hexane) 0.858 g (58%), mp 73–74°, of **20**. This gave a single spot on thin layer chromatographic analysis (Merck silica gel G; 45:8:4 benzene–methanol–acetic acid).

Anal. Calcd for $C_{14}H_{20}O_6S_2$: C, 48.27; H, 5.79; S, 18.39. Found: C, 48.01; H, 5.65; S, 18.24.

This dimesylate (**20**, 0.800 g, 2.3 mmoles, in 10 ml of THF) was added to a slurry of lithium aluminum hydride (1.5 g, 39 mmoles) in anhydrous THF (10 ml). After the mixture was refluxed for 1 hr, it was hydrolyzed with sodium sulfate solution and the solvent was removed under vacuum from the combined, dried (Na_2SO_4) THF layer and ether extracts. The crude product was purified by evaporative distillation to give 0.336 g (91%): mp 38.5–40.0°; ν_{max}^{KBr} 3101, 2910, 2875, 1495, 1465, 1435, 735 cm^{-1}. This product gave a single peak on vpc analysis (retention time, 39 min) and a single spot on thin layer chromatography under the same conditions indicated for the *cis* isomer; pmr spectrum is reported in Table I.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.63; H, 10.02.

***cis*-3,4-Dimethylcyclohexene** (**24**).—This isomer was synthesized by methods delineated in the literature. *cis*-Cyclohexene-4,5-dicarboxylic anhydride[26,40] (**21**) was reduced with lithium aluminum hydride to give the *cis*-diol[41] (**22**, 87% yield, $n^{20}D$ 1.5091) which was converted to the *cis* dimesylate[15,28] (**23**, 60% yield) which in turn was treated with lithium aluminum hydride to give *cis*-dimethylcyclohexene (42% yield). The product[15,28,29] ($n^{20}D$ 1.4462; ν_{max}^{film} 3024, 2950, 2880, 1650, 1450, 1380, 1020, 750 cm^{-1}) gave a single peak on vpc analysis (Carbowax 20 M, 20 ft × 0.25 in. column at 70°, He flow at 25 ml/min, R_t 47 min) and the correct carbon hydrogen analysis. The pmr spectrum is reported in Table I.

***trans*-3,4-Dimethylcyclohexene** (**28**).—*trans*-Cyclohexene-4,5-dicarboxylic acid methyl ester was made from methyl fumarate and butadiene in 88% yield by the method of Petrov and Sopov.[27] This was converted by the method of Walborsky, Barash, and Davis[42] by lithium aluminum hydride to the *trans*-diol (**26**, 99% yield), then to the *trans* dimesylate (**27**, 97% yield) and finally to the *trans*-4,5-dimethylcyclohexene by lithium aluminum hydride displacement (48% yield). The product[42,43] was purified by vpc under the same conditions as the *cis* isomer (R_t 44 min; ν_{max}^{film} 3040, 2970, 2890, 1660, 1450, 1430, 1370, 1010, 880, 650 cm^{-1}) and analyzed correctly for carbon and hydrogen. The pmr spectrum is reported in Table I.

Registry No.— *cis* **5**, 10074-95-0; *trans* **5**, 10294-74-3; **8**, 10074-96-1; **9**, 10074-97-2; **14**, 10074-98-3; **15**, 10074-99-4; **19**, 10075-00-0; **20**, 10075-01-1; **24**, 4300-00-9; **28**, 3685-01-6.

Acknowledgment.—We acknowledge with gratitude our appreciation to Dr. L. J. Durham for the nmr determinations and many helpful discussions concerning them, and to Parke, Davis and Co. for fellowship support.

(40) A. C. Cope and E. C. Herrick, *Org. Syn.*, **30**, 29 (1950).

(41) W. J. Bailey and J. Rosenberg, *J. Am. Chem. Soc.*, **77**, 73 (1955); private communication; the physical properties in the reference should read $n^{25}D$ 1.5090 and d^{25}_4 1.0980.

(42) H. M. Walborsky, L. Barash, and T. C. Davis, *Tetrahedron*, **19**, 2333 (1963).

(43) H. Pines and C. Chen, *J. Am. Soc.*, **81**, 928 (1959).

The Decarboxylation of 3-Carboxy-2-isoxazolines. 3β,17α-Dihydroxypregn-5-en-20-one-16α-carbonitrile

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The pyrolysis of [16,17-d]-3′-carboxyisoxazolinopregn-5-en-3β-ol-20-one (II) has been shown to yield 3β,17α-dihydroxypregn-5-en-20-one-16α-carbonitrile (III) as well as either 3β,17β-dihydroxy-17α-methyl-D-homopregn-5-en-17a-one-16β-carbonitrile (IV) or 3β,17α-dihydroxy-17β-methyl-D-homopregn-5-en-17a-one-16α-carbonitrile (VIII) according to pyrolysis conditions.

