Gladiolic Acid. Part V. Syntheses of Some Methoxybenzenetricarboxylic Acids.*

By D. GARDNER, JOHN FREDERICK GROVE, and DOREEN ISMAY.

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The synthesis of 3-methoxybenzene-1 : 2 : 4-tricarboxylic acid is described and some properties of the methoxybenzenetricarboxylic acids are compared.

THE main product of the oxidation of gladiolic acid with boiling permanganate was shown by Grove (*Biochem., J.*, 1952, **50**, 648) to be 4-methoxybenzene-1 : 2 : 3 : 5-tetracarboxylic acid whose structure was proved by synthesis; a methoxybenzenetricarboxylic acid, substance C, which gave positive results in tests for an *o*-phthalic acid and was not, therefore, methoxytrimesic acid (Ullmann and Brittner, *Ber.*, 1909, **42**, 2539), was also formed in very low yield under certain conditions. In 1946, when this acid was first obtained, only 6-methoxybenzene-1 : 2 : 4-tricarboxylic acid (Posternak, *Helv. Chim. Acta*, 1940, **23**, 1046) of the five possible methoxytrimellitic and methoxyhemimellitic acids had been described. Accordingly the synthesis of the four remaining acids was commenced, by permanganate oxidation of the methyl ethers of appropriate hydroxyacetophenones obtained by Fries rearrangement of suitable dimethylphenyl acetates. While this work was in progress 5-methoxybenzene-1 : 2 : 3-tricarboxylic acid was obtained by Wilds and Djerassi (*J. Amer. Chem. Soc.*, 1946, **68**, 1862), by a different route; and later, 4-methoxybenzene-1 : 2 : 3- and 5-methoxybenzene-1 : 2 : 4-tricarboxylic acid were described by Buehler, Spees, and Sanguinetti (*ibid.*, 1949, **71**, 11). None of these acids was identical with the acid obtained from gladiolic acid which must therefore be 3-methoxybenzene-1 : 2 : 4-tricarboxylic acid, and this has now been confirmed by synthesis. Methylation of 2-hydroxy-3 : 4-dimethylacetophenone, prepared by Fries rearrangement at 130° of 2 : 3-dimethylphenyl acetate (von Auwers and Mauss, *Annalen*, 1928, **460**, 240), proved difficult, but was achieved by prolonged heating with methyl iodide and potassium carbonate in acetone. Oxidation with permanganate then gave the desired acid, identical with the gladiolic acid oxidation product.

When the Fries rearrangement of 2 : 3 dimethylphenyl acetate was carried out in nitrobenzene at 20°, the *p*-hydroxy-ketone, 4-hydroxy-2 : 3-dimethylacetophenone, was the sole product. von Auwers and his collaborators showed that 3 : 5-dimethylphenyl acetate gave an *o*-hydroxy-ketone while 2 : 5-dimethylphenyl acetate gave a *p*-hydroxy-ketone in the Fries rearrangement at 100°. These findings were confirmed in the present study; in addition it was observed that 3 : 5-dimethylphenyl acetate yielded the *o*-hydroxy-ketone and no *p*-hydroxy-ketone under mild conditions (nitrobenzene solution at 0°), whereas 2-hydroxy-3 : 6-dimethylacetophenone was not obtained from 2 : 5-dimethylphenyl acetate even under conditions sufficiently drastic to cause migration of the alkyl substituents.

Permanganate oxidation of 4-methoxy-2 : 3-dimethylacetophenone gave 4-methoxybenzene-1 : 2 : 3-tricarboxylic acid. 5-Methoxybenzene-1 : 2 : 4-tricarboxylic acid was obtained similarly from both 2-methoxy-4 : 5- and 4-methoxy-2 : 5-dimethylacetophenone; from the last compound the intermediate 2 : 5-dicarboxy-4-methoxyphenylglyoxylic acid was also isolated.

In the preparation of 5-methoxybenzene-1 : 2 : 3-tricarboxylic acid essentially according to the method of Wild and Djerassi (*loc. cit.*), esterification during continuous extraction with ethyl acetate led to the isolation of the monoethyl ester, from which the acid was obtained by hydrolysis.

