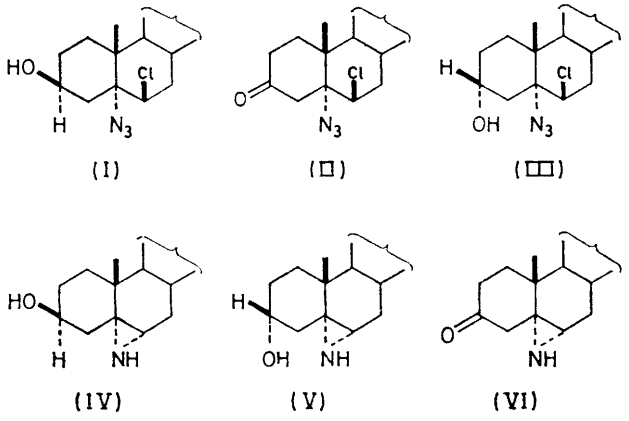
Intramolecular Catalysis. Part III.[1] Effect of a Neighbouring Hydroxy-group on the Opening of Steroidal Aziridines with Azide Anions

By **Yoram Houminer**, Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

5α,6α-Iminocholestan-3β-ol (IV) and its 3α-hydroxy-isomer (V) have been prepared and their structures established. Their reactions with sodium azide in acetone–water (2 : 1) produce the corresponding *trans*-diaxial amino-azides. The ratio of the reaction rates is *ca.* 1 : 2, respectively. The mechanisms of the reactions of the steroidal aziridines are discussed and comparison is made between these compounds and the related epoxides.

WE have recently reported that 5α,6α-epoxycholestan-3α-ol reacts with sodium azide in acetone–water faster than its 3β-hydroxy-isomer.[1] A similar phenomenon has also been observed with the 7β- and 7α-hydroxy-4α,-5α-epoxycholestanes.[1,2] It has been suggested that the neighbouring hydroxy-group reacts as an internal electrophile and facilitates the opening of the epoxide ring by delocalization of the negative charge which develops on the ring oxygen atom in the transition state.[1] The present investigation extends this study to 5α,6α-iminocholestan-3α-ol and its 3β-hydroxy-isomer, steroidal aziridines possessing similar stereochemistry. We were also interested in comparing the reactivities of aziridines and epoxides of similar structures. The aziridines were synthesized from the corresponding 5α-azido-6β-chlorocholestane derivatives. 5α-Azido-6β-chlorocholestan-3β-ol (I) was prepared by basic hydrolysis of its known acetate.[3] Oxidation of (I) with sodium dichromate in acetic acid gave the ketone (II) in almost quantitative yield. Reduction of (II) with an excess of sodium borohydride at room temperature gave a mixture of two main products, of which the major one (50%), isolated by t.l.c., was 5α-azido-6β-chlorocholestan-3α-ol (III). The minor product (33%) was the 3β-ol (I). The n.m.r. spectrum of (III) indicated its stereochemistry. The C*H*·OH signal in (III) was a multiplet, of $W_{1/2}$ <7.2 Hz (the signal overlaps with that of the 6α-proton, and both give a multiplet of $W_{1/2}$ 7.2 Hz), characteristic of an equatorial proton[4] [the multiplet corresponding to the 3α-proton in (I) has $W_{1/2}$ *ca.* 24 Hz]. Chemical evidence for the structure (III) was obtained by its smooth oxidation to regenerate the ketone (II). It is well known that reduction of a 3-oxo-group in the cholestane skeleton with sodium borohydride gives the 3β-hydroxy-isomer as the major product.[5] However, it has been shown[6] that the presence of a substituent at the 5α-position affects the stereochemical course of the reduction so that the relative amount of the 3α-hydroxy-isomer is increased, and in some cases it even becomes the major product. The reduction of (II) to (III) and (I) further demonstrates this phenomenon.

