Synthesis and Properties of Methyl 3,4-Dihydro-4-oxo-1*H*-2-benzothiopyran-3-carboxylate and Related Thiopyrano-compounds

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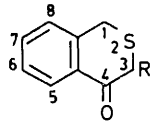
Methyl 3,4-dihydro-4-oxo-1*H*-2-benzothiopyran-3-carboxylate (2) [or its tautomer (3)] has been obtained by Dieckmann cyclisation of methyl(*o*-methoxycarbonylbenzylthio)acetate. It reacts with hydrazine and with phenylhydrazine to give 1,2-dihydro-5*H*-[2]benzothiopyrano[4,3-*c*]pyrazol-3-one (7) and the 2-phenyl derivative (6), respectively, but does not give an isoxazolone with hydroxylamine. Methylation of the pyrazolone (6) with various reagents has been investigated.

Methyl 6,7-dihydro-7-oxo-4*H*-thieno[3,2-*c*]thiopyran-6-carboxylate (12) and methyl and ethyl 3,4-dihydro-8-nitro-4-oxo-1*H*-thiopyrano[4,3-*b*][1]benzothiophen-3-carboxylate [(15) and (16) or their respective tautomers] have been obtained by the appropriate Dieckmann cyclisations. Compound (16) may also be obtained in a single step by treatment of 2-bromo-2'-chloro-5'-nitroacetophenone with ethyl mercaptoacetate (2 mol. equiv.). Improved procedures for carrying out some well known chemical transformations are described.

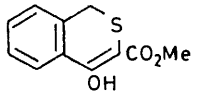
DERIVATIVES of 1*H*-2-benzothiopyran-4(3*H*)-one (1) have been used widely as a source of 2-benzothiopyrylium salts and thianaphthalene (2-substituted 2-benzothiopyran-S^{IV}) derivatives;[1-4] such compounds have been examined extensively in order to ascertain the role of sulphur *d* orbitals in their bonding. Substituted 1*H*-2-benzothiopyrans[5] and related compounds in which the benzene ring is replaced by a heterocyclic residue[6] have shown a wide range of useful biological activities.

1*H*-2-Benzothiopyran-4(3*H*)-one (1) and its derivatives are usually obtained by cyclisation of the appropriate (benzylthio)acetic acid, $ArCH_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$,[3,4,7] or of the corresponding acyl chloride.[2,5,8-11] This method suffers from the disadvantages that the cyclisation generally proceeds in low yield and that the thiols, $ArCH_2{\cdot}SH$, which are subsequently condensed with chloroacetic acid or its ester, are not readily accessible. We now describe a synthesis of the 1*H*-2-benzothiopyran-4(3*H*)-one derivative (2) (or its tautomer) from methyl *o*-toluate, which gives a high overall yield and is experimentally straightforward. *N*-Bromosuccinimide reacted sluggishly with methyl *o*-toluate, and the product contained some unwanted dibromomethyl compound; photobromination in carbon tetrachloride gave methyl α-bromotoluate quantitatively. This condensed with methyl mercaptoacetate in basic solution to yield the diester (4) (95%), which underwent Dieckmann cyclisation with sodium methoxide in benzene, to give the β-oxo-ester (2) (90%). It was not necessary to purify either the bromomethyl compound or the diester (4). The oxo-ester (2) could also be obtained in low yield (35%) by treatment of the ketone (1)[7] with dimethyl carbonate; conversely, conventional hydrolysis and decarboxylation of (2) gave the ketone (1) in high yield (79%). The oxo-ester (2) existed entirely in the enol form (3) in the solid phase (i.r. spectrum) or in solution in chloroform [n.m.r. signal at δ 12.4 (enolic OH); no 3-H signal]; in trifluoroacetic acid solution, only 50% of the enol (3) was present.

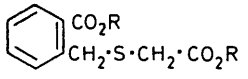
The n.m.r. spectrum of the oxo-form (2) was characteristic in that, in addition to showing the expected singlet for 3-H (δ 4.52), it showed an AB quartet (δ 3.78 and 4.24, *J* 17.5 Hz) for 1-H_2 [*cf.* singlets for (1) and (3)]. Other workers[12] have observed a similar phenomenon in the



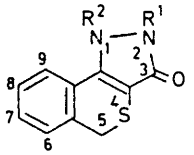
(1) R = H
(2) R = CO_2Me



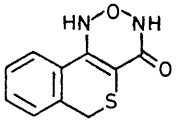
(3)



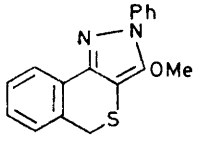
(4) R = Me
(5) R = H



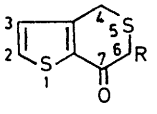
(6) R^1 = Ph, R^2 = H
(7) R^1 = R^2 = H
(8) R^1 = Ph, R^2 = Me



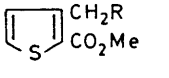
(9)



(10)



