Reactions of Relevance to the Chemistry of Aminoglycoside Antibiotics. Part 6.† A Simple Preparation of Chlorohydrin Benzoates from 1,2- and 1,3-Glycols

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Treatment of 1,2-diols and of one 1,3-diol with the imidoyl chloride derived from dimethylbenzamide afforded, at room tempreature, in excellent yields and regiospecifically the corresponding chlorohydrin benzoates. The reaction is considered to proceed *via* the appropriate phenyl(dioxacycloalkylium) intermediate and is shown to involve inversion of configuration at the centre to which chlorine is attached. The ordinary Vilsmeier reagent from dimethylformamide gives diformates under the same conditions.

DITHIOCARBONATES (1a), thiobenzoates (1b), and selenobenzoates (1c) from secondary alcohols are readily converted into the corresponding hydrocarbons (1d) on reduction with tri-n-butyltin hydride.[1] In an extension of this work we had occasion to examine the condensation of *meso*-1,2-diphenylethane-1,2-diol (2a) with *NN*-dimethyl-α-chlorobenzylideneammonium chloride (4a) followed by treatment with sodium hydrogen selenide.[1] The major product however was not a selenobenzoate but 2-chloro-1,2-diphenylethyl benzoate (5). This formulation was consistent with spectral data [$\nu_{max.}$ 1 730 and 1 605 cm^{-1}, δ 8.2—7.3, 6.2, and 5.13, *m/e* 211 (M^+ — PhCHCl)] and elemental analysis. The reaction of the *meso*-diol (2a) and the imidoyl chloride (4a) gave, on aqueous work-up, the benzoate (5) in 77% yield.

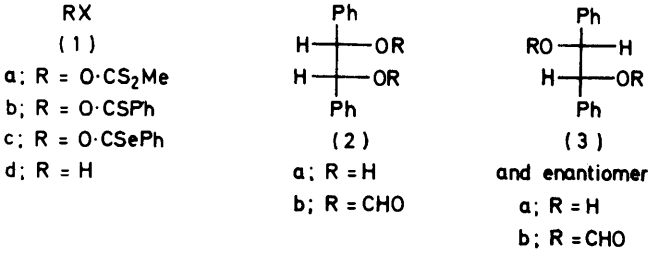
Treatment of (±)-1,2-diphenylethane-1,2-diol (3a) with the imidoyl chloride (4a) gave the epimeric 2-chloro-1,2-diphenylethyl benzoate (6) in 95% yield. Again spectral data were in full agreement with the proposed structure.

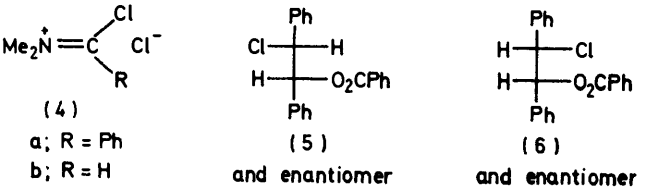
The stereochemistry of the 2-chloro-1,2-diphenylethyl benzoates (5) and (6) was determined by hydrolysis with potassium hydroxide, giving the known [2] *cis*- (7a) and *trans*- (7b) epoxides, respectively.

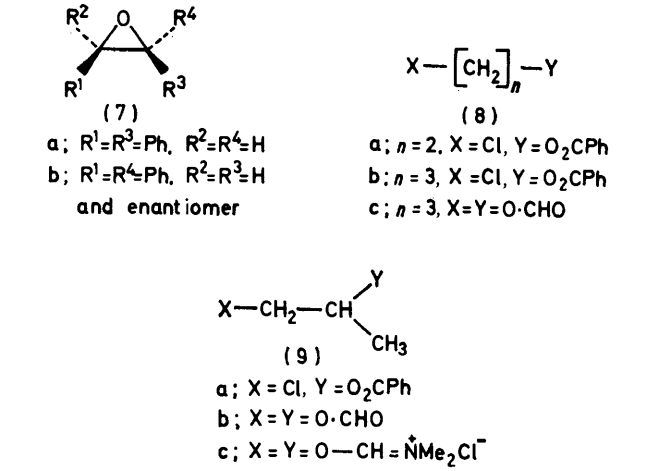
Ethane-1,2-diol, propane-1,3-diol, and propane-1,2-diol on reaction with the imidoyl chloride (4a) gave, respectively, 2-chloroethyl benzoate (8a) (96%), 3-chloropropyl benzoate (8b) (81%), and 2-chloro-1-methylethyl benzoate (9a) (88%). The chloro-benzoate derived from propane-1,2-diol was exclusively a single isomer (9a). This was supported by the methylene and methine ^1H n.m.r. signals at δ 3.6 and 5.6—5.0 respectively.

