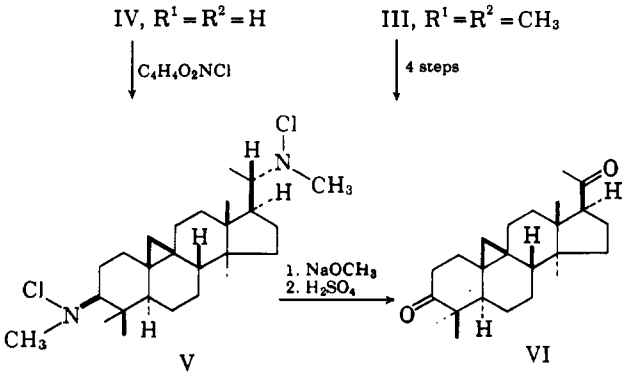
interrelation of the alkaloid with cyclovirobuxine-D and with cycloartenyl acetate. Ruschig degradation of cycloprotobuxine-D proceeded, *via* the crystalline dichloramine V, $C_{26}H_{44}N_2Cl_2$, m.p. 164–165°, to the diketone VI (4,4,14α-trimethyl-9β,19-cyclo-5α-pregnane-3,20-dione), previously obtained from cyclovirobuxine-D (III, $R^1 = R^2 = CH_3$)[9] and from cycloartenyl acetate.[16] Configurations at C-3 and C-20 were assigned on the basis of biogenetic analogy to the companion alkaloids, cyclobuxine-D (I), cyclovirobuxine-D (III, $R^1 = R^2 = CH_3$), and cyclobuxamine-H (III, $R^1 = R^2 = H$).



Methylation of cycloprotobuxine-D with formaldehyde and formic acid gave dimethylcycloprotobuxine-D (IV, $R^1 = R^2 = CH_3$), and the latter compound was found to be identical with monomethylalkaloid L.[15] Calame and Arigoni have independently assigned the cycloprotobuxine-C structure (IV, $R^1 = H$, $R^2 = CH_3$) to alkaloid L.[10,16] The interrelation of cycloprotobuxine-D and cycloprotobuxine-C by conversion to the same methylation product[17] is in accord with expectation based on the structures assigned to the respective alkaloids.

Experimental[18,19]

Separation of the Acetone-Soluble Strong Bases by Partition Chromatography.—The acetone-soluble strong base fraction (2.5 g.)[3b] was dissolved in the upper phase of the system hexane–ethylene chloride–methanol–water (50:5:15:1) and chromatographed on a column of Celite 545 impregnated with phenol red and lower phase of the solvent system.[13] Four red bands were visible on the column, at R_f 0.95 (alkaloid L[14,15] = cycloprotobuxine-C[10]), 0.72 (cycloprotobuxine-D), 0.52 (buxenine-G[1]), and 0.50 (cyclobuxine-D[3]). The R_f 0.72 band was eluted, and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and extracted with 0.5 *N* hydrochloric acid solution. The acid solution was made alkaline with ammonium hydroxide and extracted with chloroform, and the chloroform extract was evaporated to dryness. Rechromatography of the crude product using the same partition system gave a yellow semisolid material (200 mg.), R_f 0.72, which was crystallized from acetone (100 mg.). Recrystallization from acetone yielded colorless needles (80 mg.), m.p. 140–142°, $[\alpha]^{28}D$ +112° (*c* 0.94, chloroform).

Anal. Calcd. for $C_{28}H_{46}N_2$: C, 80.76; H, 11.99; N, 7.25. Found: C, 80.78; H, 12.05; N, 7.29.

N,N′-Diacetylcycloprotobuxine-D (IV, $R^1 = R^2 = COCH_3$).—A solution of cycloprotobuxine-D (25 mg.) in dry pyridine (1 ml.) and acetic anhydride (0.5 ml.) was allowed to stand at room temperature for 18 hr. After evaporation to dryness under reduced pressure the residue was crystallized from acetone to yield colorless needles (20 mg.), m.p. 276–278°. The infrared spectrum showed a very strong band at 6.18 μ.

Anal. Calcd. for $C_{30}H_{50}N_2O_2$: C, 76.54; H, 10.71; N, 6.80. Found: C, 76.60; H, 10.64; N, 6.43.

