# A New Isoquinuclidine Synthesis. A New Route to *dl*-Dioscorone[1]

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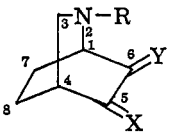
The Diels–Alder addition of 1,3-cyclohexadiene to methyleneurethan (generated *in situ*) yields 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (VII). The latter ester has been converted into isoquinuclidine (2-azabicyclo-[2.2.2]octane, I) and, in several steps, into *dl*-dioscorone (IV).

The bicyclic nucleus of isoquinuclidine (2-azabicyclo-[2.2.2]octane, I) forms an integral part of the structure of two otherwise unrelated alkaloid types. One of these is uniquely represented by dioscorine (II)[2]; the other includes the iboga-type bases, of which ibogamine (III) represents the simplest known member.[3] In this paper we describe a new synthesis of some simple isoquinuclidines and the conversion of one of these compounds to dioscorone (IV), a degradation product of dioscorine which contains the intact isoquinuclidine system.[4]

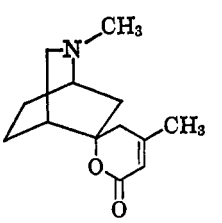
Simple isoquinuclidines containing a functional handle on one of the ethylene bridges have not been hitherto available. The original synthesis of isoquinuclidine,[5] which proceeds by way of the lactam of *cis*-4-aminocyclohexanecarboxylic acid, has been extended only to the synthesis of 2- and 6-alkylisoquinuclidines.[6,7] A number of highly substituted isoquinuclidines have been obtained as products of Diels–Alder reactions between reactive dienophiles and substituted dihydropyridines[8–11]; this general synthesis has not been of value until now for the synthesis of simple functionalized isoquinuclidines in view of the extreme instability of the parent, 1,2-dihydropyridine, and its N-alkyl derivatives.[12]

**A New Isoquinuclidine Synthesis.**—The synthesis of several tetrahydropyridines (and of a tetrahydroquinoline) has been reported making use of a new variant of the Diels–Alder reaction in which a butadiene adds to the transient intermediate methyleneurethan (V), or an equivalent species, generated by the action of boron trifluoride on the stable methylenebisurethan (VI).[13] We have found that this reaction, using 1,3-cyclohexadiene as the diene component, affords the versatile isoquinuclidine derivative, 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (VII), in fair yield (27%). Attempts to raise the yield of VII were unsuccessful owing to polymerization and disproportionation of the diene as side reactions. Under similar conditions, however, benzalbisurethan (VIII) affords the corresponding 2-carbethoxy-3-phenyl-2-azabicyclo[2.2.2]-oct-5-ene (IX) in 50% yield.

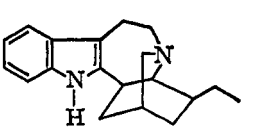
Hydrogenation of adduct VII in the presence of palladium yields 2-carbethoxy-2-azabicyclo[2.2.2]octane (X), which on vigorous alkaline hydrolysis gives isoquinuclidine (I), isolated and characterized as its crystalline picrate and as its crystalline N-benzoyl derivative (XI). Similarly, basic hydrolysis of adduct VII affords dehydroisoquinuclidine (2-azabicyclo[2.-2.2]oct-5-ene, XII), isolated as its picrate and as its crystalline N-tosyl derivative (XIII).



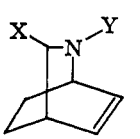
I, R = H; X = $H_2$; Y = $H_2$
IV, R = $CH_3$; X = O; Y = $H_2$
X, R = $CO_2C_2H_5$; X = $H_2$; Y = $H_2$
XI, R = $COC_6H_5$; X = $H_2$; Y = $H_2$
XVIII, R = $CO_2C_2H_5$; X = $H_2$; Y = H,OH
XIX, R = $CO_2C_2H_5$; X = H,OH; Y = $H_2$
XX, R = $CO_2C_2H_5$; X = $H_2$; Y = O
XXI, R = $CO_2C_2H_5$; X = O; Y = $H_2$
XXII, R = $CO_2C_2H_5$; X = $H_2$; Y = $-OCH_2CH_2O-$
XXIII, R = $CO_2C_2H_5$; X = $-OCH_2CH_2O-$; Y = $H_2$
XXIV, R = $CH_3$; X = $H_2$; Y = $-OCH_2CH_2O-$
XXV, R = $CH_3$; X = $-OCH_2CH_2O-$; Y = $H_2$
XXVI, R = $CH_3$; X = $H_2$; Y = O
XXVII, R = $CO_2C_2H_5$; X = $H_2$; Y = $NNHC_6H_3(NO_2)_2$
XXVIII, R = $CO_2C_2H_5$; X = $NNHC_6H_3(NO_2)_2$; Y = $H_2$