Reaction of the glucofuranose derivative (10a) with the imidoyl chloride (4a) also gave a single product, the 6-chloro-6-deoxy-5-benzoate (10b). Again assignment of the constitution followed from the n.m.r. [δ 5.6—5.1 (5 H) and 4.1—3.9 (6-H_2)] and mass spectra (M^+ 357), and elemental analysis.

The (±)- (3a) and *meso*- (2a) diphenylethanediols on reaction with *NN*-dimethylchloromethyleneammonium chloride (4b) gave the (±)- (3b) and *meso*- (2b) diformate derivatives, respectively, in high yield. The n.m.r. spectra (δ 8.0) indicated the presence of two formate functions and two equivalent methine protons.







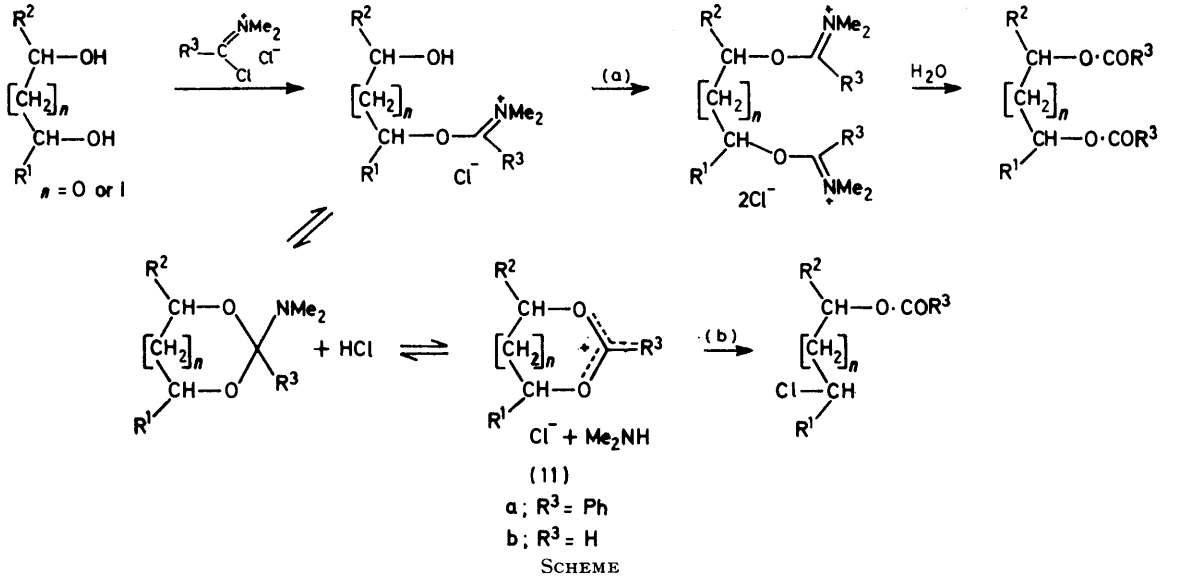
1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-glucofuranose (10a) on reaction with the Vilsmeier reagent (4b) gave the diformate derivative (10c). Propane-1,3-diol also gave the diformate derivative (8c) in modest yield with the reagent (4b).

† We have recently published several papers whose motivation is the development of reactions which would be useful in the chemistry of the aminoglycoside antibiotics. We now consider these publications, all in *J.C.S. Perkin I*, as part of a series as follows: Part 1, 1975, 1574; Part 2, 1975, 1614; Part 3, 1975, 1773; Part 4, 1976, 2112; Part 5, 1977, 1114.

[1] D. H. R. Barton and S. W. McCombie, *J.C.S. Perkin I*, 1975, 1574.

[2] M. S. Newman and D. R. Olson, *J. Org. Chem.*, 1973, **38**, 4203; see also D. A. Seeley and J. McElwee, *ibid.*, p. 1691.

