291. *A Modified Procedure for the Preparation of 3,5-Cyclosteroids.*

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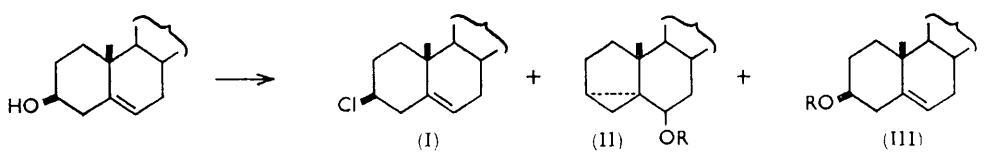
Treating a 3β-hydroxy-Δ⁵-steroid with a sulphonyl chloride in pyridine and then adding a solvolysis solvent gives good yields of several 3,5-cyclosteroids without the need to isolate the ester.

The usual preparative procedure [1] for 3,5-cyclosteroids has been the isolation of the toluene-*p*-sulphonate of the 3β-hydroxy-Δ⁵-steroid followed by buffered solvolysis of this derivative, but overall yields are not very satisfactory. It has now been found that good yields of 3,5-cyclosteroids may be obtained by adding, after a suitable time lapse, solvolysing solvent to the pyridine solution of the steroid and toluene-*p*-sulphonyl chloride or methanesulphonyl chloride without prior isolation of the toluene-*p*-sulphonate or methanesulphonate. Thus the pyridine of the reaction mixture acts in place of the usual buffer in preventing the solution from attaining the acidity required to catalyse the formation of the 3β-substituted Δ⁵-steroid derivative. The Table details the 3,5-cyclosteroids which have been prepared by the modified procedure.

	3,5-Cyclosteroid						
				Yield	Literature		
Steroid	Deriv.	M. p.	$[\alpha]_D$	(%)	M. p.	$[\alpha]_D$	Ref.
Cholesterol	6β-Hydroxy	65—67°	+46°	70	67—68°	+50°	1
	6β-Methoxy	79—80	+54	68	79	+55	2
Diosgenin	6β-Hydroxy *	185—186	−51	69	185	−48	3
Ergosterol	6,8(14),22-Triene	100—101	+91	50	102	+92	4
3β-Hydroxyandrost-5-en-17-one	6β-Hydroxy	139—141	+124	27	141	+122	5
3β-Hydroxypregn-5-en-20-one	6β-Hydroxy	179—181	+125	80	180—181	+123	6

* This product was not separated readily from unchanged diosgenin on an alumina column. The crude product was, therefore, directly oxidised by chromium trioxide in pyridine to 3α,5-cyclo-5α-spirostan-6-one.[3] The physical constants quoted are for the latter compound.

By this procedure the 3,5-cyclosteroid (II; R = H or Me) was isolated in 60—80% yield with 5—20% each of the 3β-chloride (I) (obtained from the chloride ions derived from the sulphonyl chloride) and of the 3β-substituted-Δ⁵-steroid (III) derivative. Preparations of the 6β-methoxy- and of the 6β-hydroxy-3,5-cyclosteroids were equally satisfactory. An attempt to prepare 6β-acetoxy-3α,5-cyclo-5α-cholestane by adding an excess of acetic acid to a solution of cholesterol and methanesulphonyl chloride in pyridine gave only



cholesteryl acetate. Attempts to modify the procedure further in order to render it an alternative and rapid method for the isolation of 3β-halides by, for instance, solvolysing with hydrochloric acid in methanol, gave impure products. Since there are many other procedures for the preparation of 3β-halides the method was not further investigated.

[1] Kosower and Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 4347.
[2] Fieser and Fieser, " Steroids," Reinhold Publ. Corpn., New York, 1959, p. 314.
[3] Burn, Ellis, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4092.
[4] Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397.
[5] Barton and Klyne, *Nature*, 1948, **162**, 493.
[6] Patel, Petrow, and Stuart-Webb, *J.*, 1957, 665.

In these conditions ergosterol yielded only the hydrocarbon, 3α,5-cyclo-5α-ergosta-6,8(14),22-triene. This is in conformity with the work of Nes and Steele [7] who found that the sensitive 3α,5-cyclo-5α-ergosta-7,22-dien-6β-ol gave this triene on treatment with pyridine. 3β-Hydroxyandrost-5-en-17-one was the only steroid tested by this procedure which failed to give a good yield of the 3,5-cyclosteroid.

Experimental

Light petroleum had b. p. 60—90°. $[\alpha]_D$ are for chloroform solutions. Characterisation of the products was, in all cases, confirmed by determination of their infrared spectra (Perkin-Elmer Infracord spectrophotometer, model 137).

6β-*Methoxy*-3α,5-*cyclo*-5α-*cholestane*.—Cholesterol (5 g.) and methanesulphonyl chloride (4 ml.) were left overnight in pyridine (65 ml.). After the addition of methyl alcohol (500 ml.) the reactants were refluxed for 1 hr. The methanolic solution was evaporated to dryness under reduced pressure and the residue dissolved in ether. The ethereal solution was washed successively with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and taken to dryness. The residue was chromatographed on an alumina column from a light petroleum solution. Elution with light petroleum yielded a gum (0·684 g.) which gave a positive Beilstein test, indicating the presence of cholesteryl chloride. Further elution with this solvent gave 6β-methoxy-3α,5-cyclo-5α-cholestane (3·51 g.) which, after recrystallisation from methyl alcohol–ethyl acetate, had m. p. 79—80°, $[\alpha]_D^{25}$ +54° (*c* 1·01). Further elution with light petroleum–benzene (10 : 1) yielded 3β-methoxycholest-5-ene [6] (0·13 g.), m. p. 80—82°, $[\alpha]_D^{25}$ −41° (*c* 1·6).

