Reactions of the Sodium Salts of Some Heterocyclic β-Ketoesters with Dimethyl Acetylenedicarboxylate

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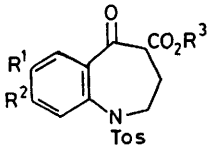
The sodium salts of several 1,2,3,4-tetrahydro-4-methoxycarbonyl-1-benzazepin-5-ones were treated with dimethyl acetylenedicarboxylate to give 1,2,3,6-tetrahydro-1-tosyl(and methyl)-4,5,6-trismethoxycarbonyl-1-benzazonin-5-ones. The sodium salt of 3-methoxycarbonylindol-3-one, on similar treatment, gave a red adduct which was converted by silica into a lactone whose structure was elucidated by *X*-ray crystallography. When the same sequence was applied to 3-methoxycarbonyl-γ-butyrolactone, the Michael adduct was obtained in good yield but other *N*-alkyl and *N*-aryl β-ketoesters from tetrahydroquinol-4-one, pyrrolidin-2-one, and piperidin-4-one gave intractable mixtures.

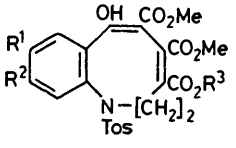
In the accompanying paper [1] we described the successful application of a novel ring-expansion involving reaction of the sodium salts of carbocyclic β-ketoesters with acetylenic esters. Here we report attempts to extend this method to heterocyclic β-ketoesters.

RESULTS AND DISCUSSION

β-Ketoesters in the tetrahydro-1-benzazepine (*e.g.* 1; $R^1 = R^2 = H$) series are readily available by Dieckmann cyclisation [2] of the appropriate diesters, and it was in this case (1; $R^1 = R^2 = H$, $R^3 = Et$) that reaction of the anion was first held [2] to give a ring-expanded product. Confirmation of this belief was established by treating the anion from (1; $R^1 = H$, $R^2 = Cl$, $R^3 = Me$) with dimethyl acetylenedicarboxylate (DMAD) and isolating a product (2; $R^1 = H$, $R^2 = H$, $R^2 = Cl$, $R^3 = Me$) whose n.m.r. spectrum included a low-field (δ 12.5) exchangeable proton indicative of an enolic system. The *X*-ray data on this substance, which confirms the benzazonine formulation, has been published separately.[3] In a similar fashion the dimethoxy-analogue [4] gave compound (2; $R^1 = R^2 = OMe$, $R^3 = Et$) in 70% yield.



(1)



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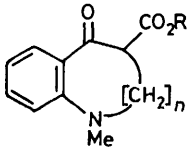


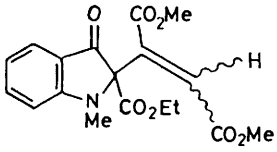
(3)

Turning to heterocycles containing basic nitrogen atoms, it was found that the anion from the β-ketoester (3; $n = 2$, R = Me) reacted with dimethyl acetylenedicarboxylate quite rapidly at 20 °C, giving several products. With some difficulty a crystalline adduct (30%) was isolated and deduced to be the benzazonine (2; $R^1 = R^2 = H$, $R^3 = Me$, Me instead of Tos), particularly since it has an exchangeable proton at δ 12.85 in the n.m.r. spectrum. A small amount of red oil was also isolated and tentatively identified as the 'Michael' adduct: although it was not obtained analytically pure, there was an n.m.r. resonance at δ 5.22 attributable to a vinyl proton as in other similar cases.[5] The homologous ketoester (3; $n = 1$, R = Me) was also obtained by Dieckmann reaction but although its anion reacted with DMAD, many products were detected and none obtained pure.

The indolone ester (3; $n = 0$, R = Et) was obtained in one step from methyl *N*-methylanthranilate and ethyl bromoacetate; the anion of the ketoester (3; $n = 0$, R = Et) reacted with DMAD at −10 °C to 0 °C yielding a gummy adduct $C_{18}H_{19}NO_7$ (4) as an inseparable mixture of *cis*- and *trans*-isomers. [Formulation of this adduct as (4) rather than as (7a), is preferred since its n.m.r. spectrum contains no exchangeable proton signals, and acidic treatments failed to convert it to the lactone (6).] However, at 5—10 °C, the reaction took a different course. The primary product was a red crystalline substance, $C_{18}H_{19}NO_7$, whose n.m.r. spectrum contained a resonance at δ 5.58 suggestive of structures (4) or (5) involving Michael addition; however, it was found that the peak at δ 5.58 was slowly exchangeable with D_2O. In an attempt to purify a substantial quantity of this red compound, chromatography on silica was discovered to convert it into yellow crystals, $C_{17}H_{15}NO_6$, apparently the result of loss of methanol. ^{13}C N.m.r. spectroscopy indicated that the red compound included a ketone carbonyl group whereas the yellow artefact did not; this latter evidence precluded a silica-induced Friedel–Crafts type of cyclisation [*e.g.* from (5)] which seemed plausible.

