Synthetic Experiments in the cyclo*Heptatrienone Series. Part III.* Syntheses of Puberulic Acid and* iso*Stipitatic Acid.*

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

[Reprint Order No. 4687.]

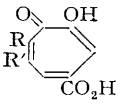
Puberulic acid has been synthesised from stipitatic acid by hydrolysis of 5-monobromostipitatic acid. The synthesis of stipitatic acid itself has been improved by isolation of the intermediate 3 : 4 : 6-trimethoxy*cyclo*heptatrienecarboxylic acid. *iso*Stipitatic acid, α-hydroxytropolone-γ-carboxylic acid, has been prepared from resorcinol dimethyl ether by ring expansion to 3 : 5-dimethoxy*cyclo*heptatrienecarboxylic acid, treatment with bromine to give 4-bromo-3-methoxy-5-oxo*cyclo*heptatrienecarboxylic acid and subsequent hydrolyses of the bromine and methoxyl groups.

One of the synthetic methods for the preparation of tropolone derivatives involves ring expansion of alkoxybenzenes with diazoacetic ester and subsequent oxidation with bromine of the *cyclo*heptatrienecarboxylic esters so formed (Part I, *J.*, 1951, 2352). In a later paper (*J.*, 1952, 4461) it was shown that the yields of tropolones obtained by this method could be improved if the intermediate *cyclo*heptatrienecarboxylic acids were purified before the bromine oxidation and in the present studies the yield of stipitatic acid (I;

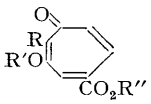
* Part II, *J.*, 1952, 4461.

R = H, R′ = OH) was 62% from the intermediate 3 : 4 : 6-trimethoxy*cyclo*heptatriene-carboxylic acid or 4·5% overall yield from 1 : 2 : 4-trimethoxybenzene.

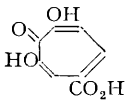
Attempts to synthesise puberulic acid (I; R = R′ = OH) (Birkinshaw and Raistrick, *Biochem. J.*, 1936, **26**, 441; Corbett, Johnson, and Todd, *J.*, 1950, 6) from 1 : 2 : 3 : 4-tetramethoxybenzene by the same method yielded a complex mixture from which neither puberulic acid nor any of its derivatives has so far been isolated. However with larger quantities of synthetic stipitatic acid at our disposal, a straight-forward method for the introduction of the extra hydroxyl group has been developed, which completes the synthesis of puberulic acid.



(I)



(II)



(III)

Birkinshaw, Chambers, and Raistrick (*Biochem. J.*, 1942, **36**, 242) described the bromination of stipitatic acid to a monobromo-derivative which was not orientated. This compound would be expected to be the 5-bromo-derivative (I; R = Br, R′ = OH) because of the combined directive influence of the carboxyl group and the tropolone ring. This was confirmed when treatment of the bromostipitatic acid with potassium hydroxide gave puberulic acid in 58% yield. This acid is known to be stable to potassium hydroxide even at 300° (Johnson, Corbett, and Todd, *loc. cit.*) and no formation of benzenoid derivatives was observed in the final stage.

