Conversion of Benzopyrones into Spiro[benzopyran-2,2′-furan]s; a Route to 2-(1,3-Dioxoalkyl)benzopyrones

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The reaction of a 5-substituted 4-oxo-1-benzopyran-2-carbonyl chloride with diethyl ethoxymagnesiomalonate gave the required acylmalonate. However, the reaction of the acid chloride with the ethoxymagnesio-derivatives of ethyl acetoacetate and acetylacetone gave spiro[benzopyran-2,2′-furan] derivatives which were identified by n.m.r. and mass spectroscopy. Treatment of these spiro-compounds with either ethanol–concentrated hydrochloric acid or propionic acid–concentrated sulphuric acid gave benzopyrones having 1,3-dicarbonyl substituents at the 2-position.

THE pyrone ring of chromones is readily opened [1] by nucleophilic attack at C-2. We now report an intramolecular nucleophilic attack which resulted, not in this typical ring opening, but in the formation of a spirochromanone. These compounds were obtained during work on the synthesis of benzopyrones having a 1,3-dicarbonyl group at the 2-position. There is only one reported route to compounds of this type, involving acylation of enamine derivatives of cyclic ketones with 4-oxo-1-benzopyran-2-carbonyl chloride (1; R = H).[2] By use of similar reaction conditions, we obtained cyclic 1,3-diketone derivatives of benzopyrones. However, attempts to apply this route to open-chain 1,3-diketones and β-oxo-esters were unsuccessful, and other routes were therefore sought.

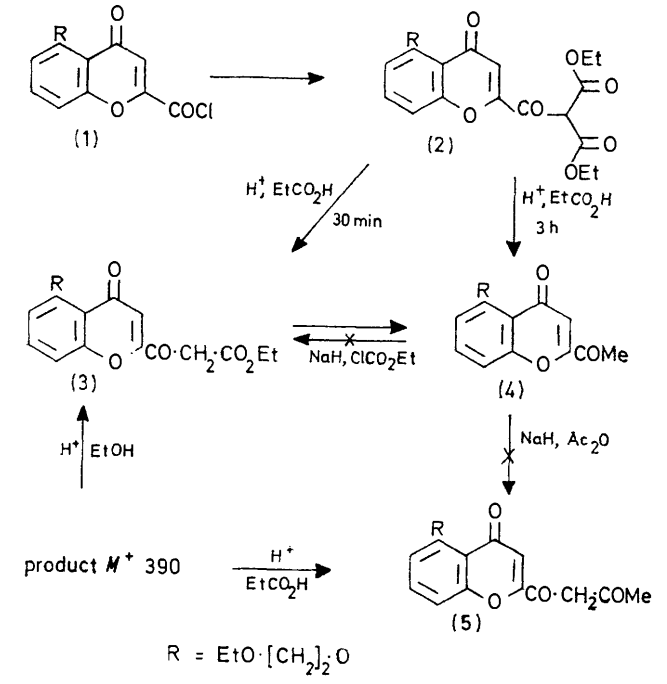
Our next approach to the 1,3-dicarbonyl compounds (3) and (5) (Scheme 1) was *via* the 2-acetylbenzopyrone (4). This was prepared by acylation of diethyl ethoxymagnesiomalonate with a substituted benzopyrone acid chloride; the product (2) was hydrolysed and decarboxylated. Unexpectedly, efforts to acylate and to ethoxycarbonylate this compound failed.