An *X*-ray analysis of the yellow crystalline compound (see Experimental section) identified it as the lactone (6). Although the red crystals were not suitable for *X*-ray analysis, it would appear from the foregoing that the structure might be (7a) or (7b). We favour the latter formulation both because of the similarity of the colour to that of isatin, and because formulation (7b) allows of

ready cyclisation to the lactone (6). There are precedents for the preferential protic attack on a methyl rather than an ethyl ester. Thus, in the following scheme, we



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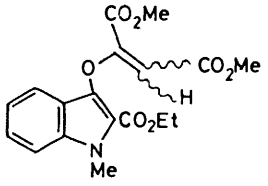

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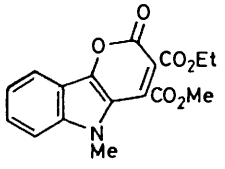
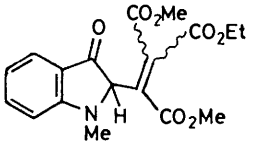
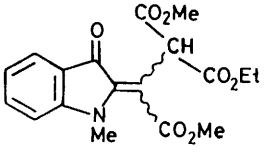


(6)



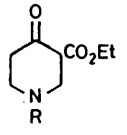
(7a)



(7b)

visualise a series of steps leading from (3; $n = 0$, R = Et) to (7b) which have precedent in work on the 'abnormal' Michael reaction [6] (8)→(9)→(7b).

What has already [1] been said about suppression of the ring-expansion mode by a strategically placed electron-donating group (OMe) is reinforced by the present study:



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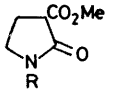

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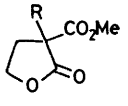

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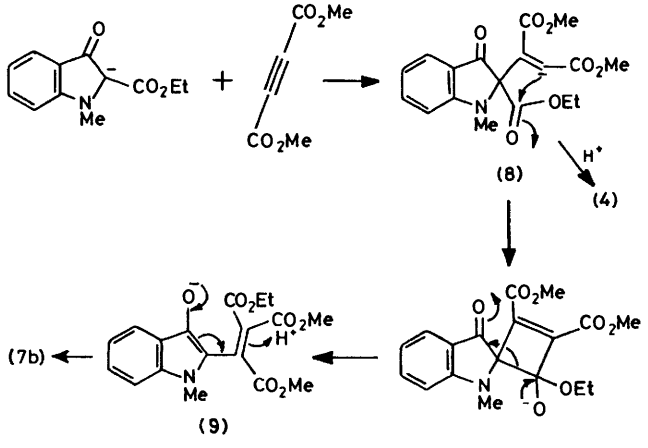


SCHEME

thus the aryl carbonyl group in (8) is of low electrophilic activity due to conjugation with the nitrogen atom, so that cyclisation to the cyclobutene required for ring-expansion is inhibited. It seemed appropriate to study heterocyclic β-ketoesters in which the nitrogen atom was either acylated or removed from the proximity of the reaction site. Accordingly the ketoesters [(10; R = $PhCH_3$ or PhCO) and (11; R = Me or *m*-MeOPh)] were studied but in every case their anions reacted with DMAD to yield intractable mixtures.

On the other hand, the salt of oxa-analogue (12; R = H) reacted cleanly with DMAD yielding the Michael adduct (12; R = CO_2Me–C=$CHCO_2Me$) exclusively (*cis*- and *trans*-isomers) in 70% yield. We conclude from these studies that, where available, *N*-tosyl β-ketoesters would be expected to undergo ring-expansion provided they are not able to undergo tosyl elimination reactions.[7] It would appear that either use of other protecting groups or utilisation of free bases will be of only limited application.

EXPERIMENTAL

10-Chloro-2,3-dihydro-4,5,6-trismethoxycarbonyl-7-hydroxy-1-p-tolylsulphonyl-1H-1-benzazonine (2; R^1 = H, R^2 = Cl, R^3 = Me).[3]—The ketoester (1; R^1 = H, R^2 = Cl, R^3 = Me or Et) (3 g) [8] was refluxed with methanol (60 ml) and sodium methoxide [from sodium (0.25 g)] for 2 h. After removal of solvent *in vacuo* and addition of toluene (60 ml), dimethyl acetylenedicarboxylate (1.5 g) in toluene (20 ml) was added dropwise with stirring. Next day work-up gave the product (2.4 g) as *colourless needles*, m.p. 152—153 °C (from methanol) (Found: C, 54.45; H, 4.3; N, 2.55%; M^+, 551.083 9, 549.084 2. $C_{25}H_{24}ClNO_9S$ requires C, 54.7; H, 4.4; N, 2.55% *M*, 551.083 1, 549.086 0); δ 12.85 (1 H, s, exchangeable, OH), 7.2—7.3 (6 H, m, aryl), 6.77 (1 H, d, *J* 2 Hz, 11-H), 3.78 (3 H, s, OMe), 3.6 (6 H, s, OMe), 2.5—3.25 (m, 4 H, 2- and 3-H), and 2.43 (3 H, s, Me); $\nu_{max.}$ (Nujol) 1 725 cm^{-1} (ester). Traces of the ethyl ester (2; R^1 = H, R^2 = Cl, R^3 = Et) were detected by mass spectroscopy (M^+, 565.098 3, 563 102 0. $C_{26}H_{26}ClNO_9S$ requires *M*, 565.098 7, 563,101 7) and n.m.r. (triplet at δ 1.1).

