The hydrogen uptake having slowed considerably, the catalyst was filtered and the filtrate made basic with 10% sodium hydroxide solution and extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated. Crystallization of the residue, 120 mg, from ethyl acetate yielded 85 mg of 16-isoretuline (**1a**): mp and mmp 194–202°; thin layer chromatogram and infrared and pmr spectra identical with those of the sample described above.

Retuline (3d).—A solution of 120 mg of dihydroakuammicine (**3b**)[10] in 10 ml of anhydrous ether was added dropwise with stirring to a solution of 40 mg of lithium aluminum hydride in 50 ml of ether and the mixture refluxed for 22 hr. The excess hydride was decomposed with water, whereupon 20 ml of 20% sodium hydroxide was added. The aqueous solution was extracted with ether and the combined organic extracts washed with water, dried over magnesium sulfate and evaporated. The non-crystalline residue **3a**, 91 mg, was homogeneous on thin-layer chromatography and revealed no carbonyl group in the infrared spectrum. A solution of this substance and 2 ml of acetic anhydride in 3 ml of pyridine was heated on a steam bath for 1 hr. The solution was evaporated under vacuum and an ether solution of the residue filtered through a short column of basic alumina yielding 107 mg of retuline acetate (**3c**) as pale yellow gum: pmr three-proton singlets 1.98, 2.29 ppm (acetyls Me), three-proton broad doublet 1.68 ppm (J = 6 cps) (ethylidene Me).

A solution of 97 mg of crude **3c** and 0.3 ml of 10% sodium hydroxide in 10 ml of methanol was allowed to stand at room temperature for 3 hr. Water, 4 ml, was added and the mixture concentrated to a small volume under vacuum and extracted first with ether and then with methylene chloride. The latter extract was dried over magnesium sulfate and evaporated. Crystallization of the residue from ethyl acetate gave 69 mg of a solid, 150–162°, whose recrystallizations and sublimation yielded retuline (**3d**): mp and mmp 167–173° (lit.[2] mp 165–170°); $[\alpha]_D$ +23° (c 0.7, MeOH); thin layer chromatogram and infrared and mass spectra[16] identical with those of the authentic alkaloid.[12]

Amino Alcohol 1f.—A mixture of 4.20 g of Wieland–Gumlich aldehyde (**2a**), 5 ml of 95% hydrazine and 2.0 g of powdered potassium hydroxide in 50 ml of diethylene glycol was refluxed (bath temperature *ca.* 130°) for 1.5 hr. The temperature was increased to 220° allowing excess hydrazine and water to distil off and maintained there for 6 hr. After cooling and dilution with 150 ml of water the mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated giving 4.09 g of a foam. Crystallization from ethyl acetate produced 2.30 g of crystals, mp 190–196°, whose sublimation yielded **1f**: mp 200–202°; infrared spectrum (Nujol) OH, NH 3.08 (w) μ, C=C 6.10 (vw), 6.25 (m) μ.

Anal. Calcd for $C_{19}H_{24}ON_2$: C, 76.99; H, 81.6. Found: C, 76.95; H, 8.22.

Treatment with ethanolic hydrogen chloride yielded a hydrochloride salt, mp 320° dec (crystallization from ethanol).

Anal. Calcd for $C_{19}H_{25}ON_2Cl$: C, 68.71; H, 7.57; N, 8.41. Found: C, 68.70; H, 7.66; N, 8.37.

Amine 1g.—A mixture of 1.10 g of **1f** hydrochloride, 0.5 ml of 70% perchloric acid, and 500 mg of active palladium–charcoal catalyst[8] in 75 ml of 2:1 water–acetic acid was hydrogenated at room temperature and atmospheric pressure. The hydrogen uptake ceased after 1.1 mole, whereupon the catalyst was filtered and the filtrate made basic with 10% sodium hydroxide and extracted with benzene. The extract was dried over magnesium sulfate and evaporated leaving 653 mg of residue. Crystallization of the latter from hexane–ether gave a solid, mp 163–167°, which on sublimation afforded **1g**: mp 168–170°; spectra: infrared (Nujol) NH 3.12 (m) μ, C=C 6.24 (m) μ; pmr three-proton doublet 0.93 ppm (J = 7 cps) (16-Me), three-proton pair of doublets 1.58 and 1.59 ppm (J = 7 cps) (ethylidene Me).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.20; H, 8.81; N, 10.26.

The dihydrochloride was crystallized from aqueous acetone, mp 302–303° dec.

Anal. Calcd for $C_{19}H_{26}N_2Cl_2$: C, 64.58; H, 7.42. Found: C, 64.72; H, 7.52.

(16) The authors are indebted to Dr. N. Danieli (Department of Organic Chemistry, The Weizmann Institute of Science, Rehovoth, Israel) for taking the mass spectra of natural retuline, synthetic retuline, and 16-isoretuline.