Treatment of the 3β-ol (I) with a large excess of lithium aluminium hydride in bis-(2-methoxyethyl) ether afforded 5α,6α-iminocholestan-3β-ol (IV) in good yield. Similarly, the 3α-ol (III) was almost quantitatively converted into 5α,6α-iminocholestan-3α-ol (V). The configuration of the aziridine ring in both (IV) and (V) has to be 5α,6α, since it is well established that the ring retains the original configuration of the azido-group.[3,7] In the n.m.r. spectrum of (IV) the C*H*·OH signal occurs at δ 3.75, as a multiplet, $W_{1/2}$ 23 Hz. The corresponding



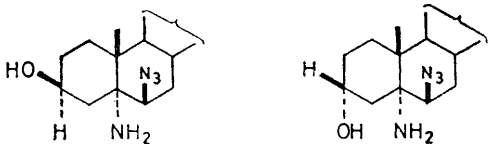
proton in the spectrum of (V) resonates at δ 4.09 with $W_{1/2}$ 6.8 Hz. This then establishes the configurations of the hydroxy-group in (IV) and (V) as equatorial and axial, respectively. The C-18 protons of both (IV) and (V) appear as singlets at δ 0.61, but the corresponding protons of cholestan-3β-ol resonate at δ 0.65. This difference is due to a long-range shielding effect and can be ascribed to the 5α,6α-aziridine ring current. A similar phenomenon is also observed in the n.m.r. spectra of the corresponding 5α,6α-epoxycholestanes, in which the singlets corresponding to the 18-protons appear at δ 0.62.

It has been shown[1] that reduction of 5α,6α-epoxycholestan-3-one with sodium borohydride gives a t.l.c.-separable mixture of the 3α- and 3β-hydroxy-epoxides. The same reaction was attempted as an alternative route for the preparation of (V). Oxidation of (IV) by Jones' method afforded 5α,6α-iminocholestan-3-one (IV), treatment of which with sodium borohydride in methanol gave a mixture of (IV) and (V). However, the

[1] Part II, Y. Houminer, *J.C.S. Perkin I*, 1975, 1663.
[2] D. H. R. Barton and Y. Houminer, *J.C.S. Chem. Comm.*, 1973, 839.
[3] G. Snatzke and A. Veithen, *Annalen*, 1967, **703**, 159.
[4] L. M. Jackman and S. Sternhell, 'Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, London, 1969, p. 288.
[5] O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, 1962, **27**, 3803; O. H. Wheeler and J. L. Mateos, *Canad. J. Chem.*, 1958, **36**, 1049.
[6] Y. Houminer, *J. Org. Chem.*, 1975, **40**, 1361, and references cited therein.
[7] G. J. Matthews and A. Hassner, *Tetrahedron Letters*, 1969, 1833; A. Hassner and L. A. Levy, *J. Amer. Chem. Soc.*, 1965, **87**, 4203.

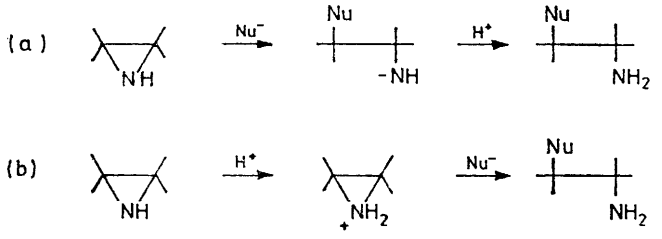
two isomers could not be separated by t.l.c. The n.m.r. spectrum of the mixture indicated that (IV) was its major component.

The reaction of either (IV) or (V) with sodium azide in acetone–water (2 : 1) gave the corresponding amino-azides, (VII) and (VIII) respectively. In the n.m.r.



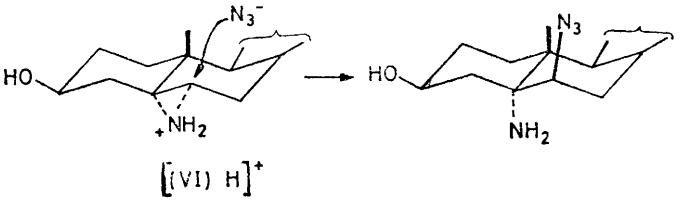
(VII) (VIII)

spectra of these the CHN_3 signals appear as multiplets at δ 3.26 with $W_{1/2}$ 5.0 Hz and at δ 3.28 with $W_{1/2}$ 5.6 Hz, respectively. These values are characteristic of equatorial protons,[4] thus establishing that in both compounds the 6-azido-group is axial and in the β-configuration. The formation of both (VII) and (VIII) indicate that the ring opening of the 5α,6α-imines with sodium azide produces the *trans*-diaxial amino-azides. This result fits the general pattern of the uncatalysed and acid-catalysed ring opening of aziridines, which usually proceeds stereospecifically *trans*.[8,9]



