Synthesis of 2-Methansulfonyloxy-1-propanol and Some Related Esters

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A number of alkyl alkansulphonates have been used as mutagenic agents in plants and in other organisms during the last decades.[1-3] Their mutagenic action is, however, accompanied by more or less serious toxic side effects.

In a series of investigations the toxicity and mutagenic activity of some unsubstituted and substituted alkyl methansulphonates have been studied.[3,4] The compounds have been further characterised, following the Swain-Scott [5] approach, by the determination of their reactivities towards representative nucleophiles. The results obtained give support to the assumption that the inducement of gene mutations requires alkylation of reactive oxygen or nitrogen atoms of DNA whereas toxic side effects are caused primarily by alkylations of essential enzymes at sites of high nucleophilicity, *e.g.* divalent sulphur atoms.[1,3,4]

Among the methansulphonates studied, the ethyl ester exhibits the highest mutagenic efficiency. The higher alkyl esters are less efficient but especially the very reactive isopropyl ester deserves interest. For example, in marked contrast to the other compounds studied it exhibits a linear dose-response relationship.

The present paper describes the syntheses of four substituted esters (I—IV) derived from propyl or isopropyl methansulphonate which were judged to be of interest with respect to their biological effects. 2-Methansulphonyloxy-1-propanol (I) was prepared from propane-1,2-diol *via* tritylation, mesylation and subsequent cleavage [6] of the trityl ether group. The isomer, 3-methansulphonyloxy-1-propanol (II), was prepared by partial mesylation of 1,3-propanediol with subsequent column chromatography. 2-Methansulphonyloxy-1-methoxypropane (III) was obtained by mesylation of 1-methoxy-2-propanol.[7] 1,2-Epoxy-3-methansulphonyloxypropane (IV) was prepared from 1-bromo-2,3-epoxypropane and silver mesylate.

The introduction of a hydroxyl or ether function in an alkyl methansulphonate will modify its properties in several ways. The increased hydrophilic character should affect the intracellular distribution of the ester causing increased concentration in the region around the solvated nucleotide chains. Especially substitution in the β-position to the sulphonate group will decrease the reactivity, provided neighbouring group effects can be excluded. Finally, the hydroxyesters I and II, on reaction with DNA-phosphate, will introduce 2-hydroxyisopropyl and 3-hydroxypropyl groups, respectively. Phosphate triesters containing a hydroxyl group in the 2-position to the P—O-bond are known to hydrolyse at high rates even in neutral solution due to a neighbouring group effect (*cf.* Ref. 8). Such a mechanism might be responsible for the pronounced chromosome breaking activity (*cf.* Ref. 4) of 2-hydroxyethyl methansulphonate [9] and ethylene oxide.

The epoxyderivative IV is of additional interest as a bifunctional alkylating agent.

Experimental. Infrared spectra were measured on a Perkin-Elmer IR 257 spectrophotometer.

1-Triphenylmethoxy-2-propanol. Trityl chloride [10] (50 g) and 1,2-propanediol (13.5 g) were stirred for 48 h at 20° with pyridine (*p.a.*; 100 ml). The reaction mixture was dissolved in chloroform (300 ml) and the solution was extracted with 4 M HCl (300 ml), washed with water and 1 M $NaHCO_3$, dried and evaporated to dryness. The crude product (52 g) was crystallised from hexane to give 1-triphenylmethoxy-2-propanol as prisms, m.p. 96—97°. (Found: C 83.3; H 6.96. $C_{22}H_{22}O_2$ (318.4) requires C 83.0; H 6.96).

