Some Reactions of Soft Electrophiles with Esters and Other Compounds containing the Thiocarbonyl Group

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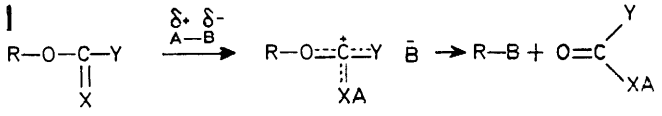
The reaction of a number of easily prepared hydroxy-derivatives containing the thiocarbonyl or selenocarbonyl group with soft electrophilic reagents has been studied. The products are derivatives with carbon bonded to the anionic fragment of the electrophile. The reactions occur under mild, neutral conditions and, in appropriate cases, afford good yields.

RECENTLY [1] we described the reaction of the soft electrophile methyl iodide with diol thiocarbonates, and applied this reaction in the synthesis of 6-deoxy-sugars. Since alcohols can be readily converted in high yield into xanthates (I), thiobenzoates [2] (II), thiocarbamates (III),[2] and selenobenzoates (IV),[2] the reactions of these esters with soft electrophiles [3] were expected to provide an alternative pathway to hydroxy-group replacement.

Recently Zehavi [4] has described improvements in steroid functionalisation by nucleophilic displacement of arenesulphonate esters by enhancing the leaving group ability. Our approach to hydroxy-group replacement *via* the esters (I)—(IV) seeks to create improved leaving groups in the presence of an appropriate nucleophile.

Although xanthate esters are frequently applied in olefin synthesis (Chugaev reaction [5]) their reaction with

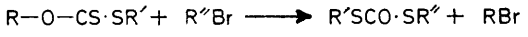


(I) X = S, Y = SR′
(II) X = S, Y = Ph
(III) X = S, Y = NR'_2
(IV) X = Se, Y = Ph

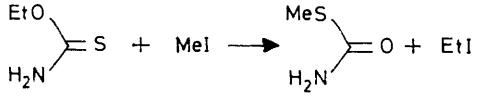
electrophiles has not been studied in detail. Reactions with alkyl bromides have been described [6] (Scheme 1).

[1] D. H. R. Barton and R. V. Stick, *J.C.S. Perkin I*, 1975, 1773.
[2] D. H. R. Barton and S. W. McCombie, *J.C.S. Perkin I*, 1975, 1574.
[3] T.-L. Ho, *Chem. Rev.*, 1975, **75**, 1.
[4] U. Zehavi, *J. Org. Chem.*, 1975, **40**, 3870.
[5] H. R. Nace, *Org. Reactions*, 1962, **12**, 57.
[6] E. Biilmann and J. Bjerrum, *Ber.*, 1917, **50**, 503; E. Biilmann, *Annalen*, 1909, **364**, 314.

Thiocarbamates have also been treated with alkyl halides [7] (Scheme 2). Douglass and Osborne have



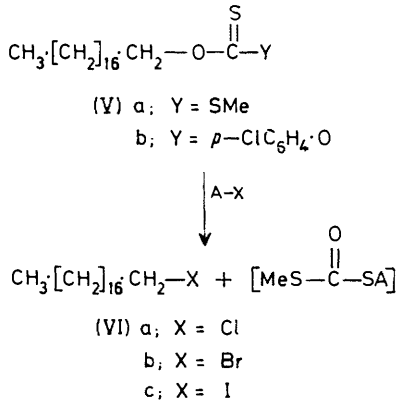
SCHEME 1



SCHEME 2

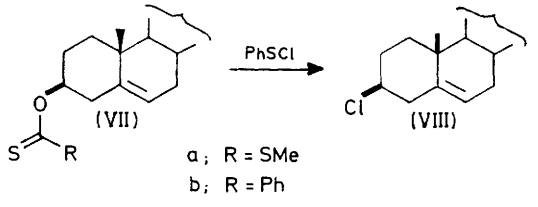
described the chlorination of simple xanthates giving sulphenyl chlorides and alkylsulphur trichlorides.[8]

S-Methyl *O*-stearyl dithiocarbonate (Va)[9] reacted with a range of halide derivatives in dichloromethane solution to give the corresponding stearyl halides in 50—100% yield. The results are tabulated. The reaction with methyl iodide was conveniently carried out in a sealed tube. Stearyl chloride (VIa), bromide (VIb), and



iodide (VIc) were also prepared in high yield by the reactions of the thiocarbonate (Vb) with benzenesulphenyl chloride, bromine, and methyl iodide, respectively.