SCHEME 1

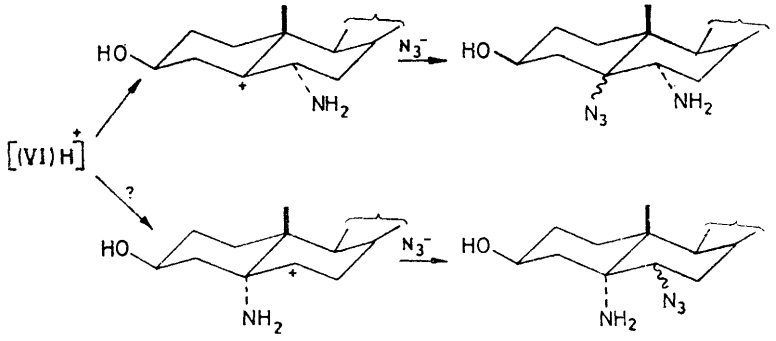
Based-catalysed ring opening of aziridines, unless they have electron-withdrawing *N*-substituents, is rare.[8] The imino-group, being a poor leaving group can react only with very strong bases such as carbanions and amide ions.[9] There is a significant body of data[9] concerning the opening of aziridines by various nucleophiles and in the light of this it has been emphasized[9] that, for aziridines to undergo ring opening with a nucleophile under ordinary conditions, the nitrogen atom must first be protonated. Thus, reaction *via* Scheme 1(a) is almost impossible and the route shown in Scheme 1(b) is always preferred. Indeed, most known reactions of this type are carried out under acidic catalysis.[9] However, there are several examples,[10,11] including our own work, in which aziridines react with nucleophiles in neutral aqueous solutions. These observations do not necessarily imply that under these conditions the reactions proceed *via* route (a) in Scheme 1, since water is sufficiently acidic to provide a very low concentration of aziridinium ions.[9] Our results support this conclusion (see preceding discussion).



SCHEME 2

The *trans*-diaxial structure of both amino-azides (VII) and (VIII) suggests an S_N2 mechanism for the reaction of (IV) and (V) with azide anions, as shown in Scheme 2 for the case of (IV). An S_N1 mechanism (Scheme 3) would afford the corresponding 5-azido-6α-amino-compound resulting from the more stable tertiary cation. This compound is not formed, thus indicating that an S_N1 mechanism is not important in our case. A similar stereochemical argument was taken as evidence for an S_N2 mechanism in the reaction of 2β,3β-imino-cholestane with nucleophiles.[8]

The kinetics of the reactions of both (IV) and (V) with sodium azide in aqueous acetone were followed by n.m.r. The 18-protons in both (IV) and (V) resonate at δ 0.61, whereas those in the corresponding amino-azides (VII) and (VIII) both resonate at δ 0.69. Integration of the two separate signals made possible the



SCHEME 3

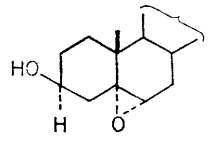
[8] A. Hassner and C. Heathcock, *J. Org. Chem.*, 1965, **30**, 1748 and references cited therein.

[9] O. C. Dermer and G. E. Ham, 'Ethylenimine and Other Aziridines, Chemistry and Applications,' Academic Press, New York, 1969, pp. 203—300, and references cited therein.

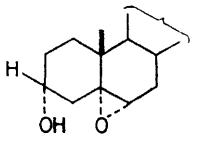
[10] R. D. Guthrie, D. Murphy, D. H. Buss, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 1963, 84.

[11] R. Ghirardelli and H. J. Lucas, *J. Amer. Chem. Soc.*, 1957, **79**, 734.

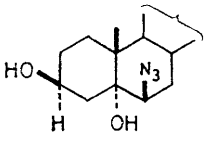
determination of the amounts of the starting material and the product in the reaction mixture. For comparison, the kinetics of the reactions of the epoxides (IX) and (X) with sodium azide to give the corresponding hydroxy-azides (XI) and (XII) [1] were followed by a



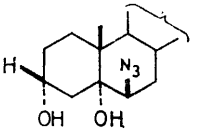
(IX)



(X)



(XI)



(XII)

similar method. The 18-protons in the epoxides resonate at δ 0.62 and in the hydroxy-azides at δ 0.68. Since the kinetics of the reactions of the epoxides are more simple we shall first discuss these results. The reactions of both (IX) and (X) with a 10—120 fold excess of sodium azide in acetone–water (2 : 1 v/v) were found in each case to be first order in the epoxide [plots of $\ln(100/100 - x)$ against t, where x is the reaction percentage, gave straight lines with correlation coefficients >0.9995]. The results with various concentrations of sodium azide (Table 1) show that the reaction is also first

