Synthesis and Ring Opening of Fused Steroidal Aziridines*,[1]

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A search for synthetic approaches to fused steroidal aziridines lead to a synthesis of 2β,3β-iminocholestane (IV) in 75% from 2-cholestene. Addition of iodine isocyanate to 2-cholestene gave the *trans* diaxial 3α-iodo-2β-cholestanyl isocyanate (I) which can be converted into methyl 3α-iodo-2β-cholestanylcarbamate (II) or the iodoamine hydriodide III upon heating with methanol or aqueous hydroiodic acid, respectively. Both II and III give the aziridine IV upon treatment with base. The structure of IV was proved by n.m.r. spectra and by opening of the aziridine with acetic acid and subsequent acetylation to 3α-acetoxy-2β-acetamidocholestane (VIII) prepared independently. The stereochemistry of ring opening of a 2,3-fused three-membered ring in steroids is discussed. Several derivatives of IV were prepared.

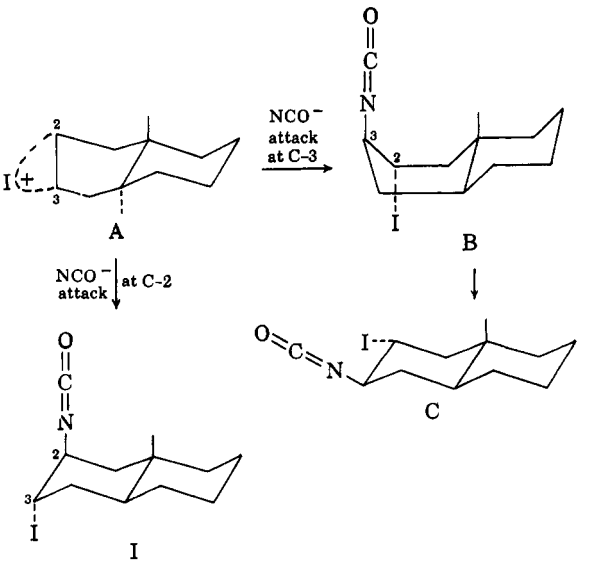
The chemistry and stereochemistry of three-membered rings with their highly compressed bond angles has long intrigued the organic chemist. These strained cyclic compounds have a propensity toward ring opening. In fact the ability of aziridinium salts to undergo facile ring opening by nucleophiles can be used to explain the action of aziridines and of related β-haloamines as carcinostats, possibly by alkylating enzyme sites.

One approach which has recently proven fruitful in cancer chemotherapy is the incorporation of functional groups such as the aziridine ring or the nitrogen mustard moiety into compounds which are themselves biologically active. Thus, "Fenesterin" an ester of cholesterol containing the β-haloamine moiety has shown favorable carcinostatic activity in a number of tumor systems.[2] In connection with our work on stereospecific introduction of nitrogen-containing functions into the steroid nucleus we were interested in the synthesis of fused steroidal aziridines and the stereochemistry of their ring-opening reactions.

Three important methods came into consideration for the synthesis of fused aziridines of type IV: the Gabriel synthesis,[3] the Wenker method,[4] and the Neber rearrangement.[5] The treatment of 3α-amino-2β-cholestanol with sulfuric acid according to the Wenker method failed to lead to an aziridine. Similarly, the Neber rearrangement of cholestanone oxime could not be accomplished because attempts to prepare the oxime tosylate invariably led to Beckmann rearrangement. The Baumgarten modification[6] of the Neber rearrangement *via* an N,N-dichloroamine likewise was unsuccessful. These failures led us to seriously consider the ring closure of β-haloamines, the Gabriel synthesis. This oldest and most general synthesis of aziridines is stereospecific, requiring a *trans* configuration for the halogen and amine functions,[7] but suffers from the disadvantage that β-haloamines are not readily available.

Addition of nitrosyl chloride, which is stereospecific for Δ^5 steroid olefins[8] and can lead to β-haloamines, gave a mixture of compounds when applied to 2-cholestene. Attempts to convert 3α-amino-2β-cholestanol by means of thionyl chloride to a 2-chloro-3-aminocholestane were likewise unsuccessful. We finally succeeded in introducing stereospecifically the desired halogen and the nitrogen function by addition of iodine isocyanate to 2-cholestene. It has been demonstrated that such additions proceed stereospecifically *trans*, presumably *via* an iodonium ion intermediate.[8a] Of the eight possible stereoisomers only one was isolated in 90% yield. It proved to be the *trans* diaxial 3α-iodo-2β-cholestanyl isocyanate (I) (see below) and its formation can be explained as follows.

Electrophilic attack on 2-cholestene is known to occur preferentially from the α side because of the shielding of the β side of the molecule by the angular methyl groups. Thus, reaction with iodine isocyanate should lead to a 2α,3α-iodonium ion (A) which can be opened by isocyanate from the β side in two ways. Attack at C-3 would lead *via* a boat transition state to B which would convert to the more stable diequatorial conformer



C. On the other hand attack of isocyanate at C-2 leads *via* a chair transition state to I. It appears that the chair transition state leading to the diaxial isomer

* To Professor Louis F. Fieser.