N,N′-Dichlorocycloprotobuxine-D (V).—A solution of cycloprotobuxine-D (250 mg.) in chloroform (10 ml.) was cooled to 0° and treated dropwise with stirring with a solution of N-chlorosuccinimide (180 mg.) in chloroform (5 ml.). After stirring for 10 min. at 0° the solution was washed with water (three 20-ml. portions) and evaporated to dryness under reduced pressure. Crystallization of the residue from acetone gave colorless plates (277 mg.), m.p. 164–165°.

Anal. Calcd. for $C_{26}H_{44}Cl_2N_2$: C, 68.60; H, 9.67; N, 6.15. Found: C, 68.77; H, 9.83; N, 6.04.

Ruschig Degradation of N,N-Dichlorocycloprotobuxine-D.—The dichloramine V (100 mg.) was treated with a solution of sodium (0.5 g.) in methanol (20 ml.), and the mixture was heated under reflux for 2 hr. After evaporation to dryness under reduced pressure, the residue was treated with 0.5 *N* hydrochloric acid and chloroform. The chloroform extract was evaporated to dryness, the residue was dissolved in ethanol (10 ml.) and 6 *N* sulfuric acid (5 ml.), and the solution was allowed to stand at room temperature for 12 hr. The mixture was diluted with water and extracted with chloroform, and the chloroform extract was evaporated to dryness. The residue was chromatographed on Woelm neutral alumina (5 g.) using benzene (50 ml.) and 5% ethyl acetate in benzene (30 ml.) as eluents. The latter solvent mixture yielded a residue which was crystallized from acetone to yield colorless needles (29 mg.), m.p. 193–196°. The infrared spectrum was superimposable upon that of an authentic sample of 4,4,14α-trimethyl-9β,19-cyclo-5α-pregnane-3,20-dione (VI),[9] and the melting point was not depressed upon admixture with the authentic sample.

N,N-Dimethylcycloprotobuxine-D (IV, $R^1 = R^2 = CH_3$).—A solution of cycloprotobuxine-D (15 mg.) in 40% formaldehyde (15 mg.) and 88% formic acid (30 mg.) was heated under reflux for 12 hr. The reaction mixture was poured into 0.5 *N* hydrochloric acid solution; the acid solution was washed with ether, made alkaline with ammonium hydroxide, and extracted with chloroform. Evaporation to dryness gave a residue which was crystallized from chloroform–acetone to yield colorless plates (12 mg.), m.p. 208–211°. The melting point was not depressed upon admixture of a sample (m.p. 209–211°) of monomethylalkaloid L,[15] and the infrared spectra of the respective samples were identical.

Anal. Calcd. for $C_{28}H_{50}N_2$: C, 81.09; H, 12.15; N, 6.76. Found: C, 81.24; H, 12.27; N, 6.91.

(16) J. P. Calame and D. Arigoni, *Helv. Chim. Acta.*, in press. We thank Professor Arigoni cordially for informing us of these results prior to publication.

(17) Dr. R. Goutarel has kindly informed us of his isolation from *Buxus balearica* Willd. of cycloprotobuxine-A (= monomethylalkaloid L = dimethylcycloprotobuxine-D; IV, $R^1 = R^2 = CH_3$).

(18) Melting points are corrected to the nearest degree. Infrared spectra were measured in chloroform solution on a Beckman Model IR-5A spectrophotometer. Rotations have been approximated to the nearest degree. N.m.r. spectra were determined on a Varian A-60 spectrometer. Microanalyses were performed by Mr. Joseph Alicino (Metuchen, N. J.).

(19) We are grateful to Ciba Pharmaceutical Company for procurement and large-scale extraction of plant material, and especially thank Drs. E. Schlittler, D. Dickel, and K. Heusler for their kind interest and cooperation in this project.

Steroids. CCLXXV. The Aromatization of 10β-Acetoxyestr-4-ene-3,17-dione in the Presence of Amines*,[1]

FRANCISCO S. ALVAREZ[2] AND AUGUSTO B. RUIZ

The Research Laboratories, Syntex, S. A., Apartado 2679, Mexico, D.F., Mexico

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In a recent publication[3] we described the facile aromatization of 10β-acetoxyestr-4-ene-3,17-dione and 10β-acetoxy-19-norpregn-4-ene-3,20-dione in alcoholic

* To Professor Louis F. Fieser.

(1) Steroids. CCLXXIV: A. D. Cross, E. Denot, R. Acevedo, and P. Crabbe, *Steroids*, submitted for publication.

(2) To whom correspondence should be addressed to the Syntex Research Center, Stanford Industrial Park, Palo Alto, Calif.

