to those used for the conversion of resorcinol dimethyl ether into 3-hydroxytropone (Part IV, *loc. cit.*). Application of the Buchner ring-expansion method to quinol dimethyl ether and subsequent hydrolysis of the ester mixture gave 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acid (X or a double-bond isomer) as bright yellow needles, together with relatively high yields of *p*-methoxyphenoxyacetic acid (Johnson, Langemann, and Murray, *J.*, 1953, 2136). Oxidation of the product (X) with bromine (1 mol.) gave 4-methoxytropone-6-carboxylic acid (XI ; R = Me) and hydrolysis of this acid gave 5-hydroxytropone-3-carboxylic acid (XI ; R = H) as pale yellow needles which could be sublimed only with difficulty (cf. Johnson and Todd, Abs. 12th Int. Congr. I.U.P.A.C., 1951, p. 398). The structure of this acid was confirmed by the alkaline rearrangement of its methyl ether to 5-hydroxy*iso*phthalic acid. Despite numerous attempts however the acid (XI ; R = H) could not be decarboxylated and in this respect is in line with the other troponecarboxylic acids.



(X)



(XI)



(XII)

Treatment of the acid (X) with larger quantities of bromine caused brominative decarboxylation, as in the 3-hydroxytropone series, and there was isolated a dibromo-4-hydroxytropone, possibly (XII), though in amount insufficient for structural determination. However, it appears that one of the bromine substituents must be in the 3-position, formerly occupied by the carboxyl group, and the other is probably in an α-position to the carbonyl, preference being given to (XII) on steric grounds. Experiments on decarboxylation of the dimethoxy-acid (X) and oxidation of the product are in progress.

In connection with the general formation of phenoxyacetic esters from the reaction of alkoxybenzenes with ethyl diazoacetate (Johnson, Langemann, and Murray, *loc. cit.*) it was of interest to find that a similar reaction occurred with dimethylaniline which gave *N*-methyl-*N*-phenylglycine ester together with an unidentified basic yellow liquid ester, the latter possibly being a product of ring expansion. The reaction of aliphatic diazo-compounds, R_2CN_2, with tertiary amines, $R'{\cdot}NMe_2$, is also known to give products of the type $R_2R'C{\cdot}NMe_2$ in certain cases (Bamford and Stevens, *J.*, 1952, 4675).

EXPERIMENTAL

Except where otherwise stated, ultra-violet absorption spectra have been determined in 95% ethanol and infra-red spectra determined as Nujol mulls.

4-*Methoxy*cyclo*hepta*-1 : 3 : 5-*trienecarboxylic Acid and Derivatives* (cf. Part II, *loc. cit.*).—Distilled anisole (580 g.) was treated with ethyl diazoacetate (32 g.; b. p. 38°/8 mm.) in a glass-lined autoclave at 160—165° for 5 hr. under oxygen-free nitrogen (25 atm.). At the end of the reaction the pressure had risen to 47 atm. The excess of anisole was removed at 100° under reduced pressure and the residual viscous brown oil distilled, giving (i) a pale yellow liquid, b. p. 99—111°/0·5 mm. (30·4 g., 58% calc. on ethyl diazoacetate), (ii) a viscous yellow liquid, b. p. 126—143°/0·5 mm. (5·3 g.), and (iii) residual brown tar (7·9 g.). Hydrolysis of fraction (i) (5 g) with methanolic potassium hydroxide gave 4-methoxy*cyclo*hepta-1 : 3 : 5-trienecarboxylic acid as described in Part II. The *methyl ester* was obtained from the acid (453 mg.) and ethereal diazomethane, as a light yellow oil (476 mg.; distilled at 0·2 mm.), n_{D}^{18} 1·5625 (Found : C, 66·8; H, 7·0. $C_{10}H_{12}O_3$ requires C, 66·65; H, 6·7%). Light absorption :

max. at 223—225 and 314—315 mμ (log ε 4·17 and 4·05 respectively). The *amide* was obtained by keeping a suspension of the methyl ester (752 mg.) in 35% aqueous ammonia (10 c.c.) for 3 weeks at room temperature with frequent shaking; the crystals were then separated (348 mg.) and washed with a little ether, and the filtrate extracted with ether (3 × 15 c.c.). Removal of the solvent from the dried extract gave a semi-crystalline product which was recrystallised from ether as colourless plates (279 mg.), m. p. 141—142°, which were combined with the first amount. For analysis a sample was sublimed at 125°/0·1 mm. (Found: C, 65·7; H, 7·0. $C_9H_{11}O_2N$ requires C, 65·45; H, 6·7%).