(1) (a) Stereochemistry of Organic Nitrogen Compounds. III; for paper I, see ref. 8a; for paper II, see ref. 8b. (b) Support of this work by Grant CY-4474 of the National Cancer Institute of the National Institutes of Health is gratefully acknowledged. (c) For a preliminary report of this work, see A. Hassner and C. Heathcock, *Tetrahedron Letters*, 393 (1963). (d) Presented in part before the Symposium on Heterocyclic Steroids of the Medicinal Chemistry Division at the 149th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964; Abstracts, p. 19M.

(2) International Cancer Congress, Moscow, 1962; see S. A. Dyogteva, *Angew. Chem., Intern. Ed. Engl.*, **1**, 600 (1962).

(3) J. S. Fruton, "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 61–77.

(4) H. Wenker, *J. Am. Chem. Soc.*, **57**, 2328 (1935).

(5) (a) P. W. Neber and A. Friedolsheim, *Ann.*, **449**, 109 (1926); (b) D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953).

(6) H. E. Baumgarten and J. M. Petersen, *ibid.*, **82**, 459 (1960).

(7) A. Weissberger and H. Bach, *Ber.*, **64**, 1095 (1931).

(8) (a) A. Hassner and C. Heathcock, *Tetrahedron Letters*, 1125 (1964); (b) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

I is more favorable here than the boat transition state, although the latter ultimately would lead to the more stable diequatorial isomer C.[9a]

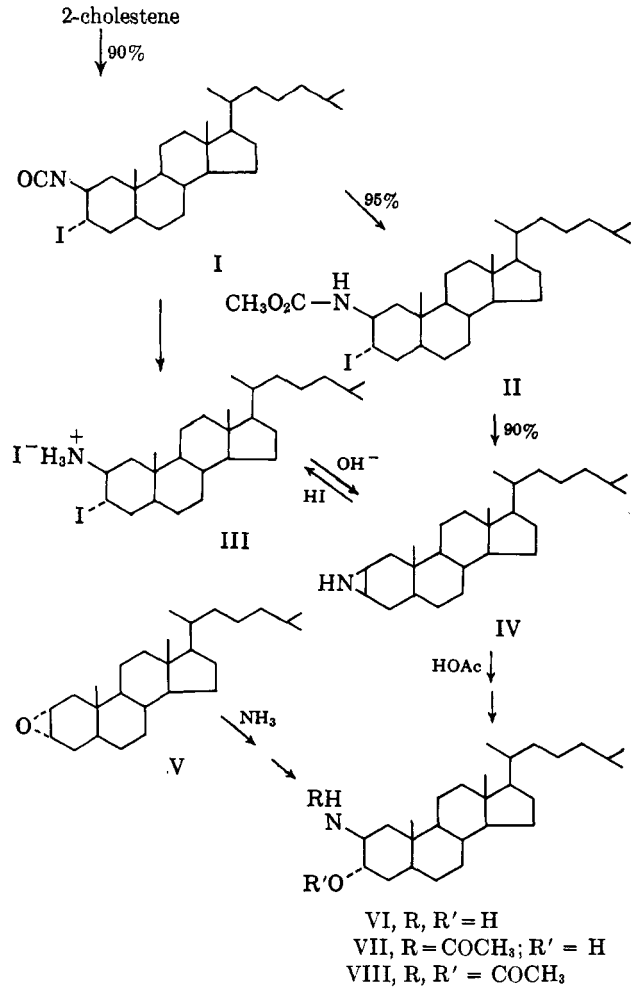
The exclusive formation of the diaxial product I from iodine isocyanate addition to 2-cholestene is analogous to the formation of diaxial dibromide on bromine addition to steroid olefins[9b] and to the diaxial ring opening of epoxides.[10]

The structure of I was inferred from its n.m.r. spectrum and from chemical conversions. Thus the 2α- and 3β-hydrogens appear as broad bands at τ 5.75 and 5.43 with half-widths of 8 and 6 c.p.s., respectively,[11] indicating that the iodine and the isocyanate groups are both axial.

