Synthesis of 3,7-Dimethyl-1,9-dioxo-1*H*,9*H*,10*H*-pyrano[3,2-*c*:5,6-*c*']-dipyran-10-ylacetic Acid and its Ethyl Ester

By **S. F. Tan** • and **T. H. Tjia**, Chemistry Department, University of Singapore, Singapore 10

3,7-Dimethyl-1,9-dioxo-1*H*,9*H*,10*H*-pyrano[3,2-*c*:5,6-*c*']dipyran-10-ylacetic acid (Ia) and its ethyl ester (Ib) have been synthesized by a double Michael addition of two molecules of triacetic acid lactone (4-hydroxy-6-methylpyran-2-one) to one of ethyl propiolate followed by intramolecular etherification. An intermediate Michael adduct, ethyl *trans*-β-(6-methyl-2,4-dioxopyran-3-yl)acrylate (II), was isolated from the reaction under milder conditions. The ^{1}H n.m.r. spectra of these products are discussed.

MICHAEL condensations of suitable nucleophiles with αβ-acetylenic esters have offered routes to a variety of heterocycles.[1-3] In some of these syntheses, successive Michael additions of one molecule of the nucleophile to two of the acetylenic compound have been reported.[4,5] A mechanism involving successive Michael additions of two molecules of nucleophile to one of acetylenic ester is now postulated for the synthesis of the pyranodipyran (Ia) and its ethyl ester (Ib), by the condensation of triacetic acid lactone with ethyl propiolate in the presence of Triton B as catalyst. Dehydroacetic acid [3-acetyl-6-methylpyran-2,4(3*H*)-dione] was isolated as a by-product.

That the major product (Ib) was the ethyl ester of compound (Ia) was demonstrated by their interconversion through esterification/hydrolysis. The acid (Ia) was previously isolated as one of the by-products from the condensation of triacetic acid lactone with malic acid in concentrated sulphuric acid but its structure was not then elucidated.[6] The identity of (Ia) with this compound was established by comparison of m.p.s and i.r. data, as well as by formation of an identical methyl ester (Ic)[6] from the acids prepared by the two different methods.

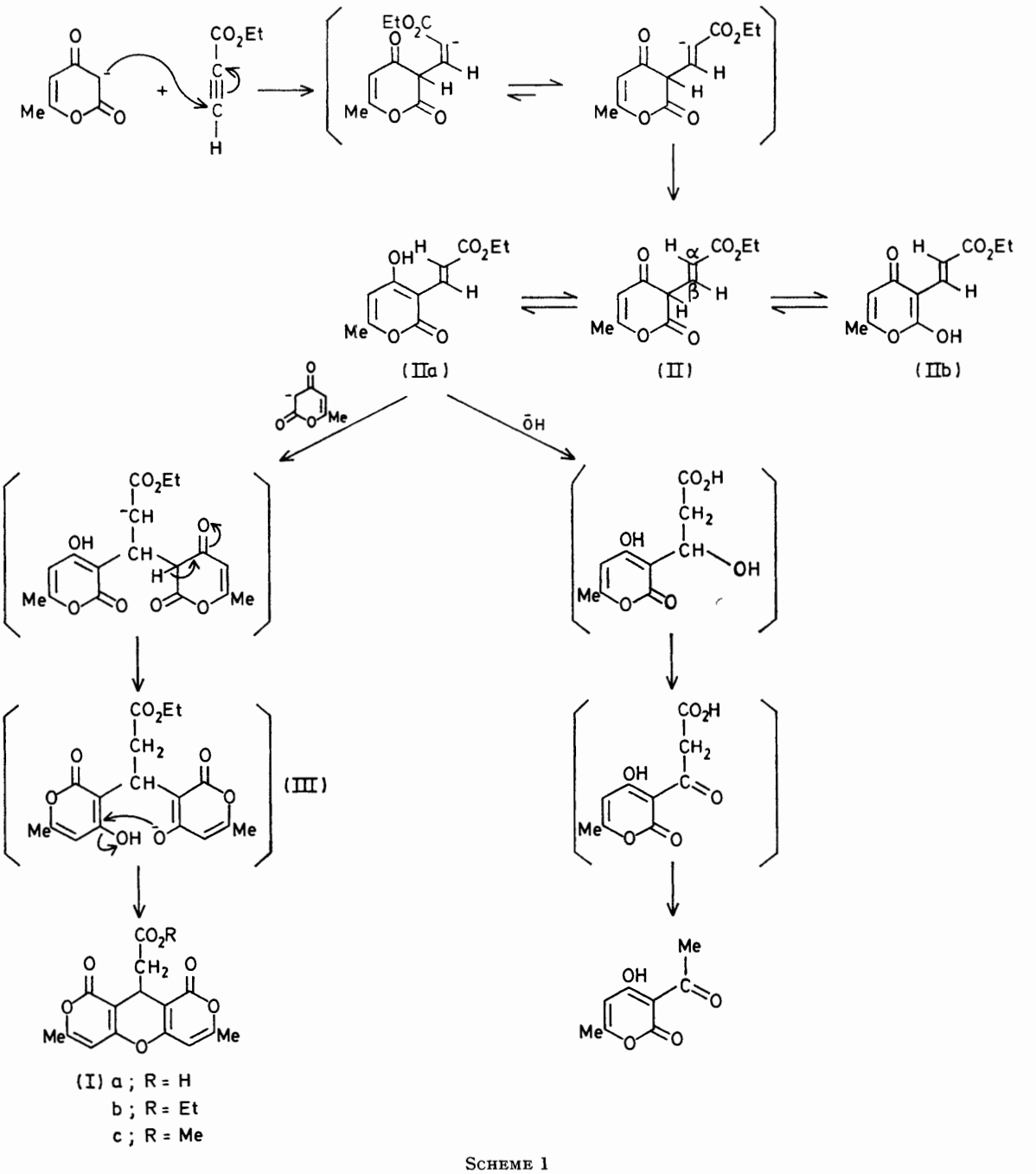
Compounds (Ia—c) are all insoluble in both dilute and concentrated hydrochloric acid, indicating the absence of a γ-pyrone ring in their structures.[7] Compound (Ia), but not (Ib) or (Ic), dissolves with effervescence in aqueous 10% sodium hydrogen carbonate, but all three are soluble in cold, aqueous 10% sodium hydroxide to give yellow solutions which, on acidification, precipitate the respective compounds unchanged. Their i.r. spectra