In an earlier publication,[1] we described the reaction sequence shown below for the hydrolysis and decarboxylation products of [16,17-*d*]-3′-carbethoxyisoxazolino steroids (see Scheme I).

The normal steroid structure of IIIa was assigned principally from the nmr data, and the structure of III was assigned on the basis of analogy with IIIa.

In this paper we present evidence showing that the compound thought to have the normal structure III has a D-homo structure, 3β,17β-dihydroxy-17α-methyl-D-homopregn-5-en-17a-one-16β-carbonitrile (IV). We also show that pyrolysis of II yields, in addition to IV, the product with the normal steroid structure 3β,-17α-dihydroxypregn-5-en-20-one-16α-carbonitrile (III). An independent synthesis of III was devised using the 20-ethylenedioxy function to avoid rearrangement during the pyrolytic decarboxylation step. Compound IIIa retains the normal steroid structure as shown.

[16,17-*d*]-3′-Carbethoxyisoxazolinopregn-5-en-3β-ol-20-one 3β-acetate[1] (I, Scheme I) was converted to the 20-ethylenedioxy derivative (VIa) prior to alkaline hydrolysis to [16,17-*d*]-3′-carboxyisoxazolino-20-ethylenedioxypregn-5-en-3β-ol (VIb). Pyrolytic decarboxylation of the latter yielded 3β,17α-dihydroxy-20-ethylenedioxypregn-5-en-16α-carbonitrile (VII) in 43% yield, after crystallization (see Chart I). Acid hydrolysis now furnished 3β,17α-dihydroxypregn-5-en-20-one-16α-carbonitrile (III) in 75% yield. The nmr spectra of both III and III acetate showed normal steroid characteristics (Table I).

The ORD data for III and for IIIa show positive single Cotton effect curves.[2] Djerassi[3,4] indicates that the positive single Cotton effect curve for a normal steroidal C_{20} ketone is qualitatively unchanged by the introduction of a 17α-hydroxyl.

In contrast to III and IIIa, IV showed an abnormal, negative ORD curve.[2] Klyne[5] has reported that a 17a-oxo-D-homo steroid (3β-hydroxy-5α-D-homoandrostan-

(1) G. W. Moersch, E. L. Wittle, and W. A. Neuklis, *J. Org. Chem.*, **30**, 1272 (1965).

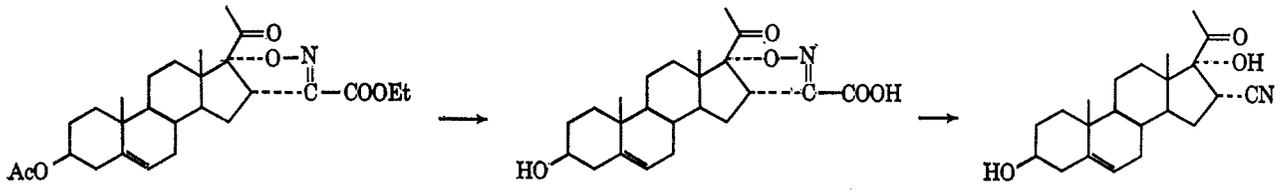
(2) We are indebted to Dr. W. Nagata and his colleagues for first determining the ORD and CD curves of our sample (IV) and for supplying ORD and 100-Mc nmr measurements on subsequent samples. Dr. Nagata's use of our sample in establishing the structure of the epimeric material [W. Nagata, M. Yoshioka, and T. Okumura, *Tetrahedron Letters*, 847 (1966)] and his correspondence during the work are deeply appreciated.

(3) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co. Inc., New York, N. Y., 1959, p 51.

(4) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, and Ch. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

(5) W. Klyne, *Advan. Org. Chem.*, **1**, 332 (1960).