As an alternative approach to puberulic acid, the preparation of *iso*stipitatic acid (I; R = OH, R′ = H or a tautomeric form) has been effected but the hydroxylation of this acid in the 6-position could not be accomplished. Diazoacetic ester ring expansion of pyrogallol trimethyl ether and subsequent brominative oxidation of the product did not yield *iso*stipitatic acid, which was eventually prepared by a method similar to that used for puberulic acid. Resorcinol dimethyl ether and diazoacetic ester gave a mixture of esters from which 3 : 5-dimethoxy*cyclo*heptatrienecarboxylic acid and *m*-methoxyphenoxyacetic acid (Johnson, Langemann, and Murray, *J.*, 1953, 2136) were obtained. The position of the double bonds in the *cyclo*heptatriene acid could not be determined by ozonolysis and hydrolysis to a dimethoxybenzoic acid, a method used in the anisole series (Part II, *loc. cit.*), as more extensive decomposition occurred during ozonolyses even at −80°, and the only recognisable product was oxalic acid. A chloroform solution of 3 : 5-dimethoxy*cyclo*heptatrienecarboxylic acid gave a solid complex with bromine (cf. Cook, Gibb, and Raphael, *J.*, 1951, 2244) which decomposed when heated or, better, when dissolved in polar solvents, to give a small quantity of the expected 3-methoxy-5-oxo*cyclo*heptatrienecarboxylic acid (II; R = R″ = H, R′ = Me) but mainly the corresponding monobromo-derivative (II; R = Br, R′ = Me, R″ = H), the structure of which was proved by its rearrangement to 5-hydroxy*iso*phthalic acid after treatment with potassium hydroxide at 150°. Treatment of methyl 3 : 5-dimethoxy*cyclo*heptatriene-carboxylate with bromine similarly gave the methyl ester (II; R = Br, R′ = R″ = Me) which could not be obtained by direct methylation of the free acid with diazomethane possibly because of preferential reaction with the halogen atom. As 2-bromo*cyclo*heptatrienones, the acid (II; R = Br, R′ = Me, R″ = H) and its ester contain moderately reactive bromine atoms which were readily hydrolysed by alkali, giving the corresponding hydroxy-compound, α-methoxytropolone-γ-carboxylic acid (*iso*stipitatic acid *O*-methyl ether) (II; R = OH, R′ = Me, R″ = H). A lower-melting isomeric compound was also isolated from this reaction and it is possible that it is α-methoxytropolone-β′-carboxylic acid, arising from hydrolysis of the alternative methoxy-group in the original 3 : 5-dimethoxy*cyclo*heptatrienecarboxylic acid, but the very low yield of this compound precluded proof of its structure.

*iso*Stipitatic acid *O*-methyl ether was unchanged after treatment with potassium hydroxide at 150° but at 200° gave 5-hydroxy*iso*phthalic acid, showing that no rearrangement had occurred during replacement of the bromine. The *O*-methyl ether was hydrolysed

with hydrogen bromide in acetic acid and gave *iso*stipitatic acid itself (II; R = OH, R′ = R″ = H, or the tautomer III). The comparatively vigorous conditions (6 hours at 100—110°) required for this hydrolysis support the view that the *O*-methyl group of *O*-methyl*iso*stipitatic acid is in the α-position to the tropolone group, as the alternative tropolone ether structure probably would be readily hydrolysed by acids.

Bromination of *iso*stipitatic acid has proved to be unexpectedly difficult and no monobromo-derivative has been isolated. Likewise we have been unable to introduce other bromine atoms into the nucleus of 4-bromo-3-methoxy-5-oxo*cyclo*heptatrienecarboxylic acid (II; R = Br, R′ = Me, R″ = H). The directive effects of the carboxyl group and the tropolone ring are evidently opposed in *iso*stipitatic acid, and further studies on its substitution reactions were postponed when puberulic acid was obtained from stipitatic acid.

Experimental

Ultra-violet absorption spectra were determined in 95% ethanol except where otherwise stated.