The trimethyl esters of the five methoxyhemimellitic and trimellitic acids were prepared and are to be preferred as reference compounds, in agreement with the views of earlier workers. The acids have characteristic infra-red spectra and can be identified by this means but their decomposition points vary with the rate of heating and in general are not

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depressed on admixture with an acid of higher though similar decomposition point. The esters, on the other hand, depressed each other's melting points when these lay close together. Their infra-red spectra are also characteristic, and have been deposited with the Society.

EXPERIMENTAL

M. p.s are corrected. Some microanalyses are by Messrs. W. Brown and A. G. Olney. Infra-red spectra were determined by using the apparatus described in earlier papers (Duncanson, Grove, and Zealley, *J.*, 1331, 1953).

Fries Rearrangement of 2 : 3-*Dimethylphenyl Acetate*.—(a) *At* 20°. Powdered anhydrous aluminium chloride (15 g., 1·8 mols.) was added in portions with stirring to 2 : 3-dimethylphenyl acetate (10·0 g.; b. p. 120°/15 mm.) (Smith and Opie, *J. Org. Chem.*, 1941, **6**, 427) in nitrobenzene (50 g.), at < 20° (ice-cooling). After 48 hr. the mixture was poured over cracked ice and concentrated hydrochloric acid, ether was added, and after separation the ether–nitrobenzene layer was extracted with 2N-sodium hydroxide. Acidification of the alkaline extract, extraction with ether, and recovery furnished 4-*hydroxy*-2 : 3-*dimethylacetophenone*, colourless prisms (from ethanol), m. p. 145° (5·3 g.) (Found: C, 73·2; H, 7·3. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%). It was insoluble in light petroleum, and gave no colour with ferric chloride in ethanol. The *semicarbazone* formed prisms, m. p. 226° (decomp.), from ethanol (Found: N, 18·7. $C_{11}H_{15}O_2N_3$ requires N, 19·0%).

The 4-hydroxy-ketone (2·0 g.), methyl sulphate (2 g.), and 20% aqueous sodium hydroxide (6 ml.) were shaken vigorously. The resulting alkali-insoluble oil was extracted with ether, and treated with light petroleum, furnishing 4-*methoxy*-2 : 3-*dimethylacetophenone* (2·0 g.), plates, m. p. 33° [Found: C, 73·8; H, 7·8%; *M* (Rast), 168. $C_{11}H_{14}O_2$ requires C, 74·1; H, 7·9%; *M*, 178]. The *semicarbazone* formed prisms, m. p. 216° (decomp.), from ethanol (Found: N, 18·4. $C_{12}H_{17}O_2N_3$ requires N, 17·9%).

(b) *At* 130°. 2 : 3-Dimethylphenyl acetate (10 g.) and anhydrous aluminium chloride (15 g.) were heated 1 hr. at 130°, the complex was decomposed with ice and hydrochloric acid, and the oily product extracted with ether. Recovery followed by distillation *in vacuo* yielded 2-hydroxy-3 : 4-dimethylacetophenone, a yellow oil, b. p. 140°/12 mm. (6·2 g.) (Smith and Opie, *loc. cit.*). It was miscible with light petroleum, and gave an intense green colour with ferric chloride in ethanol, becoming violet on dilution with water.

2-*Methoxy*-3 : 4-*dimethylacetophenone*.—The 2-hydroxy-ketone (2·5 g.), methyl iodide (12 g.), and potassium carbonate (2·5 g.) in acetone (50 ml.) were heated under reflux for 6 days, further quantities of methyl iodide being added from time to time. After concentration and addition of water (50 ml.), the solution was extracted with ether. Removal of the organic solvents left an oil which was taken up again in ether and exhaustively extracted with aqueous sodium hydroxide (20%; 10 × 50 ml.). Unchanged 2-hydroxy-ketone (1·0 g.) was recovered from the alkaline extract. The neutral fraction on recovery furnished 2-*methoxy*-3 : 4-*dimethylacetophenone*, a colourless oil (0·8 g.), b. p. 104°/2 mm. ($>C{=}O$ absorption at 1690 cm.$^{-1}$) (Found: C, 74·1; H, 7·9%), characterised as its *semicarbazone*, plates (from ethanol), m. p. 196° (Found: C, 61·4; H, 7·1; N, 17·4; OMe, 13·5. $C_{12}H_{17}O_2N_3$ requires C, 61·25; H, 7·3; N, 17·9; OMe, 13·2%). The methoxyacetophenone gave no colour with ferric chloride.