1,2,3,4-Tetrahydro-1-methyl-4-methoxycarbonylbenazazepin-5-one (3; n = 2, R = Me).[5]—The necessary diester [5] (30 g: prepared from methyl *N*-methylanthranilate and methyl γ-bromobutyrate), sodium hydride (9.5 g 50%), methanol (2 ml), and toluene (500 ml) were stirred and heated to 90 °C for 18 h. The usual work-up gave the product (22 g) which crystallised from light petroleum (b.p. 60—80 °C), m.p. 100 °C (Found: C, 67.2; H, 6.65; N, 6.0. $C_{13}H_{15}NO_3$ requires C, 67.3; H, 6.65; N, 5.9%); $\nu_{max.}$ (Nujol) 1 730 cm^{-1} (ester); δ 7.66 (1 H, dd, *J* 10 and 2 Hz, 6-H), 6.6—7.3, (3 H, m, aryl), 3.7—4.0 (1 H, m, 4-H), 3.6 (3 H, s, NMe), 3.1—3.4 (2 H, m, CH_2), 7.0 (3 H, s, OMe), and 2.35—2.6 (2 H, m, CH_2). No exchange with D_2O was detectable.

4-Ethoxycarbonyl-7-hydroxy-9,10-dimethoxy-5,6-bis-methoxycarbonyl-2,3-dihydro-1-p-tolylsulphonyl-1H-1-benzazonine (2; R^1 = R^2 = OMe, R^3 = Et).—Sodium hydride (100%; 0.32 g, 0.013 mol) was placed in anhydrous toluene (50 cm^3) under nitrogen and to this stirred suspension was added the ketoester (1; R^1 = R^2 = OMe, R^3 = Et) (5.9 g, 0.01 mol) [4] dropwise during 1 h. The mixture was heated to 70 °C for 18 h and the sodium salt then cooled to 0—5 °C.

Dimethyl acetylenedicarboxylate (1.56 g, 0.011 mol) was added during 1 h and the reaction mixture heated at 90 °C for 24 h, and then cooled in ice. An excess of methanol was added followed by an excess of 2M hydrochloric acid, and the layers separated. The aqueous layer was washed with toluene (50 cm^3) and the combined organic phase washed with water (30 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to leave a gum which crystallised to give the *product* (5.1 g, 70%), m.p. (ethanol) 169—170.5 °C (Found: C, 56.6; H, 5.65; N, 2.5%; M^+, 589.159 0. $C_{28}H_{31}NSO_{11}$ requires C, 57.1; H, 5.3; N, 2.4%; *M*, 589.161 8); δ 12.82 (1 H, s, OH), 7.60—7.20 (4 H, m, aromatic), 6.64 (1 H, s, aromatic), 6.11 (1 H, m, aromatic), 4.30—3.60 (4 H, m, CH_2 plus CH_2Me), 3.75 (6 H, 2 × s, OMe), 3.50 (6 H, S × s, OMe), 2.80—2.50 (2 H, m, CH_2), 2.40 (3 H, s, Me), and 1.04 3 H, t, CH_2Me); $\nu_{max.}$ (Nujol) 3 600—2 500 (OH, chelated), 1 720 (C=O, ester), and 1 640 cm^{-1} (H-bonded C=O).

2,3-*Dihydro*-7-*hydroxy*-1-*methyl*-4,5,6-*trismethoxycarbonyl*-1H-1-*benzazonine* (2; $R^1 = R^2 = H$, R^3 = Me, Me *instead of* Tos).—To sodium hydride (100%; 0.4 g, 0.017 mol) in anhydrous toluene (50 cm^3) under nitrogen, was added 1,2,3,4-tetrahydro-4-methoxycarbonyl-1-methylbenzazepin-5-one (3.2 g, 0.014 mol) in anhydrous toluene (10 cm^3) over 0.5 h with constant stirring. After 1 h at room temperature, the resultant sodium salt was cooled to −78 °C in a solid CO_2–acetone bath and dimethyl acetylenedicarboxylate (2.5 g, 0.017 mol) was added dropwise during 0.5 h. Several hours at this temperature converted only a small quantity of the starting material into apparently one product (t.l.c.). The temperature was then increased to room temperature and the reaction mixture stirred for 1 h, when there appeared to be no remaining starting material. The red liquor was then cooled to 0—5 °C and glacial acetic acid (5 cm^3) slowly added, followed by ice–water–2M HCl (5 cm^3). The aqueous layer was separated and washed with toluene (3 × 25 cm^3) and the combined organic phase was washed with water (25 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to leave a bright-red gum. The latter failed to crystallise and t.l.c. indicated that along with a substantial quantity of polar material there was a major component with a minor impurity of similar R_F. A primary purification was achieved through column chromatography on silica [gradient elution, light petroleum (60—80 °C), benzene, and finally ethyl acetate] to give the product (1.5 g, 30%) as *yellow needles*, m.p. (methanol) 124—125 °C (Found: C, 60.3; H, 5.5; N, 3.5%; M^+, 375.131 2. $C_{19}H_{21}NO_7$ requires C, 60.7; H, 5.6; N, 3.7%; *M*, 375.131 8); δ 12.85 (1 H, s, OH), 7.20—6.50 (4 H, m, aromatic), 3.66 (3 H, s, OMe), 3.54 (3 H, s, OMe), 3.42 (3 H, s, OMe), 2.78 (3 H, s, Me), and 3.60—2.20 (4 H, m, CH_2); $\nu_{max.}$ (Nujol) 1 740 (C=O, ester), 1 710 (C=O), 1 650, 1 630 (C=O, H-bonded), and 1 610 cm^{-1} (C=C). A small quantity of a red oil was also isolated and tentatively identified as the Michael addition compound, due to its possession of a vinylic resonance at δ 5.22.

