Photochemical Transformations. Part XXXI.[1] Photolysis of Thiobenzoic Acid *O*-Esters. Part II.[1] General Methods for the Preparation of Thiobenzoic Acid *O*-Esters

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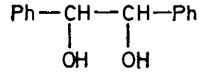
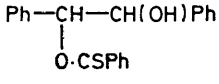
Treatment of alkoxides with (thiobenzoylthio)acetic acid gives thiobenzoic acid *O*-esters in high yield. Similarly, the reaction of alkoxides with 2,4-dinitrophenyl dithiobenzoate (IX) gives the corresponding thiobenzoic acid *O*-ester. Imidate salts react with hydrogen sulphide in pyridine to give thioacid *O*-esters in good yields.

THE study of the photochemistry of thiobenzoic acid *O*-esters [1] is restricted by the fact that they are difficult to prepare. We have used some of the existing methods for their synthesis and have developed new methods that offer advantages, particularly in yield.

Thiobenzoyl chloride can be prepared by a variety of methods. For example, treatment of phenylmagnesium bromide or phenyl-lithium with carbon disulphide followed by reaction of the resulting dithio-acid with thionyl chloride gives thiobenzoyl chloride in yields of 40—50%.[2-4] Treatment of dithiobenzoic acid with *o*-phenylenephosphorus trichloride also gives thiobenzoyl chloride.[5] Other methods available for the preparation of dithiobenzoic acid do not appear to have any advantage over the Grignard method.[6] It is difficult to obtain pure thiobenzoyl chloride. During the preparation rigorous exclusion of oxygen is required or benzoyl chloride is formed. Thiobenzoyl chloride must be stored at −78° to avoid decomposition. Thiobenzoylation of alcohols with thiobenzoyl chloride in dry pyridine gives 50—90% yields of thiobenzoic acid *O*-esters [1] but the yields are less if the alcohols are hindered. *meso*-Dihydrobenzoin (I) gave only the monothiobenzoic acid *O*-ester (30%) (II).



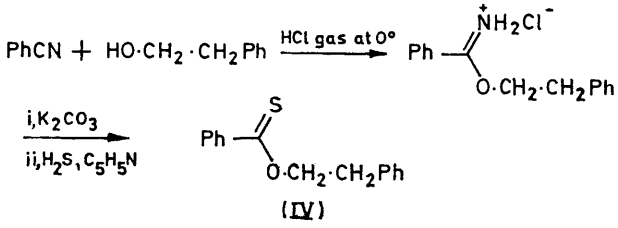
(I)



(II)

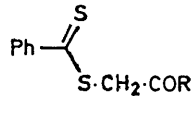
Acid-catalysed condensation of an alcohol and benzonitrile followed by thiolysis of the resulting benzimidate (Scheme 1) gives good yields of thiobenzoic acid *O*-esters.[7,8] This method is particularly useful for the preparation of *O*-phenethyl thiobenzoate [9] (Scheme 1). Yields (40—70%) were *ca.* 20% higher than in the overall thiobenzoyl chloride procedure.

(Thiobenzoylthio)acetic acid (III; R = OH) has been reported as a particularly effective thiobenzoylating agent for amines and their derivatives.[10] Treatment of sodium alkoxides with this reagent in tetrahydrofuran gave the corresponding thiobenzoic acid *O*-esters in >90% yields. Reactions with sterols and diols gave 40—50% yields. Addition of imidazole to the alkoxide

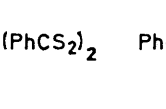


SCHEME 1

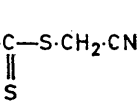
before the (thiobenzoylthio)acetic acid resulted in improved yields, and milder reaction conditions were needed. For the preparation of *O*-phenethyl thiobenzoate (IV), sodium hydride (2 equiv.) was added to



(III)



(VI)

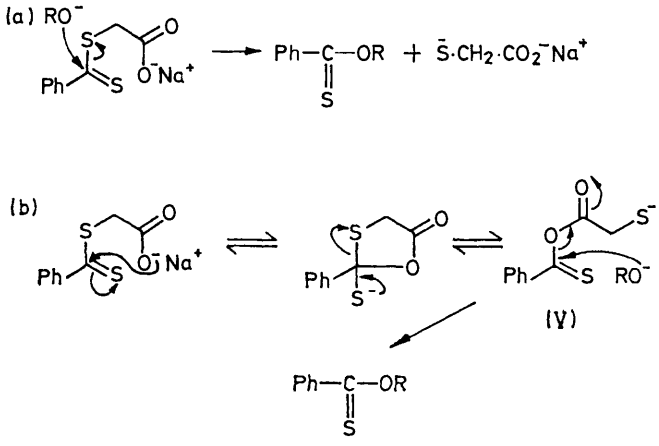


(VII)

