SOLVOLYSIS OF SOME POTASSIUM STERYL SULFATES BY METHANOL/BORON TRIFLUORIDE AND DIMETHYL SULFOXIDE

S.I. Bayyuk and A.M. Juraydini

Department of Chemistry,
American University of Beirut,
Beirut, Lebanon

Received May 20, 1967

In this work the BF_3-catalyzed methanolysis of some potassium steryl sulfates and their solvolytic cleavage by dimethyl sulfoxide were investigated. Whereas the salts were solvolyzed by $MeOH/BF_3$ at a faster rate than by dimethyl sulfoxide/water, the latter reagent seems to be milder. Unlike $MeOH/BF_3$, it does not effect dehydration of Δ^4-Cholesten-3α-ol.

In recent years, considerable interest has been shown in the solvolysis of sterol sulfates. In a procedure designed to prevent structural alterations resulting from drastic treatment, Lieberman and coworkers (1-3) liberated the free sterols from pure steryl sulfate conjugates by protracted hydrolysis at room temperature with aqueous HCl and continuous extraction with ether. In 1950 Grant and Beall (4) observed that sodium estrone sulfate underwent rapid and complete hydrolysis in dioxane at room temperature. Later, in an investigation of the hydrolysis of the pyridinium and potassium sulfates of cholesterol, β-cholestanol and estrone by a number of ethers and other solvents, McKenna and Norymberski (5) found that the rate

was fastest in dioxane, and decreased in other ethers as the basic character of the solvent diminished. Other solvents generally exhibited low reactivity.

In this work, we report results of the chemical solvolysis of certain potassium steryl sulfates in MeOH/BF_3 and DMSO/H_2O, in the hope that they may have useful application to biological extracts.

Results and Discussion

Since the ethanolysis of salts of steryl sulfates is known to proceed by nucleophilic attack at the S atom (5), it was assumed, in this investigation, that any factor which increases the susceptibility of the S atom to nucleophiles will accelerate the reaction. The potassium sulfates of three different 3-hydroxy sterols (cholesterol, β-cholestanol, epiandrosterone) and a 17-hydroxy sterol (testosterone) were synthesized from their parent alcohols (6), and were then methanolyzed in the presence and absence of BF_3 at about 65° and at room temperature.

TABLE I

Time(hr)[a] required for complete solvolysis by:

Potassium Sulfate of	MeOH/BF_3, at reflux[b]	DMSO/H_2O at 100°
Cholesterol	3/4	2
β-Cholestanol	1	5
Epiandrosterone	1½	1½
Testosterone	2	6

From the results obtained by methanolysis at 65° (Tables I and II), it is obvious that the presence of BF_3 has markedly increased the rate of the reaction. The maximum time limits required to achieve complete

TABLE II

Potassium Sulfate of	Extent of solvolysis (%) by: MeOH reflux (1 hr.)	MeOH room temp[c] (10 hr.)	MeOH/BF_3 room temp (10 hr.)	DMSO/H_2O room temp (10 hr.)
Cholesterol	15	42	80	0
β-Cholestanol	0	0	53	0
Epiandrosterone	4.5	20	65	0
Testosterone	0.6	14	56	0

[a] Each result is an average of at least two determinations.
[b] Approximately 65°.
[c] About 20°.

methanolysis of the different salts ranged between 3/4 - 2 hours, and were shorter than those required by many of the previously reported solvent systems. The catalytic effect of BF_3 could also be observed when methanolysis was effected at room temperature (Table II). In all cases the parent sterols were isolated with complete retention of configuration as evidenced from optical rotation and mixture melting point determinations. Evidently, cleavage occurred at the S-O bond. The catalyst, most likely, acted by attacking one of the exposed O atoms of the sulfate group, thus increasing the formal positive charge on the S atom and facilitating attack by MeOH.