[1] E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, 1959, **10**, ch. 3.
[2] R. A. Raphael, 'Acetylenic Compounds in Organic Synthesis,' Butterworths, London, 1955, ch. 5.
[3] J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, 1964, **86**, 107.
[4] R. M. Acheson, *Adv. Heterocyclic Chem.*, 1963, **1**, 125.
[5] R. M. Acheson and A. O. Plunkett, *J. Chem. Soc.*, 1964, 2676.
[6] F. C. Cheng and S. F. Tan, *J. Chem. Soc.* (*C*), 1968, 543.
[7] G. G. Badcock, F. M. Dean, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1950, 903.

show similar =CH–, C=O, and C=C absorptions but that of (Ia) also shows a broad, weak band characteristic of the carboxylic OH group.

The ^{1}H n.m.r. spectrum of (Ia) in $CDCl_3$–CD_3OD confirms the symmetry of the structure. The 3- and 7-Me protons give a sharp singlet at δ 2.24(6 H) and H-4 and -6 give another singlet at δ 5.94(2 H); these compare well with the chemical shifts of Me-6 and H-5, respectively, of dehydroacetic acid.[8] The methylene and methine protons of the side-chain give rise respectively to a doublet at δ 3.02(2 H) and a triplet at 3.95(1 H) each with a coupling constant of 4 Hz. Owing to the relatively low solubility of (Ia) in the above solvent, its spectrum was also obtained in trifluoroacetic acid, which shows the corresponding signals at δ 2.41(6 H, s), 6.32(2 H, s), 3.30(2 H, d, *J* 4 Hz), and 4.28(1 H, t, *J* 4 Hz).