(11) R = H
(12) R = CO_2Me



(13) R = Br
(14) R = S·CH_2·CO_2Me

[1] C. C. Price and D. H. Follweiler, *J. Org. Chem.*, 1969, **34**, 3202.
[2] A. Lüttringhaus and N. Engelhard, *Chem. Ber.*, 1960, **93**, 1525.
[3] C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.*, 1963, **85**, 2278.
[4] G. Canalini, I. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Italy)*, 1971, **61**, 504.
[5] *E.g.* R. R. Crenshaw, A. T. Jeffries, G. M. Luke, L. C. Cheney, and G. Bialy, *J. Medicin. Chem.*, 1971, **14**, 1185.
[6] *E.g.* G.P. 1,908,497/1969 (*Chem. Abs.*, 1970, **72**, 31,837u); U.S.P. 3,142,678/1964 (*Chem. Abs.*, 1964, **61**, 8314d).
[7] A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, 1951 1909
[8] R. Lesser and A. Mehrländer, *Ber.*, 1923, **56**, 1642.
[9] J. v. Braun and K. Weissbach, *Ber.*, 1929, **62**, 2416.
[10] P. Cagniant and D. Cagniant, *Bull. Soc. chim. France*, 1959, 1998.
[11] P. Cagniant, G. Jecko, and D. Cagniant, *Bull. Soc. chim. France*, 1961, 2225.
[12] P. Cagniant and D. Cagniant, *Bull. Soc. chim. France*, 1967, 2597.

n.m.r. spectra of related compounds. It seems that the two 1-protons become anisochronous only when the 3-position is a chiral centre. Perchloric acid was added to a solution of tautomers (2) and (3) in trifluoroacetic acid in the hope that the enol form (3) might lose a proton to give the corresponding 2-benzothiopyrylium salt (*cf.* ref. 5). However, although the solution became brightly coloured and some change took place, there was no n.m.r. evidence for such a deprotonation.

We now illustrate how use of the β-oxo-ester function in (2) provides easy access to polycyclic systems of potential biological interest; such reactions should also be common to related compounds of type (12) and (15).

The oxo-ester (2)* reacted readily with phenylhydrazine to give a pyrazolone, which was formulated as 1,2-dihydro-2-phenyl-5*H*-[2]benzothiopyrano[4,3-*c*]-pyrazol-3-one (6), rather than as the 2,3a-dihydro-isomer, or as an enol tautomer, on the basis of i.r. (C=O absorption at 1 650 cm^{-1}) and n.m.r. evidence (no enolic OH signal at low field; no 3a-H signal). An analogous pyrazolone (7) was obtained by treatment of (2) with hydrazine. The oxo-ester (2) did not react with hydroxylamine under conventional conditions (NH_2·OH,HCl–NaOAc), in an attempt to prepare the isoxazolone corresponding to the pyrazolone (7). Use of hydroxylamine hydrochloride in pyridine gave a complex mixture of products, from which the oxime of 1*H*-2-benzothiopyran-4(3*H*)-one (1) (15%), formed *via* demethoxycarbonylation of (2), and the oxime of the oxo-ester (2) (10%), were obtained pure. Two amorphous, but apparently homogeneous products, appear to be the hydroxamic acid derived from the enol (3) (10%) and the 1,2,6-oxadiazine derivative (9) (5%), presumably formed by cyclisation of the hydroxyimino-hydroxamic acid corresponding to the oxo-ester (2). Evidence for these proposed structures is cited in the Experimental section. The required oxime was finally obtained (42%) by treatment of the oxo-ester (2) with hydroxylamine hydrochloride in the presence of Dowex 1 anion-exchange resin under carefully controlled conditions. Surprisingly, however, it did not cyclise to give the expected isoxazolone derivative. The oxo-ester (2) did not react with urea or thiourea, did not form a Schiff's base with aniline, and did not undergo the von Pechmann reaction with resorcinol under mild acidic conditions; under more forcing conditions, only polymeric material was obtained.

We next methylated the pyrazolone (6) in order to prepare the *N*-methyl derivative (8)—an analogue of the febrifuge, antipyrin (2,3-dimethyl-1-phenyl-Δ^3-pyrazolin-5-one). Dimethyl sulphate in aqueous methanolic sodium hydroxide, a reagent which methylates simple pyrazolones essentially on nitrogen,[13] gave a mixture (1 : 1) of the *N*-methyl derivative (8) (δ 2.51, NMe) and the *O*-methyl derivative (10) (δ 4.10, OMe). A similar mixture (3 : 2), in which the *N*-methyl compound (8) predominated, was obtained by using methyl iodide in the presence of sodium hydride and dimethylformamide. Use of methyl iodide and sodium methoxide,[14] however, provided the *N*-methyl product (8) (>95%). Treatment with ethereal diazomethane gave the *O*-methyl compound (10) in quantitative yield. The 5-protons gave rise to an AB quartet in the n.m.r. spectrum of the *N*-methyl compound (8), but to a singlet in that of the *O*-methyl compound (10). The 3a-position in (8) is not chiral and therefore, according to the argument used earlier, the 5-H_2 signal might be expected to appear as a singlet. Had *C*-methylation of the pyrazolone (6) occurred (*i.e.* in the 3a-position), and thus generated a chiral centre, the observed splitting of the 5-H_2 signal might have been expected. However, the signal at δ 2.51 is at a field strength too low for a *C*-methyl group, showing that other factors must be operative in this case.