Attempts to mono-decarboxylate the diethyl acylmalonate (2) to give the β-oxo-ester (3) were generally unsuccessful. Usually the only product obtained was the acetylbenzopyrone (4), but in one experiment compound (3) was isolated in low yield. This observation, however, suggested that if a β-oxo-ester, rather than diethyl malonate, was initially treated with a benzopyrone acid chloride, then hydrolysis and decarboxylation of the product [*e.g.* (7)] would result in a benzopyrone 1,3-diketone [*e.g.* (5)]. Thus, treatment of ethyl ethoxymagnesioacetoacetate with the benzopyrone acid chloride (1; R = EtO·[CH_2]$_2$·O) gave, in good yield, a white solid having a molecular weight of 390, equal to that of the expected product (7) (Scheme 2). However, the n.m.r. spectrum of this compound did not show the

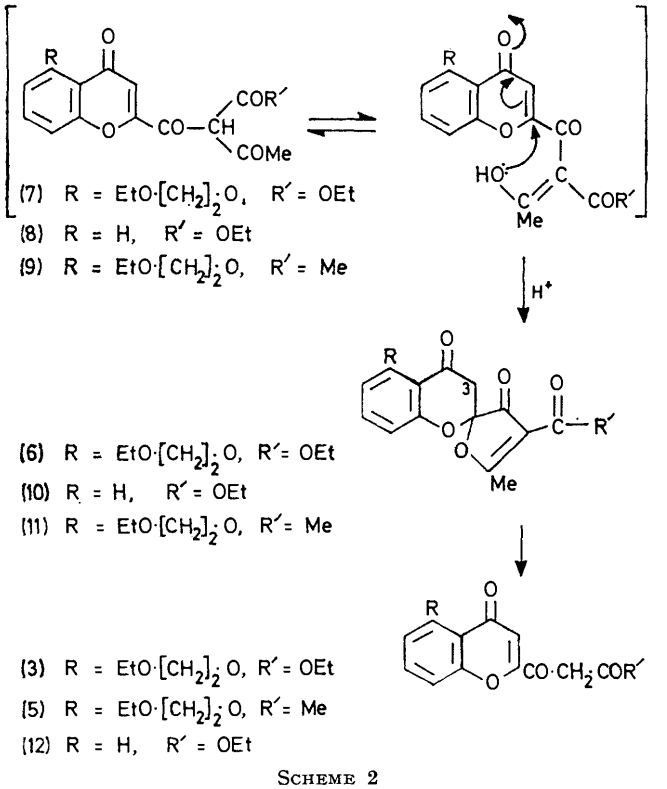
[1] N. Campbell, ' Chemistry of Carbon Compounds,' ed. E. H. Rodd, Elsevier, Amsterdam, 1959, vol. IVB, p. 888; S. Wawzonek, ' Heterocyclic Compounds', ed. R. C. Elderfield, Wiley, New York, 1950, vol. 2, p. 229.

[2] V. A. Zagorevskii, Sh. M. Glozman, and S. M. Klynev, *Khim. geterotsikl. Soedinenii*, 1967, **3**, 592 (*Chem. Abs.*, 1968, **68**, 29636b).

presence of a tautomeric mixture arising from the enolisability of the methine proton, which had been expected by analogy with compounds similar to (2)



SCHEME 1



SCHEME 2

previously studied in these laboratories. Neither did the spectrum contain an olefinic proton signal characteristic of the 3-proton of 4-oxobenzopyran-2-carboxylic acids.[3]

Although this compound was not the expected intermediate (7) the required 1,3-dicarbonyl derivatives were readily obtained from it (Scheme 1). Thus, when the compound was heated at reflux in ethanol containing a few drops of concentrated hydrochloric acid the β-oxo-ester (3) was isolated. Alternatively, when the compound was heated at reflux in propionic acid containing a few drops of concentrated sulphuric acid the 1,3-diketone (5) was obtained.

The compound was assigned the structure (6) on the basis of n.m.r. and mass spectral evidence. The n.m.r. spectrum ($CDCl_3$) displayed the expected signals for the three aromatic protons, the ethyl ester group, and the methyl group (a singlet). In addition it contained a 2 H pair of doublets (J 16 Hz) centred at τ 7.05 assigned to the non-equivalent 3-protons. This non-equivalence is well established [4] for chromanones having either a single substituent or two different substituents at the 2-position. The formation of (6) is considered to occur as shown in Scheme 2, by an intramolecular Michael addition. This sort of mechanism has recently [5] been proposed for the formation of an intermediate in the synthesis of carlosic acid.

