

REACTION OF SOME STEROIDAL TOSYLHYDRAZONES WITH LITHIUM ALKYLs

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Several short communications¹⁻³ have recently described the formation of olefins from tosylhydrazones by treatment with alkyllithium compounds.

The proposed mechanism^{1,2} involves the formation of an intermediate carbanion. The reported examples seem to indicate that the preferred product formed is the less substituted olefin, which is often difficult to synthesize. We were therefore interested in applying this reaction to a number of steroid tosylhydrazones, expecting to obtain some less accessible olefins.

In Table 1 are listed the cholestenes obtained.

TABLE 1
5 α -CHOLESTENES OBTAINED

Tosylhydrazone	Product	M.P.	[α] _D	Yield
5 α -Cholestan-3-one	Δ^2	69° (lit. ⁴ 75°)	+66° (lit. ⁴ +70°)	78%
-4-one	Δ^3	75° (lit. ⁴ 73°)	+55° (lit. ⁴ +57°)	73%
-6-one	Δ^6	87° (lit. ⁴ 87°)	-95° (lit. ⁴ -88°)	70%
5 α -Cholest-1-en-3-one	$\Delta^{1,3}$	64° (lit. ⁴ 63°)	+75° (lit. ⁴ +75°)	60%

^a λ_{\max} (EtOH) 262 m μ (ϵ 5930) [lit.⁴ 262 (5500)].

The steroid olefins formed were identified (cf.⁴) by melting points and optical rotation, and since their retention volumes by gas chromatography are very nearly the same, the olefins were ozonized, the ozonides reduced with lithium aluminium hydride and the trimethylsilyl derivatives subjected to gas chromatography.

Table 2 lists the constants of the alkyl cholestanes obtained and Table 3 the retention volumes of the olefins and of the tetramethylsilyl ethers of the diols obtained by ozonization, as well as the R_F on silica gel impregnated with silver nitrate of the olefins, developed with methylene chloride-cyclohexane (3 : 1).

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¹ Shapiro, R. H., and Heath, M. J., *J. Am. chem. Soc.*, 1967, **89**, 5734.

² Kaufman, G., Cook, F., Shechter, H., Bayless, J., and Friedman, L., *J. Am. chem. Soc.*, 1967, **89**, 5736.

³ Dauben, W. G., Lorben, M. E., Vietmeyer, N. D., Shapiro, R. H., Duncan, J. H., and Tomer, K., *J. Am. chem. Soc.*, 1968, **90**, 4762.

⁴ Scott, F. J., *Chem. Abstr.*, 1965, **63**, 16410; Henbest, H. B., and Wilson, R. A. L., *J. chem. Soc.*, 1956, 3289.

The reaction was also successfully applied to the preparation of 5 α -cholesta-1,3-diene, which previously had only been prepared laboriously and in low yield.⁴

It was found that the proportion of alkyllithium reagent to tosylhydrazone is critical; best yields of olefin are obtained using no more than 3 equiv. of lithium compound per mole of steroid tosylhydrazone; with increasing excess of alkyllithium compound increasing amounts of non-olefinic products are obtained, most of which are oils.

TABLE 2
ALKYLATED CHOLESTANES OBTAINED

Tosylhydrazone	Reagent	M.P.	$[\alpha]_D$	R_{vol}^a	Yield
5 α -Cholestan-3-one	MeLi	oil	+3.4°	1.08	70%
-3-one	BuLi	66°	+22°	2.45	75%
-4-one	MeLi	oil	+12°	1.17	64%
-6-one	MeLi	oil	$\pm 0^\circ$	1.15	66%

^a On HIEFF-8BP.