Isocyanate I is readily converted by heating with methanol to the carbamate II or by heating with hydriodic acid in aqueous acetone to the amine hydriodide III. The n.m.r. spectra of II and III likewise indicate that the functional groups at C-2 and C-3 are in an axial conformation. For the iodocarbamate II the half-width of the absorption at τ 5.88 for the C-2 proton is wider (13 c.p.s.) than for most equatorial hydrogens (6–12 c.p.s.).[11] This is apparently due to additional coupling of the C–H with the carbamate N–H as indicated by the doublet at τ 4.8 for the N–H. As expected, ring closure of the β-iodoamine salt III to aziridine IV proceeded smoothly and in 75% yield upon treatment with potassium hydroxide at room temperature. A 90–95% yield of 2β,3β-iminocholestane (IV) was obtained by heating the β-iodo carbamate II with alcoholic potassium hydroxide. This surprisingly facile, base-catalyzed breakdown of methyl carbamate II is due to neighboring group participation and proceeds *via* a N-carbomethoxy aziridine.[12] This route makes available aziridine IV in 75% over-all yield from the olefin 2-cholestene. The aziridine IV was also characterized by way of its N-methyl, N-carbomethoxy, N-carbethoxy, and N-phenylcarbamoyl derivatives.

Proof that the nitrogen function in I–IV is β rather than α came from ring-opening experiments on aziridine IV. Thus heating with acetic acid transformed IV to a diaxial β-amino alcohol derivative which upon acetylation gave diacetyl compound VIII. The latter was identical in all respects with the product obtained in low yield from ring opening of the epoxide V with ammonia followed by acetylation. Since ring opening of steroidal epoxides is known to proceed in a diaxial manner,[10] but certainly *trans*, the nitrogen function in VI, and consequently in IV, as well as in I–III must be β. Furthermore, since it has been shown[13] that *cis*-β-haloamines give ketones on treatment with base, II and III must have their functional groups *trans*. These conclusions, coupled with the n.m.r. data (discussed above), are sufficient to prove the assigned structures for I–IV.

The diacetyl compound VIII was partially hydrolyzed after 2-hr. refluxing with base to the acetamido alcohol



VI, R, R′ = H
VII, R = $COCH_3$; R′ = H
VIII, R, R′ = $COCH_3$

VII in essentially quantitative yield, or upon heating for 48 hr. it was converted to β-amino alcohol VI in 94% yield. 2β-Amino-3α-cholestanol (VI) shows in the infrared evidence for intramolecular hydrogen bonding. Svoboda, *et al.*,[14a] who observed the same phenomena, took this as evidence that ring A in VI and especially in its N,N-dimethyl derivative exists at least partially in a boat conformation. However, such an arrangement would place both the amino and hydroxyl groups equatorial and is inconsistent with the observed n.m.r. spectra. Based on the coupling constants of J_{ea} = 3 c.p.s. and J_{ee} = 2.7 c.p.s., found by Anet[14b] for *cis*-4-butylcyclohexanol, the half-width of the equatorial C-2 and C-3 protons in VI is expected to be 8.4 c.p.s. For the axial protons the half-width would be expected to amount to 19.6 c.p.s. The experimental value of 10 c.p.s. for the half-width of the C-2 and the C-3 proton in VI agrees well with equatorial protons at these positions. The apparent discrepancy between infrared and n.m.r. data can be rationalized by assuming that there is a relatively small percentage of the boat conformation present, which is more easily detected by infrared than by n.m.r. spectra.

With the structure of aziridine IV established, it became of interest to investigate the stereochemistry of reactions of this fused three-membered ring. Weissberger and Bach[15a] as well as others[15b,c] have shown

(9) (a) For an example of formation of diequatorial products on ring opening of a steroid epoxide where the boat transition state is favored, see D. H. R Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957). (b) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(10) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(11) Half-widths of less than 12 c.p.s. are characteristic of equatorial protons; see ref. 8.

(12) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 3640 (1964).

(13) O. E. Paris and R. E. Fanta, *J. Am. Chem. Soc.*, **74**, 3007 (1952).

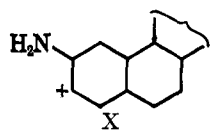
(14) (a) M. Svoboda, F. Sipos, J. Fajkos, and J. Sicher, *Tetrahedron Letters*, 717 (1962); (b) F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962).

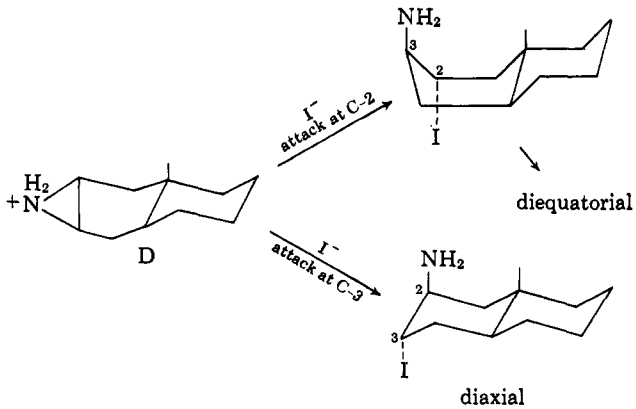
(15) See for instance (a) A. Weissberger and H. Bach, *Ber.*, **65**, 631 (1932); (b) F. Winternitz, M. Mousseron, and R. Dennilauler, *Bull. soc. chim. France*, 382 (1956); (c) P. E. Fanta, L. J. Pandya, W. R. Groskopf, and H. F. Su, *J. Org. Chem.*, **28**, 413 (1963).