2,3-*Dihydro*-1-*methyl*-3-*methoxycarbonylquinolin*-4-*one* (3; *n* = 1, R = Me).[9]—Methyl 3-(*o*-methoxycarbonylanilino)-propionate (8 g, 0.033 mol), dimethyl sulphate (6 g, 0.047 mol), AnalaR acetone (20 cm^3), and roasted potassium carbonate (8 g) were stirred at reflux for 18 h. T.l.c. indicated the presence of a lower R_F spot but a considerable quantity of starting material remained. Dimethylformamide (20 cm^3) was added and the reaction mixture again raised to reflux, a further portion of dimethyl sulphate (6 g, 0.047 mol) was added and reflux continued for 18 h. T.l.c. indicated that the maroon reaction mixture contained one major product with no starting material remaining, and after cooling to room temperature and filtering off the potassium carbonate, methylene chloride (100 cm^3) was added. This was washed with water (3 × 20 cm^3) and dried (Na_2SO_4) before evaporating under reduced pressure to leave a gum (4 g), which was distilled *in vacuo* to give, after a slight forerun of methyl anthranilate, a yellow oil as the product, b.p. 160—200 °C at 0.4 mmHg. I.r. spectroscopy showed the disappearance of the NH stretch and, without further purification, the oil was used as distilled.

To sodium hydride (100%; 10 g, 0.4 mol) in anhydrous toluene (1 000 cm^3) under nitrogen was added the above diester (20 g, 0.08 mol) in anhydrous toluene (100 cm^3) along with a catalytic quantity of methanol during 0.5 h. A brilliant yellow precipitate formed immediately, and after 3 h at 40 °C t.l.c. indicated that all the starting material had been consumed. The reaction mixture was then cooled in ice, an excess of methanol added, and it was carefully acidified with 2M hydrochloric acid. The layers were separated and the organic layer washed with toluene (2 × 100 cm^3) and organic layer then washed once with water (100 cm^3), dried (Na_2SO_4), and the solvent evaporated under reduced pressure leaving a yellow residue, which solidified on cooling to leave the product (6 g, 30%) which recrystallised as *yellow needles*, m.p. (methanol) 76 °C (Found: C, 66.0; H, 6.2; N, 6.0. $C_{12}H_{13}NO_3$ requires C, 65.8; H, 6.0; N, 6.4%); δ 7.78—6.50 (4 H, m, aromatic), 3.90—3.40 [3 H, m, CH_2 plus CH (exchangeable)], 3.64 (3 H, s, OMe), and 2.92 (3 H, s, Me); $\nu_{max.}$ (Nujol) 3 500—2 300 (br OH), 1 730 (C=O, ester), 1 665 (C=O, H-bonded), and 1 600 cm^{-1} (C=C).

Reaction of 2,3-*Dihydro*-3-*methoxycarbonyl*-1-*methylquinolin*-4-*one* (3; *n* = 1, R = Me) *with Dimethyl Acetylenedicarboxylate*.—Sodium hydride (50% dispersion; 0.64 g, 0.013 mol) in anhydrous toluene (30 cm^3) was stirred under nitrogen and the title ketoester (2.19 g, 0.01 mol) was added dropwise during 0.5 h. Stirring was continued at room temperature for 1 h and the resultant sodium salt was then cooled to 0—5 °C. Dimethyl acetylenedicarboxylate (1.56 g, 0.011 mol) was run in during 0.5 h keeping the temperature below 10 °C and the reaction mixture then stirred at room temperature for 3 h. The red liquor was cooled to 0—5 °C and glacial acetic acid (5 cm^3) slowly added followed by ice–water–2M HCl (10 cm^3). The layers were separated and the aqueous phase washed with toluene (3 × 15 cm^3). The combined organic extracts were washed once with water (15 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to yield a dark red gum which was shown by t.l.c. to be a complex mixture, and no identifiable material could be isolated from this.

2-*Ethoxycarbonyl*-1,2-*dihydro*-1-*methylindol*-3-*one* (3; *n* = 0, R = Et).—Methyl *N*-methylanthranilate (35.0 g, 0.212 mol) was heated to 120 °C and ethyl bromoacetate (42.4 g, 0.253 mol) added in one portion followed by roasted anhydrous sodium carbonate (41 g, 0.386 mol). The mixture was heated at 160 °C for 24 h, when t.l.c. indicated that the green liquor contained no remaining starting material, cooled, and poured into an excess of water. Toluene (250 cm^3) was added and the organic layer separated, dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow-green gum (37 g), which was purified by chromatography on silica and by crystallisation from light petroleum (b.p. 60—80 °C) giving the product (25 g) as yellow needles, m.p. 73—75 °C (Found: C, 65.75; H, 5.85; N, 6.65. $C_{12}H_{13}NO_3$ requires C, 65.8; H, 6.0; N, 6.4%); $\nu_{max.}$ (Nujol)

3 300—3 380 (enolic OH), 1 740 (sh, ester), 1 685 (ketone), and 1 650 (bonded ester) cm^{-1}; δ 8.1—8.7 (1 H, br, exchangeable), 7.7 (1 H, d, *J* 10 Hz, 4-H), 6.7—7.5 (3 H, m, aryl), 4.4 (2 H, q, CH_2Me), 3.8 (3 H, s, NMe), and 1.4 (3 H, t, *Me*-CH_2).