TABLE 1

Rate coefficients for the reactions of 5α,6α-epoxycholestanes with sodium azide in acetone–water (2 : 1 v/v) at 50 °C

Steroid [a]	10[NaN_3]/mol l^{-1}	$10^6 \times k_2'$ [b]/s^{-1}	$10^6 \times k_2$/l mol^{-1} s^{-1}
5α,6α-Epoxycholestan-3β-ol	0.31	0.16 ± 0.005	5.16
	1.54	0.78 ± 0.02	5.06
	3.08	1.60 ± 0.02	5.19
	3.08 [c]	1.62 ± 0.03	5.26
	6.16	2.48 ± 0.04	4.03
5α,6α-Epoxycholestan-3α-ol	0.31	1.16 ± 0.03	37.42
	1.54	5.63 ± 0.10	36.56
	3.08	11.40 ± 0.13	37.01
	3.08 [c]	11.64 ± 0.15	37.80
	6.16	18.55 ± 0.23	30.11

[a] Steroid concentration 2.49 × 10^{-3} mol l^{-1}. [b] Pseudo-first-order rate coefficient ($k_2' = k_2[NaN_3]$). [c] In the presence of NaOH (4.84 × 10^{-3} mol l^{-1}).

order in the sodium azide. Therefore, the reaction kinetics fit the equation: rate = $k_2[St][N_3^-]$ (St = steroid). The results in Table 1 suggest that at concentrations of sodium azide up to 3.08 × 10^{-1} mol l^{-1} the sodium azide is fully dissociated. At higher concentrations, the observed rate coefficient is less, and this may indicate that some of the sodium azide exists as ion pairs. Table 1 also shows that the reaction rates are not depressed by additions of sodium hydroxide.

The Figure shows pseudo-first-order plots for the reactions of the aziridines (IV) and (V) with sodium azide. For both aziridines the rate decreases with the progress of the reaction. Table 2 summarizes the

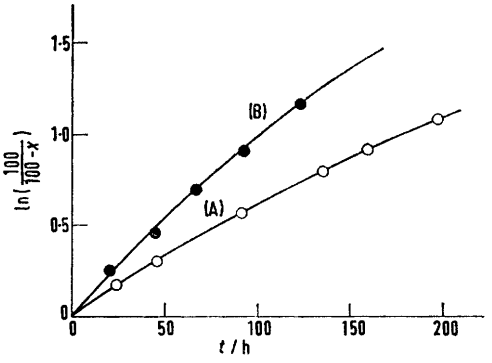
TABLE 2

Initial rates for the reactions of 5α,6α-iminocholestanes with sodium azide in acetone–water (2 : 1 v/v) at 50 °C

Steroid [a]	10[NaN_3]/mol l^{-1}	10^9 × initial rate [b]/l mol^{-1} s^{-1}
5α,6α-Iminocholestan-3β-ol	3.08	4.63
	3.08 [c]	<0.50
	1.54	4.00
	0.31	3.10
5α,6α-Iminocholestan-3α-ol	4.62	8.26
	3.08	8.07
	3.08 [c]	0.65
	1.54	6.81

[a] Steroid concentration 2.49 × 10^{-3} mol l^{-1}. [b] ±4%. [c] In the presence of NaOH (4.84 × 10^{-3} mol l^{-1}).

initial rates for the reactions of the aziridines with sodium azide at various concentrations; it is clear that the reaction for both (IV) and (V) is less than first-order in sodium azide. Table 2 shows also that the reaction rates are markedly lowered in the presence of sodium hydroxide.



Reactions of (A) 5α,6α-iminocholestan-3β-ol and (B) the 3α-ol (2.49 × 10^{-3} mol l^{-1}) with sodium azide (3.08 × 10^{-1} mol l^{-1}) in acetone–water (2 : 1 v/v) at 50 °C

In view of the above results, we propose a mechanism for the reaction of both epoxides and aziridines as demonstrated in Scheme 4 for the 3β-hydroxy-isomers of these compounds. Under our conditions, water or hydroxide anions are not involved as nucleophiles, since the only products are the azides. The reaction rate is given by equation (1).