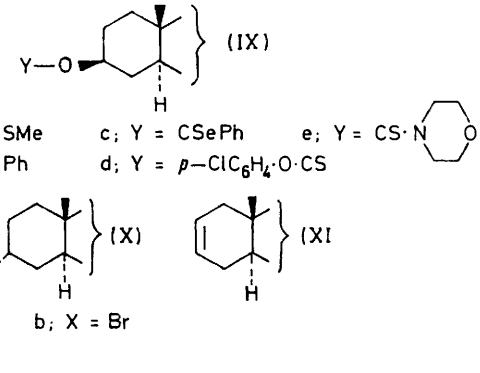
Treatment of *O*-cholest-5-en-3β-yl *S*-methyl dithiocarbonate (VIIa) or *O*-cholest-5-en-3β-yl thiobenzoate (VIIb) with benzenesulphenyl chloride gave 3β-chloro-



cholest-5-ene (VIII). Retention of stereochemistry at C-3 is consistent with the usual π-participation. In contrast the xanthate (IXa) and the thiobenzoate (IXb) derived from 5α-cholestan-3β-ol gave 3α-halides on reaction with halogens and halide derivatives (see Table).

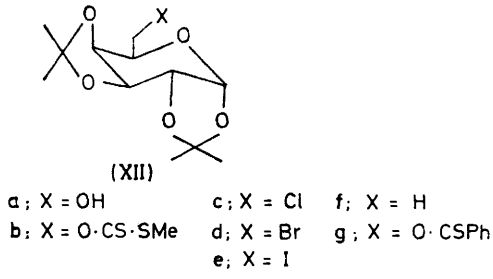
[7] E. E. Reid, 'Organic Chemistry of Bivalent Sulphur,' vol. IV, Chemical Publishing Co., New York, 1962, pp. 204—205 and references therein.

5α-Cholest-2-ene (XI) accompanied the 3α-chloride (Xa). The yield of olefin (XI) (26%) was greatest in the reaction between the xanthate (IXa) and benzeneselenenyl chloride. 5α-Cholest-2-ene (XI) was not formed during the preparation of 3α-bromo- (Xb) or 3α-iodo-5α-cholestane (Xc). This is consistent with the increased nucleophilicity–basicity ratio for bromide and iodide anions. Since selenoesters are now easily prepared in



high yield [2] we examined the reactions of *O*-5α-cholestan-3β-yl selenobenzoate (IXc) with soft electrophiles. Both 3α-chloro-5α-cholestane (Xa) and 5α-cholest-2-ene (XI) were formed in reactions with benzene-sulphenyl and -selenenyl chlorides.

The reaction of the thiocarbonate (IXd) with electrophiles was also investigated. With methyl iodide 3α-iodo-5α-cholestane (Xc) was obtained in 58% yield. The more nucleophilic thiocarbamate (IXe) [2] reacted with methyl iodide at room temperature (instead of 90 °C) to give the iodide (Xc). The chloride (Xa) and the bromide (Xb) were obtained from reactions with benzenesulphenyl chloride and bromine, respectively.



1,2:3,4-Di-*O*-isopropylidene-6-*O*-[(methylthio)thiocarbonyl]-α-D-galactose (XIIb) was prepared from 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (XIIa) in the usual way. The reactions of this xanthate with benzenesulphenyl chloride, bromine, and methyl iodide gave, respectively, the derived chloride (XIIc), bromide (XIId), and iodide (XIIe) in moderate yields. The structure of the bromide (XIId) was confirmed by reduction with tri-n-butyltin hydride,[2] giving 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactose (XIIf). The

[8] I. B. Douglass and C. E. Osborne, *J. Amer. Chem. Soc.*, 1953, **75**, 4582.

[9] D. L. Vincent and C. B. Purves, *Canad. J. Chem.*, 1956, **34**, 1302.

thiobenzoate (XIIg) also gave the bromide (XIId) and the iodide (XIIe) on reaction with bromine and methyl iodide, respectively.

In order to compare the reactivity of diol thiocarbonates [1] and bis-xanthates, the reaction of methyl derivative. The analysis ($C_{13}H_{22}O_5S_3$) and spectral data were consistent with its formulation as 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*,6-*S*-[bis(methylthio)methylene]-6-thio-α-D-glucose (XIV). The mass spectrum gave an intense ion at *m/e* 307 due to loss of MeS [ion (XV)].