The mechanism of the reaction of Vilsmeier salts with diols can be summarized as in the Scheme. Since the phenyl-substituted cation (11a) is more stable than the parent cation (11b), reactions of diols with the benzimidoyl chloride (4a) proceed *via* the novel path (b). The reactions of the formimidoyl analogue (4b) favour path (a). Consistent with this hypothesis, the *meso*- (2a) and (±)- (3a) diphenylethanediols gave, respectively, the chloro-benzoate derivatives (5) and (6) with inversion of stereochemistry. Since path (b) involves an S_N2 displacement by chloride, substitution at the primary is favoured over substitution at the secondary position. Thus propane-1,2-diol and the glucofuranose derivative



SCHEME

(10a) gave regiospecifically the chloro-benzoates (9a) and (10b), respectively.

The diequatorial diol methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (12a) gave the 3-benzoate (12b) as major product on reaction with the benzimidoyl chloride (4a). The structure of (12b) followed from comparison with authentic material. Clearly the cyclic intermediate (12c) would be *trans*-fused and thus not favoured. Presumably steric congestion prevents ready formation of the bis-Vilsmeier salt (12d) and thus of the dibenzoate (12e).

The conversion of vicinal diols (13a) into the chloroacetate derivatives (13b) in reactions of orthoacetates (13c) with chlorotrimethylsilane in dichloromethane has been reported.[2] Moffatt has described [3] a conversion of the 2,3-diol system of ribose nucleosides into the corresponding chloro- or bromo-acetate. For example the nucleoside (14a) and the acid chloride (15a) gave both chloro-acetates (14b and c).

The synthesis of 2-chloroalkyl benzoates described herein has the advantages of high yield, inexpensive reagents, and simple manipulation. Provided that the intermediate cation [of type (11)] is stereochemically allowed and sufficiently stabilised, the reaction should be general.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were recorded with tetramethylsilane as internal reference. Organic extracts were dried over sodium sulphate and evaporated under reduced pressure. Chromatography was carried out on Hopkin and Williams MFC silica gel. Light petroleum refers to the fraction with b.p. 60—80 °C.

Reaction of meso-1,2-*Diphenylethane*-1,2-*diol* (2a) *with the Imidoyl Chloride* (4a).—The imidoyl chloride (4a) prepared from *NN*-dimethylbenzamide (4.47 g), was dissolved in dichloromethane (100 ml) at 0 °C. The *meso*-diol (2a) (3.21 g) was added in portions and the solution was stirred for 18 h at room temperature. Pyridine (4.75 ml) was added at −20 °C and the mixture poured into a solution of sodium hydrogen selenide [1] [from selenium (2.6 g)] at −20 °C. After 1 h at room temperature, the solution was washed with aqueous 10% potassium carbonate, 2N-hydrochloric acid, and water, dried, and evaporated to furnish a yellow oil. Chromatography (eluant light petroleum–diethyl ether, 5 : 1) gave the less polar benzoate ester followed by *NN*-dimethylbenzamide (5%) (i.r., n.m.r., t.l.c.). The ester was crystallized from methylene chloride–light petroleum to provide the 2-*chloro*-1,2-*diphenylethyl benzoate* (5) (77%), m.p. 97—98.5°, $\nu_{max.}$ (CCl_4) 3 100, 3 070, 3 040, 2 960, 1 730, and 1 605 cm^{-1}, δ (CCl_4) 8.2—7.3 (5 H, m, PhCO), 7.13 (5 H, s, aryl-H), 7.10 (5 H, s, aryl-H), 6.20 (1 H, d, *J* 8 Hz, O·CH), and 5.13 (1 H, d, *J* 8 Hz, ClCH), *m/e* 211 (M^+ − PhCHCl), 105 (PhCO), and 77 (Ph). Recrystallization from ethanol–water and methylene chloride–light petroleum gave white needles, m.p. 100—101° (Found: C, 74.7; H, 4.9; Cl, 10.8. $C_{21}H_{17}ClO_2$ requires C, 74.9; H, 5.1; Cl, 10.5%). Reaction of the imidoyl chloride (4a), with the *meso*-diol in (2a) and pyridine in dichloromethane as above gave, on aqueous work-up, the 2-chloro-1,2-diphenylethyl benzoate (5) (77%).