II



III



VII, X = H; Y = $CO_2C_2H_5$
IX, X = $C_6H_5$; Y = $CO_2C_2H_5$
XII, X = H; Y = H
XIII, X = H; Y = $-SO_2-C_6H_4-CH_3$
XIV, X = H; Y = $CH_3$
XV, X = $C_6H_5$; Y = $CH_3$
XVI, X = $CF_3$; Y = $SO_2C_6H_5$

(1) (a) Taken in part from the Ph.D. Dissertation of C. K. Wilkins, Jr., The Ohio State University, 1964. (b) Presented at the Gordon Research Conference on Steroids and Other Natural Products, New Hampton, N. H., Aug. 1964. (c) For a preliminary report of a portion of this work, see M. P. Cava and C. K. Wilkins, Jr., *Chem. Ind.* (London), 1422 (1964). (d) Reprints may be obtained from M. P. Cava at the Department of Chemistry, Wayne State University, Detroit, Mich.

(2) W. A. McDavies, I. G. Morris, and A. R. Pinder, *Chem. Ind.* (London), **35**, 1410 (1961).

(3) For a review of the iboga-type alkaloids, see H.-G. Boit, "Ergebnisse der Alkaloid Chemie bis 1960," Akademie-Verlag, Berlin, Germany, 1961, pp. 631–642.

(4) A totally unrelated synthesis of dioscorone and its reconversion to dioscorine have been reported recently: C. B. Page and A. R. Pinder, *J. Chem. Soc.*, 4811 (1964). We are grateful to Dr. A. R. Pinder for the private communication of his results to us prior to publication.

(5) E. Ferber and H. Bruchner, *Ber.*, **75B**, 425 (1952); **76B**, 1019 (1943).

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(7) W. Schneider and R. Dillmann, *Chem. Ber.*, **96**, 2377 (1963).

(8) O. Mumm and J. Diedrichsen, *Ann.*, **538**, 195 (1939).

(9) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960 (1959); **45**, 1344 (1962).

(10) M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).

(11) T. Agawa and S. I. Miller, *J. Am. Chem. Soc.*, **83**, 449 (1961).

(12) During the preparation of this manuscript, a total synthesis of ibogamine was announced in which an unstable 1,2-dihydropyridine served as the key starting material: G. Büchi, D. L. Coffen, D. Docsis, P. E. Sonnet, and F. Ziegler, *J. Am. Chem. Soc.*, **87**, 2073 (1965).

(13) R. Merten and G. Muller, *Angew. Chem.*, **74**, 866 (1962).

$CH_2{=}N{-}CO_2C_2H_5$ (V) $CH_2(NHCO_2C_2H_5)_2$ (VI)

$C_6H_5{-}CH(NH{-}CO_2C_6H_5)_2$ (VIII) $C_6H_5{-}SO_2{-}N{=}CHCF_3$ (XVII)

Lithium aluminum hydride reduction of adducts VII and IX afford the respective N-methyl analogs, 2-methyl-2-azabicyclo[2.2.2]oct-5-ene (XIV) and 2-methyl-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene (XV).

After the completion of the work described above, a report appeared describing the synthesis of the substituted isoquinuclidine XVI by the Diels–Alder addition of cyclohexadiene to the sulfonimine XVII.[14] It may be noted, however, that the presence of the trifluoromethyl group in imine XVII is essential for the success of the Diels–Alder reaction.