Due to its aprotic character, anhydrous dimethyl sulfoxide could not exert any detectable solvolytic action on cholesteryl potassium sulfate. In the presence of H_2O however (5 x molar concentration of the salt), the steryl sulfates were solvolyzed at 100°. Similar to MeOH/BF_3, solvolysis by DMSO/H_2O afforded the parent sterols without any detectable change in structure or configuration. This could be taken

as evidence of cleavage at the S-O bond of the salt by a mechanism similar to that postulated for solvolysis by ethers (5). Unlike $MeOH/BF_3$, this solvent system did not exhibit any detectable activity at room temperature.

In conclusion, $MeOH/BF_3$ is more effective than $DMSO/H_2O$ since it solvolyzed the salts faster at a lower temperature. The latter solvent system, however, has the advantage of being a milder reagent toward sterols with allylic-OH groups. Unlike $MeOH/BF_3$, it did not dehydrate Δ^4-Cholesten-3α-ol even after two hours of heating at 100°, and it may prove useful in the solvolysis of steryl sulfates containing functional groups susceptible to Lewis acids.

Experimental

All melting points are uncorrected. Ultraviolet spectra were measured in EtOH and rotations in $CHCl_3$ at about 20°. Infrared spectra were determined on a Model 137 Perkin-Elmer Infracord.

Solvents. All were chemically pure and anhydrous unless otherwise specified. Petroleum ether had a boiling point range 35 - 70°.

β-Cholestanol. Cholesterol was repeatedly hydrogenated in glacial acetic acid at 75° and 50 p.s.i. using freshly prepared platinic oxide catalyst (7). The product had $[\alpha]_D$ + 23.4° and m.p. 140 - 142°.

Δ^4-Cholesten-3α-ol. Δ^4-Cholesten-3-one was prepared from cholesterol (8) and then reduced with sodium borohydride (9,10). Δ^4-Cholesten-3α-ol was separated from its epimer and purified by two consecutive digitonin precipitations. The alcohol melted at 130 - 131° and had $[\alpha]_D$ + 43°.

Preparation of the Potassium Steryl Sulfates (6). The sterols were treated with pyridine sulfur trioxide (11). The resultant pyridinium sulfates were then converted to the corresponding potassium salts by treatment with 10% aqueous KCl. After recrystallization from MeOH, cholesteryl potassium sulfate melted with decomposition at 236° [reported values (5,6): 226 - 227°, 210° and 239°]; the β-cholestanyl salt at 236° with decomposition [lit. (5,12): 234 - 235° and 236°]; the epiandrosteryl salt at 225° with decomposition; and the testosteryl salt at 235 - 236° with decomposition. The identities of the salts were further ascertained by examination of the infrared spectra.

Solvolysis by MeOH/BF_3. In a typical run, an accurately weighed specimen of about 220 mg of the potassium steryl sulfate was dissolved in 22.5 ml of MeOH, and 0.3 ml of boron trifluoride etherate was added. After heating the solution at reflux, ($\sim 65^0$) the methanol content was rapidly removed under reduced pressure at room temperature. The residue was extracted with about 100 ml of petroleum ether, and the extract was washed with water, dried, and finally evaporated. The weight of the final dry crystalline product was used to calculate the extent of methanolysis (%). The identities of the sterols were established by melting point, mixture melting point and specific rotation determinations, and by comparisons of UV and IR spectra.

Methanolysis of the salts under the other conditions was effected in a similar manner.

Treatment of potassium cholesteryl sulfate with anhydrous dimethyl sulfoxide. A solution of 230 mg of cholesteryl potassium sulfate in 50 ml of anhydrous DMSO was heated at 100^0 under a nitrogen atmosphere for 10 hr. The reaction mixture was then extracted with two 125 ml portions of petroleum ether, and the extract was worked up as previously described in the preceeding section. There was no detectable solvolysis.