3α,5-*Cyclo*-5α-*pregnan*-6β-*ol*.—3β-Hydroxypregn-5-en-20-one (1 g.) and methanesulphonyl chloride (0·8 ml.) were left overnight in pyridine (13 ml.). Water (10 ml.) in acetone (90 ml.) was added, and the mixture was refluxed for 1 hr. and then evaporated under reduced pressure. The residue was dissolved in chloroform, washed in the usual way, dried, and taken to dryness. The residue was chromatographed on alumina from 1 : 1 benzene–light petroleum. Elution with this solvent gave 42 mg. of crystalline product, m. p. 139—145°, with a positive Beilstein test (3β-chloropregn-5-en-20-one,[8] m. p. 148—150°). Elution with benzene and benzene–chloroform yielded 3α,5-cyclo-5α-pregnan-6β-ol (798 mg.), m. p. 179—181°, $[\alpha]_D^{25}$ +125° (*c* 0·7), after crystallisation from benzene–light petroleum.

3α,5-Cyclo-5α-cholestan-6β-ol, m. p. 65—67°, $[\alpha]_D^{25}$ +46° (*c* 0·7), was prepared in a similar manner. It was also obtained by using toluene-*p*-sulphonyl chloride in place of methanesulphonyl chloride. By this procedure diosgenin with either methanesulphonyl chloride or toluene-*p*-sulphonyl chloride gave, on chromatographic separation of the products, crude 3α,5-cyclo-5α-spirostan-6β-ol, m. p. 158—165°, $[\alpha]_D^{25}$ −63° (*c* 0·45). Petrow *et al.*[3] give m. p. 165—166°, $[\alpha]_D^{25}$ −44°. The crude compound was converted in good yield into 3α,5-cyclo-5α-spirostan-6-one, m. p. 185—186°, $[\alpha]_D^{25}$ −51° (*c* 0·54), by the chromium trioxide–pyridine reagent.[3]

3α,5-*Cyclo*-5α-*ergosta*-6,8(14),22-*triene*.—Ergosterol (590 mg.) was left overnight in dry pyridine (13 ml.) containing toluene-*p*-sulphonyl chloride (900 mg.). A solution of water (10 ml.) in acetone (90 ml.) was added. After 1 hr. the solution was evaporated under reduced pressure at 20°. The residue was dissolved in ether, washed in the usual way, dried, and recovered. The product (460 mg.) was refluxed for 3 hr. in redistilled n-pentyl alcohol [4] and then recovered under reduced pressure, dissolved in light petroleum, and filtered through alumina. Evaporation of the light petroleum gave 3α,5-cyclo-5α-ergosta-6,8(14),22-triene (285 mg.), m. p. 100—101°, $[\alpha]_D^{25}$ +91° (*c* 0·77), ε_{261} 24,400 (in ethanol), after recrystallisation from ethyl acetate.

6β-*Hydroxy*-3α,5-*cyclo*-5α-*androstan*-17-*one*.—3β-Hydroxyandrost-5-en-17-one (300 mg.) was dissolved in pyridine (4 ml.) containing toluene-*p*-sulphonyl chloride (600 mg.) and left overnight. Acetone (50 ml.) and water (5 ml.) were added and the mixture was refluxed for 30 min. After the solvents had been removed under reduced pressure, the residue was dissolved in ether. The ether solution was washed in the usual way, dried, and concentrated. The product was chromatographed from light petroleum–benzene (1 : 1) on alumina. Elution with this solvent

[7] Nes and Steele, *J. Org. Chem.*, 1957, **22**, 1457.
[8] Daus and Hirschmann, *J. Amer. Chem. Soc.*, 1953, **75**, 3840.

gave 3β-chloroandrost-5-en-17-one (58 mg.), m. p. 157—158° (Shoppee [9] reports m. p. 157°). Elution with benzene gave a gum (42 mg.) followed by 6β-hydroxy-3α,5-cyclo-5α-androstan-17-one (82 mg.), m. p. 139—141°, $[\alpha]_D^{25}$ +124° (*c* 1·0), after recrystallisation from benzene–light petroleum. Further elution with benzene gave more gum (m. p. 115—130° after crystallisation from light petroleum–benzene). Elution with benzene–chloroform and chloroform gave crude unchanged starting material (46 mg.), m. p. 139—148° (identified from its characteristic infrared spectrum).

A poor yield of 6β-hydroxy-3α,5-cyclo-5α-androstan-17-one was also obtained when methanesulphonyl chloride was used in place of toluene-*p*-sulphonyl chloride in a similar experiment.

Attempt to Prepare 6β-*Acetoxy*-3α,5-*cyclo*-5α-*cholestane*.—Cholesterol (2·0 g.) was left overnight with methanesulphonyl chloride (1·60 ml.) in pyridine (26 ml.). After addition of acetic acid (150 ml.) the mixture was refluxed for 1 hr., cooled, and poured with vigorous stirring into aqueous sodium hydrogen carbonate solution. The product was extracted into ether, washed, dried in the usual way, recovered, and chromatographed from light petroleum on alumina. Elution with light petroleum gave cholesteryl chloride (0·176 g.), m. p. and mixed m. p. 92—96°. Elution with light petroleum–benzene (20 : 1) gave cholesteryl acetate (1·080 g.), m. p. and mixed m. p. 114—115° (from methyl alcohol–ethyl acetate).

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[9] Shoppee, *J.*, 1948, 1043.