TABLE 3
 R_{vol} AND R_F VALUES OF OLEFINS AND DIOLS

	Δ^2	Δ^3	Δ^4	Δ^5	Δ^6
Olefins					
R_F (SiO ₂ -AgNO ₃)	0.44	0.41	0.66	0.73	0.40
R_{vol} (HIEFF-8BP)	1.15	1.16	1.09	1.13	1.15
Diols from ozonization					
R_{vol} (HIEFF-8BP)	1.59	1.65	1.32	1.10	1.33
R_{vol} (OV-17)	2.29	2.41		2.74	
R_{vol} (SE-30)	3.14	3.21			

Experimental

5 α -Cholestan-3-one Tosylhydrazone

According to Mitsuhashi and Harada,⁵ 1 g of steroid was made to react with 1 g tosylhydrazine in 30 ml glacial acetic acid at 30° for 16 hr. The crystalline product was filtered, washed with hexane, and recrystallized from methanol, m.p. 168–170° (dec.) (lit.⁶ 173–175°). Yield 1.2 g (85%) (Found: C, 74.1; H, 9.7; N, 5.2. Calc. for C₃₄H₄₆N₂O₂S: C, 73.6; H, 9.8; N, 5.05%).

5 α -Cholestan-4-one Tosylhydrazone

This was prepared according to Chang⁷ by refluxing 1 g cholestan-4-one and 1 g tosylhydrazine in 100 ml ethanol containing 1.7 ml conc. HCl. The product was precipitated in ice and filtered and crystallized from ethanol-hexane, m.p. 174–175° (dec.). Yield 1.1 g (78%) (Found: C, 73.7; H, 9.7; N, 5.15. Calc. for C₃₄H₄₆N₂O₂S: C, 73.6; H, 9.8; N, 5.05%).

⁵ Mitsuhashi, H., and Harada, S., *Tetrahedron*, 1966, **22**, 1033.

⁶ Caglioti, L., Grazelli, P., and Selva, A., *Gazz. chim. ital.*, 1964, **94**, 537.

⁷ Chang, F. C., *J. org. Chem.*, 1965, **30**, 2053.

5 α -Cholestan-6-one Tosylhydrazone

This was prepared in the same manner as the 3-tosylhydrazone. Crystallized from ethanol-hexane it had m.p. 151–152° (dec.). Yield 1.3 g (92%) (Found: C, 73.6; H, 9.7; N, 5.25. Calc. for C₃₄H₄₆N₂O₂S: C, 73.6; H, 9.8; N, 5.05%).

5 α -Cholest-1-en-3-one Tosylhydrazone

5 α -Cholest-1-en-3-one (1.5 g, 3.9 mmoles) was dissolved in 10 ml glacial acetic acid and 1.5 g (8.1 mmoles) *p*-toluenesulphonylhydrazine added. The solution was kept at 30° for 5 hr. The product began to precipitate after about 5 min. The precipitate was filtered off, washed with cold hexane, and air-dried. Crystallization first from ethanol and then from chloroform-hexane gave 1.85 g (89%) of product, m.p. 168–170° (dec.) (Found: C, 72.5; H, 8.9; N, 5.3. Calc. for C₃₄H₄₄N₂O₂S.H₂O: C, 72.6; H, 8.24; N, 5.0%).

Preparation of the Steroid Olefins

The tosylhydrazone (2 g), dissolved in 20 ml dry tetrahydrofuran, was cooled in an ice-bath in an atmosphere of nitrogen and 8 ml 2*N* methylithium in hexane (Aldrich) added dropwise with stirring. After 2 hr of reaction, the mixture was precipitated on ice, dilute HCl added, and the steroid extracted with pentane. To separate the olefins from the saturated by-product the reaction mixture was chromatographed on silica gel impregnated with 25% silver nitrate. The saturated alkylcholestanes eluted with cyclohexane, the olefins with *n*-hexane.

Ozonization of the Steroidal Olefins

About 50 mg of olefin were dissolved in 10 ml methylene chloride and ozone from a Welsbach ozonizer bubbled through the solution at –70° until the blue colour of dissolved ozone appeared. The solution was then evaporated in vacuum at as low a temperature as possible and the residue treated with a solution of 100 mg LiAlH₄ in 10 ml tetrahydrofuran for 1 hr at room temperature. The excess hydride was destroyed by addition of ethyl acetate and aqueous acid. The steroid was extracted with ether, the solvent evaporated, and the residue transformed into the trimethylsilyl derivative in the usual way.