Ring Expansion of Thiochroman-4-one and Isothiochroman-4-one with Ethyl Diazo(lithio)acetate to Tetrahydrobenzothiepin β-Oxoesters

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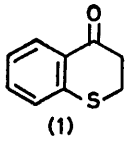
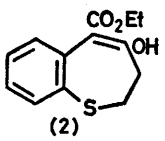
When thiochroman-4-one (1) and isothiochroman-4-one (3) were treated with ethyl diazo(lithio)acetate, ethyl 2,3-dihydro-4-hydroxy-1-benzothiepin-5-carboxylate (2) and ethyl 1,3-dihydro-4-hydroxy-2-benzothiepin-5-carboxylate (4), respectively, were formed. An improved procedure for the two-step addition–ring expansion sequence is described. The preparation of 2,3-dihydro-1-benzothiepin-4(5*H*)-one (7) and of 1,3-dihydro-2-benzothiepin-4(5*H*)-one (8) from the esters (2) and (4), respectively, is reported. Deoxygenation of (7) and (8) to 2,3,4,5-tetrahydro-1-benzothiepin (9) and 1,3,4,5-tetrahydro-2-benzothiepin (10) by Caglioti reduction is described.

THE wide range of pharmacological properties exhibited by several fused thiepin derivatives has aroused interest in this area.[1] We report here the synthesis of ethyl 2,3-dihydro-4-hydroxy-1-benzothiepin-5-carboxylate (2) and ethyl 1,3-dihydro-4-hydroxy-2-benzothiepin-5-carboxylate (4) which provide easy access to polycyclic systems of potential biological interest.

The synthetic route involves ring homologation of thiochroman-4-one (1) and isothiochroman-4-one (3) by ethyl diazoacetate.


(1)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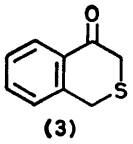
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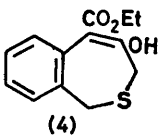
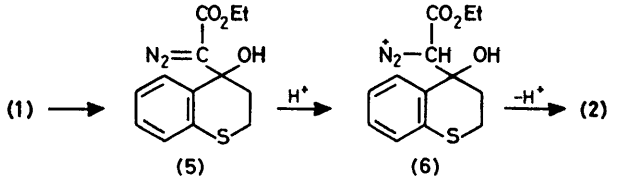

(4)

A plausible mechanism leading to the enolic β-oxo-ester (2) from thiochroman-4-one (1) is represented in the Scheme. The α-diazo-β-hydroxy-ester (5) initially formed by nucleophilic addition of ethyl diazoacetate to the carbonyl group of (1) decomposes with loss of


(5) (6)

nitrogen when refluxed in methanolic hydrogen chloride to give (2) as the product of phenyl 1,2-migration *via* the protonated intermediate (6). An analogous sequence accounts for the formation of the enolic β-oxo-ester (4) from isothiochroman-4-one (3).

Although several attempts to add ethyl diazoacetate to the ketones (1) and (3) with catalysis by bases † or Lewis acids ‡ have failed, α-diazo-β-hydroxy-esters were

† Reactions in ethanol solution catalysed by triethylamine [2] or potassium hydroxide led only to recovery of starting material.

‡ Aluminum chloride,[3] zinc chloride,[4] and boron trifluoride [5] were tried as catalysts.

[1] For references, see V. J. Traynelis in 'The Chemistry of Heterocyclic Compounds,' vol. 26, ed. A. Rosowsky, Wiley–Interscience, New York, 1972, pp. 667 *et seq.*

[2] B. Eistert and G. Borggrefe, *Annalen*, 1968, **718**, 142.

[3] E. Müller and M. Bauer, *Annalen*, 1962, **654**, 92.

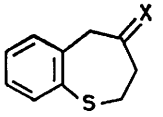
[4] B. Eistert, F. Haupter, and K. Schank, *Annalen*, 1963, **665**, 55.

[5] H. J. Liu and S. P. Majumdar, *Synth. Comm.*, 1975, **5**, 125.

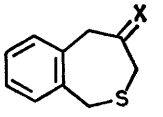
formed when ethyl diazo(lithio)acetate was employed.* The equilibrium nature of this reaction and its close analogy to the aldol condensation limited the choice of solvent to an aprotic medium. The best yields were obtained when ethyl diazo(lithio)acetate was produced *in situ* by addition of n-butyl-lithium to ethyl diazoacetate at −78 °C in tetrahydrofuran.[6] The α-diazo-β-hydroxy-esters thus formed were not isolated, but the residues obtained after evaporation of the solvent were stirred with methanolic hydrogen chloride. The enolic β-oxo-esters (2) and (4) so obtained were contaminated with the starting ketones, from which they were separated by extraction with aqueous sodium hydroxide in yields (after crystallization) of 33 and 22.2%, respectively.

Spectroscopic studies revealed that compounds (2) and (4) existed entirely in the enol form in the solid phase (i.r. spectrum) or in solution in chloroform [n.m.r. signals at δ 12.88 and 12.5 for (2) and (4), respectively; no 5-H signals].

