Michael Condensation of 4-Hydroxy-6-methylpyran-2-one with Dimethyl Acetylenedicarboxylate

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Methyl 7-methyl-2,5-dioxo-2*H*,5*H*-pyrano[4,3-b]pyran-4-carboxylate (I) has been synthesised by a Michael condensation of triacetic acid lactone (4-hydroxy-6-methylpyran-2-one) with dimethyl acetylenedicarboxylate. By-products of this reaction were dimethyl (6-methyl-2,4-dioxopyran-3-yl)maleate (II), dimethyl αβ-bis-(4-hydroxy-6-methyl-2-oxopyran-3-yl)succinate (III), and dehydroacetic acid (3-acetyl-6-methylpyran-2,4-dione). The differences between the products of this reaction and those previously obtained from a parallel condensation of triacetic acid lactone with ethyl propiolate are discussed in relation to the mechanism of Michael addition and the structures of the two acetylenic esters.

THE Michael condensation of triacetic acid lactone with ethyl propiolate, in the presence of Triton B as catalyst, yielded 3,7-dimethyl-1,9-dioxo-1*H*,9*H*,10*H*-pyrano[3,2-*c*:5,6-*c*']dipyran-10-acetic acid and its ethyl ester.[1] When similar condensations were carried out with dimethyl acetylenedicarboxylate in place of ethyl propiolate, analogous tricyclic pyran derivatives were not formed. Instead, a bicyclic pyran derivative, methyl 7-methyl-2,5-dioxo-2*H*,5*H*-pyrano[4,3-*b*]pyran-4-carboxylate (I), was the main product. By-products from this reaction were dimethyl (6-methyl-2,4-dioxopyran-3-yl)maleate (II), dimethyl αβ-bis-(4-hydroxy-6-methyl-2-oxopyran-3-yl)succinate (III), and a small amount of dehydroacetic acid.

Compound (I) is probably formed by a Michael addition of the carbanion of triacetic acid lactone to dimethyl acetylenedicarboxylate, followed by cyclisation of the intermediate adduct (VI). This cyclisation could conceivably have occurred in either of two ways giving structure (I) or (Ia). On the other hand, the possibility that an enolate ion of triacetic acid lactone, rather than its carbanion, has added to the acetylenic ester, with subsequent cyclisation to structure (Ib) or (Ic) should also be considered. However, compound (I) is soluble in cold, dilute aqueous sodium hydroxide but insoluble in dilute or concentrated hydrochloric acid. Thus structures (Ia—c) are less probable, since each contains at least one γ-pyrone, and γ-pyrones are known to be soluble in hydrochloric acid.[2,3] Moreover, the u.v. spectrum is similar to those of 7-methyl and 4,7-dimethyl derivatives [4,5] of pyrano[4,3-*b*]pyran-2,5-dione.

Structure (I) was supported by its conversion into the known [4] 7-methylpyrano[4,3-*b*]pyran-2,5-dione. As pyrone rings are sensitive to alkali, the methoxycarbonyl group of (I) was hydrolysed with concentrated sulphuric acid,[6] leading to the acid (IV), which was decarboxylated with quinoline and copper powder.[7]

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[4] F. C. Cheng and S. F. Tan, *J. Chem. Soc.* (*C*), 1968, 543.
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[6] R. H. Wiley and N. R. Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 3534.
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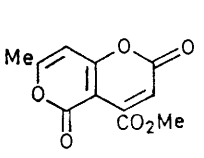
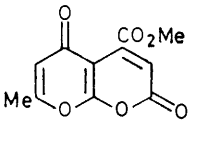
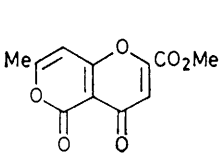
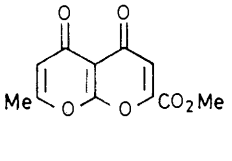
The ^{1}H n.m.r. spectrum of compound (I) in $CDCl_3$ shows three singlets, at δ 2.37 (3 H), 3.97 (3 H) and 6.22 (2 H), attributable respectively to Me-7, the CO_2Me group, and H-3 and H-8. A solution in $CDCl_3$–CD_3OD shows two singlets at δ 4.00 (3 H) and 6.35 (1 H), a doublet at δ 2.45 (3 H, *J* 0.8 Hz), and a quartet as δ 6.43 (1 H, *J* 0.8 Hz). Not only do the two ring protons now show different chemical shifts, but Me-7 and H-8 are shown to be involved in allylic coupling. Thus the signals at δ 6.35 and 6.43 can be separately assigned to H-3 and H-8, respectively.