Derivatives of Tropone-4-carboxylic Acid.—*Silver salt.* The acid (3·7 g.; Part II) was suspended in water (20 c.c.) and neutralised to pH 7 with 4N-sodium hydroxide. A saturated aqueous solution of silver nitrate (4·6 g.) was added and the brown precipitate separated and crystallised from water to give the silver salt as pale yellow needles (4·29 g.). The infra-red spectrum showed max. at 1634, 1555, 1541, 1418, 1277, 1227, 1105, 1034, 952, 907, 876, 849, 819, 810, 801, 777, and 749 cm.$^{-1}$.

Methyl ester. (*a*) Tropone-4-carboxylic acid (767 mg.) was dissolved in dry methanol (50 c.c.) and pyridine (0·5 c.c.) and a solution of di*cyclo*hexylcarbodi-imide (Schmidt, Hitzler, and Lahde, *Ber.*, 1938, **71**, 1933) in dry ether (30 c.c.) was added. After 30 min. at room temperature the solvents were removed at reduced pressure and the light brown residue was extracted with hot ether (3 × 50 c.c.). Evaporation of the ether gave a brown semi-crystalline product which on sublimation at 67°/0·2 mm. gave the ester as colourless needles, m. p. 90° (Found: C, 65·8; H, 5·1. $C_9H_8O_3$ requires C, 65·85; H, 4·9%). The infra-red spectrum showed max. at 1715, 1634, 1610, 1587, 1435, 1364, 1277, 1227, 1214, 1186, 1111, 1083, 1030, 943, 899, 867, 847, 813, 800, and 773 cm.$^{-1}$. Recrystallisation of the ester from light petroleum (b. p. 40—60°) gave a slightly coloured product. (*b*) The silver salt of the acid (615 mg.) was shaken with methyl iodide (2 c.c.) overnight. The precipitate was separated and washed with methanol (3 × 2 c.c.) and the combined filtrates were evaporated *in vacuo*, leaving a light brown semi-crystalline residue. Sublimation as above gave the ester as pale yellow needles (41 mg.), m. p. and mixed m. p. 88°.

Dibromotropone-4-carboxylic Acid.—A solution of tropone-4-carboxylic acid (601 mg.) in glacial acetic acid (30 c.c.) was treated with bromine (0·85 c.c.), and the brown solution heated under reflux for 1 hr. Removal of the solvent *in vacuo* on the steam-bath gave a light yellow solid which on recrystallisation from benzene–*cyclo*hexane gave pale yellow needles (882 mg.), m. p. 182—183° (decomp.) (Found: C, 31·6; H, 1·7. $C_8H_4O_3Br_2$ requires C, 31·2; H, 1·3%).

2-*Aminotropone*-5-*carboxylic Acid.*—Tropone-4-carboxylic acid (634 mg.) was heated in ethanol (20 c.c.) under reflux for 15 min. with hydroxylamine hydrochloride (0·9 g.) and pyridine (3 c.c.). After cooling, the dark brown mixture deposited a yellow crystalline precipitate which was separated. Concentration of the mother-liquors gave a further amount of crystals, and the combined material was recrystallised from ethanol, to give the *amino-acid* as short yellow needles (587 mg.), m. p. 280—282° (decomp.), which gave a green ferric reaction (Found: C, 58·5; H, 4·5; N, 8·2. $C_8H_7O_3N$ requires C, 58·2; H, 4·3; N, 8·5%). The infra-red spectrum showed max. at 3279, 3155, 1704, 1647, 1616, 1585, 1355, 1280, 1224, 1156, 1087, 897, 866, 823, 761, and 745 cm.$^{-1}$.