This reaction appears to be of general applicability since similar products have been obtained from substituted or unsubstituted benzopyrones and with acetylacetone in place of ethyl acetoacetate (Scheme 2). The spiro-compound (6) was also obtained by using the ethyl sodioacetoacetate but the yield was only 10%.

The difference in results obtained upon treatment of the spiro-ester (6) with hydrochloric acid–ethanol and with sulphuric acid–propionic acid may be interpreted as follows. In acidic medium an equilibrium is set up between the spiro and the open-chain form. Upon treatment with sulphuric acid–propionic acid, trans-esterification may occur, generating a carboxy-group β to a carbonyl group, resulting in spontaneous decarboxylation and formation of the 1,3-diketone (5). On the other hand, conditions prevailing in refluxing ethanol–hydrochloric acid prevent formation of the carboxylic acid. The ethanol is free to attack the most electrophilic centre, eventually resulting in loss of the acetyl group as ethyl acetate and formation of the β-oxo-ester (3). This sequence could conceivably occur with the spiro-ester or the open-chain tricarbonyl compound.

EXPERIMENTAL

M.p.s were determined with a Büchi apparatus. Mass spectra were recorded with a Hitachi–Perkin-Elmer RMU6 spectrometer. ^1H N.m.r. spectra were recorded with a Perkin-Elmer R12 spectrometer (Me_4Si as internal standard).

4-Oxo-1-benzopyran-2-carbonyl Chlorides (1).—A suspension of the 4-oxo-1-benzopyran-2-carboxylic acid (0.1 mol) in dry 1,2-dichloroethane (200 ml) containing thionyl chloride (13.1 g, 0.11 mol) and dimethylformamide (3 drops) was heated at reflux until complete dissolution had

[3] H. Cairns, D. Hunter, J. King, and N. H. Rogers, *Tetrahedron*, 1974, **30**, 79.
[4] G. F. Katekar, *J. Heterocyclic Chem.*, 1970, **7**, 187.
[5] A. Svensen and P. M. Boll, *Tetrahedron Letters*, 1974, 2821.

occurred and then for 1 h more. The solution was evaporated to dryness leaving the acid chloride as a red oil sufficiently pure for further reactions.

Diethyl [5-(2-*Ethoxyethoxy*)-4-*oxo*-4H-1-*benzopyran*-2-*ylcarbonyl*]*malonate* (2; R = EtO·[CH_2]$_2$·O).—To a stirred solution of diethyl ethoxymagnesiomalonate (22.2 g, 0.1 mol) in dry 1,2-dichloroethane (200 ml) was added, all at once, a solution of the appropriate acid chloride (0.1 mol) in dry 1,2-dichloroethane (100 ml). There was an immediate yellow precipitate and the mixture was heated at reflux for 30 min, then cooled. N-Hydrochloric acid (200 ml) was added and the mixture was stirred for 5 min; the organic layer was then separated, washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness, leaving an orange oil. This was triturated with ether giving a white *solid* which was filtered off and dried (29.2 g, 69%); m.p. 91—92° (Found: C, 60.25; H, 5.9. $C_{21}H_{24}O_9$ requires C, 60.0; H, 5.75%).

2-*Acetyl*-5-(2-*ethoxyethoxy*)-1-*benzopyran*-4-*one* (4; R = EtO·[CH_2]$_2$·O).—A solution of the foregoing acylmalonate (27.0 g, 0.064 mol) in propionic acid (200 ml) containing concentrated sulphuric acid (2 drops) was heated at reflux for 3 h. The solvent was removed and a solution of the residue in ethyl acetate was treated with charcoal, filtered, and left to crystallise, giving pale brown *needles* (5.5 g, 31%), m.p. 127—128° (Found: C, 64.9; H, 5.9. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%), τ ($CDCl_3$) 2.4 (1 H, t, *J* 9 Hz, H-7), 2.95 (2 H, m, H-6 and -8), 3.2 (1 H, s, H-3), 6.1 (6 H, m, O·[CH_2]$_2$·O·CH_2), 7.42 (3 H, s, Ac), and 8.75 (3 H, t, *J* 7 Hz, Me).