Conventional hydrolysis and decarboxylation yielded 2,3-dihydro-1-benzothiepin-4(5*H*)-one (7) and 1,3-dihydro-2-benzothiepin-4(5*H*)-one (8), respectively.



(7) X = O
(9) X = H_2



(8) X = O
(10) X = H_2

Finally both ketones (7) and (8) were transformed by successive treatments with tosylhydrazine and sodium borohydride into the known 2,3,4,5-tetrahydro-1-benzothiepin (9) and 1,3,4,5-tetrahydro-2-benzothiepin (10), respectively.

EXPERIMENTAL

M.p.s were determined with a Kofler micro hot stage apparatus. N.m.r. spectra were recorded with a JEOL INM-C-60 HL spectrometer (Me_4Si standard), and i.r. spectra with a Perkin-Elmer 257 spectrophotometer. Microanalyses were performed by the Laboratoire P. Jacquignon, Gif-sur-Yvette, France. The addition reactions were carried out under dry nitrogen. Tetrahydrofuran was distilled from lithium aluminium hydride prior to use. Apparatus for experiments requiring dry conditions was dried either by flaming under reduced pressure or in a nitrogen stream.

Thiochroman-4-one was purchased from Aldrich. Isothiochroman-4-one was prepared by cyclization of *S*-benzylthioglycolic acid.[7] Ethyl diazoacetate was prepared as described.[8] Column chromatography was performed with Merck silica gel (0.063—0.200 mm).

Ethyl 2,3-*Dihydro*-4-*hydroxy*-1-*benzothiepin*-5-*carboxylate* (2).—A solution of thiochroman-4-one (1) (7.0 g, 42.5 mmol) and ethyl diazoacetate (6.80 g, 59.4 mmol) in tetrahydrofuran (250 ml; freshly distilled from lithium aluminum hydride) was cooled to −78 °C (under nitrogen). With vigorous stirring 2M-n-butyl-lithium in hexane (29.65 ml, 59.3 mmol) was added dropwise over 20 min. The mixture was stirred for 15 min, then acetic acid (3.7 ml) in ether (100 ml) was added, the cooling bath was removed, and the mixture was allowed to reach room temperature. The organic phase was separated, washed with water, dried (Na_2SO_4), and evaporated, and the residue (12 g) was immediately dissolved in methanol (100 ml). To this solution kept at room temperature, aqueous 2.4N-hydrochloric acid (10 ml) was added over 15 min and stirring was continued for 18 h. Water (300 ml) was then added, the mixture was extracted with chloroform (5 × 80 ml) and the combined organic solutions were extracted with aqueous 3% sodium hydroxide (10 × 20 ml). The combined aqueous alkaline layers were neutralized with aqueous 12N-hydrochloric acid and extracted with ether (8 × 30 ml). The organic extracts were combined, washed with brine and water, dried (Na_2SO_4), and evaporated under vacuum, and the oily residue was crystallized from hexane to give the *ester* (2) (3.51 g, 33%), m.p. 90° (Found: C, 62.95; H, 5.8; S, 12.45. $C_{13}H_{14}O_3S$ requires C, 62.4; H, 5.65; S, 12.8%); $\nu_{max.}$ (neat) 1 710m, 1 640s, and 1 610s cm^{-1} (C=O); δ ($CDCl_3$) 1.23 (3 H, t, *J* 9 Hz, CH_2Me), 2.37 (2 H, t, *J* 9 Hz, H-2), 3.45 (2 H, t, *J* 9 Hz, H-3), 4.23 (2 H, q, *J* 9 Hz, $MeCH_2$), 7.29 (4 H, m, aromatic), and 12.88 (1 H, s, enolic OH).

Ethyl 1,3-*Dihydro*-4-*hydroxy*-2-*benzothiepin*-5-*carboxylate* (4).—Similarly treatment of isothiochroman-4-one (3) (5.0 g, 30.4 mmol) with ethyl diazoacetate (4.9 g, 43 mmol) and n-butyl-lithium (21.5 ml, 43.0 mmol) in tetrahydrofuran (240 ml) followed by crystallization of the crude product from hexane gave the *ester* (4) (1.69 g, 22.2%), m.p. 60—61° (Found: C, 62.25; H, 5.65; S, 12.9 $C_{13}H_{14}O_3S$ requires C, 62.4; H, 5.65; S, 12.8%); $\nu_{max.}$ (neat) 1 710m, 1 640s, and 1 600s cm^{-1} (C=O); δ ($CDCl_3$) 1.24 (3 H, t, *J* 9 Hz, $MeCH_2$), 2.81 and 3.12 (2 H, ABq, *J* 9 Hz, H-3), 3.3 and 3.92 (2 H, ABq, *J* 12 Hz, H-1), 42.4 (2 H, q, *J* 9 Hz, CH_2Me), 7.2 (4 H, s, aromatic), and 12.5 (1 H, s, enolic OH).