(I)


(Ia)


(Ib)


(Ic)

Compound (II) is analogous to ethyl *trans*-β-(6-methyl-2,4-dioxopyran-3-yl)acrylate (IIa), obtained as a minor product in the triacetic acid lactone–ethyl propiolate condensation in the absence of solvent, but as the major product when the condensation was carried out in benzene.[1] Similarly, the yield of (II) from the present condensation also increased [at the expense of that of (I)] when methanol was used as solvent. Thus, compound (II), like (IIa), is probably a Michael adduct formed from equimolar quantities of reactants. Now, Michael additions to acetylenic compounds are known to give either *trans*- or *cis*-adducts, or both, depending on the structures of the reactants and on experimental conditions.[8–13] In this case, the *trans*-adduct (VI), though not isolated, is the probable intermediate which leads to the pyranopyrandione (I) by intramolecular cyclisation. Attempts to convert compound (II) into compound (I) by heating with polyphosphoric acid or in diphenyl ether were unsuccessful, suggesting that (II) is the *cis*-adduct. A lower reaction temperature, as with methanol as solvent, favours the isomerisation (VI) ⟶ (II); a higher reaction temperature, as attained in the absence of solvent, favours the cyclisation (VI) ⟶ (I).

One difference between the ethyl propiolate and the dimethyl acetylenedicarboxylate condensations may now be rationalised: namely the isolation of a pyranopyrandione from the latter but not from the former.[1] This could have been the result of the greater difference in stability between the *trans*- and the *cis*-Michael adducts formed in the former than between those formed in the latter condensation. From ethyl propiolate, the *trans*-Michael adduct has the unstable *cis*-configuration (VIa) and may be expected to isomerise readily to the much more stable isomer (IIa); such isomerisation could occur too rapidly for (VIa) to undergo cyclisation to give a pyranopyrandione in any significant yield. On the other hand, the adducts (VI) and (II) are of more comparable stabilities because of the presence of the additional ester group. In either adduct, two bulky substituent groups are present on the same side of the C=C bond. Thus, in this case, cyclisation of (VI) to a pyranopyrandione (I) can compete effectively with its isomerisation to (II).

The structure of compound (II) is supported by its ^{1}H n.m.r. spectrum ($CDCl_3$). The doublet at δ 2.27 (3 H, *J* 0.5 Hz) is given by Me-6. The two singlets at δ 3.76 (3 H) and 3.87 (3 H) are assigned to the methoxycarbonyl groups at C-8 and C-7, respectively, the latter being more deshielded by the pyrone ring. The doublet at δ 5.28 (1 H, *J* 2 Hz) and the multiplet centred at δ 6.0 (1 H) are assigned to H-3 and H-5, respectively. The remaining signal, a singlet at δ 6.77 (1 H), must be that of the side-chain olefinic proton, H-8, which is deshielded by the pyrone and the ester groups. The spectrum remained unchanged when D_2O was added, showing that compound (II) exists predominantly in the dioxo-form, at least in chloroform solution.

In the above spectrum, the protons H-3 and H-5 are involved in long-range ^4J coupling,[14,15] and H-5 is further involved in allylic coupling with Me-6. This complex ABX_3 spin system could be simplified by decoupling.[16] Irradiation with the frequency corresponding to X_3 (Me-6) simplified the AB region to an isolated AB pattern, the H-3 doublet remaining unchanged and the H-5 multiplet being simplified to a doublet with the same coupling constant (*J* 2 Hz). On the other hand, irradiation with the frequency corresponding to B (H-5) simplified both the A (H-3) and the X_3 (Me-6) doublets to singlets.