The spectrum of (Ic) in $CDCl_3$ contains signals at δ 2.23



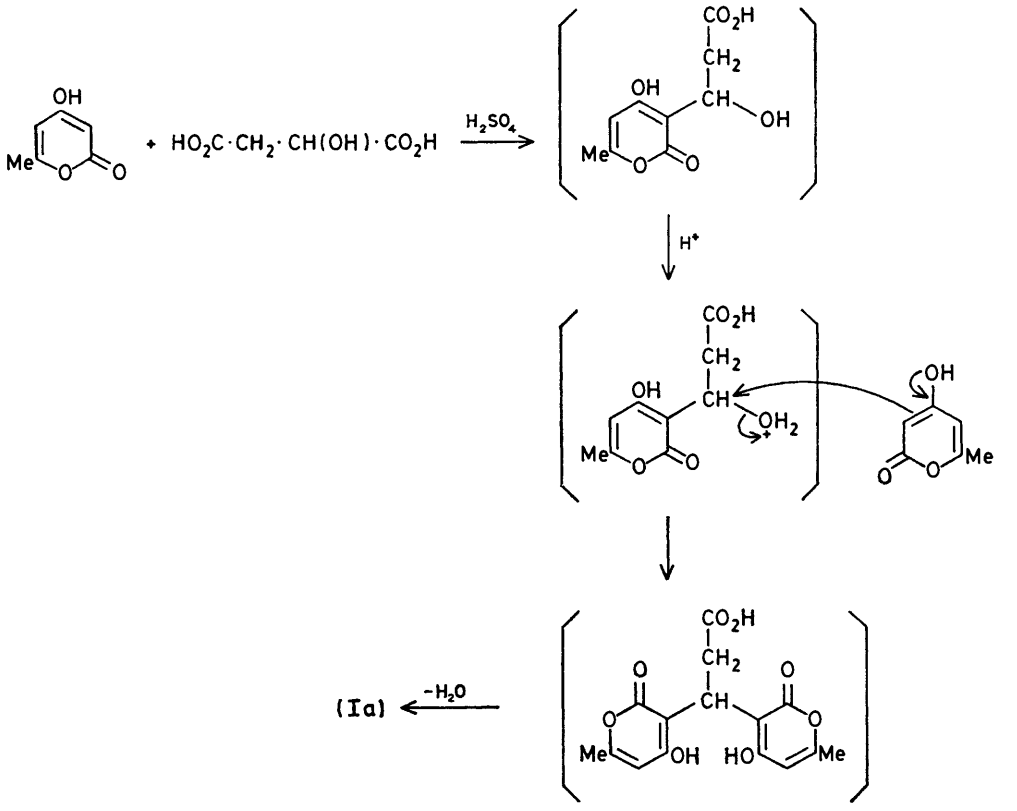
SCHEME 1

[8] N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, 'NMR Spectra Catalog,' Varian, Palo Alto, California, 1963, vol. 2, no. 504.

(6 H, s), 5.93(2 H, s), 3.05(2 H, d, J 3.5 Hz), and 3.95(1 H, t, J 3.5 Hz) corresponding to those of (Ia), and an additional singlet at δ3.51(3 H) (CO_2Me). The spectrum of (Ib) in $CDCl_3$ shows the expected peaks at δ 2.28(6 H, s), 5.95(2 H, s), and 3.09(2 H, d, J 5 Hz), but the triplet due to the methine proton, expected near δ 3.95, is obscured by a quartet at δ 4.00(3 H, q, J 7 Hz) ($CO_2{\cdot}CH_2Me$). The $CO_2{\cdot}CH_2{\cdot}CH_3$ signal is observed at δ 1.15(3 H, t, J 7 Hz).

Compound (Ib) is evidently formed by a double Michael addition of two molecules of triacetic acid lactone to one

The intermediate (II) was isolated from condensations carried out in benzene as solvent, together with smaller amounts of compounds (Ia and b), the yields of which increased at the expense of (II) on prolonged refluxing. When heated with triacetic acid lactone and a trace of Triton B, compound (II) was converted into a mixture of (Ib and a). Attempts to cyclize (II) to the previously synthesized 7-methylpyrano[4,3-*b*]pyran-2,5-dione [6] with polyphosphoric acid or by refluxing in diphenyl ether failed, suggesting that it probably had the *trans*-configuration shown which is unfavourable for cyclization.



SCHEME 2

of ethyl prepiolate through the intermediates ethyl *trans*-β-(6-methyl-2,4-dioxopyran-3-yl)acrylate (II) and (probably) ethyl 3,3-bis-(4-hydroxy-6-methyl-2-oxopyran-3-yl)propionate (III), although the latter has not been isolated. The intermediate (III) then cyclizes by intramolecular etherification as shown in Scheme 1.