SCHEME I

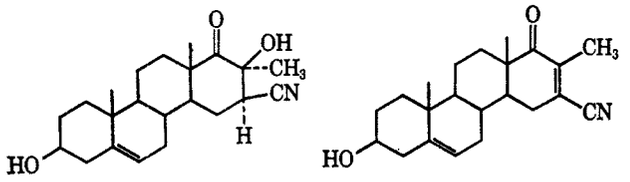


I
Ia, Δ^4-3-keto

II
IIa, Δ^4-3-keto

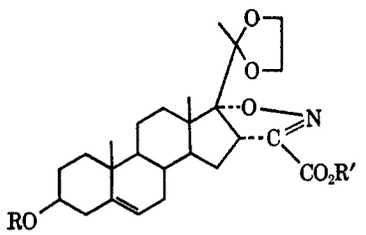
III
IIIa, Δ^4-3-keto

CHART I

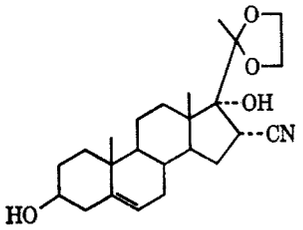


IV

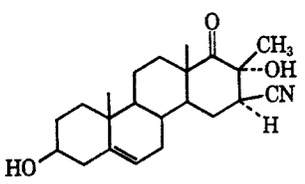
V
Va, Δ^4-3-keto



VIa, R = CH_3CO; R' = C_2H_5
b, R = R' = H



VII



Nagata's XVII

TABLE I

CHEMICAL SHIFTS (δ VALUES, PARTS PER MILLION)

Compd	Solvent	C_{19}-Me	C_{18}-Me	C_{17}-Me	Acetate	C_{20}-Me
IV	Pyridine	1.00	1.47	1.71		
IV acetate	$CDCl_3$	1.03	1.32	1.50	2.02	
IV acetate	Pyridine	0.96	1.48	1.76	2.06	
Nagata's XVII (acetate)[a]	$CDCl_3$	1.02	1.15	1.57	2.01	
Ruschig's XIV[b]	Pyridine	1.06	0.99	1.70		
VIII	Pyridine	1.06	0.99	1.68		
Ruschig's XIV acetate[b]	$CDCl_3$	1.04	1.15	1.50	2.01	
VIII acetate	$CDCl_3$	1.03	1.14	1.50	1.01	
VIa	$CDCl_3$	1.04	0.98		2.04	1.42
VIb	Pyridine	1.06	1.10			1.55
VII	Pyridine	1.04	0.92			1.50
I	$CDCl_3$	1.04	0.76		2.04	2.27
II	Pyridine	1.03	0.78			2.35
III	Pyridine	1.04	0.69			2.37
III acetate[c]	$CDCl_3$	1.04	0.63		2.02	2.26
IIIa	Pyridine	1.04	0.70			2.37
IIIa	$CDCl_3$	1.20	0.68			2.28
V	$CDCl_3$	1.06	1.06	2.08		
Va	$CDCl_3$	1.20	1.05	2.08		

[a] Reference 20. [b] Reference 14. [c] An exchange of nmr data with Nagata has shown the nonidentity of III acetate and Nagata's XXIV,[2] the C_{16} epimeric structure.

17a-one) gives an unusual dispersion curve, lacking the ketone wave, whereas the 17-oxo-D-homo steroids have single Cotton effect curves. 3β-Acetoxy-17α-hydroxy-17β-methyl-D-homo-5α-androstan-17a-one, however, a 17a-oxo-D-homo steroid, has been reported to have a single Cotton effect curve.[4] It is, however, opposite in sign to the negative curves reported for the 17a- (α- or β-) hydroxy-17a- (β- or α-) methyl-D-homo-17-ones.

Nmr data were obtained for compound IV in pyridine and for its acetate in deuteriochloroform. The significant characteristics are listed in Table I. The absence of the 21-methyl-20-keto grouping and the presence of a methyl group of the CH_3COH type confirm the D-homo structure indicated by the ORD data. The previously reported conversion of IV to V[1] is further evidence for a D-homo structure of type IV, and the chemical shifts for the C_{18}-methyl protons in IV and in V support the assignment of the 17a-one system.[6] Compound V therefore appears to result from IV by the base-catalyzed elimination of water.