Absolute Stereochemistry of Nimbin. "Complex" Optical Rotary Dispersion of Pyronimbic Acid

H. ZIFFER, U. WEISS,

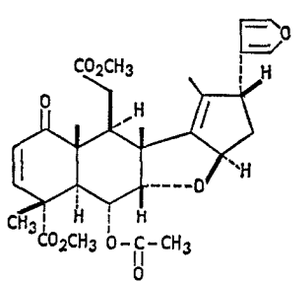
National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

G. R. NARAYANAN, AND R. V. PACHAPURKAR

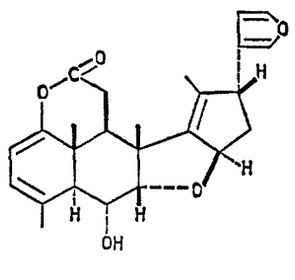
National Chemical Laboratory, Poona, India

Received March 9, 1966

The structure and relative configuration of the bitter principle nimbin (I) have recently been elucidated.[1,2]



I



II

This structure suggests a biogenetic origin through oxidative modification of a triterpenoid skeleton of the euphol type, and hence the relative stereochemistry shown in I. The available information on the absolute stereochemistry of I is given by Narayanan, *et al.*,[3] who report that the ORD curve of hexahydronimbin (double bonds in furan ring and ring A reduced) is very similar to that of cholestan-1-one, suggesting that the compound, and hence I, likewise have the $5\alpha,10\beta$ configuration. However, a recent study of the circular dichroism of cholestan-1-one[4] has shown its CD curve to be very complex, *i.e.*, composed of asymmetrically shaped negative *and* positive components of roughly the same rotational strength. As the origin of such multiple CD curves is incompletely understood, and as small shifts in the position and intensity of these CD bands could reverse the sign of the ORD curve, it was desirable to have additional evidence for the assignment of absolute configuration.

The compound of choice is pyronimbic acid (II), which contains a conjugated cisoid-diene system; the ORD of systems of this kind have been extensively investigated both theoretically and experimentally.[5] In addition to its contribution of determining the

(1) R. Henderson, R. McCrindle, and K. H. Overton, *Proc. Chem. Soc.*, 269 (1963).

(2) (a) C. R. Narayanan, R. V. Pachapurkar, S. K. Pradhan, and V. R. Shah, *Chem. Ind.* (London), 322 (1964); (b) C. R. Narayanan and R. V. Pachapurkar, *Tetrahedron Letters*, **No. 48**, 4333 (1965).

(3) C. R. Narayanan, R. V. Pachapurkar, S. K. Pradhan, and V. R. Shah, *Chem. Ind.* (London) 324 (1964).

(4) K. M. Wellman, R. Records, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 492 (1964).

(5) (a) A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *ibid.*, **83**, 4661 (1961). (b) U. Weiss, H. Ziffer, and E. Charney, *Tetrahedron*, **21**, 3105 (1965). Several examples of dienes in which one of the double bonds is enolic are given in this paper. The resulting dienes have been shown to follow the diene rules and hence the comparison with the nonenolic dienes is valid.

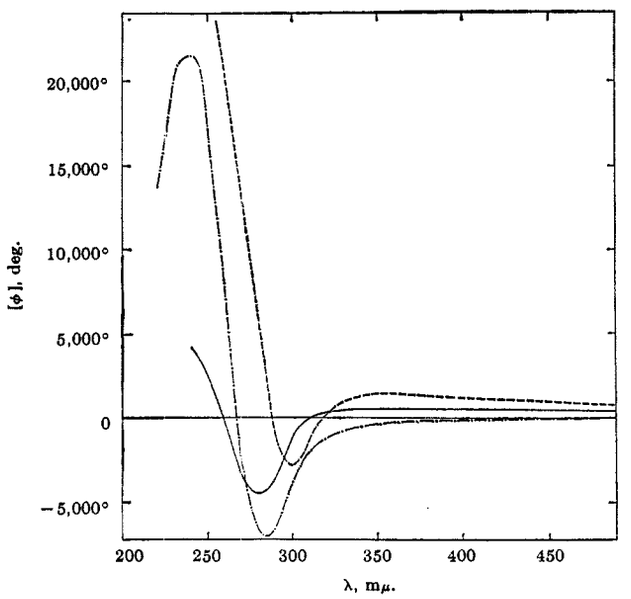


Figure 1.—1,3-Cholestadiene (III), ———; pyronimbic acid (II), - - - -; 3,17 β-diacetoxy-1,3-androstadiene (IV), - · - ·.