Triton B was used in catalytic amount to promote the formation of the resonance-stabilized carbanion of triacetic acid lactone without causing extensive opening of the pyrone ring. Its presence probably also causes partial hydrolysis of the ester (Ib) to the acid (Ia) although the possibility of hydrolysis of the ester group at one of the intermediate stages prior to the intramolecular etherification cannot be excluded. Nucleophilic addition of hydroxide ion to the intermediate (II) followed by hydrolysis, oxidation, and decarboxylation could have led to the small amount of dehydroacetic acid isolated as by-product.

The structure and configuration of (II) were confirmed by its ^1H n.m.r. spectrum (in $CDCl_3$). The ethyl proton signals appear at δ 1.3(3 H, t, J 7.5 Hz) and 4.25(2 H, q, J 7.5 Hz) and that of the ring methyl protons at δ 2.3 (3 H, s). The two olefinic protons give doublets at δ 5.85 (1 H) and 7.7(1 H) (each J 12 Hz), consistent with the proposed *trans*-configuration. The latter doublet is assigned to the β-proton since it is deshielded by the electron-withdrawing pyrone ring as well as by conjugation with the ester group. The other doublet, which is therefore assigned to the α-proton, is not symmetrical, the branch on the higher field side being equivalent to 0.5 H and that on the lower field side slightly broadened and with intensity equivalent to 1.5 H. This indicates the superimposition of another signal at δ 5.92, which could be attributed to H-5 as the chemical shift is comparable to those of similarly situated protons in compounds (Ia—c). Compound (II) could in theory exist in two other

tautomeric forms (IIa and b). The remaining absorption in the spectrum at δ 5.65(1 H, d, *J* 2 Hz), is assigned H-3 of form (II), coupled with H-5 (in the *meta*-position), although the splitting of the latter signal is obscured through overlap with one branch of the doublet at δ 5.85. Moreover, when the solution of (II) in $CDCl_3$ was shaken with D_2O, its n.m.r. spectrum remained unchanged, showing the absence of exchangeable protons such as those in structures (IIa and b). Thus, at least in chloroform solution, compound (II) exists predominantly in the dioxo-form. In alcoholic solution, compound (II) gives a negative test with iron(III) chloride.

The structure of compound (Ia) having been established, its formation from triacetic acid lactone and malic acid [6] may now be rationalized as in Scheme 2.

EXPERIMENTAL

Triacetic acid lactone was prepared from dehydroacetic acid by reaction with concentrated sulphuric acid.[9] Commercial ethyl propiolate was redistilled (b.p. 119°) and Triton B was a 40% solution of *N*-benzyltrimethylammonium hydroxide in methanol.

I.r. spectra were recorded with a Perkin-Elmer 337 grating spectrophotometer, the u.v. spectrum was obtained with a Hitachi UV spectrophotometer, and ^1H n.m.r. spectra were obtained with a Perkin-Elmer R-12 spectrometer.

Condensation between Triacetic Acid Lactone with Ethyl Propiolate in the Presence of Triton B.—(a) *In the absence of added solvent.* A mixture of triacetic acid lactone (5 g), ethyl propiolate (5 ml), and Triton 6 (0.5 ml) was heated under reflux, with a calcium chloride guard-tube, on a steam-bath for 48 h. Chloroform (50 ml) was added to the cooled mixture. The chloroform layer (extract A) was washed with aqueous 5% sodium hydrogen carbonate (2 × 30 ml), aqueous 5% sodium carbonate (2 × 20 ml), and water, and dried. The sodium hydrogen carbonate washing was cooled, acidified with hydrochloric acid, and extracted with ethyl acetate (extract B). The sodium carbonate washing was similarly acidified and extracted with chloroform (extract C).

Extract A, when distilled to dryness, gave a yellowish residue which was recrystallized from methanol to yield *ethyl* 3,7-*dimethyl*-1,9-*dioxo*-1H,9H,10H-*pyrano*[3,2-c:5,6-c′]*dipyran*-10-*ylacetate* (Ib) (1.9 g), m.p. 216° (Found: C, 61.1; H, 5.1. $C_{17}H_{16}O_7$ requires C, 61.4; H, 4.8%), $\nu_{max.}$ (Nujol) 3 085 (aromatic C–H), 1 725, 1 705—1 685 (C=O of CO_2Et and pyrone), 1 650, 1 620, and 1 590 cm^{-1} (C=C).