Substrate	Reagent and conditions	Product(s) (yield in parentheses)
Xanthate (Va) [g]	Chlorine (1.5 equiv.), 0 °C, 4 h	(50%) Stearyl chloride (VIa) [a]
	NCS (1.5 equiv.), 20 °C, 12 h	(55%)
	Disulphur dichloride (1.5 equiv.), −20 to 20 °C, 45 min	(85%)
	Benzenesulphenyl chloride (1.5 equiv.), −20 to 20 °C, 30 min	(95%)
	Phenylmethanesulphenyl chloride (1.5 equiv.), −20 to 20 °C, 30 min	(80%)
	Trichloromethanesulphenyl chloride (1.5 equiv.), −20 to 20 °C, 30 min	(98%)
	Benzenesulphinyl chloride (1.5 equiv.), −20 to 20 °C, 1 h	(72%)
	Thionyl chloride (1.5 equiv.), 0 °C, 10 h	(70%)
Xanthate (Va)	Bromine (4 equiv.), trace pyridine, 0 °C during addition, 2 h at 20 °C	(100%) Stearyl bromide (VIb) [b]
	Benzyl bromide (4 equiv.), MeCN solvent, 80 °C, 6 h	(100%)
	p-Methoxybenzyl bromide (4 equiv.), MeCN solvent, 80 °C, 6 h	(100%)
Xanthate (Va)	Methyl iodide, 90 °C, 30 h	(60%) Stearyl iodide (VIc) [c]
	Methyl toluene-4-sulphonate, tetra-n-butylammonium iodide (1.5 equiv.), 20 °C, 4 h	(60%)
Thiocarbonate (Vb)	Benzenesulphenyl chloride (2 equiv.), trace pyridine, −20 to 20 °C, 45 min	(85%) Stearyl chloride (VIa)
	Bromine (3 equiv.), 0 °C during addition, 2 h at 20 °C	(70%) Stearyl bromide (VIb)
	Methyl iodide, 90 °C, 32 h	(80%) Stearyl iodide (VIc)
Xanthate (VIIa) [d]	Benzenesulphenyl chloride (1.5 equiv.), −60 to 20 °C, 1 h	(63%) 3β-Chlorocholest-5-ene (VIII) [e]
Thiobenzoate (VIIb) [2]	Benzenesulphenyl chloride (1.5 equiv.), −60 to 20 °C, 1 h	(60%) 3β-Chlorocholest-5-ene (VIII)
Xanthate (IXa) [2]	Chlorine (in large excess), 0° C, 1 h	(60%) 3α-Chloro-5α-cholestane (Xa) [f]
	NCS (1.5 equiv.), 20 °C, 12 h	(45%)
	Disulphur dichloride (1.5 equiv.), −20 to 20 °C, 45 min	(70%)
	Benzenesulphenyl chloride (3 equiv.), −20 to 20 °C, 1 h	(90%)
	Trichloromethanesulphenyl chloride (2 equiv.), −20 to 20 °C, 1 h	Chloride (Xa) (78%), 5α-Cholest-2-ene (XI) [g] (4%)
	Benzeneselenenyl chloride (1.4 equiv.), −20 °C during addition, 1 h at 20 °C, trace pyridine	Chloride (Xa) (40%) Alkene (XI) (26%)
	Thionyl chloride (1.5 equiv.), 0 °C, 6 h	Chloride (Xa) (50%)
	Bromine (4 equiv.), 15 min at 0 °C, 2 h at 20 °C	3α-Bromo-5α-cholestane (Xb) [h] (88%)
	Methyl iodide, 90 °C, 36 h	(62%), 3α-Iodo-5α-cholestane (Xc) [i]
Thiobenzoate (IXb) [2]	Benzenesulphenyl chloride (1.5 equiv.), −20 to 20 °C, 1 h	Chloride (Xa) (70%) Alkene (XI) (8%)
Selenobenzoate (IXc)	Benzenesulphenyl chloride (1.5 equiv.), −20 to 20 °C, 45 min	Chloride (Xa) (70%) Alkene (XI) (11%)
	Benzeneselenenyl chloride (1.4 equiv.), −20 to 20 °C, 45 min	Chloride (Xa) (50%) Alkene (XI) (16%)
	Methyl iodide, 90 °C, 34 h	(84%) 3α-Iodo-5α-cholestane (Xc)
Thiocarbonate (IXd)	Methyl iodide, 90 °C, 34 h	(58%) 3α-Iodo-5α-cholestane (Xc)
Thiocarbamate (IXe) [2]	Benzenesulphenyl chloride (1.5 equiv.) −20 to 20 °C, 45 min	(75%) 3α-Chloro-5α-cholestane (Xa)
	Bromine (4 equiv.), CCl_4 solvent, 0 °C during addition, 4 h at 20 °C	(72%) 3α-Bromo-5α-cholestane (Xb)
	Methyl iodide, room temp. overnight	(78%) 3α-Iodo-5α-cholestane (Xc)
Xanthate (XIIb)	Benzenesulphenyl chloride (1.5 equiv.), −20 to 20 °C, 45 min	Chloride (XIIc) [j] (50%)
	Bromine (5 equiv.), CCl_4 solvent, trace pyridine, 0 °C during addition, 6 h at 2 0°C	Bromide (XIId) (45%)
	Methyl iodide, 80 °C, 38 h	Iodide (XIIe) [k] (75%)
Thiobenzoate (XIIg)	Bromine (5 equiv.), CCl_4 solvent, 0 °C during addition, 3 h at 20 °C	Bromide (XIId) (50%)
	Methyl iodide, 90 °C, 40 h	Iodide (XIIe) (50%)

