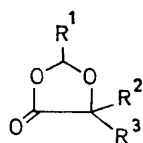


Citric Acid Chloralide

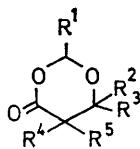
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Citric acid chloralide is shown to be 5,5-bis(carboxymethyl)-2-trichloromethyl-1,3-dioxolan-4-one by chemical and spectroscopic methods. The preparation and spectroscopic properties of 2,6-bis(trichloromethyl)-1,3-dioxan-4-one are described.

CITRIC ACID reacts with chloral to give the 'chloralide', $C_8H_7Cl_3O_7$, which could be either the 1,3-dioxolan-4-one (I; $R^1 = CCl_3$, $R^2 = R^3 = CH_2 \cdot CO_2H$) or the 1,3-dioxan-4-one (II; $R^1 = CCl_3$, $R^2 = CH_2 \cdot CO_2H$, $R^3 =$



(I)



(II)

CO_2H , $R^4 = R^5 = H$), but which has always been formulated as the former.¹ The reaction of paraformaldehyde with symmetrical dimethyl citrate gives the dimethyl ester of 'methylene citric acid' which must therefore be the 1,3-dioxolan-4-one (I; $R^1 = H$, $R^2 = R^3 = CH_2 \cdot CO_2H$).² 'Malic acid chloralide' has been estab-

¹ (a) J. Boeseken, *Versl. Akad. Wetenschap. Amsterdam*, 1926, **35**, 1084 (*Chem. Abs.*, 1927, **21**, 1962); (b) A. N. Meldrum and D. M. Bhatt, *J. Univ. Bombay*, 1934, **3**, 149 (*Chem. Abs.*, 1935, **29**, 4734).

lished as the 1,3-dioxolan-4-one (I; $R^1 = CCl_3$, $R^2 = CH_2 \cdot CO_2H$, $R^3 = H$) rather than the alternative structure (II; $R^1 = CCl_3$, $R^2 = CO_2H$, $R^3 = R^4 = R^5 = H$) by a chemical method³ and confirmed by n.m.r. spectroscopy,⁴ and the 'dimethylene tartrates' have recently been shown to be bidioxolanyldiones by i.r. spectroscopy.⁵ We now report chemical and spectroscopic evidence which confirms that citric acid chloralide is, as hitherto assumed, 5,5-bis(carboxymethyl)-2-trichloromethyl-1,3-dioxolan-4-one (I; $R^1 = CCl_3$, $R^2 = R^3 = CH_2 \cdot CO_2H$).

'Citric acid chloralide,' m.p. 161–162°, was the only product (*cf.* ref. 1a) isolated from the condensation of citric acid with chloral hydrate in sulphuric acid. Direct esterification with methanol^{1b} gave the dimethyl ester, which was identical (mixed m.p., n.m.r. spectrum) with

² C. A. Nau, E. B. Brown, and J. R. Bailey, *J. Amer. Chem. Soc.*, 1925, **47**, 2596.

³ H. Katsura, *Nippon Kagaku Zasshi*, 1956, **77**, 1105 (*Chem. Abs.*, 1959, **53**, 5126).

⁴ M. Baron and D. P. Hollis, *Rec. Trav. chim.*, 1965, **84**, 1109.

⁵ L. A. Cort and R. A. Stewart, *J. Chem. Soc. (C)*, 1971, 1386.

material obtained by the condensation of chloral in sulphuric acid with either trimethyl citrate⁶ or symmetrical dimethyl citrate; the latter route to the diester demonstrates that it has the structure (I; $R^1 = CCl_3$, $R^2 = R^3 = CH_2 \cdot CO_2Me$).