**A New Synthesis of Dioscorone.**—Adduct VII was subjected to oxidative hydroboration[15] to afford a noncrystalline mixture of alcohols (XVIII and XIX). Attempted separation of the alcohol mixture in the form of the *p*-nitrobenzoate esters was unsuccessful; one *p*-nitrobenzoate was obtained in pure crystalline form, but its structure was not further investigated.

Chromic acid oxidation[16] of the alcohol mixture (XVIII and XIX) gave a mixture of a crystalline ketone (XX) and a liquid ketone (XXI); the liquid ketone, free from the crystalline isomer, was obtained by preparative gas–liquid chromatography. Each purified ketone was converted to the corresponding ethylene ketal (XXII and XXIII), and then reduced with lithium aluminum hydride. The resulting N-methyl ketals (XXIV and XXV) were hydrolyzed by dilute acid to the corresponding N-methyl ketones (XXVI and IV). The N-methyl ketone (IV) derived from the liquid N-carbethoxy ketone (XXI) proved to be identical (infrared and n.m.r.) with a sample of *dl*-dioscorone prepared by the method of Page and Pinder[4]; comparison of the crystalline methiodide with *dl*-dioscorone methiodide further confirmed the identity of IV.

The crystalline N-carbethoxy ketone (XX) and further products derived from it (XXII, XXIV, and XXVI) were assigned 6-oxygenated isoquinuclidine structures on the basis of the method of synthesis of XX. A comparison of the n.m.r. spectra of the crystalline 2,4-dinitrophenylhydrazones (XXVII and XXVIII) of the two N-carbethoxy ketones (XX and XXI) supported the structures assigned to the latter isomers. Thus, the bridgehead hydrogen at C-1 in the derivative (XXVII) of the solid ketone XX appears at a lower field ($\delta$ 4.81) than the corresponding proton ($\delta$ 4.68) in the spectrum of the derivative XXVIII of the liquid ketone XXI. The unlikely possibility that carbethoxy ketone XX contained a rearranged isoquinuclidine system was ruled out by its catalytic reduction to N-carbethoxyisoquinuclidine (X) in the presence of platinum.

## Experimental Section[17]

**Methylenebisurethan (VI).**—Urethan (178 g., 2.0 moles) was dissolved in cold water (1.0 l.), and formaldehyde (37% solution, 81 g., 1.0 mole) and hydrochloric acid (concentrated, 2–3 ml.) were added. The mixture was allowed to stand at room temperature for 3 days during which time white needles (140 g., 65%) of methylenebisurethan deposited, m.p. 127–130° (lit.[18] m.p. 131°).

**2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (VII).**—Boron trifluoride etherate (5.0 g., 2.035 moles) and crude methylenebisurethan (24 g., 0.126 mole) were added to benzene (200 ml.). The mixture was heated to reflux and 1,3-cyclohexadiene[19] (12.5 g., 0.125 mole) was added, dropwise, over a period of *ca.* 30 min. The resulting mixture was allowed to reflux 1 hr. before cooling to room temperature. The brown solution was repeatedly washed with saturated sodium bicarbonate solution until the acid had been completely removed and then twice with distilled water (100-ml. portions). The organic phase was dried with sodium sulfate and the solvent was removed with the aid of the rotary evaporator. The residue distilled at reduced pressure yielding 6.0 g. (27%) of a colorless oil, b.p. 58–64° (3 mm.).

*Anal.* Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.33; H, 8.40; N, 7.71.

**Benzalbisurethan (VIII).**—Benzaldehyd (26.5 g., 0.25 mole), urethan (49.9 g., 0.50 mole), and boron trifluoride etherate (1.42 g., 0.01 mole) were added to benzene (250 ml.). The resulting mixture was allowed to reflux 10 hr. in an apparatus equipped with a water separator. Cooling resulted in precipitation of the benzalbisurethan (31.0 g.). An additional crop of crystals (18.0 g.) was obtained on evaporation of the mother liquors. Total yield was 64%, m.p. 177–184°. Recrystallization was effected from benzene–chloroform to yield white needles, m.p. 182–184° (lit.[20] m.p. 178–179°).