2-Methansulphonyloxy-1-propanol (I). A mixture of crude 1-triphenylmethoxy-2-propanol (40 g) and dry pyridine (25 ml) was stirred while mesyl chloride (14.5 g) was added over a period of 2 h and the temperature was kept at *ca.* —5°. The mixture was stirred overnight at 2° and was then dissolved in chloroform (300 ml). The solution was extracted with 4 M HCl (100 ml) and washed with water and 1 M $NaHCO_3$ and dried. Evaporation *in vacuo* gave the crude tritylated ester which was detritylated [6] by treatment for 4 h at 20°C with HCl (7 g) in dry chloroform (800 ml). The solution was evaporated *in vacuo* and the mesylate was separated from trityl chloride and minor amounts of 1,2-

propanediol by column chromatography. The column (4×36 cm) was prepared from Silica gel Merck (0.05–0.20 mm). Ethyl acetate was used as eluent. The eluate was analysed by TLC as described below. The appropriate fractions were combined and the solution was evaporated *in vacuo* to give chromatographically pure 2-mesyloxy-1-propanol (11 g, 58 %) which was dried at 20°, 10^{-3} mm. It could not be distilled and was stored at −15°C. (Found: C 31.7; H 6.49; S 20.2. $C_4H_{10}O_4S$ (154.2) requires C 31.2; H 6.54; S 20.8). $\nu_{max}(CHCl_3)$ 3450(br), 1350, 1175 cm^{-1}.

3-Methansulphonyloxy-1-propanol (II). Mesylchloride (26 g, 0.23 mol) was added with stirring at −5° over 2.5 h to a mixture of propane-1,2-diol (23.5 g, 0.31 mol) and dry pyridine (24 g). The reaction mixture was left at 2° overnight and was then poured, with cooling, into 4 M HCl (60 ml). The solution was extracted with chloroform (12×150 ml) and the combined extracts were dried and evaporated *in vacuo*. The crude product (30 g) was chromatographed on a column (4×36 cm; Silica gel Merck, <0.08 mm) in portions of 15 g. Ethyl acetate was used as eluent. The appropriate fractions from both columns were combined and evaporated. A further amount was obtained by running a second column on initial fractions (yield, 37 %). Distillation gave 3-mesyloxy-1-propanol, b.p. 85–86°/10^{-4} mm, n_D^{25} 1.4498. (Found: C 31.2; H 6.54; S 20.5. $C_4H_{10}O_4S$ (154.2) requires C 31.2; H 6.54; S 20.8). $\nu_{max}(CHCl_3)$ 3550, 3400, 1350, 1170 cm^{-1}.

2-Methansulphonyloxy-1-methoxypropane (III). 1-Methoxy-2-propanol [7] was prepared from 1,2-epoxypropane and fractionated. The main fraction (b.p. 120.5°–121°) was shown to contain <0.05 % methanol (GLC). Mesyl chloride (11.0 g) was added over a period of 4 h to a mixture of 1-methoxy-2-propanol (9.0 g) and dry pyridine (20 ml), kept at *ca.* −5°. The mixture was stirred for 12 h at 2° and was then poured, with cooling, into 4 M HCl (100 ml). The solution was extracted with chloroform (3×100 ml). The combined extracts were dried and evaporated and the residue was distilled in the presence of $CaCO_3$ to give III (11.4 g), b.p. 71–71.5°/0.2 mm, ν_{max}(pure) 1350, 1178, 1115 cm^{-1}. (Found: C 35.6; H 7.22; S 19.4; $C_5H_{12}O_4S$ (168.2) requires C 35.7; H 7.19; S 19.1).

1,2-Epoxy-3-methansulphonyloxypropan (IV). 1-Bromo-2,3-epoxypropane (Light; 13.7 g) was added to a solution of silver mesylate (35 g) in acetonitrile (*p.a.*; 100 ml). The mixture was refluxed for 52 h. The solution was filtered and the precipitate was washed with acetonitrile. The combined filtrate and washings were evaporated to dryness and the residue was extracted with ethyl acetate. Fractionation gave IV, b.p. 78–79°/0.1 mm, n_D^{25} 1.4505 (Found: C 31.6; H 5.28; S 21.0. $C_4H_8O_4S$ requires C 31.6 H 5.30 S 21.1). $\nu_{max}(CHCl_3)$ 3030; 1420; 1360; 1180 cm^{-1}.

Thin layer chromatography. TLC was performed on Silica gel HF_{254} (Merck) using ethyl acetate as eluent. The spots were located by means of UV-light or by spraying with 1 % $KMnO_4$ solution.

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