3 : 4 : 6-*Trimethoxy*cyclo*heptatrienecarboxylic Acid.*—The crude ester mixture (5 g.; b. p. 110—144°/0·2 mm.) obtained from the reaction of diazoacetic ester and 1 : 2 : 4-trimethoxybenzene (Part I, *loc. cit.*; in the present work 145 g. of trimethoxybenzene were recovered from an original 174·5 g. together with 33·8 g. of mixed esters) was mixed with a solution of potassium hydroxide (3·3 g.) in aqueous methanol (2·5 c.c. of water + 27·5 c.c. of methanol) at 0°. After 15 min. the potassium salt which had crystallised was separated and dried (580 mg.; m. p. 132—134°). Acidification gave 2 : 4-dimethoxyphenoxyacetic acid (295 mg.) which, after crystallisation from *cyclo*hexane–benzene and sublimation *in vacuo*, had m. p. 120°, not depressed with an authentic specimen (Johnson, Langemann, and Murray, *J.*, 1953, 2136). The filtrate from the potassium 2 : 4-dimethoxyphenoxyacetate was heated on the water-bath for 2 hr. at 60°, diluted with water (50 c.c.), acidified with hydrochloric acid (11N), further diluted until a faint turbidity appeared (total vol., *ca.* 100 c.c.), and kept at 0°. 3 : 4 : 6-*Trimethoxy*cyclo*heptatrienecarboxylic acid* (420 mg.) separated as pale yellow needles and was recrystallised from *cyclo*hexane–benzene (1 : 1) and sublimed at 130°/0·1 mm. It then had m. p. 152—153° (Found: C, 58·4; H, 5·9. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). Light absorption: max. at 217—218 and 318—319 mμ (log ε 4·14 and 3·84 respectively). The infra-red spectrum of the acid, as a mull in Nujol, showed maxima at 2632, 1684(s), 1613(s), 1534(s), 1433(s), 1401, 1344(s), 1289(s), 1259(s), 1236(s), 1193(s), 1176, 1153(s), 1147(s), 1124(s), 1080, 1028(s), 1006(s), 995(s), 948, 932, 903, 855, 818, 789, 756(s), 725, 683, and 657 cm.$^{-1}$.

Stipitatic Acid.—A solution (0·6 c.c.) of bromine (1 c.c.) in carbon tetrachloride (10 c.c.) was added dropwise to 3 : 4 : 6-trimethoxy*cyclo*heptatrienecarboxylic acid (0·2 g.) in chloroform (6·5 c.c.) at 0°. The pale orange precipitate, probably a complex with bromine, was separated, heated in ethyl acetate (3 c.c.) for 3 min., and cooled in ice. Stipitatic acid *O*-methyl ether contaminated with stipitatic acid itself separated as a pale yellow solid. This mixture was hydrolysed directly with hydrobromic acid (2·5 c.c. of 48%) at 110° for 12 hr. and on cooling stipitatic acid (100 mg.) was obtained. After crystallisation from aqueous ethanol and sublimation at 180°/0·1 mm. it had m. p. and mixed m. p. 280° (Found: C, 52·4; H, 3·4. Calc. for $C_8H_6O_5$: C, 52·7; H, 3·3%).

Monobromostipitatic Acid (cf. Birkinshaw, Chambers, and Raistrick, *loc. cit.*).—A solution of bromine (0·1 c.c.) in glacial acetic acid (5 c.c.) was added with stirring to a solution of stipitatic acid (0·39 g.) in acetic acid (100 c.c.). After 5 min. water (20 c.c.) was added and after a further 15 min. the volume of the solvent was reduced to small bulk by evaporation under reduced pressure. The monobromostipitatic acid which separated was removed by filtration and crystallised from methanol, forming small pale yellow needles, decomp. 270°. For analysis it was sublimed at 180°/0·1 mm. (Found: C, 37·0; H, 2·2. Calc. for $C_8H_5O_5Br$: C, 36·8; H, 1·9%). Light absorption: max. at 276 and 349 mμ (log ε 4·48 and 3·70 respectively). The infra-red spectrum (Nujol mull) showed maxima at 3268, 2591, 1733(s), 1582(s), 1515(s), 1266(s), 1227(s), 1170(s), 1096, 1015, 925, 889, 850, 769, 737, 707 and 685 cm.$^{-1}$.