**2-Carbethoxy-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene (IX).**—Boron trifluoride etherate (5.9 g., 4.2 mmoles) and benzalbisurethan (39.5 g., 0.148 mole) were added to benzene (240 ml.) and the solution was allowed to warm to reflux. 1,3-Cyclohexadiene[19] (16.8 g., 0.167 mole) was added and the reaction was treated as described above to yield IX, 18.6 g. (50%), b.p. 118.5–121° (3 mm.).

*Anal.* Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.61; H, 7.55; N, 5.44.

**2-Carbethoxy-2-azabicyclo[2.2.2]octane (X).**—Redistilled 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (5.0 g., 27.8 mmoles) was dissolved in cyclohexane (55 ml.) in a Parr bottle and palladium on carbon (10%, 60 mg.) was added. Hydrogen (2.0 lb.) was absorbed in 30 min. and the catalyst was removed by filtration. Evaporation of the solvent yielded 3.7 g. (74%) of colorless oil, b.p. 87–90° (5 mm.).

*Anal.* Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.24; H, 9.40; N, 7.62.

**Isoquinuclidine (I).**—2-Carbethoxy-2-azabicyclo[2.2.2]octane (X, 2.55 g., 1.4 mmoles) was heated strongly with potassium hydroxide (12 g.) in triethylene glycol (50 ml.) in a flask equipped with a distilling head. A colorless liquid distilled between 150 and 240° (bath temperature). This distillate was treated with solid potassium carbonate until two distinct layers formed and then extracted with benzene. The benzene extract was dried over sodium sulfate and after filtration treated with a saturated solution of picric acid–benzene. A picrate, m.p. 240–243°, 3.0 g. (52%), rapidly formed. Recrystallization from ethanol produced needles, m.p. 244–247° (lit.[5] m.p. 247–249°).

**Benzoylisoquinuclidine (XI).**—2-Carbethoxy-2-azabicyclo[2.2.2]octane (2.0 g., 1.1 mmoles) was hydrolyzed with potassium hydroxide (10 g.) and triethylene glycol (40 ml.) as above. The distillate was added to sodium hydroxide (200 mg.) and benzoyl chloride (4 ml.) and allowed to stir overnight. A yellow oil, which spontaneously crystallized, separated on standing. Recrystallization from cyclohexane yielded 1.1 g. (47%) of material, m.p. 115–118° (lit.[5] m.p. 118–120°). The infrared spectrum was superimposable with an authentic sample[5] and a mixture melting point was undepressed.

(14) G. Kresze and R. Albrecht, *Chem. Ber.*, **97**, 490 (1964).

(15) H. C. Brown, *J. Am. Chem. Soc.*, **83**, 2550 (1961).

(16) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(17) All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured in potassium bromide pellets, chloroform solution, or on sodium chloride plates with a Perkin-Elmer Model 237 recording spectrophotometer. N.m.r. spectra were taken on a Varian Associates A-60 spectrometer in deuteriochloroform and values ($\delta$) were measured in parts per million from tetramethylsilane at 0. Elemental analyses were carried out by Dr. A. Bernhardt, Mülheim, Germany, and by Midwest Microlab Inc., Indianapolis, Ind.

(18) M. Conrad and K. Hock, *Chem. Ber.*, **36**, 2206 (1903).

(19) J. Hine, J. A. Brown, L. H. Zalkow, W. E. Gardner, and M. Hine, *J. Am. Chem. Soc.*, **77**, 594 (1955).

(20) F. Lehman, *Chem. Ber.*, **34**, 366 (1901).

**2-Azabicyclo[2.2.2]oct-5-ene (XII).**—2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (1.0 g., 0.55 mmole) was hydrolyzed as above with potassium hydroxide (5.0 g.) and triethylene glycol (20 ml.). The distillate was treated with potassium carbonate and the amine was extracted into benzene. Addition of a saturated solution of picric acid in benzene yielded the crude picrate. Recrystallization from ethanol yielded 0.8 g. (44%) of yellow needles, m.p. 223–223.5°.