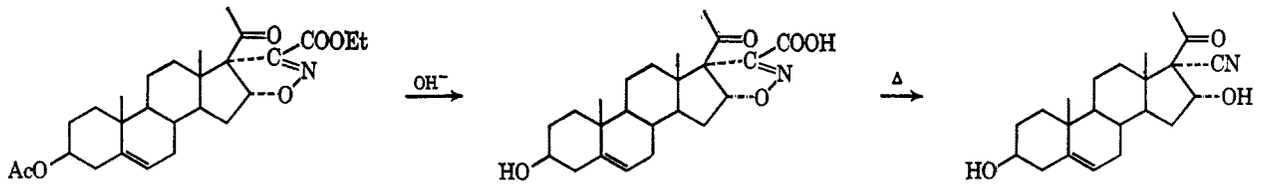
Since the downfield shift of the C_{18}-angular methyl (1.32 ppm) in IV requires nonidentity with the product (XVII, 17β-methyl) obtained by Nagata,[2] the C_{17} epimeric structure (IV, 17α-methyl) is indicated. The D ring of IV is considered to be in the chair conformation. Bible[7] points out that a 1,3-diaxial relationship of hydroxyl to an angular methyl produces a downfield shift of about 15 cps, and the incremental C_{18}-methyl chemical shifts given by Trenner[6] show a 0.11-ppm downfield shift difference of the 17β-hydroxy-17α-methyl-D-homo-17a-one structure relative to the 17β-methyl-17α-hydroxy-D-homo-17a-one. The chemical shift value for compound IV acetate C_{18} methyl (1.32 ppm) should thus be between 0.11 and 15/60 = 0.25 ppm farther downfield from the C_{18}-methyl value of 1.15 ppm for Nagata's XVII. The actual difference is 0.17 ppm. These arguments give support to the assignment of an axial hydroxyl and the chair conformation in ring D.

The configuration of the C_{16} cyano substituent in IV appears to be β, even though an equilibration about this center would be required to attend the C_{16}–C_{17} bond migration during D homologation. Nagata[2] assigned the β configuration to the cyano group of his product (XVII) on the basis of the apparent J values (4 and 12) measured both at 60 and 100 Mc. We find a corresponding set (J^{ap} = 5 and 11 cps) for IV acetate in

(6) N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961).

(7) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1695, p 59.

SCHEME II[a]



substance VII substance XI substance XIV

[a] Reference 14.

deuteriochloroform solution at 60 and also at 100 Mc.[8] The ABX system most probably has an axial–equatorial and an axial–axial arrangement. Since the direction of the effect of the cyano group electronegativity will be to decrease the J values,[9] however slightly, the most reasonable assignment for IV, as for Nagata's XVII, would be the chair conformation of the D ring with the C_{16} proton axial and α.

3β,17α-Dihydroxypregn-5-en-20-one-16α-carbonitrile (III) has been mentioned (as the 3-acetate) in patent generic claims,[10] but has not been characterized. Pike[11] has reported the preparation of 17α-hydroxy 6α-methyl-3,20-dioxopregn-4-en-16α-carbonitrile from the 16α-formyl analog. The product showed nmr peaks (in deuteriochloroform) at 0.67 ppm for C_{18} methyl, 1.18 ppm for C_{19} methyl, and at 2.26 for C_{21} methyl.

The mass spectra[12] of III, IIIa, IV, and V showed that both normal and D-homo steroidal systems produced M − 43 ion peaks but that these were relatively intense for the normal 17α-hydroxy-16α-cyano steroids (III and IIIa) and weak for the dehydrated D-homo structure (V) with IV intermediate. The presence of the 16β-cyano group apparently facilitates formation of the M − 43 ion perhaps by a route already recognized for β-hydroxynitriles.[12,13]

Stache, Fritsch, and Ruschig[14] have published a series of chemical operations identical with our own[1] but have assigned the alternate structures as shown in Scheme II. The products were obtained in corresponding yields and the melting points are in agreement with those obtained by ourselves, except for the pyrolytic decarboxylation product (substance XIV). A sample of substance XIV, kindly supplied to us by Dr. Ruschig, was found not be be identical with either III or IV, by comparison of the nmr spectra of the compounds and of their monoacetates.

Starting with our product (II), we attempted to perform the pyrolysis as described by Ruschig, *et al.*[14] We were able to isolate both III and IV by ethyl acetate crystallizations, but found no evidence of a fraction with the 0.99-ppm nmr signal (pyridine solution) which differentiates Ruschig's XIV from these products. Further experimentation ultimately resulted in the obtaining of a material identical with Ruschig's XIV when the sample of II used in the pyrolysis was obtained by precipitation with sulfuric acid and was not purified by acetone crystallization. Pyrolysis resulted in a dark reaction mixture which was separated by column chromatography on Florisil. The products obtained in this case were III and a material (VIII) which showed the nmr and infrared characteristics of Ruschig's XIV. Acetylation by pyridine and acetic anhydride gave a monoacetate with spectra in agreement with those of the acetylation product of Ruschig's XIV. Product VIII was converted quantitatively to V by brief warming in methanolic KOH. The close agreement of the chemical shifts for the C_{18} and C_{19} methyl protons of VIII with those for Nagata's XVII indicates a D-homo structure and the corresponding C_{17} configuration, while the slightly different position of the C_{17} methyl chemical shift and the downfield position (3.36 ppm) of the C_{16} proton relative to Nagata's material (2.80 ppm) indicates the probable equatorial C_{16} β proton.[9] Confirmation is found in measuring the signal breadth, $J_{AX} + J_{BX} = 7.5$ cps, which is compatible with the equatorial 16-proton assignment.[12] These considerations suggest structure VIII for Ruschig's XIV. We have found no evidence for the opposite direction of 1,3-cycloaddition proposed by Stache, Fritsch, and Ruschig, a direction which is contrary to the addition to steroidal Δ^{16}-20 ketones found in this and previous work.[1,15] Further, acetylation of III with acetic anhydride in pyridine yields clearly a monoacetate rather than the diacetate to be expected from a 3,16-diol[16] such as would have resulted had the structure of the starting material been that of substance VII rather than that of I.