(3) F. S. Alvarez, *Steroids*, **3**, 13 (1964).

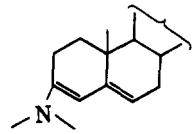
media, leading to the corresponding ring A aromatic 3-alkoxy ethers.

We now report a similar aromatization of 10β-acetoxyestr-4-ene-3,17-dione[4] in the presence of primary and secondary amines.

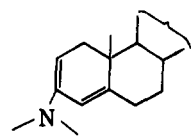
Earlier[3] we postulated formation of the intermediate enol ether III as a precursor of the ring A aromatic 3-alkoxy ethers. It seemed reasonable to suppose therefore that amines might similarly react at C-3 leading to aromatization of ring A. In fact, when 10β-acetoxyestr-4-ene-3,17-dione[4] (I) in benzene solution was treated with a slight excess of pyrrolidine complete aromatization of ring A occurred, yielding 3-(N-pyrrolidinyl)estra-1,3,5(10)-trien-17-one (VIIa). The product showed the characteristic ultraviolet absorption maxima of N,N-dialkyl-substituted anilines[5] at 258 mμ (ε 18,100), and 310–312 mμ (ε 2820), as well as a strong absorption in the infrared at 1363 cm.$^{-1}$ for the C–N bond stretching vibration of an aromatic amine.

When piperidine, diethylamine, and N,N-diethyl-1,2-ethylenediamine were used in neutral media, no aromatization occurred, only starting material was recovered from the reaction mixtures. However, when traces of acid were present, the reaction proceeded to completion after a few hours at reflux temperature. In these three cases, the aromatic amine was contaminated with estrone owing to the parallel direct acid-catalyzed aromatization of 10β-acetoxyestr-4-ene-3,17-dione. This side reaction was minimized by the use of a weak acid. The crude reaction products were purified by elution chromatography on alumina. In this manner there were obtained the 3-amino derivatives (VIIa–d).

Others workers[6] have shown that Δ^4-3-keto steroids on reaction with secondary amines yield 3-amino-3,5-dienes (A) rather than the alternative -2,4-dienes (B).



A



B

The same authors reported that only pyrrolidine was capable of enamine formation with Δ^4-3-keto steroids in the absence of acid catalysis, in contrast to other secondary amines.

On the basis of these findings, it appears likely that the mechanism of aromatization of the 10β-acetoxyestr-4-ene-3,17-dione (I) proceeds *via* enamine formation (IV), followed by anchimerically assisted elimination of acetate (IV → VII).

Aromatizations of ring A in the presence of other reagents containing SH, OH, and NH functions will be the subject of later communications.

Experimental[7]

3-(N-Pyrrolidinyl)estra-1,3,5(10)-trien-17-one (VIIa).—A solution of 250 mg. of 10β-acetoxyestr-4-ene-3,17-dione[4] (I) in 25 ml. of anhydrous benzene was treated with 286 mg. of pyrrolidine under reflux for 1 min. The reaction mixture was then kept at room temperature for 16 hr. The mixture was diluted with 75 ml. of benzene, washed twice with 25 ml. of water, and dried over anhydrous sodium sulfate. After concentration to dryness under vacuum, the residue was dissolved in methylene dichloride, de-

(4) M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. L. Mihailovic, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2674 (1962).

(5) See J. A. C. T. Browers, *et al.*, in "Organic Electronic Spectral Data," Vol. IV, Interscience Publishers, Inc., New York, N. Y., 1963, p. 304.

(6) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Am. Chem. Soc.*, **78**, 430 (1956); M. E. Herr and F. W. Heyl, *ibid.*, **75**, 5927 (1953).

(7) Melting points are corrected, optical rotations are for chloroform solutions, and ultraviolet spectra were obtained in methanol solutions. Infrared spectra were determined in potassium bromide disks. Microanalyses were performed either by Mid-West Microlaboratories, Indianapolis 20, Ind., or by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

colorized with charcoal, and crystallized from methylene dichloride–methanol, yielding 160 mg. (65%) of the amine VIIa, m.p. 187°. The analytical specimen was prepared by several crystallizations from methylene dichloride–ethanol and showed m.p. 190–192°; λ_{max} 258 mμ (ε 18,300) and 310–313 mμ (ε 2820); $[\alpha]_D$ +140°; ν_{max} 1363 (C–N), 1610, 1562, 1510 (aromatic ring), and 1739 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33; O, 4.95. Found: C, 81.76; H, 9.22; N, 4.38; O, 5.07.