4*H*-Thieno[3,2-*c*]thiopyran-7(6*H*)-one (11) has been obtained [12,15] by a method analogous to that already described for the benzo-homologue (1). This method suffers from the disadvantage that the intermediate 3-thienylmethanethiol is unstable and difficult to prepare. Further, its precursor, 3-thenyl bromide, is not readily accessible because 3-methylthiophen undergoes both nuclear and side-chain bromination when treated with *N*-bromosuccinimide.[16] In our method, we first brominated methyl 3-methylthiophen-2-carboxylate with *N*-bromosuccinimide (0.9 mol. equiv.), to give a readily separable mixture of the bromomethyl compound (13) and starting material. Use of a greater quantity of *N*-bromosuccinimide led to dibromination in the side chain and the production of an inseparable mixture. The diester (14) was obtained as before and cyclised initially with sodium methoxide in hot benzene, to give the oxo-ester (12) (20%). Cyclisation took place so readily, however, that these conditions led to the formation of tar. The progress of the reaction could more readily be monitored, and a much better yield of (12) was thereby obtained, by using sodium methoxide in methanolic dimethylformamide, at or below room temperature. Such a solvent system has not, to our knowledge, been used previously for Dieckmann cyclisations. The oxo-ester (12) existed as a mixture of oxo- and enol forms (1 : 1) in the solid phase [$\nu_{max.}$ 1 740 (ester C=O), 1 718 (oxo C=O), and 1 665 cm^{-1} (chelated C=O)] and in chloroform solution [δ 5.58 (6-H) and 12.16 (OH), of equal area]. As before, the 4-H_2 signal appeared as an AB quartet (δ 3.72 and 4.18, *J* 17.5 Hz) in the n.m.r. spectrum of the oxo-form (12) and as a singlet (δ 3.60) in that of the corresponding enol.

Next we prepared the thiopyranobenzothiophen derivatives (15) and (16). Other workers [17,18] have obtained 1*H*-thiopyrano[4,3-*b*][1]benzothiophen-4(3*H*)-

* For convenience, the equilibrium mixture (2) ⇌ (3) will be designated (2) in the ensuing discussion.

[13] A. I. Vogel, 'A Text-book of Practical Organic Chemistry,' 3rd edn., Longmans, London, 1956, p. 998.

[14] *Cf.* A. J. Boulton and A. R. Katritzky, *Tetrahedron*, 1961, **12**. 41.

[15] T. E. Young and C. R. Hamel, *J. Org. Chem.*, 1970, **35**, 821.

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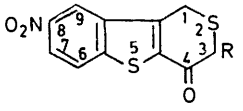
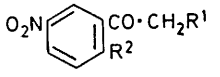
[17] P. Cagniant, *Compt. rend.*, 1970, **271C**, 1086.

[18] T. E. Young and C. R. Hamel, *J. Org. Chem.*, 1970, **35**, 816.

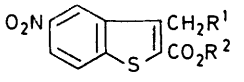
one (17) from 3-methylbenzo[*b*]thiophen by routes parallel to those used for the ketones (1) and (11), which suffer from the disadvantages already described. We



(15) R = CO_2Me
(16) R = CO_2Et
(17) R = H; no 8-NO_2 group



(18) R^1 = Br, R^2 = Cl
(19) R^1 = R^2 = S·CH_2·CO_2Et
(20) R^1 = S·CH_2·CO_2Et, R^2 = Cl



(21) R^1 = H, R^2 = Me or Et
(22) R^1 = Br, R^2 = Me or Et
(23) R^1 = S·CH_2·CO_2Me, R^2 = Me
or R^1 = S·CH_2·CO_2Et, R^2 = Et

prepared the 8-nitro-derivatives (15) and (16), partly because the starting materials were easily obtained, and partly because structures based on 5-substituted benzo[*b*]thiophens often show more pronounced biological activity than the corresponding unsubstituted compounds.[19] Further, it should be easy to transform the nitro-substituent into a wide range of other groups.

2′-Chloro-5′-nitroacetophenone readily condensed with ethyl [20] or methyl mercaptoacetate, to give the substituted benzo[*b*]thiophens (21). Photobromination of the esters (21) gave the bromo-compounds (22) (*ca.* 80%), which could not be condensed easily with methyl or ethyl sodiomercaptoacetate because of their insolubility in common solvents at room temperature. Raising the temperature or using a dipolar aprotic solvent caused partial Dieckmann cyclisation of the resulting diesters (23). However, by using piperidine as the basic catalyst, the products (23) were obtained cleanly and in high yield from (22) and the appropriate mercapto-ester. In view of the efficacy of piperidine in this reaction, it seems surprising that sulphides are invariably prepared from the alkali metal salt of a thiol and the appropriate halogeno-compound.[21] The diesters (23) were cyclised as before by using the appropriate sodium alkoxide in methanolic or ethanolic dimethylformamide. It seems that the resulting oxo-esters (15) and (16) are 50% enolised in the solid phase and in solution (see Experimental section), but owing to solubility difficulties the n.m.r. spectra could only be obtained for dilute solutions, and reliable quantitative data could not be obtained. Throughout this series we prepared the ethyl as well as the methyl esters because the former were more soluble than the latter and hence more easily handled.