'Citric acid chloralide' shows a principal absorption maximum at 1810 with a subsidiary maximum at 1818 cm^{-1} (KBr). The diethyl ester shows a single maximum in this region at 1822 cm^{-1} (liquid film) and the dimethyl ester shows a single maximum in both the liquid ($CHCl_3$; 1818 cm^{-1}) and solid (KBr; 1822 cm^{-1}) phases. These maxima at >1800 cm^{-1} are characteristic of a carbonyl group in a 2-trichloromethyl-1,3-dioxolan-4-one,^{7,8} in agreement with structure (I; $R^1 = CCl_3$, $R^2 = R^3 = CH_2 \cdot CO_2H$). 1,3-Dioxolan-4-ones lacking a 2-trichloromethyl substituent usually absorb at a slightly lower frequency^{5,7} and in agreement with this we have found that the ring carbonyl groups in 'methylene citric acid' (I; $R^1 = H$, $R^2 = R^3 = CH_2 \cdot CO_2H$) and its dimethyl ester absorb at 1804 and 1799 cm^{-1} (KBr), respectively. The carbonyl group in 2-methoxy-5,5-dimethyl-1,3-dioxan-4-one⁹ (II; $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = R^5 = Me$) absorbs at 1745 cm^{-1} , as might be expected for the six-membered ring system. To confirm that the position of the carbonyl absorption permits a valid distinction to be made between 2-trichloromethyl-1,3-dioxolan-4-ones and 2-trichloromethyl-1,3-dioxan-4-ones we have also investigated the position of the carbonyl absorption in two compounds of the latter type and shown that the principal absorption occurs at <1800 cm^{-1} . 2,6-Bistrichloromethyl-1,3-dioxan-4-one (II; $R^1 = R^2 = CCl_3$, $R^3 = R^4 = R^5 = H$) was prepared by condensing 4,4,4-trichloro-3-hydroxybutyric acid with chloral hydrate in sulphuric acid. The principal carbonyl absorption occurred at 1785 cm^{-1} (KBr or $CHCl_3$) but subsidiary maxima were also observed [at 1813 and 1767 (KBr) and at 1808 cm^{-1} ($CHCl_3$)]. α -2,6-Bistrichloromethyl-5-methyl-1,3-dioxan-4-one¹⁰ (II; $R^1 = R^2 = CCl_3$, $R^3 = R^4 = H$; $R^5 = Me$) showed a sharp carbonyl absorption in the solid phase (KBr) at 1750 cm^{-1} , but in solution ($CHCl_3$) the absorption showed a maximum at 1774 with an inflection at 1787 cm^{-1} .*

The n.m.r. spectrum of 'citric acid chloralide' (I; $R^1 = CCl_3$, $R^2 = R^3 = CH_2 \cdot CO_2H$) in perdeuterioacetone showed a broad singlet at τ 0.24, a sharp singlet at τ 4.02, and two separate AB systems, attributable to the acidic protons, the C-2 proton, and the two methylene groups respectively. One AB system had τ_A 6.31, τ_B 6.75, Δ_{AB} 0.44 p.p.m., J_{AB} -18 Hz and the other had τ_A 6.94, τ_B 7.02, Δ_{AB} 0.08 p.p.m., J_{AB} -16 Hz. The derived dimethyl and diethyl esters showed closely analogous n.m.r. spectra. Each showed two separate AB systems, the lower field systems showing a larger chemical shift difference [Δ_{AB} ($CDCl_3$) 0.49 p.p.m. (CO_2Me);