3-(N-Pyrrolidinyl)estra-1,3,5(10)-trien-17β-ol (VIIe).—A solution of 750 mg. of VIIa in 35 ml. of dioxane and 0.4 ml. of water was treated with 440 mg. of sodium borohydride. The reaction mixture was left at room temperature for 5 hr. and the excess of sodium borohydride was destroyed by careful addition of acetic acid. The mixture was diluted liberally with water, and the crystalline precipitate thus obtained was collected by filtration and washed with water to neutrality. Drying of the material then afforded 750 mg. of the 17β-alcohol VIIe, m.p. 175–178°. The analytical sample was obtained by recrystallizations from methanol and had m.p. 178–180°; λ_{max} 256 mμ (ε 17,800) and 312 mμ (ε 2750); $[\alpha]_D$ +78°; ν_{max} 1370 (C–N), 1525, 1562, 1612 (aromatic ring), and 3395 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_{22}H_{31}NO$: C, 81.18; H, 9.60; N, 4.30; O, 4.92. Found: C, 80.79; H, 9.71; N, 4.25; O, 5.17.

3-(N-Pyrrolidinyl)estra-1,3,5(10)-trien-17β-ol Acetate (VIIf).—Acetylation of 600 mg. of the above 17β-alcohol with pyridine and acetic anhydride on the steam bath in the normal manner furnished the crude acetate VIIf. The analytical sample was prepared by several crystallizations from methylene dichloride–methanol and showed m.p. 137–138°; λ_{max} 258 mμ (ε 16,600) and 312 mμ (ε 2500); $[\alpha]_D$ +51°; ν_{max} 1350, 1380 (C—N), 1520, 1560, 1630 (aromatic ring), 1245 (C—O), and 1750 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05. Found: C, 78.85; H, 9.29.

3-Diethylaminoestra-1,3,5(10)-trien-17-one (VIIb).—A solution of 750 mg. of 10β-acetoxyestr-4-ene-3,17-dione (I) in 75 ml. of benzene and 4.5 ml. of diethylamine was treated with 0.1 ml. of acetic acid under reflux for 6 hr. The reaction mixture was concentrated under vacuum to 20 ml. and filtered through a short column of alumina, eluting with benzene. The material obtained after evaporation of the solvent was purified by further column chromatography on 36 g. of unwashed alumina (system: benzene–ether). The homogeneous, less polar fractions eluted with ether–benzene (85:15) were crystallized from methylene dichloride–hexane to give 230 mg. of the amine VIIb, m.p. 122–124°. Two crystallizations from methylene dichloride–methanol afforded the analytical sample: m.p. 131.5–132.5°; λ_{max} 263 mμ (ε 14,420) and 310 mμ (ε 2145); $[\alpha]_D$ +134°; ν_{max} 1370, 1379 (C—N), 1525, 1563, 1584 (aromatic ring), and 1754 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{22}H_{31}NO$: C, 81.18; H, 9.60; N, 4.30; O, 4.92. Found: C, 81.36; H, 10.19; N, 3.95; O, 4.98.

3-N-Piperidinylestra-1,3,5(10)-trien-17-one (VIIc).—A solution of 500 mg. of I in 50 ml. of benzene, 1 ml. of piperidine, and 0.4 ml. of acetic acid was refluxed for 2.5 hr. Dilution and product isolation as described above for the 3-(N-pyrrolidinyl)-amine furnished 240 mg. of the amine VIIc, m.p. 138–140°. The analytical sample was prepared by recrystallization from methylene dichloride–methanol and showed m.p. 143–143.5°; λ_{max} 250–252 mμ (ε 11,000) and 322 mμ (ε 1620); $[\alpha]_D$ +135°; ν_{max} 1389, 1370 (C—N), 1510, 1563, 1613 (aromatic ring), and 1724 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15; O, 4.74. Found: C, 82.33; H, 9.36; N, 4.02; O, 4.60.