(thiobenzoylthio)acetic acid (1 equiv.) in tetrahydrofuran, and imidazole (1 equiv.) was added. The mixture was heated at reflux (5 min) and the 2-phenylethanol (1 equiv.) was added. After a further 5 min at reflux the thioester (IV) was isolated (>90%). When thiobenzolation was attempted with the ethyl ester or the amide of (thiobenzoylthio)acetic acid (III; R = OEt or NH_2), no thiobenzoic acid *O*-esters were formed. It seems that thioglycolic acid or a derivative is not merely a leaving group (Scheme 2a); a more reactive thiobenzoylating reagent is apparently being generated *in situ* from (thiobenzoylthio)acetic acid. Such a species could be a mixed anhydride (V) (Scheme 2b). Even if present in low equilibrium concentrations, the anhydride (V) would be an extremely reactive thiobenzoylating reagent.

[1] Part XXX, Part I, S. Achmatowicz, D. H. R. Barton, P. D. Magnus, G. A. Poulton, and P. J. West, preceding paper.
[2] H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, 1920, **3**, 824.
[3] R. Mayer and S. Scheithauer, *J. prakt. Chem.*, 1963, **4**, 21,214.
[4] R. Mayer and S. Scheithauer, *Chem. Ber.*, 1965, **98**, 829.
[5] G. Barnikow and T. Gabrio, *Z. Chem.*, 1968, **8**, 142.
[6] E. J. Hedgley and H. G. Fletcher, jun., *J. Org. Chem.*, 1965, **30**, 1282.
[7] G. J. Janz, I. Ahmad, and H. V. Venkatasetty, *J. Phys. Chem.*, 1964, **68**, 889.
[8] R. Roger and D. G. Neilson, *Chem. Rev.*, 1961, **61**, 179 and references cited therein.
[9] D. H. R. Barton, P. D. Magnus, G. A. Poulton, and P. J. West, *J.C.S. Perkin I*, 1973, 1580.
[10] (*a*) F. Kurzer, *Chem. and Ind.*, 1961, 1333; (*b*) A. Kjaer, *Acta Chem. Scand.*, 1950, **4**, 1347; 1952, **6**, 1374; (*c*) K. A. Jensen and C. Pedersen, *ibid.*, 1961, **15**, 1087; (*d*) K. A. Jensen, O. Buchardt, and C. Christophersen, *ibid.*, 1967, **21**, 1936; (*e*) A. Holm, *ibid.*, 1968, **22**, 2019.

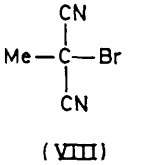
Attempts to prepare stable mixed anhydrides of thiobenzoic acid failed. Treatment of the sodium, silver, or thallium(I) salt of phenylacetic acid with thiobenzoyl chloride gave no reaction. Reaction of thiobenzoic acid



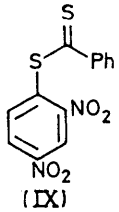
SCHEME 2

or the magnesium bromide salt of thiobenzoic acid with toluene-*p*-sulphonyl chloride gave bisthiobenzoyl disulphide (VI).

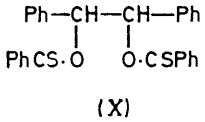
Attempts to make active esters of dithiobenzoic acid were more successful. The magnesium salt of dithiobenzoic acid was treated with bromoacetonitrile and compound (VII) was isolated in good yield, but it did not act as a thiobenzoylating reagent. Treatment of the magnesium salt of dithiobenzoic acid with cyanogen bromide gave bisthiobenzoyl disulphide (VI). Also treatment of sodium dithiobenzoate with α-bromo-α-methylmalononitrile (VIII) gave the disulphide (VI).