[19] E. Campaigne, D. R. Knapp, E. S. Neiss, and T. R. Bosin, *Adv. Drug Res.*, 1970, **5**, 1.
[20] N. B. Chapman, K. Clarke, and S. N. Sawhney, *J. Chem. Soc.* (*C*), 1968, 518.
[21] 'Methoden der Organischen Chemie,' Houben–Weyl, 1955, **9**, ch 5,

Finally, we treated 2-bromo-2′-chloro-5′-nitroacetophenone (18) with ethyl mercaptoacetate (2 mol. equiv.) in the presence of sodium ethoxide. The supposed intermediate diester (19) cyclised spontaneously, to give the thiopyrano-derivative (16) (65%) in a single step. Although the value of 2′-chloro-5′-nitroacetophenone in the synthesis of ethyl 3-methyl-5-nitrobenzo[*b*]thiophen-2-carboxylate has been appreciated for some years,[20] the synthetic potential of the bromo-ketone (18) has not been exploited. Accordingly, we treated it with ethyl mercaptoacetate (1 mol. equiv.) in piperidine, and effected preferential substitution of the bromine atom, to give the ester (20) (100%). The benzo[*b*]thiophen derivative (23; diethyl ester) was formed quantitatively when the ester (20) was treated with a further mol. equiv. of ethyl mercaptoacetate. It should be easy to treat 2-bromo-2′-chloro-5′-nitroacetophenone (18) selectively with other nucleophiles, in order to obtain compounds analogous to (20), in which R^1 is a suitable nucleophilic group; these should react further with an appropriate sulphur nucleophile to give a range of useful (3-CH_2R^1 substituted) benzo[*b*]thiophen derivatives. The scope of this potentially useful reaction is being investigated further.

EXPERIMENTAL

I.r. data refer to potassium chloride discs. N.m.r. data refer to solutions in deuteriochloroform. Molecular weights determined by mass spectrometry for bromine or chlorine containing compounds refer to the ^{79}Br or the ^{35}Cl isotope respectively. Light petroleum had b.p. 60—80°.

Starting Materials.—Methyl *o*-toluate (79%), b.p. 89—91° at 12 mmHg, was obtained by heating *o*-toluic acid overnight with methanol in the presence of sulphuric acid; with a shorter heating time the yield was appreciably lower. 2-Acetyl-3-methylthiophen (65%), obtained [22] by treatment of 3-methylthiophen with acetic anhydride in the presence of orthophosphoric acid, had b.p. 63—65° at 0.5 mmHg (lit.,[22] 79° at 4 mmHg). It was oxidised by sodium hypobromite, to give 3-methylthiophen-2-carboxylic acid (82%), m.p. 145—147° (lit.,[23] 147—148°) (from water). Overnight heating of the acid with methanol and concentrated sulphuric acid gave methyl 3-methylthiophen-2-carboxylate (70%), b.p. 66—68° at 0.5 mmHg.

Methyl (*o-Methoxycarbonylbenzylthio*)*acetate* (4).—A solution of bromine (1.01 mol. equiv.) in carbon tetrachloride was added during 5 min to a stirred, irradiated (500 W tungsten lamp) solution of methyl *o*-toluate in boiling carbon tetrachloride. The n.m.r. spectrum of the resulting solution showed that conversion into methyl α-bromotoluate was almost quantitative [δ 4.90 (2 H, s, CH_2Br); no signal at δ 2.55 (ArMe)]. Evaporation under reduced pressure at *ca.* 40 °C gave an oily residue, which formed needles, m.p. 33—34.5° [from ether–light petroleum (b.p. 40—60°)] (lit.,[24] 32—32.5°), $\nu_{max.}$ 1 720 (film) cm^{-1} (C=O).

Dry methanolic solutions of methyl mercaptoacetate (2.5

[22] H. D. Hartough and A. I. Kosak, *J. Amer. Chem. Soc.*, 1947, **69**, 3093.
[23] H. D. Hartough and L. G. Conley, *J. Amer. Chem. Soc.*, 1947, **69**, 3096.
[24] E. L. Eliel and D. E. Rivard, *J. Org. Chem.*, 1952, **17**, 1252.

g) and the crude bromomethyl compound (5.6 g) were added successively to an ice-cooled, stirred solution of sodium (0.55 g) in dry methanol (25 ml), then the mixture was allowed to attain room temperature. It was then acidified with acetic acid and evaporated, and the residue was treated with ether and water. Evaporation of the washed ($NaHCO_3$ and H_2O) and dried ethereal solution gave the product as an *oil* (5.8 g, 95%), b.p. 140—142° at 0.1 mmHg (Found: C, 56.85; H, 5.6%; *M*, 254. $C_{12}H_{14}O_4S$ requires C, 56.65; H, 5.55%; *M*, 254), $\nu_{max.}$ 1 720 (film) cm^{-1} (C=O), δ 3.08 (s, S·CH_2·CO), 3.95 (s, OMe), and 4.12 (s, ArCH_2·S).