Δ_{AB} (CCl_4) 0.51 p.p.m. (CO_2Et)] than the higher field systems [Δ_{AB} ($CDCl_3$) 0.15 p.p.m. (CO_2Me); Δ_{AB} (CCl_4) 0.17 p.p.m. (CO_2Et)] and signals due to methyl and ethyl groups were duplicated at slightly different chemical shift values in each case. The anisotropic effect of a trichloromethyl group at C-2 in a 1,3-dioxolan-4-one has been observed previously. The n.m.r. spectrum of 2-trichloromethyl-1,3-dioxolan-4-one (I; $R^1 = CCl_3$, $R^2 = R^3 = H$) shows⁸ an AB system, owing to the non-equivalence of the methylene protons, and the methyl groups in 5,5-dimethyl-2-trichloromethyl-1,3-dioxolan-4-one (I; $R^1 = CCl_3$, $R^2 = R^3 = Me$) are also non-equivalent,⁸ whereas in the unsubstituted 1,3-dioxolan-4-one (I; $R^1 = R^2 = R^3 = H$) the methylene protons at C-5 are equivalent.⁷ The n.m.r. spectra of 'methylene citric acid' (I; $R^1 = H$, $R^2 = R^3 = CH_2 \cdot CO_2H$) and the derived dimethyl and diethyl esters differ from those of the 2-trichloromethyl-substituted analogues in that the four methylene protons adjacent to the ester carbonyl groups in each case give rise to a single absorption. Whilst each pair of methylene protons would be expected to be equivalent to the other pair of methylene protons in each case, non-equivalence within a pair of methylene protons might nevertheless be observed, as is the case for example for the methylene proton pairs in trimethyl citrate, which give rise to a single AB system¹¹ owing to the presence of the central *meso*-carbon atom. In the case of compound (I; $R^1 = CCl_3$, $R^2 = R^3 = CH_2 \cdot CO_2H$) and its esters each methylene group gives rise to a separate AB system, and the chemical shift differences between the geminal protons differ for the two methylene groups within a single compound. We have also re-investigated the n.m.r. spectrum⁴ of 'malic acid chloralide' (I; $R^1 = CCl_3$, $R^2 = CH_2 \cdot CO_2H$, $R^3 = H$) and find that the methylene protons appear as an AB system, further split by the C-5 proton. The chemical shift separation [Δ_{AB} ($CDCl_3$) 0.08 p.p.m.] and the coupling constant (J_{AB} -14.5 Hz) are very similar to those of the higher field AB system in 'citric acid chloralide.' The methylene protons in the methyl ester (I; $R^1 = CCl_3$, $R^2 = CH_2 \cdot CO_2Me$, $R^3 = H$) give rise to a singlet.

The proton at C-2 in 2-methoxy-5,5-dimethyl-1,3-dioxan-4-one (II; $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = R^5 = Me$) is reported⁹ to give a singlet signal, and we have found that the protons at C-2 in the two 2,6-bistrichloromethyl-1,3-dioxan-4-ones (II; $R^1 = R^2 = CCl_3$, $R^3 = R^4 = H$, $R^5 = H$ or Me) also give sharp singlets; there is no sign of the long-range splitting observed for the analogous C-2 protons in 2-trichloromethyl-1,3-dioxolan-4-ones.^{4,5,7,8} The chemical shifts of these protons in the six-membered system are solvent-dependent, but fall within the same range as that observed in the present and in previous work^{4,5,7,8} for the chemical shifts of protons at C-2 in 2-trichloromethyl-

⁷ M. Forines and J. Soulier, *Bull. Soc. chim. France*, 1970, 332.

⁸ N. J. Turro, S. S. Edelson, J. R. Williams, and T. R. Darling, *J. Amer. Chem. Soc.*, 1968, **90**, 1926.

⁹ R. C. Blume, *Tetrahedron Letters*, 1969, 1047.

¹⁰ U.S.P. 2,854,460 (*Chem. Abs.*, 1959, 5294).

¹¹ A. Loewenstein and J. D. Roberts, *J. Amer. Chem. Soc.*, 1960, **82**, 2705.

* M. A. Saint-Martino, M. Farines, and J. Soulier, *Compt. rend. (C)*, 1971, **272**, 1438, have recently reported that three new 2-trichloromethyl-1,3-dioxan-4-ones each show carbonyl absorptions in the range 1770—1780 cm^{-1} .

⁶ L. Edenleanu and Al. Zaharia, *Bull. Acad. Sci. Roumaine*, 1895, **4**, 14.