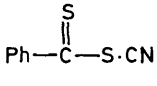
(VIII)



(IX)



(X)

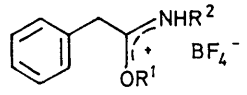


(XI)

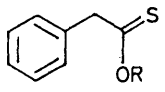
1-Chloro-2,4-dinitrobenzene reacted with sodium dithiobenzoate to give the ester (IX) (25%). Treatment of cholesterol with sodium hydride–imidazole in tetrahydrofuran followed by 2,4-dinitrophenyl dithiobenzoate (IX) gave *O*-cholesteryl thiobenzoate (80%). *meso*-Dihydrobenzoin (I) on similar treatment gave the di-*O*-ester (X) (56%), whereas (±)-dihydrobenzoin gave only the monoester, in low yield.

It has recently been reported [11] that thiobenzoyl isothiocyanate (XI) is a stable compound, although its thiobenzoylating properties have not been reported.

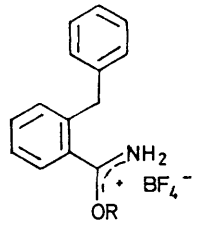
Since the reaction of 2-phenylethanol with benzonitrile followed by thiolysis gave the corresponding thiobenzoic acid *O*-ester, extension of this procedure *via* *O*-alkylation of amides was investigated. Phenylacetamide was treated with triethyloxonium fluoroborate [12] to give the crystalline imidate (XIIa) (97%).[13,14] Treatment of the imidate (XIIa) in pyridine with hydrogen sulphide gave the *O*-ester (XIIIa) (83%). The methyl analogues (XIIb) (91%) and (XIIIb)



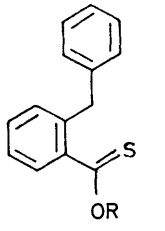
(XII) a; R^1 = Et, R^2 = H
b; R^1 = Me, R^2 = H
c; R^1 = Me, R^2 = Et



(XIII) a; R = Et
b; R = Me



(XIV) a; R = Me
b; R = Et



(XV) a; R = Me
b; R = Et

(30·5%) were similarly obtained. Alkylation of benzyl cyanide with triethyloxonium fluoroborate, followed by treatment with dry methanol gave the salt (XIIc) (44%),[15] thiolysis of which also gave the *O*-methyl ester (XIIIb) (59%). *o*-Benzylbenzamide reacted with trimethyl- or triethyl-oxonium fluoroborate to give the corresponding imidate (XIVa) (81%) or (XIVb) (67%). Thiolysis of the products gave the esters (XVa) (59%) and (XVb) (47%). Compounds (XIIIa and b) and (XVa and b) were not accessible *via* the other procedures described involving the direct condensation of a nitrile with an alcohol.

The three new procedures for thiobenzoylating alcohols have the advantage that the reagents employed are indefinitely stable and readily prepared. Furthermore the yields and simplicity of operation in general make the modified (thiobenzoylthio)acetic acid procedure the method of choice.

[11] J. Goerdeler and W. Teller, *Tetrahedron Letters*, 1972, 1513.
[12] (*a*) H. Meerwein, E. Battenberg, M. Gold, E. Pfeil, and G. Willfang, *J. prakt. Chem.*, 1939, **83**, 154; (*b*) H. Meerwin, W. Florian, N. Schon, and G. Stopp, *Annalen*, 1961, **641**, 1.
[13] U. Schmidt, E. Heymann, and K. Kabitzke, *Chem. Ber.*, 1963, **96**, 1478.
[14] (*a*) Y. Sakurada, *Mem. Coll. Sci. Kyoto Univ.*, 1926, **9**, 237 (*Chem. Abs.*, 1927, **21**, 2458); (*b*) R. Radeglia, S. Scheithauer, and R. Mayer, *Z. Naturforsch.*, 1969, **24***b*, 283; (*c*) H. Lumbroso and P. Reynaud, *Compt. rend.*, 1966, **262***C*, 1739.
[15] H. Meerwin, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.*, 1956, **89**, 209.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded for Nujol mulls. N.m.r. spectra were measured for solutions in carbon tetrachloride with tetramethylsilane as internal standard. U.v. spectra were measured for solutions in cyclohexane. All solvents were dried by standard techniques. Rotations were measured on a Perkin-Elmer 141 polarimeter for solutions in chloroform.

Only representative preparations of thiobenzoic acid *O*-esters are described. Part I and later parts of this series describe further preparations.