Thus the present work shows that the pyrolytic decarboxylation of the 3-carboxy-2-isoxazoline (II) can give rise to at least three products depending on the conditions of pyrolysis, the normal steroid structure III, and two isomeric D-homo structures (IV and VIII). Scheme III summarizes these results.

Experimental Section[17]

[16,17-*d*]-3′-Carbethoxyisoxazolino-20-ethylenedioxypregn-5-en-3β-ol Acetate (VIa).—The product (I) from carbethoxyformonitrile oxide and pregna-5,16-dien-3β-ol-20-one acetate[1]

(8) We are indebted to Varian Associates and to Dr. Nagata for supplying 100-Mc data.

(9) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(10) U. S. Patent 3,201,392 (The Upjohn Co.) (Aug. 17, 1965).

(11) J. E. Pike, *J. Org. Chem.*, **29**, 3476 (1964).

(12) We are grateful to Dr. D. C. DeJongh of Wayne State University, and to Dr. H. S. Mosher of Stanford University, for providing the mass spectra of these compounds and for their help in interpreting them. The mass spectra were determined with an ionizing potential of 70 ev and an ionizing current of 18 μa. We are also grateful to Dr. Mosher and to Dr. Lois Durham for 100-Mc nmr of our preparation of compound VIII.

(13) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p 114.

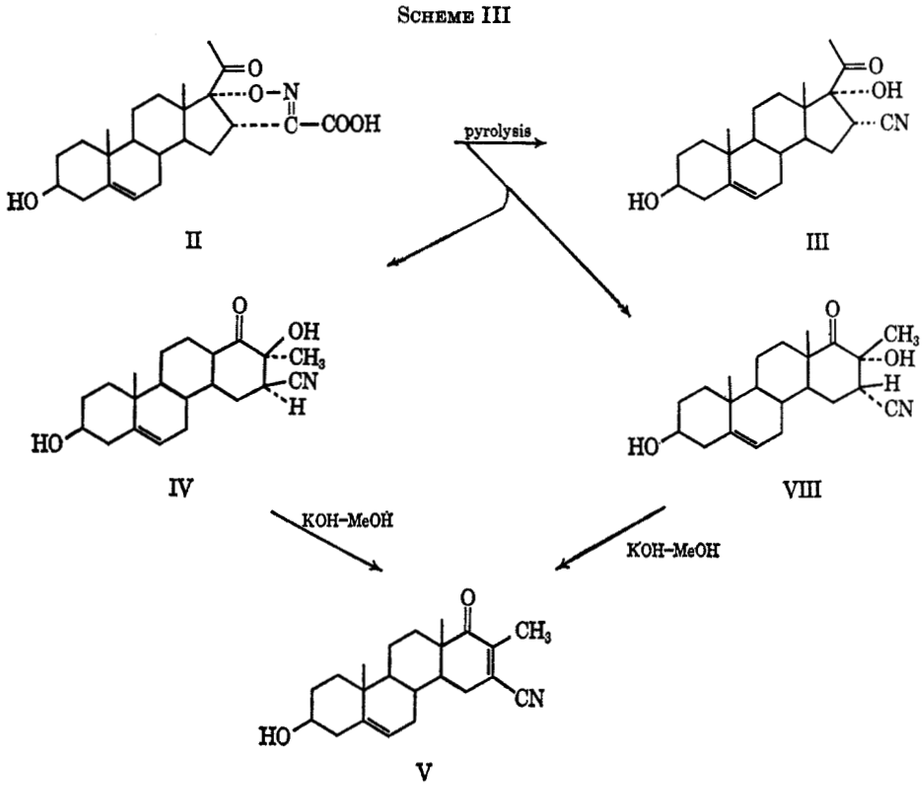
(14) U. Stache, W. Fritsch, and H. Ruschig, *Ann.*, **685**, 228 (1965).