that acid-catalyzed ring opening of aziridines usually proceeds stereospecifically *trans*. There are, however, reports that the direction of opening in unsymmetrical aziridines varies sometimes with the concentration of the acid used.[16]

It was shown above that opening of aziridine IV with acetic acid proceeded in a *trans* diaxial manner. Stronger acids such as hydrochloric or hydriodic acids likewise gave *trans* diaxially opened products. For instance 3α-chloro-2β-cholestanylamine hydrochloride (III) was obtained in 90% yield on treatment of aziridine IV with hydrochloric acid in aqueous acetone at room temperature for 45 min. The free amine, 3α-chloro-2β-cholestanylamine, could be obtained by careful neutralization of its hydrochloride salt. It was unstable and was readily coverted by base to aziridine IV. The n.m.r. spectrum of the β-chloroamine was consistent with its structure.

2β,3β-Iminocholestane IV was converted in nearly quantitative yield to N-methyl-2β,3β-iminocholestane (IX) upon heating with methyl iodide in the presence of sodium bicarbonate. Ring opening of the N-methyl aziridine IX with hydrochloric acid yielded the diaxial (by n.m.r.) N-methyl-3α-chloro-2β-cholestanylamine hydrochloride. In order to establish whether the diaxial ring opening of IV might be fortuitous and whether an equilibration between D and an open carbonium ion X was possible, we allowed aziridine IV to stand with perchloric acid in aqueous methanol, but recovered only starting material, under conditions where IV had completely reacted with hydrochloric acid. Since water and methanol are known to react readily with carbonium ions, it appears unlikely that a species such as X is involved in the ring opening of aziridine IV under acid conditions. The data are consistent, however, with stereospecific opening of a fused aziridinium ion (D), which analogously to the iodonium ion (A) prefers opening by a strong nucleophile *via* a chair transition state to give the *trans* diaxial product.





Base-catalyzed ring opening of aziridines, unless they have electron-withdrawing N-substituents, is rare. 2β,3β-Iminocholestane (IV) failed to react with lithium aluminum hydride, in contrast with the report by Mousseron and co-workers[15b] that cyclohexenimine is cleaved to cyclohexylamine by this reagent.[17] Our findings are, however, in agreement with those by Guthrie, *et al.*,[18a] and by Cram and Hatch[18b] indicating that aziridines are inert toward lithium aluminum hydride.

Even N-methyl-2β,3β-iminocholestane failed to react with lithium aluminum hydride or with methylmagnesium bromide. Thus the lack of reaction of aziridine IV with hydride was not merely due to abstraction of the N-hydrogen leading to an unreactive imino anion.

The infrared spectra of aziridine IV, of several of its N-derivatives, and of the structurally related 2β,3β-oxido and 2α,3α-oxidocholestane display some interesting absorption bands which seem to be characteristic for compounds containing a three-membered ring fused to the 2,3 positions of the steroid nucleus. The data are summarized in Table I.

TABLE I
CHARACTERISTIC INFRARED FREQUENCIES OF SOME STEROIDAL AZIRIDINES AND EPOXIDES

Cholestane derivative	C–H deformation, cm.⁻¹	C–H out-of-plane bending, cm.⁻¹
2β,3β-Imino	1418	797
N-Methyl-2β,3β-imino	1404	773
N-Acetyl-2β,3β-imino	1425	800
N-Carbomethoxy-2β,3β-imino	1416	793
N-Carbethoxy-2β,3β-imino	1419	790
N-Phenylcarbamoyl-2β,3β-imino	1410	769
2β,3β-Oxido	1428	814, 806
2α,3α-Oxido	1430	812, 802

The bands in the 1400–1430-cm.⁻¹ region are believed to be due to a C–H deformation mode of the methinyl hydrogens at the ring-fusion points. Normal C–H deformation bands appear at about 1340 cm.⁻¹,[19] but the strain involved in these compounds should increase the energy required for this vibration.

The strong bands in the 750–820-cm.⁻¹ region may be due to a C–H out-of-plane bending mode of the type normally associated with olefins. The geometry of the H–C-2–C-3–H system in these fused compounds approximates planarity and hence such modes may be expected.

Experimental

All melting points are uncorrected and were determined on a Fisher-Johns melting block. Microanalyses were performed by A. Bernhardt, Mülheim, Germany. Infrared spectra were determined on a Perkin-Elmer Model 21 infrared spectrometer. N.m.r. spectra were obtained using a Varian A-60 spectrometer and dilute solutions (*ca.* 10% by weight) of carbon tetrachloride or of deuteriochloroform; tetramethylsilane was used as an internal standard.

3α-Iodo-2β-cholestanyl Isocyanate (I).—2-Cholestene (3.01 g.) was dissolved in 20 ml. of anhydrous ether and 3.65 g. of silver

(16) W. B. Schatz and L. B. Clapp, *J. Am. Chem. Soc.*, **77**, 5113 (1955).