Preparation of the Spiro-compounds.—The ethoxymagnesio-derivatives of ethyl acetoacetate and of acetylacetone were prepared by procedures similar to that described in ref. 6. To a well stirred solution or suspension of the ethoxymagnesio-derivative (0.1 mol) in dry 1,2-dichloroethane (200 ml) was added, all at once, a solution of the acid chloride (0.1 mol) in dry 1,2-dichloroethane. There was an immediate yellow precipitate and the mixture was heated at reflux for 30 min, then cooled. N-Hydrochloric acid (200 ml) was then added and the mixture was stirred vigorously for 5 min. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness, leaving an oil. In some cases this oil was triturated with ether giving a solid which was filtered off, and in one case the oil was dissolved in ether and the solution was left to crystallise.

Ethyl 5-(2-*ethoxyethoxy*)-5′-*methyl*-3′,4-*dioxospiro*[*chroman*-2,2′(3′H)-*furan*]-4′-*carboxylate* (6) (65%) had m.p. 138—140° (after trituration with ether) (Found: C, 61.7; H, 5.7. $C_{20}H_{22}O_8$ requires C, 61.7; H, 5.7%), *M* 390, τ ($CDCl_3$), 2.55 (1 H, t, *J* 9.0 Hz, H-7), 3.35 (2 H, m, H-6 and -8), 6.2 (8 H, m, C·CH_2·O and O[CH_2]$_2$·O·CH_2·C), 7.05 (2 H, 2d, *J* 16.0 Hz, 3-H_2), 7.42 (3 H, s, MeC:), and 8.7 (6 H, 2 overlapping t, *J* 7.0 Hz, 2 × Me).

Ethyl 5′-*methyl*-3′,4-*dioxospiro*[*chroman*-2,2′(3′H)-*furan*]-4′-*carboxylate* (10) (50%) had m.p. 170—172° (after trituration with ether) (Found: C, 63.2; H, 4.7. $C_{16}H_{14}O_6$ requires C, 63.2; H, 4.7%), τ ($CDCl_3$) 1.95—3.05 (4 H, m, H-5 to -8), 5.7 (2 H, q, *J* 7.0 Hz, O·CH_2·C), 7.0 (2 H, 2d, *J* 16.0 Hz, 3-H_2), 7.4 (3 H, s, MeC:), and 8.65 (3 H, t, *J* 7.0 Hz, MeC·O).

4′-*Acetyl*-5-(2-*ethoxyethoxy*)-5′-*methylspiro*[*chroman*-2,2′-*furan*]-3′,4-*dione* (11) (28%) had m.p. 105—106° (from ether) (Found: C, 63.1; H, 5.7. $C_{19}H_{20}O_7$ requires C, 63.4; H, 5.6%), τ ($CDCl_3$) 2.55 (1 H, t, *J* 9.0 Hz, H-7), 3.4 (2 H, m, H-6 and -8), 6.2 (6 H, m, O·[CH_2]$_2$·O·CH_2·C), 7.05 (2 H, 2d, *J* 16.0 Hz, 3-H_2), 7.4 (3 H, s, MeC:), 7.55 (3 H, s, Ac), and 8.8 (3 H, t, *J* 7.0 Hz, MeC·O).