Reaction of the (±)-*Diol* (3a) *with the Imidoyl Chloride*

[3] S. Greenberg and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1973, **95**, 4016; A. F. Russell, S. Greenberg, and J. G. Moffatt, *ibid.*, p. 4025; T. C. Jain, A. F. Russell, and J. G. Moffatt, *J. Org. Chem.*, 1973, **38**, 3179; A. F. Russell, M. Prystasz, E. K. Hamamura, J. P. H. Verheyden, and J. G. Moffatt, *ibid.*, 1974, **39**, 2182.

(4a).—The (±)-diol (3a) (0.47 g) was added with stirring to the imidoyl chloride (4a) [from *NN*-dimethylbenzamide (0.75 g)] in dichloromethane (20 ml). After 22 h at room temperature evaporation and crystallization from dichloromethane–light petroleum gave the 2-*chloro*-1,2-*diphenylethyl benzoate* (6) (0.70 g, 95%), m.p. 140—142°, δ (CCl_4) 8.0—7.2 (5 H, m, PhCO), 7.13 (5 H, s, aryl-H), 7.10 (5 H, s, aryl-H), 6.3 (1 H, d, *J* 6 Hz, O·CH), and 5.3 (1 H, d, *J* 6 Hz, ClCH), *m/e* 337 (M^+), 211, 105, and 77 (Found: C, 75.05; H, 5.2%).

2-*Chloroethyl Benzoate*.—(*a*) A 10—15% solution of phosgene in dichloromethane (100 ml) was added to *NN*-dimethylbenzamide (4.47 g) in dichloromethane (20 ml). After 22 h at room temperature the mixture was evaporated to give a white solid. Dichloromethane (100 ml) was added, followed by dry ethane-1,2-diol (0.78 g) with cooling to 0 °C. After stirring for 24 h at room temperature, the solution was washed with water, dried, and evaporated, and the residue was chromatographed (eluant light petroleum–diethyl ether, 10 : 1) to afford pure (t.l.c.) 2-chloroethyl benzoate (8a) (2.22 g, 96%), b.p. 81° at 0.2 mmHg (lit.,[4] 100—102° at 1—2 mmHg), $\nu_{max.}$ (film) 1 720 cm^{-1}, δ (CCl_4) 8.2—7.2 (5 H, m, PhCO), 4.50 (2 H, t, *J* 6 Hz, O·CH_2), and 3.73 (2 H, t, *J* 6 Hz, $ClCH_2$), *m/e* 184 (M^+).

(*b*) To the imidoyl chloride (4a) [from *NN*-dimethylbenzamide (1.8 g)] in dichloromethane (30 ml), ethane-1,2-diol (0.31 g) in pyridine (3 ml) was added. After stirring for 24 h at room temperature, the mixture was worked up as before to provide 2-chloroethyl benzoate (8a) (93%), identical (i.r., n.m.r., t.l.c.) with the previous sample.

Reaction of Propane-1,3-*diol with the Imidoyl Chloride* (4a).—Reaction of propane 1,3-diol (0.76 g) with the imidoyl chloride (4a) [from *NN*-dimethylbenzamide (2.98 g)] and pyridine (1.6 g) in dichloromethane (40 ml) in the usual way gave the ether-insoluble *NN*-dimethylbenzamide and, after chromatography (eluant light petroleum–diethyl ether, 1 : 1) 3-*chloropropyl benzoate* (8b) (1.6 g, 81%), b.p. 102° at 1 mmHg, δ (CCl_4) 8.3—7.8 (2 H, m, aryl-H), 7.6—7.3 (3 H, m, aryl-H), 4.4 (2 H, t, *J* 6 Hz, O·CH_2), 3.7 (2 H, t, *J* 6 Hz, $ClCH_2$), and 2.5—2.0 (2 H, m, C·CH_2·C), *m/e* 198 (M^+), 105, and 77 (Found: C, 60.2; H, 5.3. $C_{10}H_{11}ClO_2$ requires C, 60.5; H, 5.6%).