(15) T. P. Culbertson, G. W. Moersch, and W. A. Neuklis, *J. Heterocyclic Chem.*, **1**, 280 (1964).

(16) R. Neber, P. Desaulles, E. Vischer, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1667 (1958); R. Neber, Ch. Meystre, and A. Wettstein, *ibid.*, **42**, 132 (1959).

(17) Melting points were determined in a Thomas–Hoover capillary tube apparatus. The nmr except where otherwise noted were obtained on a Varian A-60. They were determined in deuteriochloroform or in pyridine solution and the shifts are expressed as parts per million (ppm) downfield from tetramethylsilane, used as an internal standard.

SCHEME III



II III IV VIII V

(6.5 g, mp 168–170°) was dissolved in 200 ml of toluene with 25 ml of ethylene glycol, stirred, and distilled under a water separator.

p-Toluenesulfonic acid (200 mg) was then added and the distillation was resumed for 16 hr. The reaction mixture was washed with sodium carbonate solution and evaporated under reduced pressure to a white solid. Crystallization from methanol gave material (3.0 g, 42%) of mp 221–222°; ν_{KBr} 1737, 1725, 1580, 1240 cm^{-1}.

Anal. Calcd for $C_{29}H_{41}NO_7$ (515.6): C, 67.55; H, 8.01; N, 2.71. Found: C, 67.04; H, 8.06; N, 2.76.

[16,17-*d*]-3′-Carboxyisoxazolino-20-ethylenedioxy-pregn-5-en-3β-ol (VIb).—The ester (VIa, 4.0 g) was dissolved in 100 ml of methanol containing 6 g of KOH and was heated at reflux for 10 min. The cooled reaction was poured into ice–water and acidified with 3 *N* hydrochloric acid. The white precipitate was separated by filtration, washed with water, and dried in air. The product was 3.25 g of white powder (mp 188–190° with gas evolution), resolidifying and remelting at 239–244°. Crystallization from methanol–water gave material of mp 245–249°; ν_{KBr} 3430, 1720, 1592 cm^{-1}.

Anal. Calcd for $C_{25}H_{35}NO_6$ (445.5): C, 67.40; H, 7.92; N, 3.15. Found: C, 67.12; H, 8.08; N, 3.08.

3β,17α-Dihydroxy-20-ethylenedioxypregn-5-en-16α-carbonitrile (VII).—The acid (VIb, 2.0 g) was placed in a 200-ml round-bottom flask which was then connected to the oil pump and evacuated. The flask was suspended over a metal bath at 200–215° and slowly immersed. The solid evolved a gas and changed to a light brown color. After the change was complete, the flask was removed from the bath and allowed to cool before opening. The solid product was crystallized from methanol. Crop 1 (770 mg, 43%, white plates) had mp 268–270°; ν_{KBr} 3500 (hydroxyl), 2240 cm^{-1} (cyano), and absence of carbonyl.

Anal. Calcd for $C_{24}H_{35}NO_4 \cdot 0.25H_2O$ (406.0): C, 71.05; H, 8.81; N, 3.45. Found: C, 71.13; H, 8.84; N, 3.77.

3β,17α-Dihydroxypregn-5-en-20-one-16α-carbonitrile (III).—A sample of VII (1.85 g) was suspended in 250 ml of ethanol and 25 ml of water with 10 ml of concentrated hydrochloric acid and refluxed overnight under nitrogen. The reaction solution was evaporated under nitrogen, diluted with water, and refrigerated. Filtration gave 1.11 g (75%), mp 245–250°. Recrystallization from ethyl acetate gave mp 264–267°; ν_{KBr} 3440, 2200, 1708 cm^{-1}.

Anal. Calcd for $C_{22}H_{31}NO_3$ (357.5): C, 73.90; H, 8.74; N, 3.91. Found: C, 74.17; H, 8.73; N, 3.70.

III Acetate.—A 100-mg sample of III in solution in 4 ml of pyridine was treated with excess acetic anhydride (1 ml) at room temperature for 20 hr. The reaction mixture was poured into ice–water and the insoluble product was separated and crystallized from ethanol as white needles (80 mg): mp 229–231°; ν_{CHCl_3} 3560, 3420, 2238, 1722, 1710, 1250 cm^{-1}.

Anal. Calcd for $C_{24}H_{33}NO_4$ (399.5): C, 72.15; H, 8.33; N, 3.50. Found: C, 71.92; H, 8.92; N, 3.58.

