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ALKALINE HYDROLYSIS OF METHANESULFONATE ESTERS WITHOUT INVERSION

Frederic C. Chang

Department of Pharmacognosy, University of Tennessee
Memphis, Tennessee

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Alkaline hydrolysis of asymmetric sulfonate esters usually yields inverted or racemized alcoholic products, accompanied by varying but generally sizable proportions of olefinic material (1). I wish to report an alkaline room temperature hydrolytic reaction in which mesylates of equatorial conformation are converted stereospecifically and in high yield to alcohols of original configuration.[1]

3β-Cholestanyl mesylate (I) (2), $[\alpha]_D$ +13.9° (chf), 100 mg., dissolved in 1 ml. of anhydrous benzene, diluted to 4 ml. with dimethyl sulfoxide[2] (DMSO), was treated with 4 ml. of a 0.5N

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[1] No reaction of this type has been located in the literature, although reductive cleavage of sulfonate esters by reagents such as Raney nickel, sodium in liquid ammonia, and lithium aluminum hydride, is known. [G. W. Kenner and M. A. Murray, J. Chem. Soc., S178 (1949); D. B. Denny and B. Goldstein, J. Org. Chem., 21, 479 (1956); P. Karrer and A. Boettcher, Helv. Chim. Acta, 36, 837 (1953)].

[2] DMSO used in these experiments (with the exception of that used in the "wet" DMSO reactions mentioned below) was of reagent grade (J. T. Baker Co., Phillipsburg, New Jersey), dried by passage through a column of molecular sieves (Union Carbon and Carbide, Tonawanda, N. Y., Linde Sieves, 30/60 mesh, 13X grade). "Wet" DMSO was prepared by adding 0.60 ml. of water to 100 ml. of DMSO (ca. 0.33N).

solution of potassium t-butoxide[3] in DMSO[4] (equivalent ratio of base to mesylate about 9/1). After 24 hours at room temperature (about 25°), the mesylate had been almost completely consumed [reaction followed by thin-layer chromatography (TLC)]. Another 4.0 ml. of the potassium t-butoxide reagent was added and the reaction allowed to stand for 24 hours more to complete the reaction. The products, 3β-cholestanol (71 mg., 86%; identified by m.p., IR and TLC) and an olefin (3 mg., 4%; presumably a mixture[5] of 2- and 3-cholestene), were readily separated by column chromatography (3). No more than very faint traces of 3α-cholestanol were detectable by TLC.

The 5β-series equatorial compound, 3α-cholanol mesylate[6] (II), when treated identically with potassium t-butoxide-DMSO, gave analogous products, 3α-cholanol (87%) and olefin (6%). When wet[2] DMSO was used in the reactions, a small proportion of alcohol of inverted configuration was found, but the product was still predominantly uninverted alcohol.

However, when the sulfonate ester employed was 3β-cholestanol tosylate (3) instead of the corresponding mesylate I,

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[3] M.S.A. Research Corporation, Callery, Pennsylvania.

[4] Potassium t-butoxide in DMSO has been the reagent used in a number of recently reported notable reactions: (a) D. J. Cram, B. Rickborn, C. A. Kingsbury and P. Haberfield, J. Am. Chem. Soc., **83**, 3678 (1961); (b) D. J. Cram, M. R. V. Sahyun and G. R. Knox, ibid., **84**, 1734 (1962); (c) A. Schreisheim, G. E. Hoffmann and C. A. Rowe, Jr., ibid., **84**, 3160 (1962).

[5] In view of the known isomerizing properties of potassium t-butoxide-DMSO on olefins (footnote 4c), the identity of the olefinic products reported in this paper is being investigated separately.

[6] m.p. 114.5-115.5°, $[\alpha]_D$ +44.1° (chf). All new compounds mentioned in this paper have given satisfactory analyses.

under dry DMSO conditions, a surprising change in product composition was found; olefin was the major product. Elevation of temperature to 56° in the reaction of 3β-cholestanol mesylate, or change of sulfonate ester to ones of axial conformation [3α-cholestanol mesylate,[7] and 3α-cholestanol tosylate (3)], also result in predominantly olefinic products. The experiments are summarized in Table I.

TABLE I.

Reaction of Potassium t-Butoxide-Dimethyl Sulfoxide with Sulfonate Esters

Comp.[a]	Conf.[b]	D[2] or W[2]	Temp.	Products[c], %		
				β-ol	α-ol	olefin[5]
I	eq	D	25°	86[d]	0	4
I	eq	W	25°	81[d]	3[e]	6
I	eq	D	56°	19[d]	4[e]	67
II	eq	D	25°	0	87[f]	6
II	eq	W	25°	3[g]	75[f]	5
III	eq	D	25°	17[d]	2[h]	57
IV	ax	D	25°	14[d]	7[e]	77
V	ax	D	25°	9[d]	5[e]	68

[a] I, 3β-cholestanol mesylate; II, 3α-cholanol mesylate; III, 3β-cholestanol tosylate; IV, 3α-cholestanol mesylate; V, 3α-cholestanol tosylate.

[b] equatorial or axial conformation of the sulfonate ester group.

[c] Alcohols were identified by m.p., IR and TLC.

[d] 3β-cholestanol

[e] 3α-cholestanol

[f] 3α-cholanol (5)

[g] 3β-cholanol (5)

[h] Less than 1% of 3α-cholestanol t-butyl ether was also present.

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[7] m.p. 116.1-117.1° $[\alpha]_D$ +23.1° (chf).

The reaction of equatorial mesylates to stereospecifically yield uninverted alcohols must involve cleavage of the oxygen-sulfur bond, probably as a result of nucleophilic attack on sulfur by alkoxide ion[8]; and the ease with which the alkoxide-DMSO reagent reacts at room temperature is another instance of greatly enhanced reactivity of anions in DMSO as compared with hydroxylic solvents, as discussed by Cram et al.[4a]

Beyond these two fairly obvious general conclusions, a detailed understanding of the reactions awaits further studies, and discussions that follow are speculative, albeit pertinent. The appearance of the small amounts of inverted alcohol in the products of the wet DMSO reactions might be explained on the basis that addition of water is equivalent to introducing t-butyl alcohol into the solvent system.[8] The increase in proportions of olefin formed in the reaction at elevated temperature, and also in the reactions of the axial esters, is consistent with current concepts, that higher temperature of reaction generally favors elimination over substitution (5), and ionic eliminations proceed most smoothly when substituents involved are trans-diaxial (6).

The marked difference in product composition between the reactions of the two esters of 3β-cholestanol, mesylate and tosylate, reflects a decided change in reaction mechanism.

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[8] N. Pappas, J. A. Meschino, A. A. Fournier, and H. R. Nace [J. Am. Chem. Soc., **78**, 1907 (1956)], in studying the reaction of 3β-cholestanol tosylate with potassium t-butoxide in refluxing t-butyl alcohol obtained 39 to 47% of completely inverted alcoholic product, 3β-cholestanol t-butyl ether and olefin (26 to 33%). Their kinetic data did not give clear-cut evidence for a reaction mechanism, but they suggested that both ionic and bimolecular methanisms were operative at C-3. Our results thus clearly indicate that the main mesylate reaction does not involve the carbon-oxygen bond.

What factors in addition to steric ones are involved is uncertain, as nucleophilic reactions on sulfur are not well understood, although some related studies of the subject have been reported (7).

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