*Anal.* Calcd. for $C_{13}H_{14}N_4O_7$: C, 44.16; H, 4.17; N, 16.56. Found: C, 44.24; H, 4.44; N, 16.36.

Generation of the amine as above and treatment with *p*-toluenesulfonyl chloride produced a comparable yield of N-tosyl derivative (XIII), m.p. 107–108°.

*Anal.* Calcd. for $C_{14}H_{17}NO_2S$: C, 63.86; H, 6.51; N, 5.32; S, 12.15. Found: C, 64.01; H, 6.75; N, 5.53; S, 12.11.

**2-Methyl-2-azabicyclo[2.2.2]oct-5-ene (XIV).**—2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (628 mg., 0.349 mmole) was reduced with lithium aluminum hydride (200 mg., 5.25 mmoles) in dry tetrahydrofuran (20 ml.) by refluxing overnight. Excess hydride was destroyed by addition of saturated sodium sulfate solution. When precipitation of the hydroxides was complete, the solvent was removed by filtration and the residue was washed several times with fresh portions of warm solvent. The combined tetrahydrofuran solvents were evaporated to dryness and the residue, in ether, was treated with an ethereal solution of picric acid. Recrystallization of the resulting picrate from ethanol yielded yellow needles (0.4 g., 33%), m.p. 248–250°.

*Anal.* Calcd. for $C_{14}H_{16}N_4O_7$: C, 47.73; H, 4.58; N, 15.90. Found: C, 47.80; H, 4.75; N, 15.95.

**2-Methyl-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene (XV).**—2-Carbethoxy-3-phenyl-2-azabicyclo[2.2.2]oct-5-ene (IX) (628 mg., 0.245 mmole) was reduced as above utilizing lithium aluminum hydride (200 mg., 5.25 mmoles) to yield 0.45 g. (from ethanol) (43%) of picrate as yellow needles, m.p. 190–193°.

*Anal.* Calcd. for $C_{20}H_{21}N_4O_7$: C, 56.07; H, 4.71; N, 13.08. Found: C, 55.98; H, 4.89; N, 13.11.

**2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene and -6-ol (XVIII and XIX).**—2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (4.5 g., 25 mmoles) was hydroborated according to the procedure of Brown[15] using an oxidative work-up to yield a mixture of alcohols (4.7 g., 96%) which contained some olefin as the major contaminant.

Partial purification was effected through the *p*-nitrobenzoate derivative prepared as follows. The crude reaction mixture from hydroboration (3.843 g., 19.4 mmoles) in pyridine (50 ml.) was treated with *p*-nitrobenzoyl chloride (5.0 g., 27.7 mmoles) and the reaction mixture was allowed to stir at room temperature overnight, after which it was poured into a mixture of ice and concentrated hydrochloric acid. The acidic mixture was then continuously extracted with ether for 5 hr. The ether solution was evaporated, and the residue was dissolved in chloroform and washed with aqueous sodium hydroxide (10%), dilute hydrochloric acid (6 *N*), and water. Evaporation of the dried solution yielded a light yellow oil (4.971 g., 75%). Crystals were deposited from a methanolic solution (4.313 g., 65%), m.p. 70.0–110.5°. Repeated fractional crystallization yielded white crystals (0.722 g.), m.p. 138–139°. The melting point remained unchanged on further recrystallization.

*Anal.* Calcd. for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.57; H, 5.75; N, 8.22.

Hydrolysis of the crystalline mixture of *p*-nitrobenzoates was effected as follows. The *p*-nitrobenzoate mixture (1.021 g., 2.99 mmoles) in methyl alcohol (100 ml.) was treated with sodium hydroxide (0.193 g., 4.8 mmoles) in water (75 ml.) and allowed to stir at room temperature overnight. Continuous extraction with ether yielded 583.6 mg. (100%) of purified alcohol mixture which was oxidized as described below.