Reaction of 2-*Ethoxycarbonyl*-1,2-*dihydro*-1-*methylindol*-3-*one* (3; *n* = 0, R = Et) *with Dimethyl Acetylenedicarboxylate.*—(a) *At* 5—10 °C. To sodium hydride (50% dispersion; 3.3 g, 0.068 mol) in anhydrous toluene (450 cm^3) under nitrogen, was added the title ketoester (7.05 g, 0.03 mol) dropwise during 0.5 h with continuous stirring. After being stirred for 1 h at room temperature, the resultant sodium salt was cooled to 0—5 °C and dimethyl acetylenedicarboxylate (6.0 g, 0.042 mol) added over 0.5 h with the temperature being kept below 10 °C. The previously yellow reaction mixture quickly assumed a dark green colour and at the end of 4 h stirring at this temperature, t.l.c. showed the starting material to have been consumed. Glacial acetic acid (25 cm^3) was run in followed by ice–water–2M HCl (50 cm^3) and the aqueous layer was then separated and washed with toluene (3 × 50 cm^3). The organic phase was washed with water (50 cm^3), dried (Na_2SO_4), and the solvent evaporated under reduced pressure to leave a red gum. This gum was shown to contain the usual polar materials and what appears to be a major product manifesting itself on t.l.c. as a vivid red spot. Attempted crystallisation produced only a small quantity of red crystals although these corresponded to the major product remaining in the filtrate. Purification was achieved by short-path pressure column chromatography on silica. Elution [ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1)] was commenced and a distinct red band was observed to separate. The column was then left for 16 h and on resumption, no red colour was present, appearing to have been replaced by a more diffuse yellow band. Continued elution resulted in the isolation of yellow crystals of (6) (6 g), m.p. (methanol) 113—115 °C (Found: C, 61.5; H, 4.6; N, 4.0%; M^+, 329.089 5. $C_{17}H_{15}NO_6$ requires C, 61.9; H, 4.6; N, 4.3%; *M*, 329.089 9); δ 7.60—6.90 (4 H, m, aromatic), 4.40—4.17 (2 H, q, CH_2), 3.96 (3 H, s, NMe), 3.54 (3 H, s, OMe), and 1.40—1.28 (3 H, t, Me); $\nu_{max.}$ (Nujol) 1 750 (C=O, lactone), 1 730 (C=O, ester), and 1 610 cm^{-1} (C=C); δ_C ($CDCl_3$, p.p.m. downfield from $SiMe_4$) 164.47 (s, C-9, -11, -15); 163.74 (s, C-9, -11, -15); 157.56 (s, C-2); 144.455 (s, C-8); 140.27 (s, C-17); 129.11 (d, C-6); 121.10 (d, C-5 or -4); 119.52 (d, C-4 or -5); 116.00 (s, C-7); 113.70 (s, C-10); 109.99 (d, C-3); 108.84 (s, C-14); 62.19 (t, C-12); 53.39 (q, C-16); 30.15 (q, C-1); 14.135 (q, C-13).

An *X*-ray analysis of this compound appears at the end of the Experimental section.

The red crystals were identified as (7b), m.p. (methanol) 105—108 °C (Found: C, 60.45; H, 5.4; N, 3.6%; M^+, 361.113 5. $C_{18}H_{19}NO_7$ requires C, 59.8; H, 5.3; N, 3.6%; *M*, 361.116 1); δ 7.50—6.40 [5 H, m, aromatic plus OH (exchangeable)], 4.28—4.01 (2 H, q, CH_2Me), 3.80 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.15 (3 H, s, Me), 1.35—1.19 (3 H, t, CH_2Me); $\nu_{max.}$ (Nujol) 3 600—2 500 (OH), 1 735, 1 720 (C=O, ester), 1 690 (C=O), and 1 590 cm^{-1} (C=C). δ_C ($CDCl_3$, p.p.m. downfield from $SiMe_4$) 188.74 (s, C-8); 168.54 (s, C-11, -14, or -16); 167.81 (s, C-11, -14, or -16); 167.025 (s, C-11, -14, or -16); 154.89 (s, C-2); 140.76 (s, C-10); 137.42 (d, C-4); 124.92 (d, C-6); 121.22 (d, C-5); 120.37 (d, C-7); 109.75 (d, C-3); 107.87 (s, C-13); 61.76 (t, C-17); 52.66 (q, C-12 or -15); 52.24 (q, C-15 or -12); 48.11 (s, C-9); 34.76 (q, C-18); 14.075 (q, C-1).