Reaction of Propane-1,2-*diol with the Imidoyl Chloride* (4a).—Propane-1,2-diol, the imidoyl chloride (4a) and pyridine in dichloromethane gave 2-*chloro*-1-*methylethyl benzoate* (9a) (88%), b.p. 65—67° at 1 mmHg, δ (CCl_4) 8.3—7.8 (2 H, m, aryl-H), 7.6—7.2 (3 H, m, aryl-H), 5.6—5.0 (1 H, m, O·CH), 3.6 (2 H, d, *J* 7 Hz, $ClCH_2$), and 1.5 (3 H, d, *J* 7 Hz, CH*Me*), *m/e* 198 (M^+), 105, and 77 (Found: C, 60.35; H, 5.55. $C_{10}H_{11}ClO_2$ requires C, 60.45; H, 5.6%).

Reaction of 1,2-O-*Isopropylidene*-3-O-*methyl*-α-D-*glucofuranose* (10a) *with the Imidoyl Chloride* (4a).—Reaction of the glucofuranose derivative (10a) (0.35 g), pyridine (0.28 g), and the imidoyl chloride (4a) [from *NN*-dimethylbenzamide (0.45 g)] for 22 h at room temperature gave, on evaporation, a white solid. Partition between dichloromethane and water gave on evaporation of the dried organic phase, the chloro-benzoate (10b) (0.53 g, 95%), m.p. 58—60°. P.l.c. on silica (diethyl ether) gave the pure *chloro-benzoate* (10b), m.p. 63—64° (from light petroleum), δ (CCl_4) 8.2—7.8 (2 H, m, aryl-H), 7.6—7.2 (3 H, m, aryl-H), 5.8 (1 H, d, *J* 3 Hz, 1-H), 5.6—5.1 (1 H, m, 5-H), 4.6—4.4 (2 H, m, 2- and 4-H), 4.1—3.9 (2 H, m, 6-H_2), 3.75 (1 H, d, *J* 4 Hz, 3-H), 3.2 (3 H, s, OMe), and 1.4 (6 H, 2 s, CMe_2), *m/e* 357 (M^+), 340, 87, and 85 (Found: C, 57.25; H, 6.05. $C_{17}H_{21}ClO_6$ requires C, 57.2; H, 5.95%).

Reaction of (±)-1,2-*Diphenylethane*-1,2-*diol* (3a) *with the Imidoyl Chloride* (4b).—The (±)-diol (3a) (0.20 g) was added to the imidoyl chloride (4b)[1] [from dimethylformamide (0.16 g)] in dichloromethane (20 ml). After stirring for 30 min the solvent was removed and the residue stirred with dichloromethane (30 ml) and water (10 ml) for 30 min. The aqueous phase was extracted with dichloromethane (3 × 10 ml) and the combined organic extract washed with water (3 × 10 ml), dried, and evaporated to give the diformate (3b) (0.24 g, 92%), m.p. 116—125° (from CH_2Cl_2, then from MeOH–H_2O), δ (CCl_4) 8.0 (2 H, s), 7.2 (10 H, s), and 6.1 (2 H, s), *m/e* 241, 135, and 77.

Reaction of the meso-*Diol* (2a) *with the Imidoyl Chloride* (4b).—Reaction of the *meso*-diol (2a) and the imidoyl chloride (4b) gave the *diformate* (2b) (93%), m.p. 172—174° (from CH_2Cl_2), δ ($CDCl_3$) 8.0 (2 H, s), 7.2 (10 H, s), and 6.2 (2 H, s) (Found: C, 71.1; H, 5.15. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%).

Reaction of 1,2-*Isopropylidene*-3-O-*methyl*-α-D-*glucofuranose* (10a) *with the Imidoyl Chloride* (4b).—Reaction of the glucofuranose derivative (10a) with the imidoyl chloride (4b) gave, after p.l.c. (diethyl ether) the *diformate* (10c) (72%), m.p. 60° (from light petroleum), δ ($CDCl_3$) 8.0 (2 H, s, CHO), 5.9 (1 H, d, *J* 3 Hz, 1-H), 5.2—5.6 (1 H, m, 5-H), 4.8—4.0 (4 H, m, 3-H, 4-H, and 6-H_2), 4.3 (1 H, d, *J* 3 Hz, 2-H), 3.4 (3 H, s, OMe), and 1.38 (6 H, 2 s, CMe_2), *m/e* 275, 87, and 85 (Found: C, 49.85; H, 6.1. $C_{12}H_{18}O_8$ requires C, 49.65; H, 6.25%).