**2-Carbethoxy-2-azabicyclo[2.2.2]octan-5- and -6-one (XX and XXI).**—The purified alcohols (from hydrolysis of a mixture of *p*-nitrobenzoates) (1.23 g., 6.27 mmoles) were dissolved in reagent grade acetone (10 ml.) under an atmosphere of nitrogen and, with cooling and stirring, chromic acid reagent[16] (1.56 ml., 4.18 mmoles) was rapidly added. The reaction mixture was stirred for an additional 5 min. under the nitrogen atmosphere and then quenched by being poured into water (500 ml.). The green aqueous solution was continuously extracted with ether for 24 hr. and the ether was removed to yield 1.22 g. (97%) of a colorless mobile oil. The infrared spectrum indicated that no more than *ca.* 10% of unreacted alcohol remained. Crystallization of the oil could be induced by cooling and scratching an ether–hexane solution. Of the materials volatile enough to be put through v.p.c. it was clear that 55–60% consisted of crystalline isomer (m.p. 69–70°), 35–40% of noncrystallizable isomer, and about 5% of olefin. The isomers were separated by preparative v.p.c. on 10% XF-1150[21] on Chromosorb W. The crystalline isomer (XX) had m.p. 69–70°.

*Anal.* Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.74; H, 7.53; N, 7.06.

The liquid ketone could not be obtained free of small quantities of solvent. However, it formed a yellow crystalline 2,4-dinitrophenylhydrazone derivative, purified by chromatography and recrystallization, m.p. 158–160°.

*Anal.* Calcd. for $C_{16}H_{19}N_5O_6$: C, 50.92; H, 5.08; N, 18.56. Found: C, 50.79; H, 5.17; N, 18.19.

The crystalline ketone (XX) formed a yellow crystalline 2,4-dinitrophenylhydrazone derivative, purified by chromatography and recrystallization, m.p. 160–161°.

*Anal.* Calcd. for $C_{16}H_{19}N_5O_6$: C, 50.92; H, 5.08; N, 18.56. Found: C, 50.80; H, 5.14; N, 18.30.

The melting point of either of the isomers was depressed upon admixture with the other.

**Preparation of the Ketals XXII and XXIII.**—The preparation and yields were comparable in both cases. The N-carbethoxy ketone (259.1 mg., 1.32 mmoles) was dissolved in benzene (40 ml.) and ethylene glycol (10 ml.) added, along with a few crystals of *p*-toluenesulfonic acid. The mixture was stirred under reflux (using water separator) for 12 hr. The solution was allowed to cool to room temperature, made basic with 10% sodium hydroxide, and poured into water. The two-phase suspension was continuously extracted with benzene for 24 hr., and the benzene extract was evaporated to dryness to yield 317 mg. (100%) of material whose infrared and n.m.r. spectra were in accord with the expected product.

**Preparation of N-Methyl Ketals XXIV and XXV.**—The crude N-carbethoxy ketals were treated as follows. Lithium aluminum hydride (200 mg., 5.25 mmoles) was added to dry tetrahydrofuran (25 ml.) and, with stirring, a solution of the N-carbethoxy ketal (298 mg., 1.23 mmoles) in tetrahydrofuran (25 ml.) was added in a dropwise manner. When the addition was complete, the reaction mixture was allowed to stir at reflux, under nitrogen, overnight. The reaction mixture was cooled by means of an ice bath while water was slowly added to destroy the excess lithium aluminum hydride. When hydrolysis was complete, the entire reaction mixture was continuously extracted with ether for 24 hr. Evaporation of the ether yielded 220 mg. (97%) of material which possessed a characteristic amine odor and whose infrared spectrum showed no carbonyl peak.

**Hydrolysis of the N-Methyl Ketals.**—In both cases the procedure and yields were similar. The N-methyl ketal (996.4 mg., 4.15 mmoles) was added to a solution of hydrochloric acid (6 *N*, 5 ml.) and water (40 ml.) and the mixture was allowed to reflux, with stirring, overnight. When cool, the yellowish solution was made slightly basic with 10% sodium hydroxide (added dropwise). The basic solution was then continuously extracted overnight with ether. The residue (570 mg., 97%) on evaporation of the ether was dark orange and had a characteristic amine odor.