Tropolone-5-*carboxylic Acid.*—A solution of the amino-acid (307 mg.) in 4N-sodium hydroxide (15 c.c.) was heated on the steam-bath. Ammonia was evolved and after 2 hr. the solution was cooled and acidified by careful addition of concentrated sulphuric acid (3 c.c.). The pale yellow precipitate was separated and dried (283 mg.). Crystallisation from acetic acid followed by sublimation in a high vacuum gave a pale yellow, anhydrous *tropolone*-5-*carboxylic acid*, m. p. 187° (sealed tube), which gave a green ferric reaction (Cook, Raphael, and Scott, *loc. cit.*, give m. p. 222—225° for the monohydrate) (Found: C, 58·05; H, 3·9. $C_8H_6O_4$ requires C, 57·8; H, 3·6%). The infra-red spectrum showed max. at 3125, 1698, 1618, 1570, 1550, 1497, 1418, 1321, 1295, 1230, 1205, 1072, 769, 751, 731, and 691 cm.$^{-1}$. Treatment of the acid (226 mg.) in ether with excess of diazomethane, evaporation, and sublimation of the solid residue in a high vacuum gave light yellow prisms of the methyl ether methyl ester (233 mg.), m. p. 185° (Cook, Raphael, and Scott, *loc. cit.*, give m. p. 184·5°) (Found: C, 61·65; H, 5·4. Calc. for $C_{10}H_{10}O_4$: C, 61·85; H, 5·2%). The infra-red spectrum showed max. at 1724, 1631, 1585, 1513, 1404, 1362, 1299, 1277, 1255, 1215, 1176, 1120, 1082, 974, 942, 892, 861, 817, 771, 722, and 696 cm.$^{-1}$.

3 : 6-*Dimethoxy*cyclo*heptatrienecarboxylic Acid* (cf. Johnson, Langemann, and Murray, *loc. cit.*).—Quinol dimethyl ether (300 g.) was heated with ethyl diazoacetate at 150—155° for 5 hr., the product fractionated, and the fraction of b. p. 115—160°/0·2 mm. (30 g.) collected.

A portion of this fraction (5 g.) was cooled to 0° and mixed with a cooled solution of potassium hydroxide (3·3 g.) in 90% methanol (30 c.c.) with stirring. After 15 min. at 0°, the precipitated potassium *p*-methoxyphenoxyacetic acid (2·3 g.) was separated and washed with a little methanol. The filtrate was then heated at 60—70° for 2 hr. in order to complete hydrolysis of the ester and to reduce the volume of solution to 10—15 c.c. The solution was cooled (ice), water (50 c.c.) added, and then concentrated hydrochloric acid carefully (temperature of the solution held at 0°). It was preferable to induce crystallisation of the product by rubbing and scratching in the early stages of the precipitation. After the addition of a slight excess of hydrochloric acid (no further precipitation), the suspension was kept for a further hour at 0°. The bright yellow *dimethoxy-acid* (0·74 g.) was then separated, washed, and dried. It crystallised from benzene–*cyclo*hexane in yellow needles, m. p. 153—154° (previous softening), subliming at 140°/0·5 mm. (Found: C, 61·5; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). Light absorption: max. at 356—357 and 222 mμ (log ε 3·59 and 4·32 respectively).

5-Methoxytropone-3-carboxylic Acid.—A solution of bromine (0·3 c.c.) in carbon tetrachloride (3 c.c.) was added, with stirring, to a solution of 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acid (1 g.) in chloroform (10 c.c.) at 0°. The dark oily suspension was warmed at 60° on the water-bath for 5 min., hydrogen bromide being evolved. The mixture was cooled to 0°, the supernatant liquid decanted and discarded, and the dark oil dissolved in a little methanol. The solvent was then removed under reduced pressure, the residue cooled (ice), and partial solidification induced by scratching. Water (2 c.c.) was added, and the suspension well mixed and kept at 0° for 15 min. The precipitated solid was separated, washed, and crystallised from water (charcoal), the *monoether* (0·76 g.) being obtained as yellow needles, m. p. 190° (decomp.) (Found: C, 60·1; H, 4·6. $C_9H_8O_4$ requires C, 60·0; H, 4·45%). Light absorption: max. at 352—353 and 222 mμ (log ε 4·11 and 4·32 respectively).