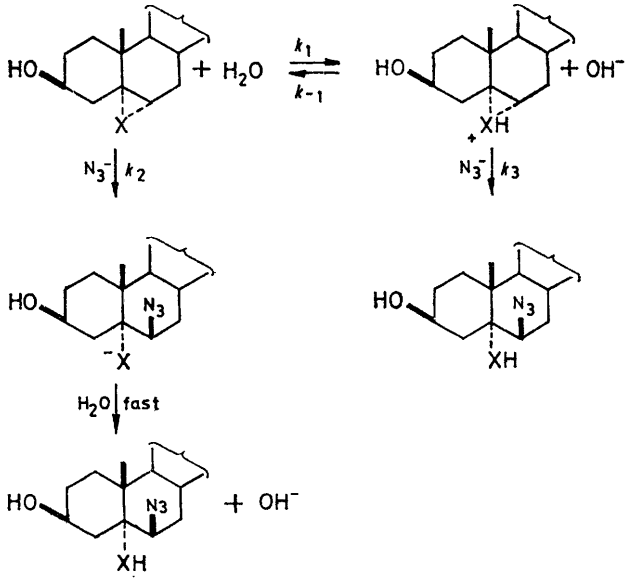
$$\text{rate} = k_2[St][N_3^-] + k_3[StH^+][N_3^-] \qquad (1)$$

Aziridines and epoxides of similar structures differ strongly in their basicities. There are no reported pK values for the epoxides (IX) and (X) or the aziridines (IV) and (V), but it can be estimated, on the basis of a comparison between ethers and secondary amines,[12] that (IV) and (IX) as well as (V) and (X) differ in their pK values at least by ten orders of magnitude. Therefore, in the case of the epoxides we can conclude that, under our conditions, which are slightly basic owing to

[12] J. March, 'Advanced Organic Chemistry, Reaction Mechanisms and Structure,' McGraw-Hill, New York, 1968, pp. 219—221.

the solvolysis of sodium azide in aqueous solutions, $[StH^+]$ is negligible, and although it is clear that $k_2 \ll k_3$ (the protonated epoxide must be more reactive towards nucleophiles) the fact that $[StH^+] \simeq 0$, simplifies equation (1) into rate $= k_2[St][N_3^-]$. This conclusion is supported both by the kinetics of the reactions and by the observation that the rates are not depressed by the presence of added sodium hydroxide, which should decrease $[StH^+]$.

The reaction kinetics in the case of the aziridines are much more complex. Although both $[N_3^-]$ and $[H_2O]$ remain practically constant during one kinetic run, the reactions have no pseudo-first-order characteristic (Figure). Therefore the decrease in rate during one kinetic run, both with (IV) and (V), is evidently due to the build-up of $[OH^-]$. Indeed, added sodium hydroxide strongly lowered the reaction rates (Table 2). These

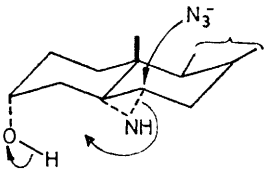


SCHEME 4 X = O for epoxides, NH for aziridines

results support our previous arguments on the mechanism of the opening of aziridines which we assumed to proceed exclusively through the protonated aziridines.

The results (Table 1) verify our previous observations [1] on the existence of electrophilic intramolecular catalysis in the opening of the epoxides (IX) and (X) with azide anions. We expected that such internal catalysis would also be shown in the related aziridines, and since the epoxy-group in the epoxides is a better leaving group than the imino group in the aziridines, we even expected to find a larger catalytic effect in the latter case. However, our results show that (V) is only slightly more reactive than (IV), and it is clear that (V) does not exhibit intramolecular catalysis. This phenomenon can be explained as follows. Electrophilic assistance by the hydroxy-group in (V) [but not in (IV)] can occur only on the unprotonated aziridine, in the transition state of which, (XIII), a negative charge is developed on the nitrogen atom. Our results suggest that the reaction proceeds exclusively *via* the protonated aziridine and therefore no such internal catalytic effect can be observed.