2,3-*Dihydro*-1-*benzothiepin*-4(5H)-*one* (7).—To a solution of concentrated sulphuric acid (16.6 ml) in ethanol–water (70 : 30; 80 ml) was added the ester (2) (1.4 g, 5.6 mmol), and the mixture was stirred at reflux for 29 h. It was then diluted with water (150 ml) and extracted with ether (5 × 40 ml). The combined extracts were washed with aqueous 3% sodium hydrogen carbonate (120 ml) and saturated brine (120 ml), and then dried (Na_2SO_4) and evaporated. Distillation of the oily residue (0.64 g) (b.p. 92—94° at 0.13 mmHg) gave the oily *ketone* (7) (0.36 g, 35.5%) (Found: C, 67.05; H, 5.75; S, 17.25. $C_{10}H_{10}OS$ requires C, 67.4; H, 5.65; S, 17.95%); $\nu_{max.}$ 1 700s cm^{-1} (C=O); δ ($CDCl_3$) 2.6—3.2 (4 H, m, H-2 and -3), 3.93 (2 H, s, H-5), and 7.19 (4 H, m, aromatic).

The *oxime* melted at 123—125° (from benzene–pentane) (Found: C, 62.2; H, 5.55; N, 7.05; S, 16.55. $C_{10}H_{11}NOS$ requires C, 62.15; H, 5.75; N, 7.25; S, 16.55%); δ ($CDCl_3$) 2.65—3.25 (4 H, m, H-2 and -3), 3.95 (2 H, s, H-5), 7.2 (4 H, m, aromatic), and 10.55 (1 H, s, NOH).

1,3-*Dihydro*-2-*benzothiepin*-4(5H)-*one* (8).—Similarly

* In one preparation the α-diazo-β-hydroxy-intermediates were isolated and their structures confirmed on the basis of i.r. evidence (N_2 and OH absorptions at 2 100 and 3 450 cm^{-1}, respectively).

[6] *Cf.* (*a*) U. Schollkopf and H. Frasnelli, *Angew. Chem.*, 1970, **82**, 291; (*b*) E. Wenkert and C. A. McPherson, *J. Amer. Chem. Soc.*, 1972, **94**, 8084; (*c*) U. Schollkopf, B. Banhidai, H. Frasnelli. R. Meyer, and H. Beckhaus, *Annalen*, 1974, 1767.

[7] K. Kiang and F. G. Mann, *J. Chem. Soc.*, 1951, 1909.

[8] N. E. Searle, *Org. Synth.*, 1956, **36**, 25.

treatment of the enolic β-oxo-ester (4) (0.6 g) with concentrated sulphuric acid (10 ml) in ethanol–water (70 : 30; 50 ml) with stirring for 24 h, and crystallization of the crude product from hexane gave the *ketone* (8) (0.3 g, 70%), m.p. 96—97° (Found: C, 67.4; H, 5.7; S, 17.7. $C_{10}H_{10}OS$ requires C, 67.4; H, 5.65; S, 17.95%); $\nu_{max.}$ 1 710s cm^{-1} (C=O); δ ($CDCl_3$) 3.06 (2 H, s, H-3), 3.66 (2 H, s, H-5), 3.85 (2 H, s, H-1), and 7.16 (4 H, m, aromatic).

The *oxime* melted at 190° (from benzene–pentane) (Found: C, 61.9; H, 5.65; N, 7.15; S, 16.4. $C_{10}H_{11}NOS$ requires C, 62.15; H, 5.75; N, 7.25; S, 16.55%); δ ($CDCl_3$) 3.26 (2 H, s, H-3), 3.72 (2 H, s, H-5), 3.90 (2 H, s, H-1), 7.15 (4 H, m, aromatic), and 10.34 (1 H, s, NOH).

2,3,4,5-*Tetrahydro*-1-*benzothiepin* (9).—A solution of the ketone (7) (0.45 g, 2.53 mmol) and *p*-tolylsulphonylhydrazine (0.84 g) in methanol (45 ml) was refluxed for 4 h, then cooled. Sodium borohydride (0.86 g) was added in small portions and the mixture refluxed for 3 h.[9] It then was poured into water (80 ml) and extracted with ether (5 × 30 ml). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue (0.3 g) on a silica gel column and elution with benzene gave the product (9) (0.14 g, 33.7%), identical with an authentic sample.[10]

1,3,4,5-*Tetrahydro*-2-*benzothiepin* (10).—A similar Caglioti reduction of the ketone (8) [0.34 g of (8), 0.63 g of $TsNHNH_2$, 40 ml of methanol, 0.65 g of $NaBH_4$] led to compound (10) (0.14 g, 44.7%), m.p. 49—50° (lit.,[11] 48—49°); δ ($CDCl_3$) 1.15 (2 H, m, H-4), 1.75 (2 H, t, H-3), 2.85 (2 H, t, *J* 6 Hz, H-5), 3.76 (2 H, s, H-1), and 7.04 (4 H, m, aromatic).

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[9] L. Caglioti, *Tetrahedron*, 1966, **22**, 487.
[10] V. J. Traynelis and R. F. Love, *J. Org. Chem.*, 1961, **26**, 2728.
[11] J. von Braun, *Ber.*, 1925, **58**, 2165.