(17) On the other hand, A. Streitwieser (private communication) found that cyclohexenimine was not opened with lithium aluminum deuteride in refluxing tetrahydrofuran.

(18) (a) R. D. Guthrie, D. Murphy, D. H. Buss, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 84 (1963); (b) D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33, 38 (1953).

(19) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962.

cyanate[20] was added. The suspension was cooled in an ice–salt bath while being stirred magnetically. When the slurry had cooled to −15°, 2.06 g. of solid iodine was added and stirring was continued for 2 hr. in the cold and then for 6 hr. at room temperature. At the end of the reaction, the slurry had a bright canary yellow color.

The ether solution was filtered through Celite 545 to remove the yellow inorganic salts, then evaporated in the cold. There was obtained 3.85 g. (88%) of light tan solid, m.p. 107–109°. This material was sufficiently pure for further use: ν_{max}^{KBr} 2260 and 2200 (sh) cm.$^{-1}$, $\nu_{max}^{CCl_4}$ 2260 cm.$^{-1}$. The n.m.r. spectrum, in CCl_4, had absorption at τ 5.43 (C-3 H, half-width 6 c.p.s., equatorial), 5.75 (C-2 H, half-width 8 c.p.s., equatorial), 8.98 (C-19 H_3, singlet), 9.13 (C-26 and C-27 H_6, doublet, J = 6.5 c.p.s.), and 9.34 (C-18 H_3, singlet).

Methyl (3α-Iodo-2β-cholestane)carbamate (II).—A solution containing 3.50 g. of β-iodo isocyanate I in 100 ml. of 1:1 ether–methanol was refluxed on the steam bath for 4 hr. On cooling the solution the carbamate precipitated as white needles. The yield was 3.11 g. (88%), m.p. 157–159°.

Carbamate II can also be obtained from 2-cholestene without the actual isolation of the iodo isocyanate I: ν_{max}^{KBr} 3430, 1740, 1725, 1504, 1227, 775, and 648 cm.$^{-1}$; $\nu_{max}^{CCl_4}$ 1720 cm.$^{-1}$; $\lambda_{max}^{CH_3OH}$ 260 mμ (ε 500).

The n.m.r. spectrum of II in deuteriochloroform has bands at τ 4.8 (N–H doublet), 5.32 (C-3 H, half-width 7 c.p.s.), 5.88 (C-2 H, half-width 13 c.p.s.), 6.33 (OCH_3, singlet), 9.05 (C-19 H_3, singlet), 9.13 (C-26 and C-27 H_6, doublet, J = 6.5 c.p.s.), and 9.35 (C-18 H_3, singlet).

The analytical sample prepared by careful crystallization from absolute methanol melted at 160–162°.

Anal. Calcd. for $C_{29}H_{50}INO_2$: C, 60.95; H, 8.82; I, 22.20; N, 2.45. Found: C, 61.15; H, 8.70; I, 21.70; N, 2.36.

3α-Iodo-2β-cholestanylamine Hydriodide (III). A. From 3α-Iodo-2β-cholestanyl Isocyanate (I).—A solution of 500 mg. of iodo isocyanate I in 50 ml. of acetone and 10 ml. of 50% hydriodic acid was stirred at room temperature for 1.5 hr., and then was diluted with 50 ml. of water. The resulting precipitate was filtered off to yield 560 mg. of product: m.p. 191–192° dec. (block preheated to 180°); ν_{max}^{KBr} 2950, 1900, 1585, and 1490 cm.$^{-1}$.

An analytical sample was prepared by recrystallization from acetone, m.p. 197–198° dec. (block preheated to 180°).

Anal. Calcd. for $C_{27}H_{49}I_2N$: C, 50.55; H, 7.70; N, 2.18. Found: C, 50.54; H, 7.83; N, 2.32.

B. From 2β,3β-Iminocholestane (IV).—To a solution of 85 mg. of the aziridine IV in 20 ml. of acetone at room temperature was added 5 ml. of 50% hydriodic acid. A gelatinous precipitate resulted. After the mass had been stirred at room temperature for 45 min., 20 ml. of water was added. The resulting yellow crystalline material was filtered and washed with ether. There was obtained 139 mg. of product (98%), m.p. 193–195° dec. (block preheated to 180°). The material was identical by infrared with the material prepared from the iodo isocyanate (I).

2β,3β-Iminocholestane (IV). A. From Methyl (3α-Iodo-2β-cholestane)carbamate (II).—The aziridine IV, m.p. 103–105°, was obtained in 90% yield on heating II with potassium hydroxide in 90% ethanol for 1–2 hr. as previously described.[21]

B. From 3α-Iodo-2β-cholestanylamine Hydriodide (II).—A suspension of the iodoamine salt II (100 mg.) in 20 ml. of 1.5 *N* methanolic potassium hydroxide was stirred at room temperature for 4 hr., then was poured into 50 ml. of water. The suspension was extracted with ether and the extracts were washed with water. After drying the ether solution over magnesium sulfate, the solvent was removed to give 45 mg. of the aziridine (75%), m.p. 103–104°, identical in all respects to IV obtained in procedure A.