ORD Data.[2]—17α-Hydroxypregn-4-en-3,20-dione-16α-carbonitrile (IIIa) showed (*c* 0.44 methanol at 23.5°) $[\phi]_{400}$ +1325°, $[\phi]_{354}$ +1777°, $[\phi]_{312}$ + 12278°, $[\phi]_{278}$ −1535°.

3β,17α-Dihydroxypregn-5-en-20-one-16α-carbonitrile (III) showed (*c* 0.494, methanol at 24°) $[\phi]_{400}$ +507°, $[\phi]_{320}$ +6227°, $[\phi]_{270}$ −12020°, $[\phi]_{255}$ −11441°, $[\phi]_{265}$ −12455°.

3β,17β-Dihydroxy-17α-methyl-D-homopregn-5-en-17α-one-16β-carbonitrile (IV) showed (*c* 0.703, methanol at 24°) $[\phi]_{342}$ −1080°, $[\phi]_{295}$ −2898°, $[\phi]_{228}$ −12102°.

Pyrolysis of [16,17-*d*]-3′-Carboxyisoxazolinopregn-5-en-3β-ol-20-one (II). A.—A sample of II, crystallized from acetone (2.0 g, mp 214–216° dec) was pyrolyzed according to the procedure of Stache, Fritsch, and Ruschig.[14] The solidified melt was crystallized from ethyl acetate to yield a first crop of 350 mg (22%, mp 246–250° identifiable as compound III by nmr and infrared. Fraction 2 (400 mg, 25%, mp 262–263°) corresponded by nmr to compound IV. Fraction 3 (300 mg, 19%, mp 243–245°) exhibited the nmr of a mixture of III and IV. Fraction 2 was recrystallized from methanol (mp 263–265°)[18] and was acetylated (100 mg) with acetic anhydride and pyridine at room temperature. The product was crystallized from ethanol–water to yield 55 mg of 3β,17β-dihydroxy-17α-methyl-D-homopregn-5-en-17a-one-16β-carbonitrile 3-acetate (IV acetate): mp 215–217°; ν_{CHCl_3} 3595, 3440, 2240, 1723, 1717, 1250 cm^{-1}; λ_{max}^{MeOH} 257 mμ (ε 2140).

Anal. Calcd for $C_{24}H_{33}NO_4$ (399.5): C, 72.15; H, 8.33. Found: C, 72.05; H, 8.42.

B.—A sample of II (27 g; obtained by sulfuric acid precipitation of the hydrolysis quench mixture, filtering, washing with water, and drying; mp 231–233° dec) was pyrolyzed according to the procedure of Stache, Fritsch, and Ruschig.[14] The melt became black and after cooling was taken into ethyl acetate and filtered. The dark solution failed to produce crystals and was passed over a 20-in. column of Florisil and the column was eluted

(18) The mp of this compound was reported earlier[1] as 275–277°. This was obtained on a Fisher-Johns hot stage at too rapid a rate and is 12° too high. Nagata[3] obtained a mp 260–262° on the hot stage.

with ethyl acetate. Ethyl acetate crystallization of the eluate residues gave crystalline material from the first four eluates. After these, only brown, noncrystalline materials were obtained. Fraction 1 (140 mg, 0.6%, mp 248–253°) corresponded by nmr to compound III. Fraction 2 (4.15 g, 17.3%, mp 228–232°) was shown by nmr to be a mixture of III and VIII (Ruschig's XIV). Fraction 3 (1.64 g, 6.8%, mp 252–255°) and fraction 4 (1.19 g, 5.0%), mp 253–255°) corresponded by infrared and nmr with Ruschig's XIV.

3β-Acetoxy-17α-hydroxy-17β-methyl-D-homopregn-5-en-17α-one-16α-carbonitrile (VIII).—A sample of Fraction 3 (from B, 200 mg) was acetylated in pyridine at room temperature with acetic anhydride. The product was crystallized from methanol–water to yield 160 mg of the 3-acetate of VIII: mp 202–205°; ν_{CHCl_3} 3480, 2245, 1730, 1708, 1255 cm^{-1}; $[\alpha]^{25}D$ −82.3° (1.05% in chloroform).

Anal. Calcd for $C_{24}H_{33}NO_4$ (399.5): C, 72.15; H, 8.33; N, 3.50. Found: C, 72.19; H, 8.29; N, 3.76.