O-Phenethyl Thiobenzoate (IV).—2-Phenylethanol (2·45 g) and benzonitrile (2·05 g) in dry ether (25 ml) were treated with dry hydrogen chloride gas at 0° for 1 h then set aside overnight at 0°. The mixture was poured into water, neutralised with solid potassium carbonate, and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated at room temperature. The residue was dissolved in dry pyridine (25 ml) and treated with dry hydrogen sulphide gas (excess) in the dark. The mixture was left overnight at room temperature, then poured into water. Extraction with ether, drying (Na_2SO_4), and chromatography over acid-washed silica gel [elution with light petroleum (b.p. 40—60°)] gave the *thioester* (IV) (2·60 g, 55%) as a yellow liquid, b.p. 116—118° at 0·1 mmHg, $\nu_{max.}$ (film) 1230 cm^{-1}, $\lambda_{max.}$ 248, 288, and 420 nm (ε 6600, 9600, and 120), τ 6·90 (2H, t, *J* 7 Hz), 5·20 (2H, t, *J* 7 Hz), 2·75 (8H, m), and 1·92 (2H, m) (Found: C, 74·7; H, 5·7; S, 13·2. $C_{15}H_{14}OS$ requires C, 74·4; H, 5·8; S, 13·2%).

This sequence illustrates the procedure used when preparing thioesters from their imino-ether derivatives (Scheme 1).

O-Phenethyl Thiobenzoate (IV) *by the (Thiobenzoylthio)acetic Acid* (III; R = OH) *Procedure.*—Sodium hydride (0·10 g) was added to (thiobenzoylthio)acetic acid (III; R = OH) (0·212 g) in dry tetrahydrofuran (25 ml). When the initial vigorous effervescence had ceased, imidazole (0·136 g) was added. The mixture was heated at reflux for 5 min and 2-phenylethanol (0·122 g) was added. After being heated at reflux for a further 5 min, the mixture was worked up as before. The residue was chromatographed on alumina (G3) [elution with light petroleum (b.p. 40—60°)] to give the thioester (IV) (0·21 g), identical with the sample previously prepared.

Application of this procedure to cholesterol gave *O*-cholesteryl thiobenzoate (90%).[1]

2,4-Dinitrophenyl Dithiobenzoate (IX).—1-Chloro-2,4-dinitrobenzene (2·02 g) and sodium dithiobenzoate (1·76 g) were mixed in acetone (40 ml) at room temperature. After 1 h the mixture was centrifuged and the acetone layer separated. Evaporation followed by chromatography gave *2,4-dinitrophenyl dithiobenzoate* (IX) (650 mg, 25%), m.p. 98—100° (from carbon tetrachloride), $\nu_{max.}$ 1600, 1240, 870, 840, 775, 760, and 680 cm^{-1}, $\lambda_{max.}$ 310 and 228 nm (ε 10,000 and 10,000) (Found: C, 48·6; H, 2·7; S, 19·9. $C_{13}H_8N_2O_4S_2$ requires C, 48·8; H, 2·5; S, 20·0%).

O-Cholesteryl Thiobenzoate.—Imidazole (0·034 g), cholesterol (0·096 g), and sodium hydride (0·012 g) in tetrahydrofuran (10 ml) were heated at reflux for 1 h. To this mixture was added 2,4-dinitrophenyl dithiobenzoate (IX) (0·080 g). After 0·5 h at reflux the mixture was evaporated and the residue chromatographed on alumina (G3) [elution with light petroleum (b.p. 40—60°)] to give *O*-cholesteryl thiobenzoate (80%).

OO'-meso-1,2-Diphenylethylene Bisthiobenzoate (X).—*meso*-Dihydrobenzoin (0·053 g), imidazole (0·069 g), and sodium hydride (0·024 g) in tetrahydrofuran (10 ml) were heated at reflux for 0·5 h. 2,4-Dinitrophenyl dithiobenzoate (0·160 g) was added and the mixture was heated at reflux for a further 0·5 h. Work-up as before gave the bisthiobenzoate (X) (0·067 g), m.p. 193—195° (from chloroform), identical with an authentic sample.[9]