**Picrate of the N-Methyl Ketone XXVI.**—The picrate, prepared from benzene and recrystallized from methyl alcohol, had m.p. 227–232° dec.

*Anal.* Calcd. for $C_{14}H_{16}N_4O_8$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.85; H, 4.56; N, 15.08.

**Methiodide of the N-Methyl Ketone XXVI.**—The methiodide, prepared from acetone, had m.p. 272–274° dec.; prepared from benzene, m.p. 279–280° dec.

*Anal.* Calcd. for $C_9H_{16}INO$: C, 28.44; H, 5.75; N, 4.98. Found: C, 28.50; H, 6.04; N, 4.81.

**Picrate of N-Methyl Ketone IV.**—The picrate, prepared from benzene and recrystallized from methanol, had m.p. 180–182°.

*Anal.* Calcd. for $C_{14}H_{16}N_4O_8$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.66; H, 4.52; N, 15.36.

**Methiodide.**—The methiodide of *dl*-dioscorone had the identical melting point (185–187° dec.)[22] and mixture melting point and infrared spectrum (potassium bromide) with a sample pre-

(21) Wilkens Instrument and Research, Inc., Walnut Creek, Calif.

(22) This melting point (previously unreported) is considerably lower than that (295° dec.) reported[4] for (+)-dioscorone methiodide obtained from the degradation of natural dioscorine; it could not be raised by recrystallization.

pared by the method of Page and Pinder.[4] Its noted[23] instability precluded accurate microanalysis.

**Reduction of 2-Carboethoxy-2-azabicyclo[2.2.2]octan-5-one (XX) to 2-Carboethoxy-2-azabicyclo[2.2.2]octane (X).**—2-Carbethoxy-2-azabicyclo[2.2.2]octan-5-one (500 mg., 2.5 mmoles) was placed in a Parr shaker bottle containing platinic oxide (83.62%) (*ca.* 1 g.), aqueous hydrochloric acid (30 ml., 2 *N*), and ethanol (30 ml.) and was hydrogenated at 26 p.s.i. overnight.

The catalyst was removed by filtration through Celite and the filtrate was evaporated to dryness. The residue was partitioned between ether and water (50 ml. each) and the aqueous phase was washed with a fresh portion (50 ml.) of ether. The combined ether phases were washed with dilute hydrochloric acid (6 *N*), dilute sodium hydroxide (10%), and water. Evaporation yielded 2-carbethoxy-2-azabicyclo[2.2.2]octane (X, 211.4 mg.) identical with that prepared by direct reduction of 2-carboethoxy-2-azabicyclo[2.2.2]oct-5-ene (VII).

Soxhlet extraction of the catalyst with methanol yielded 265.3 mg. of colorless oil, the infrared spectrum of which, in chloroform, closely resembled the mixture of alcohols XVIII and XIX. This material was not further investigated.

(23) I. G. Morris and A. R. Pinder, *J. Chem. Soc.*, 1841 (1963).

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# Steroids. IV. A Synthetic Route to A-Bisnorsteroids[1]

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A-Bisnorcholestan-1-one (XXIII) and several other 1-substituted cholestanes have been synthesized, starting with cholestan-1-one. The multistep reaction sequence included, as key steps, the photolytic Wolff rearrangement of 2-diazocholestan-1-one and 2-diazo-A-norcholestan-1-one.

A number of modified steroids are known in which one of the four rings is contracted by one carbon atom relative to the normal tetracyclic steroid nucleus.[2] We now wish to report the synthesis of some A-bisnorcholestane derivatives which represent the first examples of steroids containing a four-membered A-ring. The synthetic route employed, starting with the readily available cholest-1-en-3-one (I), represents a sequence of general applicability for the preparation of other 1-substituted A-bisnorsteroids, as well as an improved route to steroidal A-nor-1-ketones.

