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Note

Selective alkylation of glycerol: direct synthesis of 2-*O*-benzylglycerol and 2-*O*-methylglycerol

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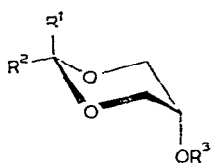
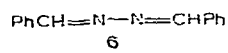
As part of acetalation studies[1], 2,2-dimethyl-1,3-dioxan-5-ol (1,3-O-isopropylideneglycerol, **1**) was required as a standard for g.l.c. Compound **1** has been synthesised[2] by acetonation of 2-*O*-benzylglycerol (**2**) followed by catalytic hydrogenolysis. It is also formed[3], but in extremely low yield, by the low-temperature, dilute acid-catalysed equilibration of 1,2-*O*-isopropylideneglycerol.



1 $R^1 = R^2 = Me$; $R^3 = H$
3 $R^1 = R^3 = H$; $R^2 = Ph$
8 $R^1 = R^2 = Me$; $R^3 = p$-phenylazobenzoyl



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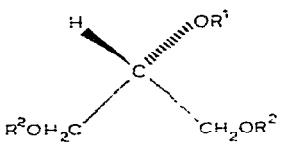

2 $R^1 = Bzl$; $R^2 = H$
4 $R^1 = R^2 = H$
5 $R^1 = Me$; $R^2 = H$
7 $R^1 = Bzl$; $R^2 = Ts$
9 $R^1 = Me$; $R^2 = p$-phenylazobenzoyl
10 $R^1 = Me$; $R^2 = p$-nitrobenzoyl

The intermediate **2** has been synthesised[4–6] from suitably protected glycerol derivatives, usually *via* 1,3-*O*-benzylideneglycerol (**3**). It has been of interest in a variety of lipid studies[7–13], mainly due to the ease of removal of the benzyl group. It has also been investigated[6] as an analogue of mephenisin [3-(2-methylphenoxy)-1,2-propanediol], an anticonvulsant and muscle relaxant. There is no direct synthesis of **2** from glycerol (**4**).

Alkylation of nucleosides[14–17] and some sugar derivatives[18–19] with diazomethane and diazo(phenyl)methane in the presence of a catalytic quantity of tin(II) chloride dihydrate showed remarkably high selectivity towards certain hydroxyl groups. A diol system of restricted steric-dimension is a necessary requirement for

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the reaction, and primary hydroxyl groups apparently do not react. These reactions have now been applied to glycerol (**4**), resulting in the direct synthesis of **2** and the corresponding 2-*O*-methylglycerol (**5**). Compound **5** is a useful reference compound[20-23] in structural studies of carbohydrates and has been synthesised[24] by methylation of **3**, followed by acid hydrolysis: from 2,5-di-*O*-methylgalactitol[22,23] or 2,5-di-*O*-methyl-L-rhamnitol[21], using periodate oxidation–borohydride reduction sequences; and also from 1,3-di-*O*-benzylglycerol[25].

Treatment of **4** in methanol–dichloromethane, containing tin(II) chloride dihydrate, with excess of diazo(phenyl)methane in ether gave a mixture of 2-*O*-benzylglycerol (**2**) and benzaldehyde azine (**6**), together with unreacted **4**. Diazo(phenyl)methane is known[26] to react slowly with methanol to yield **6**. Compound **3** could be isolated (54–58%) by fractional distillation or by chromatography on silica gel, which gave a purer product that crystallised and was characterised as the crystalline bis(toluene-*p*-sulfonate) **7**. Treatment[1] of **2** with 2,2-dimethoxypropane in 1,2-dimethoxyethane yielded the 1,3-*O*-isopropylidene derivative, which was not isolated, but was hydrogenolysed to give **1**, characterised as the known *p*-phenylazobenzoate **8**.

The yield of **2** was dependent upon the source of the diazo(phenyl)methane. When the reagent was prepared[27-28] by the oxidation of benzaldehyde hydrazone with mercuric oxide, the yield was lower (38%) and the product much more difficult to purify than when the reagent was prepared from azibenzil[29] (α-diazobenzyl phenyl ketone).

Treatment of **4** in methanol–dichloromethane with excess of diazomethane, in the presence of tin(II) chloride dihydrate, yielded one product. Fractional distillation gave unreacted **4** (26.5%) and 2-*O*-methylglycerol (**5**, 66%), which was characterised as the known bis(*p*-phenylazobenzoate) **9** and the bis(*p*-nitrobenzoate) **10**.

The formation of a disubstituted complex between a suitable diol-group and the catalyst is a requirement[18,19] for the observed, selective alkylations. Glycerol (**4**) can form complexes of the 1,3-dioxane or 1,3-dioxolane type, involving HO-1,3 and HO-1,2, respectively. It is known[19] that complexed, primary hydroxyl groups and isolated, secondary hydroxyl groups do not react with the reagent mixture, and the complex of the 1,3-dioxane type would be a non-productive intermediate. Only the complexed HO-2 group (of the 1,3-dioxolane-type structure) should react, leading to the observed, selective alkylations. The overall yields are lower than those in previous alkylations of this type and could be accounted for by the relative distribution of the two forms of complex.