1,3-dioxolan-4-ones. The protons at C-5 and C-6 in (II; $R^1 = R^2 = \text{CCl}_3$, $R^3 = R^4 = R^5 = \text{H}$) constitute an ABX system with Δ_{AB} $[(\text{CD}_3)_2\text{CO}]$ 0.20 and p.p.m. The coupling constants ($J_{AB} - 16$, J_{AB} 10.7, J_{AX} 3 Hz) are consistent with the six-membered ring adopting a chair formation with the C-6 trichloromethyl group equatorial and with axial-axial (10.7 Hz) and axial-equatorial (5.3 Hz) coupling constants similar in value to those observed in the 1,3-dioxan series.¹² Similarly the value of 5.2 Hz for $J_{5,6}$ in (II; $R^1 = R^2 = \text{CCl}_3$, $R^3 = R^4 = \text{H}$, $R^5 = \text{Me}$) is consistent with the protons at C-5 and C-6 having a *cis*-(*ax-eq*) relationship in a chair-shaped six-membered ring, but we do not feel that a full stereochemical assignment is possible for either of these compounds on the basis of the information at present available.

It is of interest that the observed n.m.r. spectrum of 'citric acid chloralide' (I; $R^1 = \text{CCl}_3$, $R^2 = R^3 = \text{CH}_2\text{CO}_2\text{H}$) is qualitatively consistent with the alternative formulation (II; $R^1 = \text{CCl}_3$, $R^2 = \text{CH}_2\text{CO}_2\text{H}$, $R^3 = \text{CO}_2\text{H}$, $R^4 = R^5 = \text{H}$), since in that structure the side-chain methylene group might give rise to an AB system analogous to that seen with 'malic acid chloralide' and the methylene protons at C-5 would be expected to give a second AB system with a somewhat larger chemical shift difference, both in the τ 6-7 region, and the proton at C-2 would be expected to give a singlet near τ 4.

EXPERIMENTAL

N.m.r. spectra were measured with a Varian HA 100 instrument except for a few measured with Varian A60 or Perkin-Elmer R12 instruments. The integrations were in every case in agreement with the proton assignments. I.r. spectra were measured with a Unicam SP 100 instrument.

1,3-Dioxolan-4-ones.—5,5-Bis(carboxymethyl)-2-trichloromethyl-1,3-dioxolan-4-one^{1a} had m.p. 161–162° (lit.,^{1a} 161°; lit.,^{1a} 166°); ν_{max} 1810 and 1730 cm^{-1} (KBr); τ $[(\text{CD}_3)_2\text{CO}]$ 0.246 (s, CO_2H), 4.02 (s, 2-H), 6.31 and 6.75 ($J_{AB} - 18$ Hz), and 6.94 and 7.02 ($J_{AB} - 16$ Hz) (Found: C, 29.6; H, 2.5; Cl, 33.3. Calc. for $\text{C}_8\text{H}_7\text{Cl}_3\text{O}_7$: C, 29.9; H, 2.2; Cl, 33.1%). 5,5-Bis(methoxycarbonylmethyl)-2-trichloromethyl-1,3-dioxolan-4-one^{1b} had m.p. 72–73° (lit.,⁶ 73°); ν_{max} 1822 and 1740 cm^{-1} (KBr), 1818 and 1740 cm^{-1} (CHCl_3); τ (CDCl_3) 4.06 (s, 2-H), 6.25 (s) and 6.28 (s) ($2 \times \text{CO}_2\text{Me}$), 6.39 and 6.88 ($J_{AB} - 18.5$ Hz), and 6.97 and 7.12 ($J_{AB} - 15$ Hz). 5,5-Bis(ethoxycarbonylmethyl)-2-trichloromethyl-1,3-dioxolan-4-one^{1b} had b.p. 202° at 17 mmHg (lit.,^{1b} 215–225° at 33 mmHg); ν_{max} 1822 and 1736 cm^{-1} (film); τ (CCl_4) 4.1 (s, 2-H), 5.82 (q) and 5.85 (q) (J 7 Hz, $2 \times \text{CO}_2\text{CH}_2\text{CH}_3$), 6.42 and 6.93 ($J_{AB} - 18$ Hz), 7.06 and 7.23 ($J_{AB} - 15$ Hz), and 8.70 (t) and 8.72 (t) (J 7 Hz, $2 \times \text{CH}_2\text{CH}_3$). 5,5-Bis(carboxymethyl)-1,3-dioxolan-4-one^{1c} had m.p. 208° (lit.,¹³ 205°); ν_{max} 1804 and 1723 cm^{-1} (KBr); τ ($\text{C}_5\text{D}_5\text{N}$) —5.16 (s, CO_2H), 4.12 (s, 2-H), and 6.68 (s, $\text{CH}_2\text{CO}_2\text{H}$). 5,5-Bis(methoxycarbonylmethyl)-1,3-dioxolan-4-one² had m.p. 67–68° (lit.,² 69.5°); ν_{max} 1799 and 1742 cm^{-1} (KBr); τ (CDCl_3) 4.47 (s, 2-H), 6.31 (s, CO_2Me), and 7.09 (s, $\text{CH}_2\text{CO}_2\text{Me}$). 5,5-Bis(ethoxycarbonylmethyl)-1,3-dioxolan-4-