3-*Methoxybenzene*-1 : 2 : 4-*tricarboxylic Acid*.—Potassium permanganate (5% solution; 25 ml.) was added dropwise during 30 min. to a stirred suspension of 2-methoxy-3 : 4-dimethylacetophenone (0·4 g.) in sodium carbonate (10 ml.; saturated solution) at 60°. The reaction was continued under reflux for 6 hr. after the addition of a further 75 ml. of permanganate solution. Excess of permanganate was then destroyed by the addition of methanol, the manganese dioxide filtered off, and the filtrate acidified with concentrated hydrochloric acid. The oil obtained by 24 hours' continuous extraction with ethyl acetate and recovery was oxidised in 3N-sulphuric acid (10 ml.) with potassium permanganate (25 ml.; 5%) at 100°, excess of permanganate removed by the addition of sodium sulphite, and the acid solution extracted with ethyl acetate. After two crystallisations from a very small volume of water, or from acetone–benzene, the solid extract formed prisms (97 mg., 18%) of 3-*methoxybenzene*-1 : 2 : 4-*tricarboxylic acid*, (C.S. 102 *), m. p. 198—200° (decomp.) [Kofler block, very rapid heating, 209—210° (decomp.)]

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* This and similar designations denote infra-red spectra which have been deposited with the Society. Photo-copies may be obtained, price 3*s*. 0*d*. each per copy, on application stating the C.S. no. to the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

[Found: C, 50·3, 49·9; H, 3·4, 3·7%; equiv. 78. $C_{10}H_8O_7$ requires C, 50·0; H, 3·4%; equiv., 80 (tribasic acid)].

The *trimethyl ester* (C.S. 103) formed in 24 hr. in methanol with excess of ethereal diazomethane crystallised from methanol in prisms, m. p. 75° (Found: C, 55·4; H, 5·1; OMe, 43·6. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0; 4OMe, 44·0%).

The *anhydride* formed by sublimation of the acid at 160—180°/10^{-1} mm. formed needles, m. p. 165—168° (Found: C, 54·1; H, 3·0. $C_{10}H_6O_6$ requires C, 54·1; H, 2·7%).

When the m. p. of the acid is taken on the Kofler block with a slow rate of heating it is found to be 165—168°, the m. p. of the anhydride. Thus the m. p. of the acid, 160—165°, originally recorded (Grove, *loc. cit.*) is actually that of the anhydride.

3-Methoxybenzene-1 : 2 : 4-tricarboxylic acid did not depress the m. p. of the methoxybenzenetricarboxylic acid obtained from gladiolic acid and the infra-red spectra were identical. The trimethyl esters of the two acids were also identical.

4-*Methoxybenzene*-1 : 2 : 3-*tricarboxylic Acid*.—4-Methoxy-2 : 3-dimethylacetophenone (0·35 g.) was oxidised with potassium permanganate, first in sodium carbonate and then in 3N-sulphuric acid as described for the preparation of 3-methoxybenzene-1 : 2 : 4-tricarboxylic acid. The acid (C.S. 104) obtained by ethyl acetate extraction crystallised from a little water in prisms (123 mg., 26%), m. p. 222° unchanged on cooling and reheating, or after 5 minutes' heating at 230° (Buehler *et al.*, *loc. cit.*, give m. p. 215—216°) (Found: C, 49·9; H, 3·5%). The trimethyl ester (C.S. 105) formed prisms, m. p. 92° (lit., 91—92°), from methanol. Sublimation of the acid at 200—210°/10^{-1} mm. gave the *anhydride*, prisms, m. p. 222° (Found: C, 54·0; H, 3·0%).