Reaction of VIII with Base.—A sample (100 mg) of fraction 3 (above) was heated on the steam bath in a solution of 500 mg of KOH in 30 ml of methanol. After 10 min, the solution was cooled under an air stream and diluted with water. The product was separated, washed with water and dried in air to yield 90 mg: mp 259–261°; λ_{max}^{MeOH} 247 mμ (ε 10,500); ν_{KBr} 3450, 2215, 1680 cm^{-1}. The identity of the product with compound V was also shown by nmr.

Registry No.—VIa, 7745-50-8; VIb, 7745-51-9; VII, 7745-52-0; III, 2472-37-9; IIIa, 2324-73-4; IV, 7745-55-3; acetate of IV, 7782-06-1; 3-acetate of VIII, 7745-56-4; V, 2472-38-0; VIII, 7745-58-6; I, 1062-03-9; II, 2324-71-2; Va, 2324-74-5.

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The Conversion of Tetrahydro-β-carbolines into 2-Acylindoles[1]

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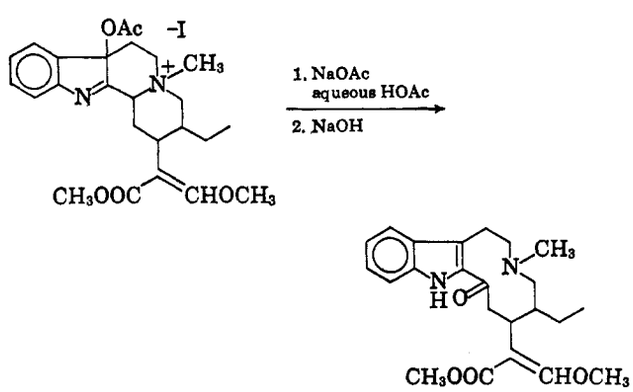
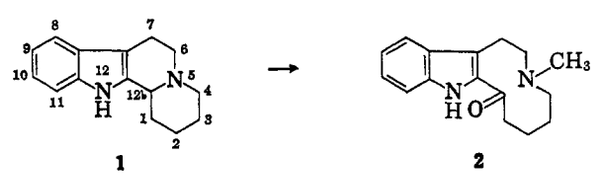
The 2-acylindole, 5-methyl-12b-keto-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**2**), has been synthesized. The mechanism of the previously reported C–D ring cleavage of dihydrocorynantheine is discussed. The 2-acylindole (**2**) has also been prepared by periodic acid oxidation of the tricyclic amine, 5-methyl-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**10**). The reaction of tricyclic ketone **2** with nucleophiles has been examined as a model for the suggested biogenesis of echitamine.

A previous report[4] from these laboratories has illustrated a new method for the C–D ring cleavage of dihydrocorynantheine derivatives.



It is the purpose of the present study to examine this process in more detail and explore new methods for effecting this transformation. We have also examined the reaction of the resulting 2-acylindoles with nucleophiles as a model for the synthesis of echitamine. To this end we have studied the conversion of the tetracyclic base, 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine (**1**), into the tricyclic ketone (**2**), 5-methyl-12b-keto-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindole-[2,3-*a*]quinolizine, by two independent routes.

The required tetracyclic base was prepared from N-(indole-3-acetyl)piperidine[5,6] by a modification of Wenkert's procedure[6] employing mercuric acetate oxidation and cyclization of N-[2-(3-indolyl)-ethyl]piperidine (see the Experimental Section).



1 **2**

Treatment of the tetracyclic amine (**1**) with *t*-butyl hypochlorite gave the expected mixture of epimeric β-chloroindolenines[7] (**3**) which were alkylated with methyl iodide to form a mixture of β-chloroindolenine methiodides (**4**). Treatment of the methiodide mixture with sodium acetate in aqueous ethanol followed by basification with sodium hydroxide gave desired tricyclic ketone **2** in yields of 10–20% from tetracyclic amine (see Scheme I).

The structure of **2** was readily confirmed by spectral data. The ultraviolet spectrum in ether solution shows normal 2-acylindole[4] absorption [$\lambda_{max}^{Et_2O}$ 308 (ε 14,900)] which is changed to an indole spectrum by the addition of acetic acid. The ultraviolet spectrum in ethanol shows combination of indole and 2-acylindole chromophores. In aqueous ethanol the ultraviolet spectrum shows only indole absorption. This pronounced solvent effect is attributed to the ring-closed dipolar species (**5**) which is favored by polar media. A similar

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(3) National Institutes of Health Predoctoral Fellow, 1965–1967.

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(7) Interestingly, treatment of the chloroindolenine epimeric mixture with potassium *t*-butoxide results in the formation of tetracyclic amine **1**, presumably arising from nucleophilic attack on chlorine.