Extract B, after drying, was distilled to dryness to give a pale yellow solid, which on recrystallization from ethyl acetate yielded the *acid* (Ia) (0.4 g), m.p. 273° (Found: C, 59.4; H, 4.3. $C_{15}H_{12}O_7$ requires C, 59.2; H, 4.0%), $\nu_{max.}$ (Nujol) 3 360—2 500br (OH of CO_2H), 3 090 (aromatic C–H), 1 725—1 690 (overlap of C=O of CO_2H and of pyrone), 1 650, 1 615, and 1 580 cm^{-1} (C=C).

Extract C, on removal of the chloroform, gave a sticky solid from which a small amount of dehydroacetic acid could be obtained by crystallization from benzene.

(b) *In benzene as solvent.* Triacetic acid lactone (5 g), ethyl propiolate (5 ml), and Triton B (0.5 ml) were dissolved in benzene (200 ml) and refluxed on a steam-bath for 20 h. The solution was then concentrated by distillation. On cooling, a pale yellow solid precipitated which, when recrystallized from ethyl acetate, gave *ethyl* β-(6-*methyl*-2,4-*dioxopyran*-3-*yl*)*acrylate* (II) (1.2 g), m.p. 88—89° (Found: C, 58.5; H, 5.7. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%), $\lambda_{max.}$ (EtOH) 292, 243, and 218 nm (log ε 3.82, 4.23, and 4.23); $\nu_{max.}$ (Nujol) 3 060 (H=CH–), 1 740—1 700 (overlap of C=O of CO_2Et and of pyrone), 1 660, 1 640, and 1 580 cm^{-1} (C=C); δ ($CDCl_3$) 1.3(3 H, t, *J* 7.5 Hz), 2.3(3 H, s), 4.25(2 H, q, *J* 7.5 Hz), 5.65(1 H, d, *J* 2 Hz), 5.85(1 H, d, *J* 12 Hz), 5.92(1 H, obscured), and 7.7(1 H, d, *J* 12 Hz).

A repeated condensation with a reflux time of 48 h yielded a mixture from which compounds (Ia) (0.2 g), (Ib) (1 g), and (II) (0.8 g) could be isolated.

Reaction of Compound (II) with Triacetic Acid Lactone.—A mixture of compound (II) (1 g), triacetic acid lactone (0.56 g), and a drop of Triton B was heated on a steam-bath for 20 h, cooled, diluted with chloroform, and extracted with aqueous 5% sodium hydrogen carbonate. The chloroform solution was washed with water, dried, and distilled to give compound (Ib) (0.5 g). The sodium hydrogen carbonate extract was then acidified and extracted with ethyl acetate to give compound (Ia) (0.1 g).

Esterification of the Acid (Ia).—(*a*) A solution of the acid (Ia) (1 g) in methanol (10 ml) containing a few drops of sulphuric acid was refluxed on a steam-bath for 1½ h. On removal of most of the methanol, *methyl* 3,7-*dimethyl*-1,9-*dioxo*-1H,9H,10H-*pyrano*[3,2-c:5,6-c′]*dipyran*-10-*ylacetate* (*Ic*) (0.9 g) was deposited; m.p. 232° (Found: C, 60.5; H, 4.7. $C_{16}H_{14}O_7$ requires C, 60.4; H, 4.4%); $\nu_{max.}$ (Nujol) 3 090 (aromatic C–H), 1 740, 1 710, 1 690 (C=O of CO_2Me and pyrone), 1 640, 1 610, 1 590, and 1 580 cm^{-1} (C=C).

(*b*) The esterification was repeated with ethanol instead of methanol. The product (1 g) had m.p. 216°, not depressed by admixture with compound (Ib). The identification was confirmed by comparison of i.r. spectra.

Hydrolysis of the Ester (Ib).—A solution of the ethyl ester (Ib) (0.2 g) in acetone (20 ml) and aqueous 5% sodium hydrogen carbonate (10 ml) was refluxed on a steam-bath for 5 h. Acidification of the cooled mixture with concentrated hydrochloric acid and evaporation of the acetone caused precipitation of a solid (0.12 g), m.p. 271—273°, identical (mixed m.p. and i.r. spectra) with compound (Ia).

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