5-*Methoxybenzene*-1 : 2 : 4-*tricarboxylic Acid*.—(*a*) 2-Methoxy-4 : 5-dimethylacetophenone (1·0 g., m. p. 56°) (von Auwers, Bundesmann, and Wieners, *Annalen*, 1926, **447**, 162) was oxidised with potassium permanganate in sodium carbonate as described above. Crystallisation of the product from ethyl acetate gave the acid (C.S. 106), m. p. 222—223° (decomp.) (675 mg., 50%) (Buehler *et al.*, *loc. cit.*, give m. p. 224—225°) (Found: C, 49·7; H, 3·9%). The trimethyl ester (C.S. 107) crystallised from light petroleum in prisms, m. p. 62° (lit., 62·5—63°) (Found: C, 55·2; H, 5·1%).

(*b*) 4-Methoxy-2 : 5-dimethylacetophenone (1·0 g.; m. p. 78°) (von Auwers *et al.*, *loc. cit.*, 1926) was oxidised as in (*a*). Treatment of the gummy ethyl acetate extract with benzene furnished a solid which crystallised from water in prisms, m. p. 216—219° (decomp.) (780 mg., 52%), of 2 : 5-*dicarboxy*-4-*methoxyphenylglyoxylic acid* [Found: C, 49·2; H, 3·2%; equiv., 87. $C_{11}H_8O_8$ requires C, 49·2; H, 3·0%; equiv., 89 (tribasic acid)]. Oxidation of this acid (200 mg.) with permanganate in sulphuric acid in the usual way gave 5-methoxybenzene-1 : 2 : 4-tricarboxylic acid (125 mg.) (overall yield 36%).

5-*Methoxybenzene*-1 : 2 : 3-*tricarboxylic Acid*.—4-Methoxy-2 : 6-dimethylbenzaldehyde (0·5 g.; m. p. 50°) (Wilds and Djerassi, *loc. cit.*) was oxidised in sodium carbonate with potassium permanganate as described above. Continuous extraction of the acidified solution with ethyl acetate and crystallisation of the solid product from water gave the *monoethyl ester* of the desired acid as needles, m. p. 177—178° (decomp.) [Kofler block, m. p. 185—187° (decomp.)] (Found: C, 54·0; H, 4·8. $C_{12}H_{12}O_7$ requires C, 53·7; H, 4·5%). Methylation with ethereal diazomethane in methanol yielded an ethyl dimethyl ester, prisms (from methanol), m. p. 96° [Found: C, 56·5; H, 5·6; OAlk (as OMe), 41·2. Calc. for $C_{14}H_{16}O_7$: C, 56·7; H, 5·4; OAlk (as OMe), 41·9%]. Wilds and Djerassi described an ethyl dimethyl ester, m. p. 98—99°. Hydrolysis of the ethyl ester with methanolic potassium hydroxide and treatment of the salt obtained with hydrochloric acid as described by Wilds and Djerassi gave 5-methoxybenzene-1 : 2 : 3-tricarboxylic acid (C.S. 108), m. p. 211—212° (decomp.) (lit., 211—212°) (420 mg., 57%) (Found: C, 49·9; H, 3·6%). Sublimation at 200°/10^{-1} mm. gave the *anhydride*, m. p. 198° (Found: C, 53·7; H, 3·2%). The trimethyl ester (C.S. 109), prisms, m. p. 85° (lit., 83—83·5°), was obtained by methylation of the acid in methanol with excess of ethereal diazomethane.

6-*Methoxybenzene*-1 : 2 : 4-*tricarboxylic acid* (C.S. 110), m. p. 258° (decomp.), was prepared according to Posternak (*loc. cit.*) [Posternak gives m. p. 251° (decomp.)]. The trimethyl ester (C.S. 111) formed prisms (cf. Berner, *J.*, 1946, 1052), m. p. 145° (lit., 144°) (Found: C, 55·5; H, 5·2; OMe, 43·0%).

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THE FRYTHE, WELWYN, HERTS.

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