Compound (III) is insoluble in both dilute and concentrated hydrochloric acid. It is, however, soluble in cold concentrated sulphuric acid and trifluoroacetic acid but can be reprecipitated unchanged on dilution of these solutions with water.

The simplicity of the ^{1}H n.m.r. spectrum of (III) in trifluoroacetic acid, which consists of four singlets at δ 2.25, 3.90, 5.05, and 6.20 (3 : 3 : 1 : 1) is in accord with the symmetry of the proposed structure. These signals may be assigned to the two ring Me groups, the two

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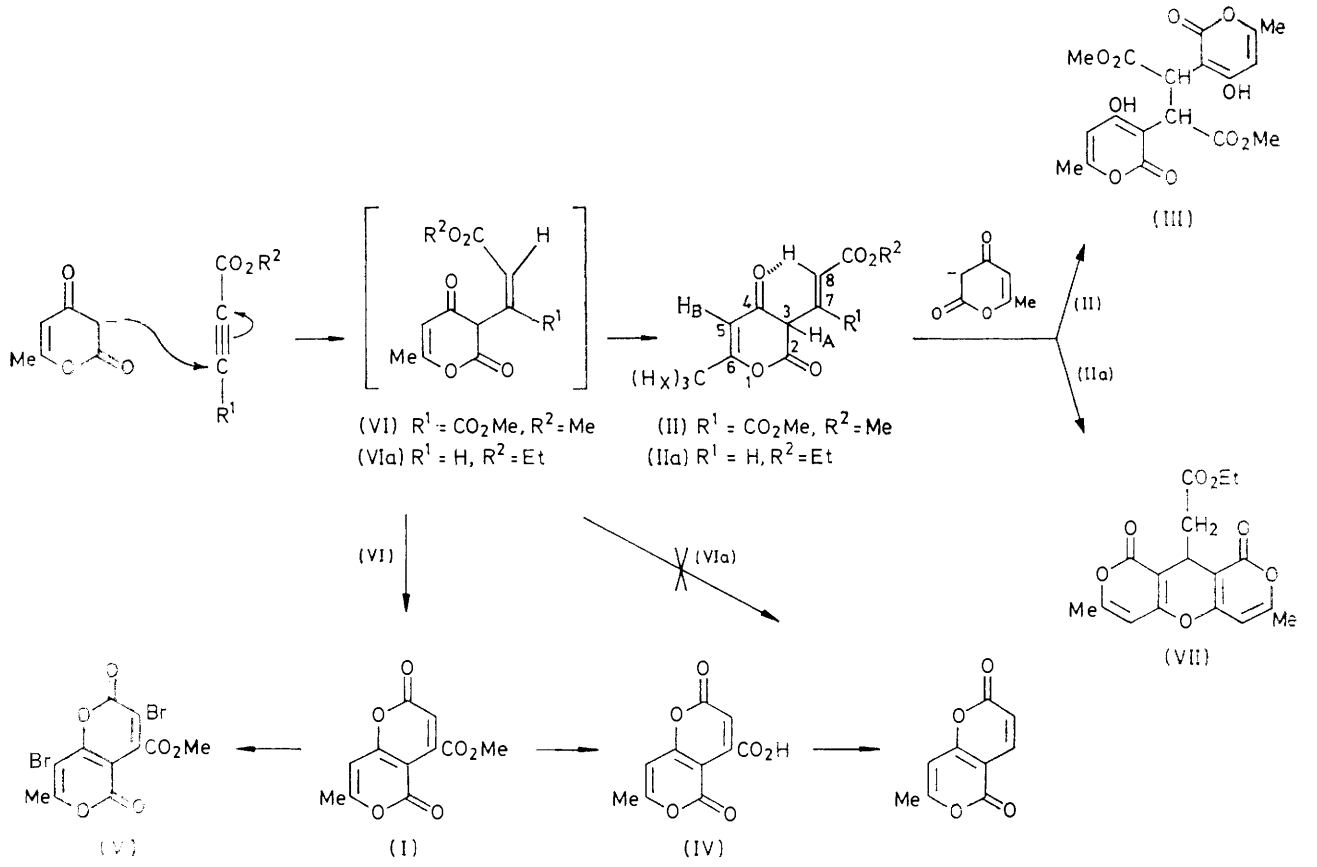
CO_2Me groups, the two methine protons, and the two ring protons, respectively. The OH signals are not observed owing to exchange with the solvent.