Puberulic Acid.—Monobromostipitatic acid (0·43 g.) was added to potassium hydroxide (3 g.) partly dissolved in water (1·5 c.c.) in a nickel crucible. At room temperature the potassium salt so obtained was not completely soluble but as the temperature of the mixture was slowly raised to 200° a homogeneous solution was obtained. The melt was maintained at 200° for 15 min. with occasional stirring, cooled, treated with 2N-sulphuric acid (20 c.c.), and finally

acidified with concentrated sulphuric acid with stirring and cooled. The precipitated puberulic acid (0·126 g.) was separated and washed with water. The combined filtrate and washings were extracted with ether (4 × 20 c.c.) and then ethyl acetate (4 × 20 c.c.), the combined extracts were dried, and the solvent was removed, to yield a further quantity of puberulic acid (0·063 g.). The product crystallised from aqueous ethanol (charcoal) as almost colourless plates, m. p. 317° alone and mixed with an authentic specimen (Corbett, Hassall, Johnson, and Todd, *J.*, 1950, 1) (Found, in a specimen sublimed at 190°/0·5 mm.: C, 48·7; H, 3·1. Calc. for $C_8H_6O_6$: C, 48·5; H, 3·05%). The ultra-violet and infra-red spectra were identical with those of the authentic specimen.

3 : 5-*Dimethoxy*cyclo*heptatrienecarboxylic Acid.*—Resorcinol dimethyl ether (180 g.) and diazoacetic ester (40 c.c.) were caused to react at 150° in the usual manner (Parts I and II, *locc. cit.*), and the product was fractionated, to give a mixed ester fraction (34·5 g.), b. p. 112—132°/0·3 mm. A cooled solution of potassium hydroxide (3·3 g.) in 90% methanol (30 c.c.) was added in small portions to these mixed esters (5 g.) at 0° with constant stirring. After a further 15 min. at 0°, the precipitated potassium *m*-methoxyphenoxyacetate (0·2—0·8 g. in various batches) (Johnson, Langemann, and Murray, *loc. cit.*) was separated and washed with a little methanol, and the combined filtrate and washings were heated on a water bath for 2 hr. The solution was cooled in ice, diluted with water (50 c.c.), and acidified by cautious addition of concentrated hydrochloric acid, a copious precipitate of 3 : 5-dimethoxy*cyclo*heptatriene-carboxylic acid being obtained. After cooling at 0° for ½ hr., the precipitate was separated, washed, dried (2·0 g.), and crystallised from benzene as pale yellow plates, m. p. 181° (Found, in a sample sublimed at 140°/0·1 mm.: C, 61·2; H, 6·0; OMe, 29·0. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2; 2OMe, 31·6%). Light absorption: max. at 222—223, 286, and 316—318 mμ (log ε 4·22, 3·69, and 3·90 respectively). The acid is slightly soluble in cold water or *cyclo*hexane, soluble in hot benzene, and very soluble in methanol.

The acid (0·5 g.) was dissolved in ether (50 c.c.) containing 1% of methanol and esterified with excess of diazomethane. The solvent was removed and the residue crystallised from *cyclo*hexane, to give the *methyl ester* as pale yellow needles, m. p. 65·5—66·5° (Found: C, 63·0; H, 6·9. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·7%). Light absorption: max. at 222—223, 287, and 319—320 mμ (log ε 4·18, 3·75, and 3·9 respectively).

4-*Bromo*-3-*methoxy*-5-*oxo*cyclo*heptatrienecarboxylic Acid.*—3 : 5-Dimethoxy*cyclo*heptatriene-carboxylic acid (0·46 g.) was dissolved in cold chloroform (10 c.c.), and a solution of bromine (0·3 c.c.) in carbon tetrachloride (3 c.c.) added slowly with stirring. Hydrogen bromide was evolved and an orange precipitate of a bromine complex (1·0 g.) was obtained. This complex was stable in non-polar solvents even when heated, but was readily decomposed in water or methanol. It was dissolved in cold methanol and kept at room temperature for 1 hr. The *product*, which separated as a very pale yellow solid (0·299 g.), recrystallised from dioxan as pale yellow needles which sintered at 270—273° without melting but with previous darkening (Found, in a sample sublimed at 180°/0·35 mm.: C, 41·7; H, 3·0. $C_9H_7O_4Br$ requires C, 41·7; H, 2·7%). Light absorption: max. at 260 and 327—329 mμ (log ε 4·49 and 3·61 respectively). The infra-red spectrum, determined as a mull in Nujol, showed maxima at 1859, 1718, 1631, 1587(s), 1548(s), 1527(s), 1443(s), 1420, 1339, 1290, 1236(s), 1224(s), 1200(s), 1170(s), 1020, 926(s), 885, 850, 767, 760, and 673 cm.$^{-1}$.