Ethyl Phenylacetimidate Hydrofluoroborate (XIIa).—Phenylacetamide (3·34 g) in dichloromethane (75 ml) was treated with triethyloxonium fluoroborate (4·68 g) in dichloromethane (5 ml) under nitrogen at room temperature. The mixture was stirred overnight. Evaporation gave the *imidate* (XIIa) (97%), m.p. (sealed tube) (from chloroform–ether) 78—79·5°, $\nu_{max.}$ 3230, 3100, 1685, and 1290 cm^{-1}, τ 8·62 (3H, t, *J* 7 Hz), 6·08 (2H, s), 5·58 (2H, q, *J* 7 Hz), 2·70 (5H, s), 1·02br (1H, s), and 0·9br (1H, s) (Found: C, 47·9; H, 5·5; N, 5·5. $C_{10}H_{14}BF_4NO$ requires C, 47·9; H, 5·6; N, 5·6%).

O-Ethyl Phenyl(thioacetate) (XIIIa).—Dry hydrogen sulphide was bubbled through a solution of the imidate (XIIa) (0·285 g) in dry pyridine (5 ml) at 0° for 1 h. The mixture was stirred for 1·5 h at 0° then for 1 h at room temperature, poured into cold saturated aqueous sodium chloride, and extracted with ether. The extract was washed successively with cold dil. hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The residue dissolved in chloroform was chromatographed on silica gel plates (60 × 20 cm). Elution with chloroform–cyclohexane (1 : 1 v/v) gave the *thioacetate* (XIIIa) (0·133 g, 83%), b.p. 20° at 10^{-4} mmHg, n_D^{25} 1·5554, $\nu_{max.}$ 1363, 1300, 1253, 1202, 1130, 1094, 1027, and 695 cm^{-1}, $\lambda_{max.}$ 377 and 243 nm (ε 45 and 8860), τ 8·66 (3H, t, *J* 7·5 Hz), 5·97 (2H, s), 5·52 (2H, q, *J* 7·5 Hz), and 2·66 (5H, s) (Found: C, 66·4; H, 7·0. $C_{10}H_{12}OS$ requires C, 66·6; H, 6·7%).

Methyl Phenylacetimidate Hydrofluoroborate (XIIb).—A suspension of trimethyloxonium fluoroborate (1·0 g) and phenylacetamide (0·91 g) in dry dichloromethane (7 ml) at room temperature was stirred overnight under nitrogen. The solvent was evaporated off to yield the *imidate* (XIIb) (1·46 g, 91%), m.p. (sealed tube) (from chloroform–ether) 64—65·5°, $\nu_{max.}$ 3345, 3230, 1704, 1604, 1206, 1120—1000, 932, and 852 cm^{-1}, τ 6·07 (2H, s), 5·92 (3H, s), and 2·74 (5H, s) (Found: C, 45·6; H, 5·2; N, 5·8. $C_9H_{12}BF_4NO$ requires C, 45·6; H, 5·1; N, 5·9%).

O-Methyl Phenyl(thioacetate) (XIIIb).—Methyl phenylacetimidate hydrofluoroborate (XIIb) (1·19 g) in dry pyridine (10 ml) at 0° was treated with hydrogen sulphide gas for 1 h. The mixture was stirred for 1·25 h at 0° then poured into cold saturated aqueous sodium chloride. The solution was extracted with ether and the extract washed successively with cold dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The residue in chloroform was chromatographed on silica plates (60 × 20 cm). Elution with chloroform–cyclohexane (1 : 1 v/v) gave the *thioester* (XIIIb) (0·255 g, 30·5%) as an oil, $\nu_{max.}$ 1494, 1453, 1441, 1302, 1254, 1207, 1118, 1018, 893, 775, 715, and 695 cm^{-1}, $\lambda_{max.}$ 376 and 240 nm (ε 43 and 8250), τ 5·90 (5H, s) and 2·62 (5H, s) (Found: C, 65·0; H, 6·4; S, 19·1. $C_9H_{10}OS$ requires C, 65·0; H, 6·1; S, 19·3%).