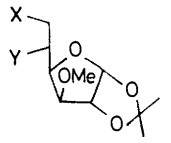
NCS = *N*-chlorosuccinimide.

[a] C. F. Mabery, *Amer. Chem. J.*, 1902, **28**, 165. [b] F. Seidel and O. Engelfried, *Ber.*, 1936, **69**, 2567. [c] N. F. Wood and F. C. Chang *J. Org. Chem.*, 1965, **30**, 2054; D. A. Shirley and J. R. Zeitz, jun., *ibid.*, 1953, **18**, 1591. [d] G. L. O'Connor and H. R. Nace, *J. Amer. Chem. Soc.*, 1953, **75**, 2118. [e] C. W. Shoppee, *J. Chem. Soc.*, 1946, 1147. [f] R. E. Marker, F. C. Whitmore, and O. Kamm, *J. Amer. Chem. Soc.*, 1935, **57**, 2358. [g] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959, p. 253. [h] G. Roberts, C. W. Shoppee, and R. J. Stephenson, *J. Chem. Soc.*, 1954, 2705. [i] A. V. Bayless and H. Zimmer, *Tetrahedron Letters*, 1968, 3811. [j] S. Hanessian and N. R. Plessas, *J. Org. Chem.*, 1969, **34**, 2163; *Chem. Comm.*, 1967, 1152. [k] C. Cone and L. Hough, *Carbohydrate Res.*, 1965, **1**, 1.

iodide with 1,2-*O*-isopropylidene-3-*O*-methyl-5,6-bis-*O*-[(methylthio)thiocarbonyl]-α-D-glucose (XIIIb) was examined. The latter, prepared from 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (XIIIa), unlike the xanthate (XIIb), was not recovered on distillation. Pyrolysis of the bis-xanthate (XIIIb) gave a crystalline

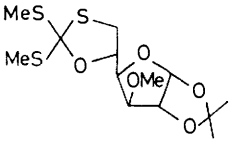
The trithio-orthocarbonate (XIV) can be considered to arise by nucleophilic attack at C-6 by the 5-thiocarbonyl group. The attachment of the sulphur at C-6 and of the oxygen at C-5 follows from the n.m.r. spectrum.

Electrophilic attack on thiocarbonyl or selenocarbonyl derivatives of alcohols provides a simple, mild and, in



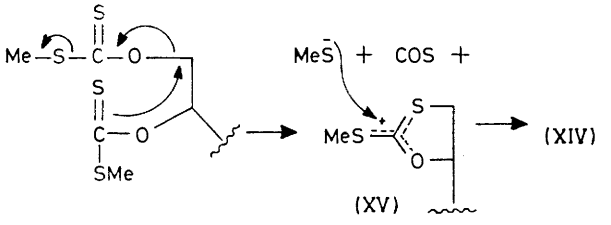
(XIII)

a; X = Y = HO b; X = Y = O·CS·SMe



(XIV)

many cases, high yield method of hydroxy-group replacement.*



EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. N.m.r. spectra were recorded (deuteriochloroform as solvent and tetramethylsilane as internal standard) with a Varian T-60 or HA-100 instrument. ' Normal ' work-up refers to addition of dichloromethane or diethyl ether, washing with water, dilute acid, or base, then water again, drying (sodium or magnesium sulphate), and evaporation under reduced pressure. Light petroleum refers to the redistilled fraction with b.p. 40—60 °C. Reactions of thiocarbonyl compounds with methyl iodide were carried out in sealed tubes without solvent at 90 °C over 2 days. All other reactions of thiocarbonyl compounds, unless stated to the contrary, were carried out in dichloromethane solution and are summarised in the Table. After normal work-up and chromatography on silica (eluant light petroleum–diethyl ether) the products were identified by comparison with authentic samples.