A further quantity of this acid was obtained by concentration of the methanol mother-liquors but the product so obtained required charcoal treatment for purification. Concentration of the mother-liquors gave 3-*methoxy*cyclo-5-*oxoheptatrienecarboxylic acid* (20 mg.) which crystallised from methanol in colourless needles, m. p. 235—237° (decomp.), and sublimed at 150°/0·1 mm. (Found: C, 60·3; H, 4·6. $C_9H_8O_4$ requires C, 60·0; H, 4·5%). Light absorption: max. at 222, 248, and 301 mμ (log ε 4·25, 4·48, and 3·73 respectively). The infra-red spectrum (Nujol mull) showed maxima at 2353, 1876, 1709, 1645, 1597, 1555, 1515(s), 1362, 1316, 1255(s), 1227(s), 1198(s), 1171(s), 1087, 1020, 985, 916(s), 887, 862, 850, 785, 772, 759, 720, 683, and 669 cm.$^{-1}$.

Methyl 4-*Bromo*-3-*methoxy*-5-*oxo*cyclo*heptatrienecarboxylate.*—Methyl 3 : 5-dimethoxy*cyclo*-heptatrienecarboxylate (0·47 g.) was dissolved in the minimum quantity of carbon tetrachloride, cooled in ice, and treated with a solution of bromine (0·3 c.c.) in carbon tetrachloride (3 c.c.). The precipitated bromine complex was separated, washed with cold carbon tetrachloride, and treated with methanol (10 c.c.) in order to decompose it. The methanol was removed and the process repeated twice more. The residual ester crystallised from methanol as pale yellow needles, m. p. 149—150° (Found, on a sample sublimed at 120°/0·1 mm.: C, 43·9; H, 3·2. $C_{10}H_9O_4Br$ requires C, 43·9; H, 3·3%). Light absorption: max. at 262, 270, and 330—333 mμ

(log ε 4·49, 4·47, and 3·62 respectively) with an inflection at 320—325 mμ (log ε 3·60). The infra-red spectrum (mull in Nujol) showed maxima at 1730(s), 1634, 1592(s), 1439(s), 1408(s), 1330, 1282(s), 1258(s), 1215(s), 1176(s), 1095, 1031(s), 1005, 962, 937, 917(s), 890, 851, 791, and 767 cm.$^{-1}$.

Alkaline Rearrangement of 4-*Bromo*-3-*methoxy*-5-*oxo*cyclo*heptatrienecarboxylic Acid*.—A mixture of this acid (0·53 g.), potassium hydroxide (4 g.), and water (0·5 c.c.) was heated in a nickel crucible at 140° (oil-bath) with intermittent stirring. When the initial effervescence had ceased, the temperature was raised to 170° for 5 min. and then 200° for 10 min. The solution, originally red, slowly changed to orange-yellow. The melt was dissolved in water (8 c.c.) and acidified with 11N-hydrochloric acid, and the solution was continuously extracted with ether for 2 days. The ethereal extract was dried and the solvent removed, to yield a solid residue (0·3 g.) which after crystallisation from aqueous ethanol had m. p. 296°, alone and mixed with an authentic specimen of 5-hydroxy*iso*phthalic acid (Found: C, 53·0; H, 3·5. Calc. for $C_8H_6O_5$: C, 52·7; H, 3·3%). The infra-red spectrum, determined as a Nujol mull, was identical with that of authentic 5-hydroxy*iso*phthalic acid.