Both Table 2 and the Figure indicate that (V) is about twice as reactive as (IV). The proximity of the



(XIII)

3α-hydroxy-group to the imino-group in (V) suggests the possibility of internal hydrogen bonding between the two groups (mainly O–H · · · NH and not HO · · · H–N; compare for example the case of ethanolamine [13]), thus increasing slightly the concentration of a quasi-protonated aziridine in the case of (V) as compared with (IV). However, the i.r. spectra of both (IV) and (V) do not indicate any intramolecular hydrogen bonding in (V), similar to the case of the related epoxides.[1] Therefore, internal hydrogen bonding in (V) is not a likely explanation for its higher reactivity. We believe that the greater reactivity results from the higher basicity of (V), *i.e.* the 3α-hydroxy-group can stabilize the positive charge on the protonated nitrogen by internal solvation, thus increasing the basicity of the amino-group.

It is clear from the results that any attempt to compare the reactivities of epoxides and aziridines of related structures towards nucleophiles is meaningless, since the two series react by two different mechanisms. If we compare (IV) and (IX), in both of which no intramolecular catalysis is possible, the reactivities are similar in the absence of sodium hydroxide but differ markedly in the presence of the base. Thus, in general, the relative reactivities of epoxides and aziridines should be strongly pH-dependent.

EXPERIMENTAL

M.p.s were determined with a Fisher–Johns apparatus. I.r. spectra were recorded with a Perkin-Elmer 254 spectrophotometer. Optical rotations were determined for solutions in chloroform with a Perkin-Elmer 141 polarimeter. N.m.r. spectra were taken for solutions in deuteriochloroform with a Varian T 60 spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a Varian MAT 311 spectrometer. T.l.c. was carried out on silica gel G. Plates were eluted with light petroleum (b.p. 60—80°) containing 20—40% acetone.

5α-Azido-6β-chlorocholestan-3β-ol (I).—A suspension of 3β-acetoxy-5α-azido-6β-chlorocholestane (1.50, g) m.p. 121—122°, $[\alpha]_D$ −48° (lit.,[3] m.p. 120—122°, $[\alpha]_D$ −50°), in methanol (250 ml) containing potassium hydroxide (2.0 g) was refluxed for 30 min (the solid had dissolved after 5 min). Water was added and the product was filtered off. Recrystallization from methanol afforded *needles* (1.30 g, 95%), m.p. 139—142°, $[\alpha]_D$ −22° (*c* 0.78), $\nu_{max.}$ (CCl_4) 3 620, 2 105, 1 165, 1 040, and 665 cm^{-1}, δ 0.70 (s, 18-H_3), 1.28 (s, 19-H_3), 3.98 (m, $W_{1/2}$ *ca.* 24 Hz, H-3α), and 4.12

[13] P. J. Krueger and H. D. Mettee, *Canad. J. Chem.*, 1965, **43**, 2970.

(m, $W_{1/2}$ 7.0 Hz, H-6α), *m/e* 465/463 (0.1/0.2%, *M*), 442(4), 437/435 (2/7, *M* − N_2), 422(2), 420(6), 400(100), 384(18), and 382(15) (Found: C, 69.5; H, 9.7; Cl, 7.55; N, 9.05. $C_{27}H_{46}ClN_3O$ requires C, 69.85; H, 10.0; Cl, 7.65; N, 9.05%).

5α-*Azido*-6β-*chlorocholest*-3-*one* (II).—To a suspension of (I) (0.60 g) in acetic acid (20 ml) at 50 °C was added a solution of sodium dichromate dihydrate (0.4 g) in acetic acid (5 ml). The mixture was stirred at 50 °C for 30 min (the solid had dissolved after 5 min). Water was added and the solution was cooled in an ice-bath. The product was filtered off and the solid was washed with water. Recrystallization from methanol afforded *plates* (0.53 g, 88%), m.p. 143—145°, $[\alpha]_D$ −25° (*c* 0.39), $\nu_{max.}$ (CCl_4) 2 100, 1 725, 910, 665, and 650 cm^{-1}, δ 0.72 (s, 18-H_3), 1.45 (s, 19-H_3), and 4.10 (m, $W_{1/2}$ 6.8 Hz, H-6α), *m/e* 442(26%), 420(15), 418(39), 400(21), 398(50), 384(70), and 382(100).