N-(Phenylcarbamoyl)-2β,3β-iminocholestane.—The phenylurea derivative of aziridine IV was prepared by adding 0.5 g. of phenyl isocyanate to the ether wash solution obtained from preparation of the analytical sample of IV. After 12 hr., the ether was evaporated leaving a sticky mass which solidified on trituration with *n*-hexane. The resulting solid was extracted with *n*-hexane, leaving 145 mg. of insoluble carbanilide, m.p. 245–246°. On cooling of the hexane solution, the product was obtained as fibrous needles: 327 mg.; m.p. 142–143°; ν_{max}^{KBr} 3300, 3200, 3100, 1645, 1595, 1535, 1500, 1410, 749, and 692 cm.$^{-1}$.

The n.m.r. spectrum, in deuteriochloroform, showed aromatic protons as a complex multiplet in the τ 2.45–3.0 region. The protons at the imine–A ring junction were found as two broad overlapping bands at about τ 7.3 and the aliphatic methyl groups were found at τ 9.12 (C-19 H_3), 9.14 (C-26 and C-27 H_6, doublet, J = 6.5 c.p.s.), and 9.35 (C-18 H_3).

An analytical sample was prepared by recrystallization from *n*-hexane, m.p. 145.5–146.5°.

Anal. Calcd. for $C_{34}H_{52}N_2O$: C, 80.90; H, 10.38; N, 5.55. Found: C, 81.07; H, 10.57; N, 5.73.

N-Methyl-2β,3β-iminocholestane (IX).—2β,3β-Iminocholestane (IV, 600 mg.) was dissolved in 100 ml. of dimethylformamide on a steam bath. A solution of 10% aqueous sodium bicarbonate (30 ml.) was added, followed by 3 ml. of methyl iodide. After addition of the sodium bicarbonate solution, a white precipitate appeared. The heating was continued for 45 min., after which time the suspension was poured into 200 ml. of water and extracted with ether. The ether extracts were washed well with water and then dried over anhydrous magnesium sulfate. Removal of solvent gave a clear oil which solidified on standing. The yield of product was 615 mg. (99%), m.p. 78–82°. This material was sufficiently pure for further preparative use: ν_{max}^{KBr} 2810, 1404, 1114, and 773 cm.$^{-1}$. The n.m.r. spectrum, in carbon tetrachloride, showed an N-methyl group at τ 7.87. The protons at the imine–A ring junction appeared as broad bands at τ 7.87 and 8.13. The aliphatic methyl peaks were found at τ 9.14 (C-26 and C-27, doublet, J = 6.5 c.p.s.), 9.20 (C-19 H_3), and 9.37 (C-18 H_3).

The analytical sample, m.p. 85–86°, was obtained by two recrystallizations from methanol.

Anal. Calcd. for $C_{28}H_{49}N$: C, 84.14; H, 12.36; N, 3.50. Found: C, 84.34; H, 12.26; N, 3.64.

N-Methyl-3α-chloro-2β-cholestanylamine Hydrochloride.—N-Methyl-2β,3β-iminocholestane (IX, 50 mg.) was dissolved in a solution of hydrochloric acid in aqueous acetone (1.2 *N* HCl). The solution deposited white needles after several minutes. After standing at room temperature for 40 min., the product was filtered and washed with cold water and ether. The yield was 48 mg. (81%) of white needles: m.p. 267–269° dec.; ν_{max}^{KBr} 2800, 1588, 716, and 696 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{51}Cl_2N$: C, 71.15; H, 10.88. Found: C, 71.35; H, 10.74.

3α-Chloro-2β-cholestanylamine Hydrochloride.—2β,3β-Iminocholestane (IV, 95 mg.) was dissolved in 22.5 ml. of acetone and 2.5 ml. of 37% aqueous hydrochloric acid was added. The solution was stirred at room temperature for 45 min. White crystals appeared after about 5 min. The slurry was diluted with 20 ml. of water and filtered. There was obtained 100 mg. (89%) of the amine hydrochloride: m.p. 261–265° dec. (block preheated to 250°); ν_{max}^{KBr} 2850, 1990, 1603, 1757, 1513, 717, and 702 cm.$^{-1}$.

An analytical sample, m.p. 261–265° dec., was prepared by recrystallization from acetone–water containing a trace of hydrochloric acid.

Anal. Calcd. for $C_{27}H_{49}Cl_2N$: C, 70.22; H, 10.77. Found: C, 70.53; H, 10.54.