Cholest-1-en-3-one (I) was converted *via* the corresponding 1$\alpha$,2$\alpha$ epoxide (II)[3] to cholest-2-en-1$\alpha$-ol (III) by use of the general method of Wharton.[4,5] Mild chromic acid oxidation of III using the general method of Brown[6] afforded the corresponding ketone (IV). The over-all yield in the conversion of cholest-1-en-3-one to cholest-2-en-1-one was as high as 50%. Catalytic reduction of IV gave cholestan-1-one (V). Base-catalyzed oximination of cholestan-1-one (V) afforded, in 70% yield, *anti*-2-oximinocholestan-1-one (VI), m.p. 198–201° dec. The *anti* configuration was assigned to oximino ketone VI on the basis of its reaction with divalent copper and cobalt ions,[7] as well as on the basis of the bathochromic shift of its ultraviolet spectrum which was observed in alkaline solution.[8]

Oximino ketone VI was converted to the corresponding $\alpha$-diazo ketone by means of the Forster reaction.[9] Thus, oximino ketone VI reacted with chloramine to give, in 78% yield, 2-diazocholestan-1-one (VII), m.p. 98–100°. Diazo ketone VII underwent a photolytic Wolff rearrangement when irradiated in aqueous tetrahydrofuran containing sodium bicarbonate. The acidic reaction product, m.p. 198–201°, obtained in 63% yield, was assigned the structure 1$\beta$-carboxy-A-norcholestane (VIII). Esterification of VIII with diazomethane afforded 1$\beta$-carbomethoxy-A-norcholestane (IX), isolated as an oil. Treatment of the nor acid (VIII) with lithium aluminum hydride in tetrahydrofuran provided, in 60% yield, 1$\beta$-hydroxymethyl-A-norcholestane (X), m.p. 104–105°.

The carboxyl group of acid VIII was expected to have the $\beta$ configuration on mechanistic grounds, since hydration of the intermediate ketene formed in the photolysis reaction should take place from the less hindered $\alpha$ side of the molecule.[10] Chemical confirmation of the stereochemistry of acid VIII was obtained by converting it into the previously described[11] 1$\beta$-amino-A-norcholestane (XI) *via* a Schmidt reaction, a transformation which is known to proceed with retention of configuration.[12] Amine XI was obtained in this manner in 89% yield as a crystalline solid, m.p. 93–95°, although it had been described previously only as an oil; synthesis of XI by the previously described procedure [lithium aluminum hydride reduction of 1-oximino-A-norcholestane (XII)] afforded, in our hands,

(1) (a) For a preliminary communication of a portion of these results, see M. P. Cava and B. R. Vogt, *Tetrahedron Letters*, **No. 39**, 2813 (1964), which is considered to be part III of this series. (b) Reprints may be obtained from M. P. Cava at the Department of Chemistry, Wayne State University, Detroit, Mich.

(2) For examples involving rings A, B, C, and D, respectively, see (a) H. R. Nace and D. H. Nelander, *J. Org. Chem.*, **29**, 1677 (1964); (b) F. Šorm and H. Dykova, *Collection Czech. Chem. Commun.*, **13**, 407 (1948); (c) N. L. Wendler, R. F. Hirschmann, H. R. Slates, and R. W. Walker, *J. Am. Chem. Soc.*, **77**, 1632 (1955); (d) M. P. Cava and E. Moroz, *ibid.*, **84**, 115 (1962).

(3) P. Streibel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).

(4) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).

(5) The conversion of II to III by Wharton's method was reported independently during the course of our investigation: C. Djerassi, D. H. Williams, and B. Berkoz, *ibid.*, **27**, 2205 (1962). Details of our procedure, however, are reported in the Experimental Section of this paper since they appear to represent both in yield and in work-up an improvement over the previously published procedure.

(6) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(7) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, Oxford, 1937, pp. 195–196.

(8) (a) D. H. R. Barton and J. Beaton, *J. Am. Chem. Soc.*, **83**, 4083 (1961); (b) A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, **27**, 1760 (1962).

(9) For some recent examples of the use of this reaction as well as some earlier references, see M. P. Cava and P. M. Weintraub, *Steroids*, **4**, 41 (1964).

(10) For a more detailed discussion of this point, see J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 5445 (1960).

(11) C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1583 (1961).

(12) A. Campbell and J. Kenyon, *ibid.*, 26 (1946).