O-*Methyl*iso*stipitatic Acid*.—4-Bromo-3-methoxy-5-oxo*cyclo*heptatrienecarboxylic acid (0·73 g.) was heated in methanol (50 c.c.) containing potassium hydroxide (0·5 g.) on a water-bath under gentle reflux for 2 hr. After cooling and acidification with 11N-hydrochloric acid, the solvent was removed and the residual solid repeatedly extracted with boiling methanol (6 × 4 c.c.) until the methanolic extracts no longer gave a colour with ferric chloride. After removal of the methanol from the combined extracts, the residue was crystallised from water (charcoal), to give colourless plates of O-*methyl*iso*stipitatic acid*, m. p. 257° (with previous softening) (Found, on material sublimed at 180°/0·5 mm.: C, 55·0, 55·3; H, 4·4, 4·3. $C_9H_8O_5$ requires C, 55·1; H, 4·1%). The product gave a pale green ferric reaction. Light absorption: max. at 216 and 308—311 mμ (log ε 4·54 and 3·54 respectively). The infra-red spectrum, determined on a mull in Nujol, showed maxima at 1825, 1706(s), 1600, 1515, 1408, 1333, 1307, 1274(s), 1124, 1105, 1055, 905, 878, 757, 748, 691, and 662 cm.$^{-1}$.

From the aqueous mother-liquors there was isolated a small quantity of a pale yellow isomeric material, m. p. 220° which gave a brown-red ferric reaction (Found: C, 55·5; H, 4·1%). The infra-red spectrum (Nujol mull) showed maxima at 1704(s), 1647, 1603, 1555, 1536, 1504, 1414, 1274(s), 1229, 1209, 1124, 1087, 1054, 1031, 920, 887, 758, 723, 691, and 664 cm.$^{-1}$.

iso*Stipitatic Acid*.—To *O*-methyl*iso*stipitatic acid (0·049 g.) in glacial acetic acid (3 c.c.), 50% hydrogen bromide in glacial acetic acid (3 c.c.) was added and the mixture was heated at 100—110° for 6 hr. After removal of the solvent the residue was twice crystallised from water, to give iso*stipitatic acid* as an almost colourless solid, m. p. 293—294° (decomp.), which gave a green ferric reaction (Found, in a sample sublimed at 180°/0·5 mm.: C, 52·5; H, 3·4. $C_8H_6O_5$ requires C, 52·7; H, 3·3%). Light absorption: max. at 216 and 312 mμ (log ε 4·53 and 3·54 respectively). The infra-red spectrum (mull in Nujol) showed maxima at 3448, 1704(s), 1675(s), 1600(s), 1493, 1420(s), 1344, 1282(s), 1209(s), 1181(s), 1111, 1000, 975, 930, 909, 901, 881, 786, 757, 735, 694, 668, and 664 cm.$^{-1}$.

Alkaline Rearrangement of O-*Methyl*iso*stipitatic Acid*.—The acid (0·38 g.) was heated with potassium hydroxide (3 g.) and water (1·5 c.c.) in a nickel crucible at 240° for 15 min. Treatment of the product as in the case of the alkaline rearrangement of 4-bromo-3-methoxy-5-oxo*cyclo*heptatrienecarboxylic acid (above) gave 5-hydroxy*iso*phthalic acid (0·13 g.) which after crystallisation from aqueous ethanol had m. p. and mixed m. p. 293°. In another experiment alkaline rearrangement of *O*-methyl*iso*stipitatic acid was effected at 200° for 5 min. and 5-hydroxy*iso*phthalic acid was isolated from the product as before.

Grateful acknowledgment is made to Professor A. R. Todd, F.R.S., for his interest, 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, September 29th,* 1953.]