Solvolysis by DMSO/H_2O. Accurately weighed samples (about 105 mg) of the salts were dissolved in a mixture of 10.5 ml of DMSO and 1.5 ml of H_2O. Heating of the solutions at 100^0 precipitated the free sterols in crystalline form. The products were isolated by extracting each reaction mixture with 100 ml of petroleum ether. When the reactions were conducted at room temperature, no detectable solvolysis could be observed even after 10 hours.

Effect of MeOH/BF_3 on Δ^4-cholesten-3α-ol. Since certain sterols containing allylic -OH groups are readily dehydrated by acids, it was essential to ascertain whether the BF_3-catalyzed methanolysis of sulfate salts of such sterols is accompanied by such a side reaction. Several attempts to prepare the pyridinium sulfate of Δ^4-cholesten-3α-ol were made using different solvent systems and different conditions. All were unsuccessful, and resulted in the dehydration of the alcohol to $\Delta^{3,5}$-cholestadiene which was identified by its m.p. 79 - 80^0; λ_{max} 235 mμ; and $[\alpha]_D$ - 121^0. This could be attributed to the ready dehydration of the alcohol by the pyridine sulfur trioxide reagent. In view of this fact, it was decided to treat Δ^4-cholesten-3α-ol directly with MeOH/BF_3 under the same conditions used for the methanolysis of the salts. To this effect, 0.3 ml of boron trifluoride etherate was added to a solution of 200 mg of Δ^4-cholesten-3α-ol in 25 ml of MeOH, and the reaction mixture was heated at reflux ($\sim 65^0$) for 1 hr. After cooling to room temperature, the crystalline product was collected, washed with a small portion of ice-cold MeOH, and finally identified as $\Delta^{3,5}$-cholestadiene by melting point determination, specific rotation, and ultraviolet absorption. Similarly, solutions containing 200 mg of the sterol in 24 ml of DMSO and 1 ml of H_2O were heated at 100^0 for 1 and 2 hours. After cooling to room temperature, the solutions were extract-

ed with petroleum ether. The crystalline product obtained consisted of Δ^4-cholesten-3α-ol. It had $[\alpha]_D$ + 44°, melted at 130 - 131°, and its melting point was not depressed on admixture with authentic Δ^4-cholesten-3α-ol.

Acknowledgment

This work was supported by Arts and Sciences Rockefeller Research Grant.

References

1. Lieberman, S., Hariton, L.B., and Fukushima, D.K., J. AM. CHEM. SOC. 70, 1427 (1948).
2. Lieberman, S., and Dobriner, K., REC. PROG. HORMONE RES. 3, 71 (1948).
3. Lieberman, S., Mond, B., and Smyles, E., REC. PROG. HORMONE RES. 9, 113 (1954).
4. Grant, G.A., and Beall, D., REC. PROG. HORMONE RES. 5, 307 (1950).
5. McKenna, J., and Normberski, J.K., J. CHEM. SOC., 3889 (1957).
6. Sobel, A.E., and Spoerri, P.E., J. AM. CHEM. SOC. 63, 1259 (1941).
7. Bruce, W.F., and Ralls, J.O., ORGANIC SYNTHESIS, Collective Vol. 2, Editor A.H. Blatt, John Wiley and Sons, Inc., New York, 1948, p. 191.
8. Fieser, L.F. ORGANIC SYNTHESIS, Vol. 35, Editor T.L. Cairns, John Wiley and Sons, Inc., New York, 1955, p. 43.
9. Dauben, W.G., Micheli, R.A., and Eastham, J.F., J. AM. CHEM. SOC. 74, 3852 (1952).
10. Haddadin, M.J., and Issidorides, C.H., J. ORG. CHEM. 25, 403 (1960).
11. Sobel, A.E., Drekter, I.J., and Natelson, S., J. BIOL. CHEM. 115, 381 (1936).
12. Sobel, A.E., and Rosen, M.J., J. AM. CHEM. SOC. 63, 3536 (1941).