5α-*Azido*-6β-*chlorocholestan*-3α-*ol* (III).—The ketone (II) (500 mg) in propan-2-ol (100 ml) was treated with a large excess of sodium borohydride, and the solution was left at room temperature for 2 h. Work-up as usual [1] and repeated t.l.c. separations afforded 5α-*azido*-6β-*chlorocholestan*-3α-*ol* (III) (250 mg, 50%). Recrystallization from methanol gave amorphous powder, m.p. 49—54°, $[\alpha]_D$ −12.5° (*c* 1.56), $\nu_{max.}$ (CCl_4) 3 625, 3 600sh, 2 105, 1 170, 930, 918, and 655 cm^{-1}, δ 0.72 (s, 18-H_3), 1.23 (s, 19-H_3), and 4.12 (m, $W_{1/2}$ 7.2 Hz, H-3β and H-6α), *m/e* 437/435 (8/21%, *M* − N_2), 422(2), 420(5), 400(100), 384(31), and 382(26) (Found: C, 69.65; H, 10.1; Cl, 7.15; N, 8.95. $C_{27}H_{46}ClN_3O$ requires C, 69.85; H, 10.0; Cl, 7.65; N, 9.05%). Also separated was 5α-azido-6β-chlorocholestan-3β-ol (I) (165 mg, 33%), m.p. 140—142° (from methanol), identical with authentic (I) (mixed m.p., $[\alpha]_D$, i.r., and t.l.c.).

Oxidation of the 3α-*Alcohol* (III).—The steroid (III) (30 mg) in acetic acid (3 ml) was treated with sodium dichromate dihydrate (30 mg) and the solution was left at 50 °C for 30 min. Work-up as usual and recrystallization from methanol afforded plates (21 mg, 70%), m.p. 142—144°, $[\alpha]_D$ −25° (*c* 0.45), identical with authentic 5α-azido-6β-chlorocholest-3-one (II) (mixed m.p., i.r., and t.l.c.).

5α,6α-*Iminocholestan*-3β-*ol* (IV).—5α-Azido-6β-chlorocholestan-3β-ol (I) (500 mg) in anhydrous bis-(2-methoxyethyl) ether (60 ml) was treated with a large excess of lithium aluminium hydride and the mixture was stirred for 2 h at 100 °C. The excess of the reducing agent was destroyed according to the procedure of Steinhardt.[14] The granular precipitate was filtered off and dried *in vacuo*. It was washed with acetone (20 ml) and then with methylene chloride (20 ml). Washings were repeated, as above, until no more organic material was eluted. The combined organic solutions were evaporated under reduced pressure. Almost pure (IV) was obtained (390 mg, 90%), m.p. 202—205°. Recrystallization from acetone afforded needles, m.p. 210—212°, $[\alpha]_D$ −50° (*c* 0.41) (lit.,[3] m.p. 210—215°, $[\alpha]_D$ −49.9°), $\nu_{max.}$ (CCl_4) 3 630, 3 260 w, vbr, and 1 032 cm^{-1}, $\nu_{max.}$ (Nujol) 3 340 and 3 265 cm^{-1}, δ 0.61 (s, 18-H_3), 1.06 (s, 19-H_3), and 3.75 (m, $W_{1/2}$ 23 Hz, H-3α), *m/e* 401 (53%, *M*), 386(100), 372(26), 368(19), 358(16), 344(16), 330(11), and 316(19).

5α,6α-*Iminocholestan*-3α-*ol* (V).—A solution of 5α-azido-6β-chlorocholestan-3α-ol (III) (500 mg) in anhydrous bis-(2-methoxyethyl) ether (60 ml) was treated with a large excess of lithium aluminium hydride and the mixture was stirred for 2.5 h at 85 °C. Work-up as above gave almost pure (V) (345 mg, 80%), m.p. 135—138°. Recrystallization from acetone afforded needles, m.p. 142—144°, $[\alpha]_D$ −70° (*c* 0.43), $\nu_{max.}$ (CCl_4) 3 610, 3460, 3 320sh, and 1 010 cm^{-1}, $\nu_{max.}$ (Nujol) 3 510 and 3 305 cm^{-1}, δ 0.61 (s, 18-H_3), 1.05 (s, 19-H_3), and 4.09 (m, $W_{1/2}$ 6.8 Hz, H-3β), *m/e* 401 (52%, *M*), 386(100), 384(31), 383(35), 372(11), 368(39), 358(11), 355(14), 344(14), 330(39), and 316(11) (Found: C, 80.5; H, 11.85; N, 3.8. $C_{27}H_{47}NO$ requires C, 80.75; H, 11.8; N, 3.5%).