As demonstrated before,[1] double Michael additions of two molecules of a donor to one molecule of an acetylenic ester are possible. Compound (III) is evidently formed by such a process. However, its structure differs from that of the product (VII) of the corresponding double Michael addition of triacetic acid lactone to ethyl propiolate, as the result of a difference in the site of attachment of the second triacetic acid lactone molecule. The double bond in the side-chain of the intermediate adduct (IIa), formed from ethyl propiolate, is polarised mainly by the one ester group, which is more strongly electron-withdrawing than the pyrone ring. Therefore, the second addition takes place at C-7 in (IIa). On the other hand, the corresponding double bond in the adduct (II), formed from dimethyl acetylenedicarboxylate, is polarised in the opposite direction, since there are now two ester groups, and the pyrone ring reinforces the electron-withdrawing effect of that ester group at C-7. Hence the second triacetic acid lactone molecule now preferentially attacks the C-8, which incidentally is also less sterically crowded.

The formation of the small amount of dehydroacetic acid probably follows a pathway similar to that previously postulated for its formation from the ethyl propiolate condensation.[1]



EXPERIMENTAL

Triacetic acid lactone was prepared from dehydroacetic acid by treatment with concentrated sulphuric acid.[17] Commercial dimethyl acetylenedicarboxylate was redistilled (b.p. 198°) 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, u.v. spectra with a Hitachi UV spectrophotometer, and ^1H n.m.r. spectra with a Perkin-Elmer R12 instrument.

Condensations of Triacetic Acid Lactone with Dimethyl Acetylenedicarboxylate.—(a) *In the absence of added solvent.* A mixture of triacetic acid lactone (5 g), dimethyl acetylenedicarboxylate (5 ml), and Triton B (0.5 ml) was heated under reflux, with a calcium chloride guard-tube, on a steam-bath for 24 h. The cooled mixture was rubbed repeatedly with chloroform (3 × 20 ml); *dimethyl αβ-bis-(4-hydroxy-6-methyl-2-oxopyran-3-yl)succinate* (III) was left as an insoluble white residue (0.65 g). It was insoluble or sparingly soluble in most common organic solvent but could be recrystallised from glacial acetic acid or by continuous extraction with acetone; m.p. 265° (Found: C, 54.3; H, 4.7. $C_{18}H_{18}O_{10}$ requires C, 54.8; H, 4.6%), $\nu_{max.}$ (Nujol) 3 440—2 340br (hydrogen-bonded O–H), 1 750, 1 710—1 690 (C=O of α-pyrone and ester), 1 660, 1 630, 1 590, and 1 540 cm^{-1} (C=C).

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The combined chloroform extract was washed with aqueous 5% sodium carbonate (2 × 30 ml), then with water, dried, and finally distilled, yielding a yellow solid which, when recrystallised from ethyl acetate, gave crystals of *methyl 7-methyl-2,5-dioxo-2H,5H-pyrano*[4,3-b]*pyran-4-carboxylate* (I) (1.8 g), m.p. 181° (Found: C, 55.4, 55.4; H, 3.7, 3.6. $C_{11}H_8O_6$ requires C, 55.9; H, 3.4%), $\lambda_{max.}$ (EtOH) 325, 285, and 230 nm, $\nu_{max.}$ (Nujol) 3 060 (aromatic C–H), 1 770, 1 750, 1 730 (C=O of α-pyrone and of ester), 1 650, 1 610, and 1 550 cm^{-1} (C=C). Dimethyl (6-methyl-2,4-dioxopyran-3-yl)maleate (II) (0.05 g) was recovered from the mother liquor.