absolute stereochemistry of nimbin, the ORD of II is also of interest in the understanding of the "complex" curves[5b] hitherto observed exclusively in a group of steroidal 1,3-dienes. The ORD curve[6] of II is given in Figure 1 and is compared with those of 1,3-cholestadiene (III) and 3,17β-diacetoxy-1,3-androstadiene[7] (IV). Dreiding models of II with both possible *trans* configurations at the juncture of rings A and B, *i.e.*, 5α,10β and 5β,10α, show that the diene system is skewed in the sense of a left-handed helix in the former, and of a right-handed one in the latter. Consequently, theory[5] predicts a negative Cottone ffect associated with the absorption band at longest wavelength (280 mμ) for the 5α,10β configuration, and a positive one for 5β,10α. Since the ORD curve of II (Figure 1) shows a *negative* Cotton effect, the former alternative applies, and II is correctly represented by the formula shown.[8] The fact that IV exhibits the negative Cotton effect predicted from the chirality of its diene proves that the presence of an enol ester group on the chromophore does not interfere with the validity of the rules connecting this chirality with the sign of the Cotton effect. Some other examples of enolic dienes obeying these rules are given in ref 5a and b.

The ORD curves of II–IV belong to the "complex" type[5b] characterized by a relatively weak Cotton effect superimposed upon a strong background of opposite rotation. Such "complex" curves had thus far been observed consistently and exclusively with steroidal 1,3-dienes; II is the only compound found up to now to give this type of curve without actually being a 1,3-dienic steroid.

Since bicyclic compounds with the same $\Delta^{1,3}$ chromophore (compounds 2–4 of ref 5b) show intense, almost symmetrical, Cotton effects with little background influence, it is tempting to assume that the tendency to avoid a marked nonbonded interaction between the hydrogens at positions 1 and 11α in the steroid $\Delta^{1,3}$-dienes leads to a flattening of the chromophore with consequent weakening[9] of the Cotton effect. The "complex" curve of II, which lacks the proton at C-1, shows that this effect can at least not be the *only* cause for the appearance of such curves.

The large molar rotation of II at the sodium D line (+478°) *opposite* in sign to that of the Cotton effect again emphasizes the danger of using [α]D values for stereochemical assignments *even in the case of dissymmetric chromophores.*

See Table I for experimental data.

TABLE I
EXPERIMENTAL DATA

Compd	$[\Phi]_{extremum}$	$\lambda_{extremum}$ mμ	Solvent	Concn, g/100 ml
1,3-Cholestadiene	−5,000	280	Cyclohexane	0.071
	+4,200	235		
Pyronimbic acid	−2,800	302	Dichloromethane	0.049
	+23,600	255		
3,17β-Diacetoxy-1,3-androstadiene	−5,900	285	Isooctane	0.050
	+21,500	240		

(6) The ORD curves of II and IV were determined on a Cary 60 spectropolarimeter, that of III on a Rudolph recording spectropolarimeter.

(7) R. Wiechert and G. Schulz, *Chem. Ber.*, **98**, 3165 (1965).

(8) Dreiding models show that the diene system in both C-9 epimers of pyronimbic acid has the same chirality. Consequently, the sign of the Cotton effect should be the same in either case.

(9) E. Charney, *Tetrahedron*, **21**, 3127 (1965).

Conformation of the 17β Side Chain of C-20 Oxygenated Pregnane Derivatives as Determined by Nuclear Magnetic Resonance Coupling Constants[1a,b]

HWALIN LEE, NORMAN S. BHACCA, AND MANFRED E. WOLFF[1c]

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94122, and Varian Associates, Palo Alto, California

February 8, 1966

Pronounced differences in the behavior of epimeric C-20 alcohols in the Barton reaction,[2] lead tetraacetate oxidation, and other reactions used in the functionalization of C-18 have been attributed to differences in the spatial relationship to the C-18 group[3] of the reactive oxygen intermediates involved. Related differences in solvolytic reactions have been rationalized on the same basis.[4]

Attempts have been made to define these relationships using calculations based on van der Waals radii and molecular rotations.[4] More recently, Klyne[5] and Diassi[6] suggested from hydrogen-bonding studies that the conformation of the 17β side chain is such that the 20-hydrogen is usually on the same side of the steroid nucleus as the C-18 methyl group. None of these studies was able to specify the exact conforma-

(1) (a) From the Ph.D. Thesis of H. Lee, University of California, San Francisco, Calif., 1966. (b) This investigation was supported in part by a Public Health Service research Grant (AM-05016) from the National Institute of Arthritis and Metabolic Disease, U. S. Public Health Service. (c) To whom inquiries concerning this work should be addresed.

(2) *Cf.*, A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, E. Townley, P. Kabasakalian, and D. H. R. Barton, *J. Am. Chem. Soc.*, **82**, 2973 (1960).

(3) *Cf.* L. Velluz, G. Muller, R. Bardoneschi, and A. Poittevin, *Compt. Rend.*, **250**, 725 (1960).

(4) D. Glick and H. Hirschmann, *J. Org. Chem.*, **27**, 3212 (1962).

(5) J. C. Danilewicz and W. Klyne, *J. Chem. Soc.*, 1306 (1965).

(6) A. I. Cohen, B. Keeler, E. Beker, and P. A. Diassi, *J. Org. Chem.*, **30**, 2175 (1965).