5-Hydroxytropone-3-carboxylic Acid.—The foregoing methoxy-acid (0·15 g.) in 48% aqueous hydrobromic acid (4 c.c.) and water (1 c.c.) was heated at 100° for 3 hr. The solvent was removed, water (3 c.c.) added, the suspension cooled in ice for 15 min., and the precipitate (0·13 g.) separated and dried. Crystallisation of the product from water (charcoal) gave *5-hydroxytropone-3-carboxylic acid* as pale yellow needles, m. p. 240° (after charring) (Found: C, 58·0; H, 3·6. $C_8H_6O_4$ requires C, 57·8; H, 3·6%). The product gave no marked ferric reaction, nor was it coloured in alkaline solution. It sublimed only with difficulty. Light absorption: max. at 356—359 and 221—223 mμ (log ε 4·09 and 4·29 respectively). The infra-red spectrum showed max. at 2941—2703 (broad band), 1786, 1715, 1647, 1629, 1595, 1531, 1486, 1422, 1379, 1351, 1238, 1098, 962, 904, 893, 850, 815, 778, 760, and 706 cm.$^{-1}$.

Alkaline Rearrangement of 5-Methoxytropone-3-carboxylic Acid.—The acid (0·2 g.), potassium hydroxide (5 g.), and water (1 c.c.) were heated at 250° in nickel crucible for 10 min. The melt was dissolved in water (10 c.c.) and acidified with sulphuric acid. The precipitated potassium sulphate was separated, and the dark filtrate thoroughly extracted with ether (8 × 25 c.c.). The solvent was removed from the dried combined ethereal extract, and the solid residue crystallised from water to give colourless 5-hydroxy*iso*phthalic acid, needles, m. p. and mixed m. p. 299° after sublimation *in vacuo*.

Dibromo-4-hydroxytropone.—Bromine (0·8 c.c.) was added dropwise to a solution of 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acid (0·45 g.) in glacial acetic acid (8 c.c.) and water (1 c.c.) at 0°. The dark red solution was then kept at room temperature for ½ hr., diluted with water (25 c.c.) and kept at 0° for 36 hr. The solvent was removed, and the residue treated with water (5 c.c.) and cooled (ice). The precipitated oil slowly solidified; the solid was separated, washed, and crystallised from aqueous dioxan (charcoal). The *dibromo-compound* (0·1 g.) was then sublimed at 140°/0·6 mm. and recrystallised from aqueous ethanol, then having m. p. 188—189° (decomp.) (Found, on a freshly sublimed sample: C, 29·8; H, 1·6. $C_7H_4O_2Br_2$ requires C, 30·0; H, 1·45%). Light absorption: max. at 370 and 247 mμ (log ε 4·16 and 4·24 respectively), inflection at 386—388 mμ (log ε 4·12). The infra-red spectrum showed max. at 1626, 1538, 1299, 1274, 1250, 1153, 1124, 993, 951, 921, 846, 781, 761, and 724 cm.$^{-1}$.

Reaction of Dimethylaniline and Ethyl Diazoacetate.—Purified dimethylaniline (168 g.) was heated to 160° and ethyl diazoacetate (40 g.) added dropwise with stirring during 2 hr. After *ca.* 15 min. a steady stream of nitrogen was evolved and after all the ethyl diazoacetate had been added the mixture was heated for a further hour. The excess of dimethylaniline was removed under reduced pressure, the residual dark yellow oil distilled, and the fraction of b. p. 117—142°/1 mm. (25·2 g.), a deep yellow oil, was collected. A portion (2·1 g.) of this fraction was shaken with aqueous ammonia (*d* 0·88; 8 c.c.) for 3 weeks and the crystalline product separated and recrystallised from aqueous methanol, to give colourless plates (214 mg.),

m. p. 162° alone and mixed with an authentic specimen of the amide of *N*-methyl-*N*-phenylglycine (Found: C, 65·8; H, 7·5; N, 17·2. Calc. for $C_9H_{12}ON_2$: C, 65·8; H, 7·4; N, 17·05%).

No other pure compound has so far been isolated from the product.

Grateful acknowledgment is made to the Royal Commissioners for the Exhibition of 1851 for an Overseas Studentship (to R. B. J.) and to the New Zealand Government for a National Research Fellowship (to J. M.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 5th*, 1954.]