O-4-*Chlorophenyl* O-*Octadecyl Thiocarbonate* (Vb).—4-Chlorophenyl chloroformate (247 mg) was added to stearyl alcohol (370 mg) and pyridine (1 ml) in dichloromethane (5 ml) at 10 °C. After 5 h at room temperature evaporation gave the *thiocarbonate* (Vb) (349 mg, 60%) as plates, m.p. 62—64° (from diethyl ether–light petroleum), $\nu_{max.}$ ($CHCl_3$) 1 560s, 1 525s, 1 450s, 1 125m, 1 085s, and 1 040m cm^{-1}, $\lambda_{max.}$ (EtOH) 234 nm (ε 3 300) (Found: C, 68.0; H, 9.5; Cl, 8.0; S, 7.05. $C_{25}H_{41}ClOS$ requires C, 68.05; H, 9.3; Cl, 8.15; S, 7.25%).

O-4-*Chlorophenyl* O-5α-*Cholestan*-3β-*yl Thiocarbonate* (IXd).—4-Chlorophenyl chloroformate (824 mg) was added with cooling to 5α-cholestan-3β-ol (1.16 g) in dichloromethane (25 ml). After 6 h at room temperature the solvent was removed under vacuum and the residue chromatographed on alumina. Elution with benzene–light petroleum gave *thiocarbonate* (IXd), m.p. 79° (from CH_2Cl_2–MeOH), $[\alpha]_D^{20}$ +14° (*c* 2.0 in $CHCl_3$) (Found: C, 73.0; H, 9.0; S, 5.55. $C_{34}H_{51}ClO_2S$ requires C, 73.15; H, 9.15; S, 5.75%).

* *Note added in proof:* Preparation of trithio-orthocarbonate (XIV) by pyrolysis of (XIIIb) has recently been described (G. Descotes and A. Fuare, *Synthesis*, 1976, 449).

O-5α-*Cholestan*-3β-*yl Selenobenzoate* (IXc).—Ethanol (12 ml) was added dropwise to a mixture of selenium powder (800 mg) and sodium borohydride (400 mg) under argon, and the mixture was stirred (15 min). *O*-5α-Cholestan-3β-yl *N*-methylbenzimidate methochloride [2] (4.40 g) in dichloromethane (40 ml) was added dropwise and the mixture warmed (25 °C; 1 h). Normal work-up and chromatography on silica gave the *selenobenzoate* (IXc) (2.45 g, 82%) as red needles, m.p. 136—137° (from EtOH–CH_2Cl_2), $\lambda_{max.}$ ($CHCl_3$) 254 (ε 9 500) and 338 nm (ε 7 700), τ 1.67—2.86 (5 H, m, Ph), 4.20br (1 H, s, H-3), and 9.37 (3 H, s, Me-13) (Found: C, 73.3; H, 9.65. $C_{34}H_{32}OSe$ requires C, 73.5; H, 9.45%).

1,2:3,4-*Di*-O-*isopropylidene*-6-O-[(*methylthio*)*thiocarbonyl*]-α-D-*galactose* (XIIb).—To 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (XIIa) (3.90 g) in tetrahydrofuran (60 ml) were added sodium hydride (600 mg) and imidazole (150 mg). The mixture was stirred (2 h), and carbon disulphide (1.8 ml) and methyl iodide (1.6 ml) were added in sequence (15 min). Normal work-up, chromatography on silica, and distillation gave the xanthate (XIIb) (4.60 g, 88%) as an oil, $[\alpha]_D^{20}$ −57.6° (*c* 0.25 in $CHCl_3$) (lit.,[10] $[\alpha]_{578}^{16}$ −67.37° in $CCl_2{=}CCl_2$), $\lambda_{max.}$ (EtOH) 221 (ε 6 900) and 278 nm (ε 10 200), τ (CCl_4) 4.51 (1 H, d, H-1, $J_{1,2}$ 5.0 Hz), 4.98—5.51 (3 H, m), 5.51—5.98 (3 H, m), 7.42 (3 H, s, SCH_3), and 8.32—8.86 (12 H, t, CMe_2) (Found: C, 47.95; H, 6.2. Calc. for $C_{14}H_{22}O_6S_2$: 48.0; H, 6.35%).