The sodium carbonate washings were acidified and extracted, first with ethyl acetate (2 × 20 ml) and then with chloroform (2 × 30 ml). The ethyl acetate extract, on distillation, gave a sticky residue from which dehydroacetic acid (0.2 g) was obtained by recrystallisation from benzene. From the chloroform extract, more of compound (III) (0.1 g) was recovered.

(b) *In methanol as solvent.* Triacetic acid lactone (5 g), dimethyl acetylenedicarboxylate (5 ml), and Triton B (0.5 ml) were dissolved in methanol (20 ml) and refluxed on a steam-bath for 24 h. The mixture, when concentrated by distillation and allowed to cool, deposited crystals of *dimethyl (6-methyl-2,4-dioxopyran-3-yl)maleate* (II), which could be further recrystallised from ethyl acetate; yield 1.2 g, m.p. 118° (Found: C, 53.4, 53.7; H, 4.4, 4.5. $C_{12}H_{12}O_7$ requires C, 53.7; H, 4.5%), $\lambda_{max.}$ (EtOH) 283 (log ε 3.72) and 218 nm (4.11), $\nu_{max.}$ (Nujol) 3 040 (aromatic C–H), 1 750, 1 730 (C=O of α-pyrone and ester), 1 650, 1 630, and 1 585 cm^{-1} (C=C). Compound (I) (0.05 g) was isolated from the mother liquor.

By prolonging the reaction to 48 h, the yield of compound (II) was increased to 2.6 g but there was no marked increase in the yield of (I).

Bromination of Compound (I).—A solution of bromine (0.5 ml) in glacial acetic acid (2 ml) was added to a solution of compound (I) (100 mg) in the same solvent (2 ml). After 4 h heating on a steam-bath, the mixture was allowed to cool and poured into crushed ice. The cloudy suspension was extracted with chloroform, and the residue obtained by distillation of the chloroform extract was recrystallised from ethyl acetate, yielding pale yellow crystals of *methyl 3,8-dibromo-7-methyl-2,5-dioxopyrano*[4,3-b]*pyran-4-carboxylate* (V) (55 mg), m.p. 188—190° (Found: C, 33.3; H, 1.6; Br, 42.1. $C_{11}H_6Br_2O_6$ requires C, 33.5; H, 1.5; Br, 40.6%), $\nu_{max.}$ (Nujol) 1 765, 1 745, 1 725 (C=O of α-pyrone and ester), 1 600, 1 580, and 1 528 cm^{-1} (C=C) [the absence of absorption in the region 3 060 cm^{-1} was in agreement with the replacement of the ring protons in compound (I) by bromine atoms].

Hydrolysis of Compound (I).—A solution of compound (I) (1 g) in concentrated sulphuric acid was warmed on a steam-bath for 5 h and then left at room temperature for 24 h. Pouring into crushed ice gave a precipitate, which could be recrystallised from ethyl acetate to give *7-methyl-2,5-dioxopyrano*[4,3-b]*pyran-4-carboxylic acid* (IV) (0.6 g), m.p. 263—265° (Found: C, 54.3, 54.1; H, 2.7, 2.8. $C_{10}H_6O_6$ requires C, 54.1; H, 2.7%), $\nu_{max.}$ (Nujol) 3 300—3 100 (OH of CO_2H), 1 760 (C=O of α-pyrone), 1 705 (C=O of CO_2H), 1 624, 1 598, and 1 540 cm^{-1} (C=C).

The hydrolysis could also be carried out by refluxing a solution of compound (I) in acetone with 5N-hydrochloric acid. However, the yield of (IV) was low and some unchanged (I) was recovered.

Decarboxylation of Compound (IV).—To a solution of compound (IV) (200 mg) in redistilled quinoline (4 ml), copper powder (100 mg) was added. After being refluxed gently for 2 h the mixture was cooled and poured gradually into ice-cold 5N-hydrochloric acid (100 ml). The mixture was then extracted with chloroform; the extract, when washed with water, dried and distilled, gave a solid product. Recrystallisation from benzene–light petroleum yielded crystals (50 mg), m.p. 182°, of 7-methylpyrano[4,3-*b*]pyran-2,5-dione, identical (mixed m.p. and i.r. spectra) with an authentic sample.

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