Attempt to Prepare the 3α-*Alcohol* (V) *by Reduction of the Ketone* (VI).—To a solution of 5α,6α-iminocholestan-3β-ol (IV) (100 mg) in acetone (70 ml) at 0 °C was added Jones reagent (0.2 ml), and the solution was stirred at 0 °C for 10 min. Water was added and the product was extracted with chloroform. The solution was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated under reduced pressure. A yellow oil was obtained which showed $\nu_{max.}$ (CCl_4) at 1 720 cm^{-1} and no absorption at 3 630 cm^{-1}. T.l.c. indicated the presence of one major product. However, the pure ketone could not be isolated either by recrystallization or by t.l.c. Therefore, the crude mixture in methanol (40 ml) was treated with a large excess of sodium borohydride, and the solution was stirred at room temperature for 15 min. Work-up as usual gave a white solid. Its n.m.r. and i.r. spectra showed the presence of both (IV) and (V). However, the two isomers could not be separated by t.l.c. under various conditions. The n.m.r. spectrum of the mixture indicated that (IV) was its major component.

5α-*Amino*-6β-*azidocholestan*-3β-*ol* (VII).—A solution of the aziridine (IV) (200 mg) in acetone (70 ml) and water (35 ml) containing sodium azide (2.0 g) was refluxed for 192 h. Water was added and the product was extracted with chloroform. The solution was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. T.l.c. gave pure 5α-*amino*-6β-*azidocholestan*-3β-*ol* (VII) [155 mg, 70%; the rest of the material was unchanged (IV)], m.p. 144—145° (needles from methanol–water), $[\alpha]_D$ −46° (*c* 1.22), $\nu_{max.}$ (CCl_4) 3 620, 3400, 3 320, 2 095, and 1 040 cm^{-1}, δ 0.69 (s, 18-H_3), 1.18 (s, 19-H_3), 3.26 (m, $W_{1/2}$ 5.0 Hz, H-6α), and 4.10 (m, $W_{1/2}$ 21.5 Hz, H-3α), *m/e* 416 (12%, *M* − N_2), 401 (31, *M* − HN_3), 386(38), 384(20), 383(19), 374(100), 368(20), 344(27), 330(31), and 316(32) (Found: C, 72.6; H, 11.0; N, 12.15. $C_{27}H_{48}N_4O$ requires C, 72.9; H, 10.9; N, 12.6%).

5α-*Amino*-6β-*azidocholestan*-3α-*ol* (VIII).—A solution of the aziridine (V) (120 mg) in acetone (60 ml) and water (30 ml) containing sodium azide (1.2 g) was refluxed for 96 h. Work-up as for the case of (VII) and t.l.c. gave pure 5α-*amino*-6β-*azidocholestan*-3α-*ol* (VIII) [105 mg, 80%; the rest of the material was unchanged (V)], m.p. 187—189° (needles from acetone–water), $[\alpha]_D$ −41°, $\nu_{max.}$ (CCl_4) 3 360 vbr and 2 105 cm^{-1}, δ 0.69 (s, 18-H_3), 1.07 (s, 19-H_3), 3.28 (m, $W_{1/2}$ 5.6 Hz, H-6α), and 4.00 (m, $W_{1/2}$ 8.8 Hz, H-3β), *m/e* 416 (18%, *M* − N_2), 401 (69, *M* − HN_3), 386 (29), 384(20), 383(20), 374(100), and 344(20) (Found: C, 73.05; H, 10.85; N, 12.3%).

Rate Measurements.—A sample (30 mg) of the 5α,6α-iminocholestane derivative was weighed into each of five or six measuring flasks. A solution of sodium azide in acetone (B.D.H. AnalaR) and water (conductivity grade) (2 : 1 v/v) was added, and the stoppered measuring flasks were introduced into a bath at 50 ± 0.1 °C, shaken to complete dissolution, and withdrawn, each after a predetermined time. The acetone was evaporated off at room

[14] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 584.

temperature under reduced pressure. Water (100 ml) was added, and the products were extracted with methylene chloride (3 × 50 ml). The combined extracts were washed with water (2 × 100 ml) and evaporated under reduced pressure. An n.m.r. spectrum of the dry reaction mixture was taken, and the reaction percentage was calculated from the ratio of the signal at δ 0.61 (18-H_3 of the 5α,6α-imino-compound) to that at δ 0.69 (18-H_3 of the 5α-amino-6β-azido-compound). A similar procedure was used for studying the reaction rates of the corresponding 5α,6α-epoxycholestanes.

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