Methyl 3,4-*Dihydro*-4-*oxo*-1H-2-*benzothiopyran*-3-*carboxylate* [(2) ⇌ (3)].—*Method A*. A solution of either the crude or the distilled diester (4) (5.08 g, 0.02 mol) in dry benzene (20 ml) was added to a stirred suspension of dry sodium methoxide [from sodium (0.95 g, 0.041 g atom)] in benzene (100 ml), then the mixture was heated under reflux for 1 h and some of the benzene (*ca.* 25 ml) was distilled off. The cooled mixture was then stirred with 2M-hydrochloric acid, the benzene layer was separated, and the acid layer was extracted with benzene. The combined benzene solutions were washed, dried, and evaporated, to give the product (1.3 g) as bright yellow *needles*, m.p. 84—85° (from methanol, then from benzene) (Found: C, 59.3; H, 4.6. $C_{11}H_{10}O_3S$ requires C, 59.45; H, 4.55%), $\nu_{max.}$ 1 642 cm^{-1} (chelated ester C=O), δ 3.74 (s, 1-H_2), 3.84 (s, OMe), and 12.42 (s, OH), *m/e* 222 (M^+), 190 (*M* — MeOH), and 162 (190 — CO, *m**138). When the mother liquors were set aside for several weeks, more pure product (2.7 g; total yield 90%) separated. It gave an intense emerald green colour with neutral aqueous iron(III) chloride.

Method B. Dimethyl carbonate (5.4 g) was added dropwise to a stirred suspension of oil-free sodium hydride (2.0 g) in dry benzene (50 ml), then the mixture was heated under reflux and 1*H*-2-benzothiopyran-4(3*H*)-one (1) [7] (5 g) was added in portions during 3 h. The cooled mixture was acidified cautiously with acetic acid, then diluted with aqueous 50% hydrochloric acid; the product (2.3 g, 35%), isolated in the usual way, was identical with that obtained by method A.

1H-2-*Benzothiopyran*-4(3H)-*one*.—The oxo-ester (2) (1.0 g) was stirred with an excess of warm (50 °C) aqueous 5% potassium hydroxide until it has dissolved (*ca.* 2.5 h). The mixture was then acidified with 2M-hydrochloric acid and heated on a steam-bath for 15 min; then neutral and acidic fractions were obtained in ether in the usual way. The neutral fraction gave the ketone (1) as needles (0.58 g, 79%), m.p. 58—59° (lit.,[7] 59—60°) (from light petroleum). The acidic fraction gave the dicarboxylic acid (5) (0.12 g, 12%), m.p. 144—145° (lit.,[8] 146—147°) (from ethanol) (Found: *M*, 226. Calc. for $C_{10}H_{10}O_4S$: *M*, 226), $\nu_{max.}$ 1 680 and 1 715 cm^{-1} (C=O). The same acid was obtained by alkaline hydrolysis of the diester (4).

Reaction of the Oxo-ester (2) *with Hydroxylamine*.—(*a*) A solution of the oxo-ester (2) (1 g) and hydroxylamine hydrochloride (0.5 g) in pyridine–methanol (1 : 1; 10 ml) was kept overnight at 100 °C, then diluted with 2M-hydrochloric acid. Brown organic material was isolated with ether and chromatographed on silica gel. Elution with benzene–light petroleum (3 : 1) gave (*a*) 1*H*-2-benzothiopyran-4(3*H*)-one oxime (0.12 g) as *needles*, m.p. 136—137° (from ethanol) (Found: C, 60.0; H, 5.15; N, 7.8%; *M*, 179. C_9H_9NOS requires C, 60.3; H, 5.05; N, 7.8%; *M*, 179), identical with the oxime formed directly from ketone (1); (*b*) methyl 3,4-dihydro-4-oxo-1*H*-2-benzothiopyran-3-carboxylate (2) oxime (0.1 g), which crystallised from ethanol as pale yellow *needles*, m.p. 168—170° (decomp.) (Found: C, 55.85; H, 4.8; N, 6.1%; *M*, 237. $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.65; N, 5.9%; *M*, 237), $\nu_{max.}$ 1 738 cm^{-1} (C=O), δ 3.95 (s, OMe), 5.12 (s, 3-H), and 8.4br (1 H, OH, exchanges with D_2O); (*c*) amorphous material (50 mg), probably the oxadiazine (9) (Found: *M*, 220.0314. Calc. for $C_{10}H_8N_2O_2S$: M^+, 220.0306), $\nu_{max.}$ *ca.* 1 700br cm^{-1} (C=O), δ 7.8br (2 H, 2 × NH); and (*d*) the hydroxamic acid from the enol (3) (50 mg), which could not be crystallised (Found: *M*, 223.0308. Calc. for $C_{10}H_9NO_3S$: M^+, 223.0303), $\nu_{max.}$ 1 635 cm^{-1} (C=O), δ 9.5—11.0br [3 H (probably 2 × OH; 1 × NH), exchanged with D_2O] (no OMe signal), giving a deep red colour with neutral aqueous iron(III) chloride.