(b) *At* −10 *to* 0 °C. The reaction was repeated as in (a) except that the addition was made at −10 to 0 °C. The product was an oil (9.6 g) purified by short-path chromatography on silica (1% ethanol, toluene) to yield a gum showing two closely spaced yellow spots on t.l.c. These were the *cis*- and *trans*-isomers of the Michael adduct (4) (Found: C, 59.5; H, 5.3; N, 4.0%; M^+, 361.116 9. $C_{18}H_{19}NO_7$ requires C, 59.8; H, 5.3; N, 3.6%; *M*, 361.116 1); δ 6.5—7.5 (5 H, m, 4 aryl + 1 vinylic proton), 4.07 (2 H, 2 q, CH_2Me), 3.64 (3 H, s, NMe), 3.51 and 3.58 (3 H, 2 s, CO_2Me), 3.95 and 4.08 (3 H, 2 s, CO_2Me), and 1.15 (3 H, 2 t, CH_2Me).

Reaction of Methyl 1,2,3,4-*Tetrahydro*-4-*oxoquinoline*-3-*carboxylate* (3; *n* = 1, R = Me, H *instead of* Me) *with Dimethyl Acetylenedicarboxylate.*—Sodium hydride (100%; 0.2 g, 0.008 mol) was placed in anhydrous toluene (25 cm^3) under nitrogen. To this stirred suspension was added the title ketoester [9] (1.02 g, 0.005 mol) dropwise over 1 h. When the addition had been completed the mixture was stirred for 1 h at room temperature, and the sodium salt thus formed cooled to 0—5 °C. Dimethyl acetylenedicarboxylate (0.78 g, 0.005 5 mol) was run in over 1 h with the temperature being kept below 10 °C. Stirring at this temperature produced very little reaction and the mixture was permitted to attain room temperature overnight, whereupon t.l.c. indicated a complex mixture. Work-up of the red tar obtained failed to give any isolable product and repetition of this reaction varying the time and temperature parameters proved fruitless.

Reaction of 1-*Benzyl*-3-*ethoxycarbonylpiperidin*-4-*one* (10; R = CH_2Ph) *with Dimethyl Acetylenedicarboxylate.*[10]—To sodium hydride (100%; 1.08 g, 0.05 mol) in anhydrous toluene (100 cm^3) under nitrogen, was added the title ketoester [10] (5.96 g, 0.002 mol) over 0.5 h with constant stirring. The mixture was heated at 60 °C for 24 h, and the resultant sodium salt then cooled to 0—5 °C. Dimethyl acetylenedicarboxylate (3.12 g, 0.022 mol) was then added during 1 h, with the temperature of the reaction mixture being kept below 10 °C. The red liquor was allowed to attain room temperature at which it was stirred for a further 2 h. Glacial acetic acid (10 cm^3) was slowly added followed by ice–water–2M HCl (10 cm^3) and the pH adjusted until just acidic before separating the layers. The aqueous layer was now extracted with toluene (3 × 25 cm^3) and the organic phase washed once with water (50 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to leave a dark-red gum. This gum was shown by t.l.c. to contain at least four components in addition to the usual accompanying polar material. Attempted separation of these components by column chromatography led to the isolation of a small quantity of red oil which could not be fully purified (M^+, 403.163 7. $C_{21}H_{25}NO_7$ requires *M*, 403.163 1); δ 7.15—7.03 (6 H, m, aromatic plus vinylic) and 4.20—2.20 (10 H, br m, CH_2); $\nu_{max.}$ (film) 1 720 (C=O, ester), 1 650 (C=O, H-bonded), and 1 600 cm^{-1} (C=C).

2-*Methoxycarbonyl*-2-(1,2-*bismethoxycarbonylvinyl*)-1,4-*butyrolactone* [12; R = (*Z*)-C(CO_2Me)=CHCO_2Me].—To sodium hydride (50% dispersion; 1.92 g, 0.04 mol) in anhydrous toluene (250 cm^3) under nitrogen, was added 2-methoxycarbonyl-1,4-butyrolactone [11,12] (8.58 g, 0.03 mol) during 0.5 h with continuous stirring. When the addition of the ester had been completed, the mixture was stirred at room temperature for 1.5 h, and the resultant sodium salt thus obtained was cooled to 0—5 °C. Dimethyl acetylenedicarboxylate (4.69 g, 0.033 mol) was now added over 0.5 h with the temperature being kept below 10 °C. After

4 h at this temperature, t.l.c. showed the reaction had essentially gone to completion. Glacial acetic acid (50 cm^3) was slowly run in followed by ice–water–2M HCl (50 cm^3) and the layers separated. The aqueous layer was extracted with toluene (2 × 50 cm^3), washed with water (50 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to give a reddish tar which was subsequently distilled *in vacuo* to afford a yellow viscous oil as product (9 g, 70%), b.p. 190—200 °C at 0.35 mmHg (Found: C, 50.7; H, 5.1%; M^+, 286.069 3. $C_{12}H_{14}O_8$ requires C, 50.3; H, 5.0%; *M*, 206.068 9); δ 6.79 (0.33 H, s, vinylic), 6.30 (0.66 H, s, vinylic), 4.60—4.30 (4 H, m, CH_2), and 3.80—3.60 (9 H, m, OMe); $\nu_{max.}$ (film) 1 780 (C=O, lactone), 1 735 (C=O, ester), and 1 645 cm^{-1} (C=O, H-bonded).