one¹⁴ had m.p. 50–51° (lit.,¹⁴ 54°); τ (CDCl_3) 4.48 (s, 2-H), C, (q, J 7 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 7.14 (s, CH_2CO_2), and 8.75 (t, J 7 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$). 5-Carboxymethyl-2-trichloromethyl-1,3-dioxolan-4-one¹⁵ had m.p. 176–177° (lit.,⁴ 176–177°); ν_{max} 1823 and 1710 cm^{-1} (KBr); τ (CDCl_3) 3.94 (d, $J_{2,5}$ 1.6 Hz, 2-H), 4.94 (dt, $J_{2,5}$ 1.6, $J_{H,\text{OH}}$ 4.0 Hz, 5-H), and 6.89 and 6.97 ($J_{AB} - 14.5$, J_{H,CH_2} 4.0 Hz, CH_2). 5-Methoxycarbonylmethyl-2-trichloromethyl-1,3-dioxolan-4-one was prepared *via* the acid chloride¹⁶ and also by direct esterification ($\text{MeOH}-\text{H}_2\text{SO}_4$) and had m.p. 72–73° (lit.,¹⁶ 72–73°); ν_{max} 1816 and 1733 cm^{-1} (KBr); 1823 and 1741 cm^{-1} (CHCl_3); τ ($\text{C}_5\text{D}_5\text{N}$) 3.75 (d, $J_{2,5}$ 1.5 Hz, 2-H), 4.91 (dt, $J_{2,5}$ 1.5, $J_{H,\text{OH}}$ 4.0 Hz, 5-H), 6.39 (s, CO_2Me), and 6.90 (d, J_{H,CH_2} 4.0 Hz, CH_2).

Reaction of Chloral with sym-Dimethyl Citrate.—*sym*-Dimethyl citrate,¹⁷ m.p. 118° (lit.,¹⁷ 125–126°; lit.,¹¹ 115–117°) (5.5 g) chloral (3.7 g, 1 mol. equiv.) and 36N-sulphuric acid (5 ml) were thoroughly mixed and kept at room temperature for 18 h. The mixture was then poured on ice and the crude product extracted with chloroform. The extract was washed with water, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Evaporation left a residue which slowly deposited crystals. Recrystallisation from light petroleum (b.p. 60–80°) gave 5,5-bis(methoxycarbonylmethyl)-2-trichloromethyl-1,3-dioxolan-4-one (2.4 g), m.p. and mixed m.p. 73°.