(*b*) A mixture of the oxo-ester (2) (2 g), hydroxylamine hydrochloride (0.5 g), Dowex-1 (OH^-) anion-exchange resin (0.5 g), and methanol (50 ml) was shaken at room temperature, further portions (0.2 g) of hydroxylamine hydrochloride and resin being added at intervals of 2 days. The reaction was stopped (*ca.* 8 days) when t.l.c. indicated that *ca.* 80% of the starting material had reacted; after this time extensive decomposition set in. The mixture was then filtered and evaporated to dryness, and the residue was chromatographed in benzene on silica gel. Elution with benzene–light petroleum (1 : 1) gave a forerun of starting material (0.2 g), then the oxime of (2) [0.8 g, 42% (allowing for recovered starting material)], identical with that obtained by method (*a*).

1,2-*Dihydro*-2-*phenyl*-5H-[2]*benzothiopyrano*[4,3-c]*pyrazol*-3-*one* (6).—A mixture of the oxo-ester (2) (2 g) and phenylhydrazine (1.5 g) was kept at 110 °C until the vigorous reaction which ensued had subsided. The cooled red residue was triturated with ether, then recrystallised from benzene or methanol, to give *needles* (2 g, 79%), m.p. 127—128° (Found: C, 68.5; H, 4.4; N, 10.1. $C_{16}H_{12}N_2OS$ requires C, 68.55; H, 4.3; N, 10.0%), $\nu_{max.}$ ($CHCl_3$) 1 650 cm^{-1} (C=O), δ 3.50 (s, 5-H_2) and 3.7br (NH) (no enolic OH signal), *m/e* 280 (M^+), 252 (*M* — CO), and 161 (*M* — PhN:C:O, base peak).

Use of hydrazine hydrate (98% w/w) in this reaction gave the *pyrazolone* (7) (62%), which formed prisms, m.p. 160—162° (decomp.) (from methanol) (Found: C, 59.0; H, 3.9; N, 13.5%; *M*, 204. $C_{10}H_8N_2OS$ requires C, 58.8; H, 3.95; N, 13.7%; *M*, 204), $\nu_{max.}$ 1 650 cm^{-1} (C=O), δ [$(CD_3)_2SO$] 3.80 (s, 5-H_2) and 6.08 (s, 2 H, 2 × NH).

Methylation of the Pyrazolone (6).—(*a*) A solution of the pyrazolone (6) (2 g) and sodium hydroxide (0.3 g) in methanol (10 ml) and water (2 ml) was treated with dimethyl sulphate (1.0 g) under the conditions described in ref. 13. An ethereal solution of the brown oily product was shaken with aqueous sodium hydroxide in order to remove a small amount of starting material, then the resulting mixture of two components [1 : 1 (t.l.c. and n.m.r.)] was chromatographed on silica gel. Elution with benzene gave the O-*methyl derivative* (10) (0.8 g, 39%), which formed pale yellow needles, m.p. 95—96° (from methanol) (Found: C, 69.4; H, 4.95; N, 9.3%; *M*, 294. $C_{17}H_{14}N_2OS$ requires C, 69.35; H, 4.8; N, 9.5%; *M*, 294), δ 3.93 (s, 5-H_2) and 4.10 (s, OMe); no C=O band in the i.r. Continued elution with benzene–ethanol (20 : 1) gave the N-*methyl derivative* (8) (0.5 g, 24%) as white needles, m.p. 193—194° (decomp.) (from benzene) (Found: C, 69.3; H, 4.55; N, 9.6%; *M*, 294), $\nu_{max.}$ 1 640 cm^{-1} (C=O), δ 2.51 (s, NMe), and 4.02 and 4.56 (dd, 5-H_2, *J* 17.0 Hz).

(*b*) Oil-free sodium hydride [from 60% suspension in oil

(0.15 g)] and methyl iodide (0.34 g) were added successively to a stirred solution of the pyrazolone (6) (0.56 g) in dry dimethylformamide (10 ml). After 5 min, water was added dropwise, then in excess, and the resulting precipitate was collected. A mixture (0.5 g) of the *O*-methyl derivative (10) (40%) and the *N*-methyl derivative (8) (60%) remained after some starting material had been removed with aqueous sodium hydroxide.

(*c*) Sodium (0.55 g) and a solution of methyl iodide (0.34 g) in methanol (5 ml) were added successively to a stirred solution of the pyrazolone (6) (0.56 g) in methanol (20 ml). After being heated under reflux for 1 h, the mixture was cooled, acidified, and diluted with water. After treatment of the resulting precipitate with alkali to remove some starting material, the product contained the *N*-methyl derivative (8) (>95%), together with traces of the *O*-methyl derivative (10).

(*d*) An excess of ethereal diazomethane was added to an ethereal solution of the pyrazolone (6). After 0.5 h, the *O*-methyl derivative (10) (100%) was isolated in the usual way.