A small amount of the salt was suspended between ether and 0.1 *N* potassium hydroxide. The ether solution was dried over magnesium sulfate and evaporated to yield the free base, **3α-chloro-2β-cholestanylamine**, m.p. 80–87°. The n.m.r. spectrum of the chloroamine, in carbon tetrachloride, has bands at τ 5.90 (C-3 H, half-width 7 c.p.s.), 6.60 (C-2 H, half-width 9 c.p.s.), 9.00 (C-19 H_3, singlet), 9.14 (C-26 and C-27 H_6, doublet, J = 6.5 c.p.s.), and 9.35 (C-18 H_3, singlet).

Attempted Ring Opening of 2β,3β-Iminocholestane (IV) with Perchloric Acid–Methanol.—A solution of 108 mg. of the aziridine IV in 20 ml. of methanol and 5 ml. of 72% perchloric acid was stirred at room temperature for 30 min., during which time white crystals appeared. The slurry was poured into 50 ml. of 10% aqueous sodium hydroxide solution and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate. Removal of solvent gave 90 mg. of recovered starting material (83%), m.p. 93–98°. The material was identified by

(20) The purity of the silver cyanate used seems to be critical. Best results were obtained using material prepared in the following manner. Silver nitrate (100 g.) in 3 l. of distilled water was added to 49.5 g. of potassium cyanate in 700 ml. of water. The white precipitate was filtered and washed with water, methanol, and ether. The product was air dried overnight and then *in vacuo* over phosphorus pentoxide for 1–2 days before use. The material can be kept in a desiccator in the dark for 3–4 weeks without appreciable loss of activity. Commercial silver cyanate had a pronounced gray color and was totally unsuitable for use in this reaction.

(21) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

comparison of its n.m.r. and infrared spectra with those of the authentic material.

Attempted Reduction of N-Methyl-2β,3β-iminocholestane (IX) with Lithium Aluminum Hydride.—A solution of 92 mg. of the N-methylaziridine IX in 20 ml. of anhydrous tetrahydrofuran was treated with 100 mg. of lithium aluminum hydride. The suspension was refluxed for 13 hr. Excess hydride was destroyed with ethyl acetate, followed by 20% aqueous sodium hydroxide solution. This solution was then extracted with ether. The ether extracts were washed well with water, then dried over anhydrous magnesium sulfate. Removal of solvent gave 86 mg. of unchanged starting material, m.p. 71–79°, identified by comparison of its infrared spectrum with that of the authentic material.

In a similar experiment 2β,3β-iminocholestane (IV) was recovered unchanged after 12 hr. heating with lithium aluminum hydride in ether.

An attempted reaction of N-methyl-2β,3β-iminocholestane with methylmagnesium bromide in ether for 3 hr. led to recovery of unchanged starting material.

2β-Acetamidocholestan-3α-ol Acetate (VIII). A. From 2α,3α-Oxidocholestane (V).—Epoxide V (128 mg.) was suspended in a mixture of 20 ml. of ethanol and 20 ml. of 15 *M* ammonium hydroxide solution. The suspension was placed in a Pyrex tube of 100-ml. capacity and sealed. The sealed tube was placed in an oil bath and heated at 120° for 14 hr. During this time there was always some insoluble oil at the bottom of the tube. At the end of the reaction, the tube was cooled and opened, and the contents were poured into an excess of water. The resulting white solid was filtered off and air dried. This material was acetylated with 5 ml. of acetic anhydride and 5 ml. of pyridine on a steam bath for 30 min. The solution was then poured into ice–water and let stand for 1 hr., then extracted with ether. The ether extracts were washed with water, saturated sodium bicarbonate solution, and dilute hydrochloric acid, then dried over anhydrous magnesium sulfate. Removal of solvent gave 112 mg. of clear oil. On adding hexane and warming briefly on a steam bath, the product separated as white needles, 23 mg. (14%), m.p. 186–188°. This material was identical by infrared and mixture melting point with the diacetate prepared by the following procedure.

B. From 2β,3β-Iminocholestane (IV).—A solution of 340 mg. of the aziridine IV in 10 ml. of glacial acetic acid was heated on a steam bath for 10 min. At this time 2 ml. of acetic anhydride and 6 drops of pyridine were added and the solution was heated for 5 min. longer. The solution was poured into ice–water and worked up as in the preceding preparation. The product was 426 mg. of clear oil. On trituration with hexane, there was obtained 260 mg. of the diacetate VIII (60%): m.p. 188–190°; ν_{max}^{KBr} 3300, 3090, 1730, 1645, 1555, 1240, 1040, and 1025 cm.$^{-1}$.

The n.m.r. spectrum, in deuteriochloroform, has bands at τ 4.3 (N–H), 5.12 (C-3 H, half-width 6 c.p.s.), 5.92 (C-2 H, half-width 15 c.p.s.), 7.97 and 8.07 (acetoxy and acetamido methyls), 9.10 (C-19 H_3, singlet), 9.15 (C-26 and C-27 H_6, doublet, J = 6.5 c.p.s.), and 9.36 (C-18 H_3, singlet).