1,3-Dioxan-4-ones.—4,4,4-Trichloro-3-hydroxybutanoic acid¹⁸ (20.8 g), chloral hydrate (16.6 g, 1.0 mol. equiv.), and 36N-sulphuric acid (40 ml) were thoroughly mixed. After 18 h at room temperature the mixture was poured on ice and the crude product extracted with ether. The extract was washed with water, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4), and the ether was distilled off. Crystallisation of the residue from carbon tetrachloride gave crystals (1.35 g) which after further crystallisation from carbon tetrachloride and then light petroleum (b.p. 60–80°) gave 2,6-bistrichloromethyl-1,3-dioxan-4-one, m.p. 148–149° (sublimes at 100° and 10 mmHg); ν_{max} 1785 cm^{-1} (KBr and CHCl_3); τ (CDCl_3) 3.95 (s, 2-H), 5.11, 6.64, and 6.82 (ABX, $J_{AB} - 16$, J_{AX} 10.7, J_{BX} 5.3 Hz, 5-H₂ and 6-H); τ $[(\text{CD}_3)_2\text{CO}]$ 3.60, 4.76, 6.42, and 6.62 (Found: C, 21.6; H, 1.5; Cl, 63.0. $\text{C}_8\text{H}_4\text{Cl}_6\text{O}_3$ requires C, 21.4; H, 1.2; Cl, 63.2%).

α -2,6-Bistrichloromethyl-5-methyl-1,3-dioxan-4-one,¹⁰ m.p. 132–133° (lit.,¹⁰ 131–133°); ν_{max} 1750 cm^{-1} (KBr), 1774 cm^{-1} (CHCl_3); τ (CDCl_3) 4.30 (s, 2-H) 5.54 (d, $J_{5,6}$ 5.2 Hz, 6-H), 6.66 (dq, $J_{5,6}$ 5.2, $J_{H,\text{Me}}$ 7.6 Hz, 5-H), and 8.25 (d, $J_{H,\text{Me}}$ 7.6 Hz, Me), τ $[(\text{CD}_3)_2\text{CO}]$ 3.75, 5.15, 6.71, and 8.28 (Found: Cl, 60.4. Calc. for $\text{C}_7\text{H}_6\text{Cl}_6\text{O}_3$: Cl, 60.7%), was prepared by the action of polyphosphoric acid on 6,6-diethoxy-5-methyl-2,4-bistrichloromethyl-1,3-dioxan,¹⁹ m.p. 81–82° (lit.,¹⁹ 81–82°), τ (CDCl_3) 4.89 (s, 2-H), 5.71 (d, $J_{4,5}$ 9.5 Hz, 4-H), 5.95–6.60 (complex, $\text{O}\cdot\text{CH}_2\text{CH}_3$), 7.55 (dq, $J_{4,5}$ 9.5, $J_{H,\text{Me}}$ 7.0 Hz, 5-H), 8.78 (t, J 7.0 Hz, $\text{O}\cdot\text{CH}_2\text{CH}_3$), and 8.80 (d, J 7.0 Hz, >CHMe) (Found: C, 31.3; H, 3.7; Cl, 50.1. Calc. for $\text{C}_{11}\text{H}_{16}\text{Cl}_6\text{O}_4$: C, 31.3; H, 3.7; Cl, 50.2%).

We thank Mr. B. Day for preparing three of the compounds, and Dr. E. Bullock for his interest.

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¹⁶ E. Vinkler and E. Borsok, *Acta Phys. et Chem. Szeged.*, 1942, **1**, 70 (*Chem. Abs.*, 1948, **42**, 1192).

¹⁷ G. Schroeter and L. Schmitz, *Ber.*, 1902, **35**, 2085.

¹⁸ K. v. Auwers and H. Wissebach, *Ber.*, 1923, **56**, 731.

¹⁹ U.S.P. 3,000,904/1961 (*Chem. Abs.*, 1962, **56**, 1459).

¹² H. Booth, *Progr. N.M.R. Spectroscopy*, 1969, **5**, 359.

¹³ W. Sternberg, *Pharm. Ztg.*, 1901, **46**, 1004.

¹⁴ D. W. S. Evans, *J. Chem. Soc.*, 1959, 1313.

¹⁵ N. M. Shah and R. L. Alimchandani, *J. Indian Chem. Soc.*, 1934, **11**, 545 (*Chem. Abs.*, 1935, **29**, 122).