Methyl 3-Bromomethylthiophen-2-carboxylate (13) (with A. De).—Freshly recrystallised *N*-bromosuccinimide (22.2 g, 0.125 mol) was added in small portions to a stirred, irradiated (200 W tungsten lamp) solution of methyl 3-methylthiophen-2-carboxylate (21.3 g, 0.14 mol) and benzoyl peroxide (0.2 g) in boiling carbon tetrachloride (300 ml). The mixture was then cooled and filtered, and the solvent was removed. Distillation of the residue gave a small forerun of starting material, then the *product* (17 g, 58%), b.p. 118—120° at 0.5 mmHg, m.p. 32—33° (Found: C, 35.8; H, 3.2%; *M*, 234. $C_7H_7BrO_2S$ requires C, 35.75; H, 3.0%; *M*, 234), $\nu_{max.}$ (film) 1 720 cm^{-1} (C=O), δ 3.85 (s, OMe) and 4.82 (s, CH_2Br).

Methyl (2-Methoxycarbonyl-3-thenylthio)acetate (14) (with A. De).—Prepared (74%) by the method used for the diester (4), this had b.p. 148—149° at 0.5 mmHg (Found: C, 46.45; H, 4.7%; *M*, 260. $C_{10}H_{12}O_4S_2$ requires C, 46.15; H, 4.65%; *M*, 260), δ 3.23 (s, $S{\cdot}CH_2{\cdot}CO$), 3.70 and 3.86 (s, 2 × OMe), and 4.23 (s, $ArCH_2{\cdot}S$).

Methyl 6,7-Dihydro-7-oxo-4H-thieno[3,2-c]thiopyran-6-carboxylate (12).—(*a*) (with A. De) Cyclisation of the diester (14) by the method described for the benzene analogue (4) gave an oil, from which yellow *needles* (20%), m.p. 165—168° (from methanol), slowly separated (Found: C, 47.15; H, 3.5. $C_9H_8O_3S_2$ requires C, 47.35; H, 3.5%), *m/e* 228 (M^+), 196 (*M* − MeOH), and 168 (196 − CO); other spectral data are discussed in the text.

(*b*) A solution of sodium methoxide [from sodium (0.54 g)] in methanol (10 ml) was added in one portion to an ice-cooled solution of the diester (14) (3 g) in dimethylformamide (10 ml). The yellow mixture was allowed to warm to room temperature and the reaction was followed by t.l.c. As soon as all the starting material had reacted (*ca.* 0.5 h), water was added, and the oily product was extracted with ether. It slowly solidified, to give a product (1.6 g, 61%) identical with that just described.

Methyl 3-Methyl-5-nitrobenzo[b]thiophen-2-carboxylate.—Prepared (100%) by a method analogous to that [20] used for the ethyl ester, this formed needles, m.p. 187° (from ethanol) (lit.,[25] 187—188°).

Ethyl or Methyl 3-Bromomethyl-5-nitrobenzo[b]thiophen-2-carboxylate (22).—Ethyl 3-methyl-5-nitrobenzo[*b*]thiophen-2-carboxylate was brominated in carbon tetrachloride as described for the bromination of methyl *o*-toluate. Removal of the solvent and recrystallisation of the residue from benzene–light petroleum gave *needles* (77%), m.p. 148—150° (Found: C, 41.8; H, 3.0; N, 4.15%; *M*, 343. $C_{12}H_{10}BrNO_4S$ requires C, 41.85; H, 2.9; N, 4.05%; *M*, 343), $\nu_{max.}$ 1 715 cm^{-1} (C=O), δ 5.23 (s, CH_2Br). The *methyl ester* (22) (83%) was obtained similarly, except that it crystallised directly from the cooled reaction mixture. It formed needles, m.p. 196—198° (from benzene) (Found: C, 40.25; H, 2.35; N, 4.15%; *M*, 329. $C_{11}H_8BrNO_4S$ requires C, 40.0; H, 2.45; N, 4.25%; *M*, 329), $\nu_{max.}$ 1 710 cm^{-1} (C=O), δ ($HCO{\cdot}NMe_2$) 5.41 (s, CH_2Br).

Ethyl or Methyl (2-Ethoxy- or Methoxy-carbonyl-5-nitro-3-benzo[b]thenylthio)acetate (23).—Piperidine (3 g) was added to a boiling solution of ethyl mercaptoacetate (3.6 g) and ethyl 3-bromomethyl-5-nitrobenzo[*b*]thiophen-2-carboxylate (10 g) in ethanol (500 ml), then the mixture was heated under reflux for 1.5 h, and cooled. The product was collected and recrystallised from ethanol, to give *needles* (9 g, 81%), m.p. 147—148° (Found: C, 50.0; H, 4.45; N, 3.5%; *M*, 383. $C_{16}H_{17}NO_6S_2$ requires C, 50.1; H, 4.45; N, 3.65%; *M*, 383), $\nu_{max.}$ 1 710 and 1 730 cm^{-1} (C=O), δ 3.30 (s, $S{\cdot}CH_2{\cdot}CO$) and 4.63 (s, $ArCH_2{\cdot}S$).