3-(2-Diethylamino)ethylaminoestra-1,3,5(10)-trien-17-one (VIId).—A solution of 720 mg. of I in 70 ml. of benzene, 0.7 ml. of N,N-diethylethylenediamine, and 0.1 ml. of acetic acid was refluxed (with water separator) for 1 hr. The mixture was concentrated to a final volume of 20 ml. and worked up further as described above to yield 550 mg. of crude amine VIId. The analytical sample was prepared by recrystallization from methylene dichloride–pentane and had m.p. 90–100°; $[\alpha]_D$ +121°; λ_{max} 248 mμ (ε 13,820) and 300–302 mμ (ε 2050); ν_{max} 1370, 1385 (C—N), 3350 (N—H), 1508, 1570, 1615 (aromatic ring), and 1738 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{24}H_{36}NO_2$: C, 78.21; H, 9.85; N, 7.60; O, 4.34. Found: C, 78.49; H, 9.81; N, 7.54; O, 4.22.

Isolation and Structure of Aeneadiol*

XORGE ALEJANDRO DOMÍNGUEZ AND VÍCTOR BARRAGÁN

Departamento de Química, Escuela de Ciencias, Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey, N.L., Mexico

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Most *Argemone* species are native to the dry regions of North and Central America.[1] Several parts of these plants have been used medicinally even in prehispanic times.[2–4] Alkaloids of the berberine and protopine group have been isolated from these plants.[5–7] Flavones have been isolated from the flowers of *A. mexicana*.[8] As part of our study of flowers used in Mexican folk medicine, several substances present in *Argemone aenea* G. B. Ownb. were investigated. From the nonsaponifiable portion of the petroleum ether extract three compounds were isolated. The most abundant, A, m.p. 115–116°, had the empirical formula $C_{30}H_{62}O_2$. Its infrared spectrum showed hydroxyl bands. It gave positive tests for a vicinal glycol and a linear aliphatic compound. A Kuhn–Roth determination gave two terminal C-methyl groups. Oxidation with periodic acid furnished two aldehydes. The steam-volatile component was identified as *n*-decanal; the nonvolatile component, m.p. 77–79°, $C_{20}H_{40}O$, as *n*-eicosanal. Therefore, A, which we have named aeneadiol, is the previously unreported 10,11-triacontanediol.[9]

Compound B, m.p. 73–74°, $C_{26}H_{52}O$, showed infrared bands of a linear aliphatic ketone. A Kuhn–Roth determination gave two C-methyl groups. The Zimmermann and other tests for carbonyl groups agreed with the infrared information. Its n.m.r. spectrum showed a methyl peak at τ 8.9 (6H) and a methylene peak at 8.75 (50–54H).

Compound C, m.p. 134–136°, $C_{26}H_{46}O$ (acetate m.p. 120–122°, $C_{28}H_{48}O_2$), gave a positive Liebermann–Burchard test and a negative tetranitromethane test. It must be a sterol which was not further investigated.

From the acetone extract two alkaloids were isolated: berberine and α-allocryptopine. Six unidentified alkaloids were detected by thin layer chromatography (t.l.c.) on silica gel, R_f 0.18, 0.21, 0.25, 0.57, 0.62, and 0.70. From the alcoholic extracts, berberine, α-

* To Professor Louis F. Fieser.

(1) G. B. Ownbey, *Mem. Torrey Botan. Club*, **21**, 50 (1958).

(2) P. C. Standley, "Trees and Shrubs of México," Part 1, Smithsonian Institution, Washington, D. C., 1920, p. 299.

(3) M. Martínez, "Plantas medicinales de México," 3rd Ed., Editorial Botas, Mexico, 1959, p. 108.

(4) F. Hernández, "Historia de las plantas de Nueva España," Imprenta Universitaria México, Mexico, 1942, p. 805.

(5) A. Santos and P. Adkilen, *J. Am. Chem. Soc.*, **54**, 2923 (1932).

(6) L. Slavikova and J. Slavik, *Collection Czech. Chem. Commun.*, **21**, 211 (1955).

(7) J. Schermerhorn and T. Soine, *J. Am. Pharm. Assoc.*, **40**, 20 (1951).

(8) W. Rahman and M. Ilyas, *J. Org. Chem.*, **27**, 153 (1962).

(9) The only previous reference to a triacontanediol is the 1,2-diol from the insect *Tenebro molitor* [W. Schulz and M. Becker, *Biochem. Z.*, **232**, 189 (1931)]. This structure would appear to be rather tenuous owing to the paucity of data used to substantiate it. It is reported to melt at the same temperature as our glycol which suggests that they may be the same. The great difference in the two sources, one animal and the other plant, however, suggests that they are different. Very few other long-chain aliphatic diols have been described [W. Karrer, "Konstitution und vorkommen der organischen Pflanzenstoffe," Birkhaeuser Verlag, Basel, 1958]; most of them are α,ω-diols.