Reaction of Propane-1,3-*diol with the Imidoyl Chloride* (4b).—Propane-1,3-diol (1.9 g) and the imidoyl chloride (4b) [from dimethylformamide (3.7 g)] in dichloromethane (100

[4] L. P. Chigogidze and R. M. Lagidze, *Soobshcheniya Akad. Nauk, Gruzin S.S.R.*, 1955, **16**, 443 (*Chem. Abs.*, 1956, **50**, 11973i).

ml) were stirred for 30 min at room temperature. After evaporation, dichloromethane (100 ml) and water (0.9 ml) were added and the mixture was stirred for 15 min. Ammonia was bubbled through, the solution was evaporated, and the mixture stirred with acetone (100 ml). After 1 h at −10 °C the mixture was filtered and evaporated, and the oily residue distilled (b.p. 41—68° at 6 mmHg), chromatographed (eluant Me_2CO–EtOH, 1 : 1), and redistilled to give the diformate (8c) (1.35 g, 40%), b.p. 50—52° at 1.4 mmHg (lit.,[5] 75° at 10 mmHg), n_D^{20} 1.4210 (lit.,[6] n_D^{25} 1.4162), δ ($CDCl_3$) 8.0 (2 H, s, CHO), 4.2 (4 H, t, *J* 6 Hz, O·CH_2), and 2.4—1.8 (2 H, fentit, *J* 6 Hz, C·CH_2·C), *m/e* 132 (M^+) and 87 (Found: C, 45.4; H, 6.25. Calc. for $C_5H_8O_4$: C, 45.45; H, 6.15%).

Reaction of 2-Chloro-1,2-diphenylethyl Benzoate with Alcoholic Potassium Hydroxide.—The benzoate isomer (5) (0.2 g; m.p. 100—101°) in ethanolic 0.5M-potassium hydroxide (10 ml) was heated to reflux for 1 h. Water (to 40 ml) and aqueous 25% acetic acid (to neutrality) were added. The solid was filtered off and crystallized from aqueous ethanol to give the *cis*-epoxide (7a), m.p. 39—41° (lit.,[7] 42°). The benzoate isomer (6), m.p. 140—142°, on similar hydrolysis gave the *trans*-epoxide (7b), m.p. 69° (from EtOH–H_2O) (lit.,[7] 69—70°).

Reaction of Methyl 4,6-O-Benzylidene-α-D-glucopyranoside (12a) *with the Imidoyl Chloride* (4a).—(*a*) The imidoyl chloride (4a) [from *NN*-dimethylbenzamide (3.0 g)] was dissolved in dichloromethane and tetrahydrofuran (1 : 2; 100 ml) and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (12a) (2.68 g) and pyridine (4 ml) were added. The mixture was stirred for 3 days at room temperature, during which an oil separated. The mixture was washed with water, the aqueous layer was extracted with ether (2 × 50 ml), and the combined organic layers were dried and evaporated. The residue was crystallized from chloroform–light petroleum to afford the 3-benzoate (12b) (0.57 g, 16%), m.p. 212—216°. Recrystallization gave material with m.p. 215—218° (lit.,[8] 217—218°). The n.m.r. spectrum was consistent with the structure. The filtrate on evaporation gave crude *NN*-dimethylbenzamide (2.5 g). The aqueous extract was cooled to give crude 3-benzoate (12b) (1.0 g, 28%, total 43%), m.p. 191—198°. T.l.c. revealed a major component with the same mobility as the pure 3-benzoate as well as several unidentified components.

(*b*) Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (12a) (0.56 g) and pyridine (1 ml) in dichloromethane and tetrahydrofuran (1 : 1; 40 ml) were added dropwise over 30 min to a refluxing solution of the imidoyl chloride (4a) [from *NN*-dimethylbenzamide (0.75 g)] in dichloromethane (30 ml). After being heated to reflux for 4.5 h, the mixture was cooled and washed with water, and the aqueous layer was extracted with chloroform (3 × 20 ml). The combined organic layers were dried and evaporated and the residue was crystallized from chloroform–light petroleum to afford the crude 3-benzoate (12b) (36%), m.p. 185—205°. Recrystallization gave material with m.p. 210—215°.

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[5] Q. E. Thompson, *J. Org. Chem.*, 1962, **27**, 4498.
[6] J. Read and I. G. Macnaughton Campbell, *J. Chem. Soc.*, 1930, 2377.
[7] G. N. Bollenback, 'Methyl Glucoside,' Academic Press, New York, 1958, p. 48.