A boiling solution of the methyl ester (22) (2 g) and methyl mercaptoacetate (0.7 g) in benzene (150 ml) and methanol (150 ml) was heated under reflux for 1 h with piperidine (0.75 g). The solvents were evaporated until crystallisation commenced, then the *dimethyl ester* (23) (1.9 g, 88%) was collected. It formed needles, m.p. 139.5—140° (from methanol) (Found: C, 47.15; H, 3.85; N, 3.9%; *M*, 355. $C_{14}H_{13}NO_6S_2$ requires C, 47.3; H, 3.7; N, 3.95%; *M*, 355), δ 3.30 and 4.63.

2-Bromo-2′-chloro-5′-nitroacetophenone (18).—A solution of bromine (8.1 g) in acetic acid (10 ml) was added dropwise during 0.5 h to a solution of 2′-chloro-5′-nitroacetophenone (10 g) in acetic acid (50 ml), to which a catalytic amount of aluminium chloride had been added, at such a rate that the temperature did not exceed 20 °C. The mixture was then poured into water and kept at 0 °C until the resulting oil had crystallised. It formed *needles* (11.2 g, 81%) (from methanol–water), m.p. 47—48° (Found: C, 34.4; H, 1.85; N, 5.15%; *M*, 277. $C_8H_5BrClNO_3$ requires C, 34.5; H, 1.8; N, 5.0%; *M*, 277), $\nu_{max.}$ 1 710 cm^{-1} (C=O), δ 4.53 (CH_2Br).

Photobromination in chloroform by the method [26] used for the 5′-chloro-2′-nitro-isomer gave an oily mixture which contained the 2,2-dibromo-compound (*ca.* 20%).

Reaction of 2-Bromo-2′-chloro-5′-nitroacetophenone with Ethyl Mercaptoacetate.—(*a*) Piperidine (0.85 g, 0.01 mol) was added to an ice-cooled, stirred mixture of the bromo-ketone (18) (2.78 g, 0.01 mol), ethyl mercaptoacetate (1.2 g, 0.01 mol), and ethanol (50 ml). The mixture was allowed to warm to room temperature, then water was added, and the *mono-ester* (20) was filtered off. It formed cream needles (3.1 g, 100%), m.p. 52—53° (from methanol) (Found: C, 45.1; H, 3.75; N, 4.4%; *M*, 317. $C_{12}H_{12}ClNO_5S$ requires C, 45.35; H, 3.8; N, 4.4%; *M*, 317), $\nu_{max.}$ 1 695 and 1 730 cm^{-1} (C=O).

(*b*) An ethanolic solution of the foregoing ester was heated under reflux for 2 h with ethyl mercaptoacetate (1 mol. equiv.) and piperidine (1.1 mol. equiv.). The benzo[*b*]thiophen derivative (23; diethyl ester) (100%) was identical with that obtained before.

[25] J. Cooper and R. M. Scrowston, *J. Chem. Soc.* (*C*), 1971, 3405.

[26] K. Schofield and J. C. E. Simpson, *J. Chem. Soc.*, 1948, 1170.

Ethyl or Methyl 3,4-*Dihydro*-8-*nitro*-4-*oxo*-1H-*thiopyrano*-[4,3-b][1]*benzothiophen*-3-*carboxylate* [(16) *or* (15)].—*Method A*. The diethyl ester (23) reacted with sodium ethoxide in ethanolic dimethylformamide under the conditions described for the thiophen analogue (14). The product (16) (67%) formed orange *microcrystals*, m.p. 270—272° (decomp.) (from benzene) (Found: C, 49.55; H, 3.3; N, 4.4. $C_{14}H_{11}NO_5S_2$ requires C, 49.85; H, 3.3; N, 4.15%), $\nu_{max.}$ 1 740 (ester C=O), 1 718 (oxo C=O), and 1 655 (chelated C=O) cm^{-1}, δ (C_5D_5N) 3.72 (s, 1-H_2 of enol form), 4.92 (s, 3-H of oxo-form), and 4.15 and 4.42 (dd, 1-H_2 of oxo-form, J 17.5 Hz), *m/e* 337 (M^+) and 291 (M — EtOH).

Prepared similarly, the methyl ester (15) (51%) formed orange-brown *needles*, m.p. 302—305° (decomp.) (from chloroform) (Found: C, 48.1; H, 3.0; N, 4.45%; M, 323. $C_{13}H_9NO_5S_2$ requires C, 48.3; H, 2.8; N, 4.35%; M, 323); spectral data are similar to those for the ethyl ester.

Method B. An ice-cooled solution of 2-bromo-2′-chloro-5′-nitroacetophenone (2.78 g, 0.01 mol) and ethyl mercaptoacetate (2.4 g, 0.02 mol) in dry ethanol (50 ml) was treated with sodium (0.69 g, 0.06 g atom). The mixture was allowed to warm to room temperature, and water was added when all the starting material had reacted. The product (16) (2.19 g, 65%) was identical with that obtained by method A.

We thank Midland-Yorkshire Holdings Ltd. for a gift of 3-methylthiophen. The work was carried out when D. C. S. was a VIth form student at Beverley Grammar School.

[5/2035 *Received*, 17*th October*, 1975]