Ethyl 3-[5-(2-*Ethoxyethoxy*)-4-*oxo*-4H-1-*benzopyran*-2-*yl*]-3-*oxopropionate* (3; R = EtO·[CH_2]$_2$·O).—*Method A.* A solution of the acylmalonate (2; R = EtO·[CH_2]$_2$·O) (5.0 g) in propionic acid (50 ml) containing concentrated sulphuric acid (1 drop) was heated at reflux for 30 min. The solvent was removed *in vacuo* and the residue was crystallised from ethanol–water to give orange *needles* (1.0 g, 24%), m.p. 106—108° (Found: C, 60.7; H, 5.8. $C_{18}H_{20}O_7$,-0.5H_2O requires C, 60.5; H, 5.8%), τ ($CDCl_3$) (*ca.* 60% enol in this solvent) 2.45 (1 H, t, *J* 9.0 Hz, H-7), 3.1 (2 H, m, H-6 and -8), 3.25 (1 H, s, H-3), 4.02 [1 H, s, CH:C·OH (enol form)], 6.0 [10 H, m, CH_2·O·[CH_2]$_2$·O, C·CH_2·O·CO, and CO·CH_2·CO (keto-form)], and 8.6 (6 H, 2 overlapping t, *J* 7.0 Hz, 2 × Me).

Method B. A solution of the spiro-compound (6) (5.0 g) in ethanol (75 ml) containing concentrated hydrochloric acid (1 ml) was heated at reflux for 2 h. The solvent was removed *in vacuo* and the residue was crystallised from ethanol–water to give the β-oxo-ester (4.4 g, 76%), m.p. 106—108°, identical with that obtained by method A.

2-(1,3-*Dioxobutyl*)-5-(2-*ethoxyethoxy*)-1-*benzopyran*-4-*one* (5; R = EtO·[CH_2]$_2$·O).—*Method A.* A solution of the spiro-compound (11) (2.5 g) in ethanol (35 ml) containing concentrated hydrochloric acid (0.5 ml) was heated at reflux for 2.5 h. The solvent was removed *in vacuo* and the residue was crystallised from ethanol–water (charcoal) to give the 1,3-*diketone* (5) as a yellow solid (1.6 g, 73%), m.p. 110—111° (Found: C, 64.0; H, 5.8. $C_{17}H_{18}O_6$ requires C, 64.1; H, 5.7%), τ ($CDCl_3$) (nearly 100% enol form in this solvent) 2.45 (1 H, t, *J* 9.0 Hz, H-7), 3.1 (2 H, m, H-6 and -8), 3.15 (1 H, s, H-3), 3.65 [1 H, s, CH:C·OH(enol)], 4.1 (6 H, m, O·[CH_2]$_2$·O·CH_2·C), 7.75 (3 H, s, MeCO), and 8.8 (3 H, t, *J* 7.0 Hz, MeC).

Method B. A solution of the spiro-compound (6) (1.0 g) in propionic acid (50 ml) containing concentrated sulphuric acid (1 drop) was heated at reflux for 20 min. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and allowed to crystallise. The solid obtained (0.1 g, 12%) was identical with that obtained by method A.

Ethyl 3-*Oxo*-3-(4-*oxo*-4H-1-*benzopyran*-2-*yl*)*propionate* (12).—A solution of the spiro-compound (10) (5.0 g) in ethanol (100 ml) containing concentrated hydrochloric acid (2 ml) was heated at reflux for 1 h. The solvent was removed *in vacuo* and the residual oil was crystallised from ethanol to give the β-*oxo-ester* as a yellow solid (2.8 g, 65%), m.p. 106—107° (Found: C, 64.4; H, 4.8. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.65%), τ ($CDCl_3$) (*ca.* 80% enol in this solvent) 1.85 (1 H, dd, *J* 10 and 2 Hz, H-5), 2.5 (3 H, m, H-6—8), 3.0 [1 H, s, H-3 (keto)], 3.1 [1 H, s, H-3 (enol)], 3.95 [1 H, s, CH:C·O (enol)], 5.75 [2 H, 2 overlapping q, *J* 7.0 Hz, CH_2·O (keto and enol)], 6.05 [2 H, s, CH_2 (keto)], and 8.65 (3 H, t, *J* 7.0 Hz, MeC).

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[6] M. Viscontini and N. Merckling, *Helv. Chim. Acta*, 1952, **35**, 2280; H. Land and A. Voigt, *Org. Synth.*, Coll. Vol. II, 1943, p. 594.