6-*Bromo*-6-*deoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactose* (XIId).—The *bromide* (XIId) was obtained as an oil, $[\alpha]_D^{20}$ −56° (*c* 2.1 in $CHCl_3$) (Found: C, 44.2; H, 5.6. $C_{12}H_{19}BrO_5$ requires C, 44.6; H, 5.85%).

6-*Deoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactose* (XIIf). Tri-n-butyltin hydride (291 mg) in dry benzene (10 ml) was added dropwise over 20 min to a refluxing solution of compound (XIId) (170 mg) in dry benzene (10 ml) under argon. Normal work-up, after 4 h, followed by chromatography on silica and elution with light petroleum, gave the 6-deoxy-compound (XIIf) as an oil (90 mg, 70%), b.p. 62° at 0.5 mmHg, $[\alpha]_D^{20}$ −47.5° (*c* 2.5 in $CHCl_3$) (lit.,[10] b.p. 68—70° at 0.5 mmHg, $[\alpha]_D$ −47°.

1,2-O-*Isopropylidene*-3-O-*methyl*-5,6-*bis*-O-[(*methylthio*)-*thiocarbonyl*]-α-D-*glucose* (XIIIb).—The bis-xanthate (XIIIb) (11.70 g, 94%), prepared from 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (XIIIa) (7.02 g) as for the xanthate (XIIb) above, was isolated by chromatography on silica and obtained as an oil, $[\alpha]_D^{20}$ −37.4° (*c* 0.62 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 222 (ε 13 300) and 277 nm (ε 20 700), τ 3.76—3.93 (1 H, octet, H-5), 4.14 (1 H, d, H-1, $J_{1,2}$ 4.0 Hz), 4.76 and 4.90 (1 H, dd, H-6′, $J_{5,6}$ 2.0 Hz), 5.17 and 5.29 (1 H, dd, H-6, $J_{5,6}$ 5.0, $J_{6,6'}$ 12 Hz), 5.44 and 5.51 (1 H, dd, H-4, $J_{4,5}$ 7.0 Hz), 5.48 (1 H, d, H-2), 6.26 (1 H, d, H-3, $J_{3,4}$ 3.0 Hz), 6.70 (3 H, s, OMe), 7.48 and 7.52 (6 H, 2s, SMe), and 8.53 and 8.71 (6 H, 2s, CMe_2), *m/e* 414 (M^+) and 307 ($M^+ - CH_3SCSO$).

Pyrolysis of the Bis-xanthate (XIIIb).—Pyrolysis (150 °C) under vacuum (10^{-4} mmHg) of the bis-xanthate (XIIIb) (410 mg) gave 1,2-O-*isopropylidene*-3-O-*methyl*-5-O,6-S-[*bis*(*methylthio*)*methylene*]-6-*thio*-α-D-*glucose* (XIV) (320 mg, 92%), m.p. 78.5—79° (from light petroleum), $[\alpha]_D^{23}$ −142° (*c* 0.80 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 207 (ε 2 000) and 227 nm (ε 600), τ 4.17 (1 H, d, H-1, $J_{1,2}$ 3.5 Hz), 5.30 and 5.33 (1 H, dt, H-5, $J_{5,6}$ 8.0, $J_{5,6'}$ 6.0 Hz), 5.43 (1 H, d, H-2), 5.73 and 5.81 (1 H, dd, H-4, $J_{4,5}$ 8.0 Hz), 6.28 (1 H, d, H-3, $J_{3,4}$ 3.0 Hz),

[10] K. Freudenberg and A. Wolf, *Ber.*, 1927, **60**, 232.

6.59 (3 H, s, OMe), 6.64—6.82 (2 H, m, H-6, -6'), 7.82 (6 H, s, SMe), and 8.51 and 8.70 (6 H, 2s, Me_2C), *m/e* 307 ($M^+ - CH_3S$) (Found: C, 44.05; H, 6.35; S, 27.1. $C_{13}H_{22}O_5S_3$ requires C, 44.05; H, 6.25; S, 27.15%).

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