It has been suggested[30] that tin(II) chloride is not involved directly in the alkylations, but reacts rapidly with diazomethane to form products that exhibit properties in the alkylation reactions identical with those ascribed to tin(II) chloride.

EXPERIMENTAL

Kieselgel 60 (Merck) was used for column chromatography. T.l.c. was per-

formed on silica gel (Merck: DC Fertigplatten), using 1,2-dimethoxyethane–cyclohexane (3:2) and detection[31] with 0.1M $KMnO_4$–M sulfuric acid (1:1) at 110°. Glycerol (Fluka, water-free) was used without further purification.

Reactions of glycerol (**4**). — (*a*) *With diazo(phenyl)methane–tin(II) chloride dihydrate.* A solution of **4** (2.5 g) in methanol (100 ml) and dichloromethane (125 ml) containing tin(II) chloride dihydrate (20 mg) was stirred with a solution of diazo-(phenyl)methane [from azibenzil[29] (10 g)] in ether (70 ml) at room temperature for 48 h. T.l.c. revealed one major component (R_F 0.26), unreacted **4**, and benzaldehyde azine (**6**) (R_F 0.76). Formic acid (98%) was added dropwise to decompose the excess of reagent, and the mixture was concentrated *in vacuo*. A suspension of the residue in water (60 ml) was extracted with light petroleum (b.p. 60–80°, 2 × 80 ml), and the aqueous solution was freeze-dried. Fractional distillation of the crude, syrupy product gave **4** (0.7 g, 28%), b.p. 164–167°/10 mmHg; and 2-*O*-benzylglycerol (**2**; 2.65 g, 54%), b.p. 188–192°/10 mmHg; lit.[6] b.p. 185–187°/10 mmHg.

In another experiment, the crude, syrupy product was chromatographed on silica gel (85 g). Elution with 1,2-dimethoxyethane–cyclohexane (3:2) gave **2** (2.87 g, 58%) which was homogeneous in t.l.c. The material crystallised on storage at 0° and, when recrystallised from benzene–cyclohexane (3:1), had m.p. 37–39°; lit.[6] m.p. 38.5–40°.

Treatment of **2** (1.5 g) in dry pyridine (20 ml) with toluene-*p*-sulfonyl chloride (1.7 g), in the usual manner, gave the bis(toluene-*p*-sulfonate) **7** (84%), m.p. 110–111° (from ethanol); lit.[8] m.p. 110–112°.

(*b*) *With diazomethane–tin(II) chloride dihydrate.* A solution of **4** (4 g) in methanol (150 ml) and dichloromethane (50 ml) containing tin(II) chloride dihydrate (8 mg) at −5° was treated with a solution of diazomethane [from 1-methyl-1-nitroso-urea[32] (15 g)]. The yellow colour of the mixture was discharged within 30 min, and the mixture was stirred at room temperature for 18 h. T.l.c. then revealed one component in addition to unreacted **4**. The solvents were evaporated *in vacuo* and the syrupy residue was fractionally distilled to give 2-*O*-methylglycerol (**5**; 3.05 g, 66%), b.p. 115–118°/6 mmHg (lit[20] b.p. 123°/13 mmHg); and **4** (1.06 g), b.p. 154–156°/6 mmHg.

Treatment[33] of **5** with *p*-phenylazobenzoyl chloride gave the bis(*p*-phenylazo-benzoate) **9**, m.p. 127–129° (from ethanol); lit.[21] m.p. 128–130°. The product **5** was further characterised as the bis(*p*-nitrobenzoate) **10**, m.p. 158–159° (from ethanol); lit.[22] m.p. 159.5–160.5°.

2,2-Dimethyl-1,3-dioxan-5-ol (**1**). — A solution of **2** (1.4 g) in 1,2-dimethoxy-ethane (12 ml) and 2,2-dimethoxypropane (7.5 ml) was heated under reflux with stirring for 65 h; t.l.c. then indicated that all of **2** had reacted. The cooled solution was concentrated *in vacuo* at 30°, and ether (2 × 25 ml) was distilled from the residue. A solution of the residue in ethanol (80 ml) was then hydrogenolysed exhaustively in the presence of palladium (from 400 mg of the oxide). The filtered mixture was concentrated *in vacuo*, and distillation of the residue gave **1** (0.69 g, 68%), b.p. 115–120°/22 mmHg; lit.[2] b.p. 130°(bath)/33 mmHg. The product was characterised[33] as the *p*-phenylazobenzoate **8**, m.p. 143–146° (from ethanol); lit.[2] m.p. 145–147.5°.

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