An analytical sample was prepared by two recrystallizations from benzene–hexane, m.p. 191–192° (lit.[22] m.p. 186°).

Anal. Calcd. for $C_{31}H_{53}NO_2$: C, 76.33; H, 10.95; N, 2.87. Found: C, 76.66; H, 11.07; N, 2.93.

2β-Acetamidocholestan-3α-ol (VII).—2β-Acetamidocholestan-3α-ol acetate (VIII, 188 mg.) was dissolved in a mixture of 30 ml. of methanol and 7 ml. of water containing 2.3 g. of potassium hydroxide (*ca.* 1.1 *N* in KOH). The solution was refluxed for 2 hr. and filtered while still hot. This initial crop of white needles weighed 90 mg. (52%) and had m.p. 214–217°. On cooling, the mother liquor deposited a second crop of needles weighing 77 mg. (45%): m.p. 212–213°; ν_{max}^{KBr} 3225, 3080, 1640, 1555, 1040, and 1018 cm.$^{-1}$.

The combined product was recrystallized from methanol–water to give 136 mg. of pure product (79%), m.p. 217° (lit.[22] m.p. 211–212°).

Anal. Calcd. for $C_{29}H_{51}NO_2$: C, 78.14; H, 11.53; N, 3.14. Found: C, 78.09; H, 11.35; N, 2.89.

2β-Aminocholestan-3α-ol (VI).—Diacetate VIII (387 mg.) was dissolved in a mixture of 18 ml. of methanol and 2 ml. of water containing 8 g. of potassium hydroxide (*ca.* 6.5 *M* in KOH). The solution was refluxed for 48 hr., poured into water, and filtered. The product weighed 300 mg. (94%) and had m.p. 212–214°; ν_{max}^{KBr} 3500–3100, 1610, 1063, 1050, 1018, 842, and 763 cm.$^{-1}$.

The n.m.r. spectrum, in deuteriochloroform, had bands at τ 6.38 (C-3 H, half-width 10 c.p.s.), 7.00 (C-2 H, half-width 10 c.p.s.), 9.05 (C-19 H_3, singlet), 9.13 (C-26 and C-27 H_6, doublet, J = 6.5 c.p.s.), and 9.36 (C-18 H, singlet).

An analytical sample was prepared by two recrystallizations from methanol, m.p. 212–214° (lit. m.p. 184–187°,[16] m.p. 206–207°[22]). After the first recrystallization the material melted at 215–216°.

Anal. Calcd. for $C_{27}H_{49}NO$: C, 80.33; H, 12.24; N, 3.47. Found: C, 79.94; H, 12.06; N, 3.32.

(22) K. Ponsold, *Ber.*, **96**, 1411 (1963).

A New Synthesis of Desacetamidocolchiceine*,[1]

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The synthesis of desacetamidocolchiceine (I) *via* a seven-membered ring closure of the dissymmetrical intermediate II (X = CN), accessible by two methods, is reported. The shorter and the easier method involves a selective monocyclization of the keto ester VII (R = CH_3) into bicyclic VIII followed by vinylogous formylation of the latter into XXII.

Although at the inception of our work several syntheses had already been published,[2] we still felt the need for a short and flexible route to desacetamidocolchiceine (I), the precursor of the physiologically interesting desacetamidocolchicine[3] and of natural colchicine.[2,4]

In the synthesis of I a main difficulty lies in the elaboration of the tropolonic ring and, more precisely, in the direct introduction of the α-diketone system in the right position of the C ring. A simple solution to this problem has already been given by Van Tamelen and his group[2b] who used the acyloin condensation to obtain a ketol whose oxidation afforded the desired diketone. We looked for a more satisfactory synthetic route and we report here our results.

From the beginning a Dieckmann-type cyclization of a bicyclic carboxylic diester like II (X = CO_2CH_3)

* To Professor Louis F. Fieser.

(1) Part of the work was reported in a preliminary form in *Compt. rend.*, **258**, 243 (1964).

(2) (a) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 540 (1961); (b) E. E. Van Tamelen, T. A. Spencer, Jr., D. S. Allen, Jr., and R. L. Orvis, *Tetrahedron*, **14**, 8 (1961); (c) A. I. Scott, F. McCapra, J. Nabney, D. W. Young, A. J. Baker, T. A. Davidson, and A. C. Day, *J. Am. Chem. Soc.*, **85**, 3041 (1963). This simulated biogenetic synthesis of colchicine was published after the completion of our work.

(3) R. Schindler, *Nature*, **196**, 73 (1962).

(4) J. Nakamura, *et al.*, *Chem. Pharm. Bull.* (Tokyo), **8**, 843 (1960); **9**, 81 (1961); **10**, 281 (1962). In these papers colchicine is obtained without using desacetamidocolchiceine as a precursor.