Reaction of 1-*Methyl*-3-*methoxycarbonylpyrrolidin*-2-*one* (11; R = Me) *with Dimethyl Acetylenedicarboxylate.*—To sodium hydride (50% dispersion; 0.72 g, 0.015 mol) in anhydrous toluene (50 cm^3) under nitrogen, was added the title [12] compound (1.6 g, 0.01 mol) during 0.5 h with continuous stirring. The reaction mixture was stirred for 1 h at room temperature and the salt then cooled in ice before adding dimethyl acetylenedicarboxylate (1.7 g, 0.012 mol) dropwise during 0.5 h. The reaction liquor was stirred below 10°C for 2 h, when t.l.c. indicated no remaining starting material. Sufficient 2M hydrochloric acid was added to achieve neutrality and the aqueous layer then washed with toluene (2 × 10 cm^3). The organic layer was washed with water (10 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to leave a red gum, which comprised several components none of which could be isolated.

Reaction of 1-(m-*Methoxyphenyl*)-3-*methoxycarbonylpyrrolidin*-2-*one* (11; R = *m*-$MeOC_6H_4$) *with Dimethyl Acetylenedicarboxylate.*[13,14]—To sodium hydride (50% dispersion; 0.36 g, 0.007 5 mol) in anhydrous toluene (30 cm^3) under nitrogen, was added the title ketoester (1.25 g, 0.005 mol) during 0.5 h with continuous stirring. After stirring at room temperature for 1.5 h, the salt was cooled in ice and dimethyl acetylenedicarboxylate (0.85 g, 0.007 mol) was added over 0.5 h with the reaction temperature being kept below 10 °C. The red liquor was stirred at this temperature for 2 h and sufficient 2M hydrochloric acid added to achieve neutrality. The separated organic layer was washed with water (10 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to leave an intractable tar.

Reaction of 1-*Benzoyl*-3-*ethoxycarbonyl-piperidin*-4-*one* (10; R = PhCO) [14] *with Dimethyl Acetylenedicarboxylate.*—To sodium hydride (50% dispersion; 0.96 g, 0.02 mol) in anhydrous toluene (100 cm^3) under nitrogen, was added the title ketoester (5.0 g, 0.018 2 mol) [14] during 0.5 h with continuous stirring. When the addition had been completed, the mixture was stirred at room temperature for 16 h. The resultant sodium salt was cooled to 0—5 °C and dimethyl acetylenedicarboxylate (3.2 g, 0.023 mol) added during 0.5 h with the temperature being kept below 10 °C. After stirring for 4 h, glacial acetic acid (20 cm^3) was run in followed by ice–water–2N HCl (20 cm^3) and the layers separated. The aqueous layer was extracted with toluene (30 cm^3) and the organic phase washed once with water (25 cm^3). The solution was dried (Na_2SO_4) and evaporated under reduced pressure to leave a red gum from which nothing could be isolated.

TABLE 1

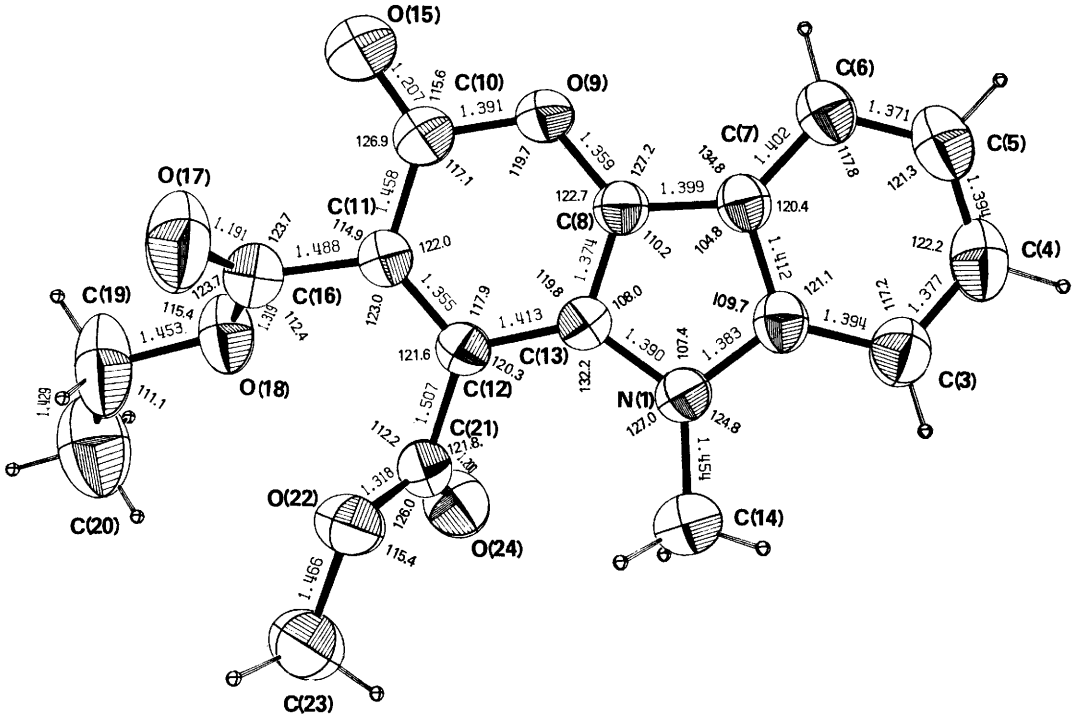
Hydrogen atom parameters (× 10^3). The absence of an estimated standard deviation indicates that the parameter was not refined