Methyl N-Ethylphenylacetimidate Hydrofluoroborate (XIIc).—A mixture of benzyl cyanide (3·66 g) and triethyloxonium fluoroborate (11·9 g) in dry dichloromethane (50 ml) was heated at reflux for 48 h under nitrogen. The mixture was evaporated and the residue cooled to 0°. Methanol (2·54 ml) was added and the solution was stirred

overnight at room temperature. Evaporation and trituration of the residue with ether gave the *imidate* (XIIc) (3·67 g, 44%), m.p. (sealed tube) (from chloroform–ether) 103—105°, $\nu_{max.}$ 3350, 3300, 1666, 1522, 1271, 1064, 1028, and 736 cm^{-1}, τ 8·70 (3H, t), 6·50 (2H, q, *J* 7 Hz), 5·82 (5H, s), 2·67 (5H, s), and 0·77br (1H, s) (Found: C, 49·7; H, 6·1; N, 5·3. $C_{11}H_{26}BF_4NO$ requires C, 49·8; H, 6·1; N, 5·3%).

Methyl *N*-ethylphenylacetimidate hydrofluoroborate (XIIc) (0·530 g) in dry pyridine (5 ml) was treated with hydrogen sulphide and the product was worked up as for (XIIIb). The thioester (XIIIb) isolated (0·197 g, 59%) was identical with the sample prepared from (XIIb).

Methyl o-*Benzylbenzimidate Hydrofluoroborate* (XIVa).—Trimethyloxonium fluoroborate (0·35 g) and *o*-benzylbenzamide (0·50 g) in dry dichloromethane (7 ml) were stirred at room temperature under nitrogen for 12 h. Evaporation left the *imidate* (XIVa) (0·60 g, 81%), m.p. (sealed tube) (from chloroform–ether) 140—141·5°, $\nu_{max.}$ 3305, 3165, 1703, 1606, 1100—1040, 763, 738, and 701 cm^{-1}, τ 5·92 (3H, s), 5·88 (2H, s), and 2·83 (11H, m) (Found: C, 57·4; H, 5·1; N, 4·3. $C_{15}H_{16}BF_4NO$ requires C, 57·6; H, 5·2; N, 4·5%).

O-*Methyl* o-*Benzyl*(*thiobenzoate*) (XVa).—The imidate (XIVa) (0·534 g) in dry pyridine (10 ml) was treated with hydrogen sulphide gas at 0° for 1 h. The solution was stirred for 1 h at 0° and then for 0·5 h at room temperature. Work-up in the usual way gave the *thiobenzoate* (XVa) (0·242 g, 59%) as an oil, $\nu_{max.}$ 1493, 1448, 1295, 1233, 1149, 1039, 764, 729, and 696 cm^{-1}, $\lambda_{max.}$ 406 and 269 nm (ε 303 and 8760), τ 5·92 (3H, s), 5·87 (2H, s), and 2·87 (9H, m) (Found: C, 74·1; H, 5·8; S, 13·3. $C_{15}H_{14}OS$ requires C, 74·3; H, 5·8; S, 13·2%).

Ethyl o-*Benzylbenzimidate Hydrofluoroborate* (XIVb).—Triethyloxonium fluoroborate (0·40 g) and *o*-benzylbenzamide (0·44 g) were treated in the usual way to give the *imidate* (XIVb) (0·46 g, 67%), m.p. (sealed tube) (from chloroform–ether) 127—129°, $\lambda_{max.}$ 3315, 3165, 1693, 1593, 1153, 1120—1000, 773, and 733 cm^{-1}, τ 8·68 (3H, t, *J* 7 Hz), 5·80 (2H, s), 5·08 (2H, q, *J* 7 Hz), 2·68 (9H, m), 0·78br (1H, s), and 0·38br (1H, s) (Found: C, 58·8; H, 5·5; N, 4·3. $C_{16}H_{18}BF_4NO$ requires C, 58·7; H, 5·5; N, 4·3%).

O-*Ethyl* o-*Benzyl*(*thiobenzoate*) (XVb).—The imidate (XIVb) (0·140 g) in dry pyridine (3 ml) was treated with dry hydrogen sulphide gas in the usual way. Work-up as for (XVa) gave the *thiobenzoate* (XVb) (0·052 g, 47%) as an oil, $\nu_{max.}$ 1608, 1504, 1455, 1302, 1240, 1042, 768, 735, and 702 cm^{-1}, $\lambda_{max.}$ 406 and 266 nm (ε 309 and 9430), τ 8·68 (3H, t, *J* 7·5 Hz), 5·80 (2H, s), 5·43 (2H, q, *J* 7·5 Hz), and 2·77 (9H, m) (Found: C, 75·0; H, 6·4. $C_{16}H_{16}OS$ requires C, 75·0; H, 6·3%).

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