Atom	*x/a*	*y/b*	*z/c*	10^2U
H-3	206(3)	314(4)	28(2)	6
H-5	177(3)	792(4)	−75(2)	6
H-14	393(3)	204(4)	174(2)	6
H-14″	367(3)	156(4)	89(2)	6
H-19′	995	663	339	8
H-20′	873	360	389	10
H-23	741(3)	151(4)	326(2)	7
H-23″	831(3)	39(4)	271(2)	7
H-4	100(3)	493(4)	−52(2)	7
H-6	366(3)	888(4)	−20(2)	5
H-14′	495(3)	153(4)	137(2)	6
H-19	999	462	306	8
H-20	869	561	421	10
H-20″	999	451	427	10
H-23′	675(3)	26(4)	268(2)	7

TABLE 2

Parameters for non-hydrogen atoms (positional parameters × 10^4, thermal parameters × 10^3). The temperature factor used had the form $\exp(-2\pi^2\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*h_ih_j)$

Atom	*x/a*	*y/b*	*z/c*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N-1	4 272(2)	3 998(3)	1 067(1)	47	41	43	−8	5	1
C-2	3 486(3)	4 867(4)	561(1)	43	52	39	0	6	−3
C-3	2 366(3)	4 295(5)	211(2)	51	67	56	−12	6	−2
C-4	1 761(3)	5 449(6)	−269(2)	47	96	56	−3	−5	−6
C-5	2 240(3)	7 116(6)	−411(2)	60	85	48	13	−1	5
C-6	3 346(3)	7 693(5)	−75(1)	55	60	43	5	4	3
C-7	3 982(2)	6 551(4)	419(1)	43	46	35	1	6	−2
C-8	5 105(2)	6 636(4)	850(1)	44	39	39	−1	7	0
O-9	5 940(1)	7 987(2)	891(1)	53	38	52	−8	−3	6
C-10	7 063(3)	7 791(4)	1 306(1)	54	46	57	−8	0	1
C-11	7 206(2)	6 228(4)	1 759(1)	42	44	43	0	1	3
C-12	6 319(2)	4 960(4)	1 753(1)	40	39	38	3	10	3
C-13	5 272(2)	5 118(4)	1 250(1)	39	38	39	−2	9	0
C-14	4 156(3)	2 140(5)	1 266(2)	68	50	69	−15	2	8
O-15	7 800(2)	8 980(3)	1 270(1)	75	58	92	−28	−14	17
C-16	8 423(3)	6 084(5)	2 193(2)	47	57	60	−4	2	5
O-17	9 386(2)	6 094(4)	1 957(1)	45	150	78	−6	7	24
O-18	8 312(2)	5 848(3)	2 864(1)	45	97	47	9	−2	0
C-19	9 456(3)	5 494(7)	3 308(2)	48	175	69	8	−15	22
C-20	9 219(4)	4 788(7)	3 970(2)	84	169	75	37	−3	2
C-21	6 392(3)	3 491(4)	2 292(1)	42	47	45	1	2	4
O-22	7 340(2)	2 425(3)	2 246(1)	59	49	60	12	19	18
C-23	7 484(4)	975(6)	2 760(2)	69	67	83	18	18	32
O-24	5 648(2)	3 359(3)	2 704(1)	60	75	61	11	28	20



X-*Ray Results*

(Note that a separate numbering system applies for these data)

Crystallographic Data.—Monoclinic, $a = 10.906(1)$, $b = 7.498(1)$, $c = 19.200(1)$ Å, $\beta = 96.54(1)°$, $U = 1\,559.83$ Å^3, $Z = 4$, space group $P2_1/c$ (C_{2h}^5), $D_c = 1.402$, $D_m = 1.39$ g cm^{-3}. Cell dimensions were obtained by least-squares analysis using reflections measured at $+\theta$ on a diffractometer (Cu-K_α radiation, $\lambda = 1.541\,8$ Å).

Data Collection.—The crystal used was a bright yellow platelet, approximately 0.2 × 0.15 × 0.1 mm and mounted roughly parallel to the longest dimension. Intensities were measured with a computer-controlled diffractometer (Nonius CAD-4) using graphite-monochromatised Cu-K_α radiation. The maximum sin θ/λ was 0.617 Å^{-1} and there were 3 063 unique reflections, 1 550 of which had $I_o > 3\sigma(I_o)$; only those meeting this intensity criterion were used in the refinement. Lorentz and polarisation corrections were applied but not absorption corrections. There was no indication of significant radiation damage during data collection.

Structure Analysis.—The structure was solved using MULTAN.[15] Standard refinement techniques,[16] with weighting following Peterson and Levy[17] and scattering factors as given in X-RAY 72,[16] allowed recognition of all hydrogen atoms. The model was refined to an R of 0.047 (based on observed reflections) with isotropic thermal parameters for hydrogen atoms and anisotropic thermal parameters for all others. Thermal parameters for hydrogen atoms were not refined and were set to the isotropic values which had been obtained for the heavy atoms to which they were attached. In view of the large anisotropic thermal parameters of atoms 16 to 20, the positions of the hydrogen atoms attached to C(19) and C(20) were not refined.

The positions used were the results of a calculation, assuming a bond length of 1.00 Å, which was in good agreement with a difference map. The atomic parameters are given in Tables 1 and 2 and the bond lengths and angles are shown in the Figure.

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