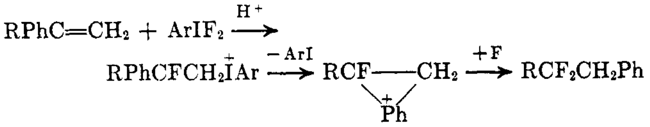
$$1 + PhCH{=}CH_2 \longrightarrow \underset{\mathbf{4}}{PhCH_2CF_2H}$$

the reaction with styrene. The structure of the product, 2,2-difluoroethylbenzene, was identified by its proton and ^{19}F nmr spectra. Again, as with 1,1-diphenylethylene, a rearrangement has occurred, probably *via* a phenonium ion intermediate. The role of



R = phenyl, H

excess hydrofluoric acid is not clear but it appears to act solely as an acid catalyst. If the solution is filtered through magnesium oxide prior to use very little reaction occurs and **1** remains unchanged. Likewise if excess pyridine is added no reaction occurs. If the hydrofluoric acid is first removed by treatment with magnesium oxide and then replaced with trifluoroacetic acid the reaction proceeds vigorously and **4** is formed in about the same yield as if hydrofluoric acid were used. Furthermore, no evidence was obtained that the trifluoroacetate ion was incorporated in the products.

Of the various aryliodosodifluorides which have been prepared, the *p*-chlorophenyliodosodifluoride is the most convenient. Its precursor, the iodosodichloride, is easily prepared in high yield and keeps well in the refrigerator. The phenyl and tolyl iodides have a tendency to become partially chlorinated on the ring during the chlorination of the iodo group. The *p*-nitrophenyliodosodichloride is not sufficiently soluble in methylene chloride to allow convenient preparation of the difluoride.

Chloroform and benzene have also been used with success in the formation of the iodosodifluorides. Saturated hydrocarbons are not good solvents. Acetonitrile and tetrahydrofuran react with the reagents.

Experimental Section

Aryliodosodichloride.—The aryliodosodichlorides were prepared according to known procedures,[5b] or adaptations thereof.

Aryliodosodifluorides.—The aryliodosodifluorides were all prepared by procedures analogous to the one shown here for *p*-chlorophenyliodosodifluoride. *p*-Chlorophenyliodosodichloride (12.3 g, 0.04 mole) and 10.8 g of finely ground yellow mercuric oxide (0.05 mole) were shaken with 100 ml of methylene chloride in a polyethylene bottle.[7] Hydrofluoric acid (48%, 10 ml) was added and the bottle shaken vigorously for about 1 min. The color of the solution turned from bright yellow to nearly colorless. In some instances a small additional amount of mercuric oxide was required to completely discharge the yellow color. The methylene chloride phase was carefully decanted. The residue was shaken with 50 ml of methylene chloride, which was then decanted and combined with the original solution. The combined solution (1 ml) was analyzed by titration of the iodine liberated by reaction with aqueous potassium iodide. From the volume of the reagent solution the yield was calculated, typically in the range of 60–90%.

1,1-Difluoro-1,2-diphenylethane.—Phenyliodosodifluoride was prepared according to directions given above with 20.9 g (0.076 mole) of phenyliodosodichloride. Iodometric analysis indicated that 0.0592 moles of the iodosodifluoride was present in the 187 ml of solution. This solution was stirred at 0° while 9.43 g (0.0524 mole) of 1,1-diphenylethylene in 35 ml of methylene chloride was added over a period of 20 min. The reaction was kept at 0° for 3 hr before being washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated to 11.3 g of dark brown viscous oil. The oil was dissolved in 100 ml of pentane and chromatographed on 50 g of alumina. In addition to iodobenzene and recovered starting material, 5.4 g (47%) of white crystals melting at 57–63° was obtained. After recrystallization from pentane they melted at 65–67°, lit.[1] mp 66°. The nmr spectrum showed peaks at τ 2.85 and 2.97 (phenyl), and τ 6.73 (CH_2), a triplet with a splitting of 0.26 ppm.

Anal. Calcd for $C_{14}H_{12}F_2$: C, 77.04; H, 5.54; F, 17.41. Found: C, 76.76; H, 5.59; F, 17.32.

1,1-Difluoro-2-phenylethane.—*p*-Chlorophenyliodosodichloride (30.95 g, 0.1 mole) was converted to the iodosodifluoride by the method described above using 200 ml of methylene chloride, 25 g of mercuric oxide, and 30 ml of hydrofluoric acid. To the decanted methylene chloride solution was added 15 g (0.14 mole) of styrene at room temperature. After 3 hr the solution was washed with aqueous sodium bicarbonate, dried by filtration through anhydrous magnesium sulfate, and concentrated to an amber oil which was then distilled. The fraction boiling at 130–150° at atmospheric pressure (11.1 g) was analyzed by gas chromatography. A 20 ft × $^3/_8$ in. column packed with 20% FS-1265 silicone fluid (10,000 cts) on Chromosorb W was maintained at 140° with a helium flow rate of 200 cc/min. 1,1-Difluoro-2-phenylethane, retention time 9.8 min, and styrene, retention time 7.1 min, were the major constituents of the mixture. A yield of 37% based on the iodosodichloride was calculated from the gc analysis by using the corrected thermal response values of all the major components. The product was collected by preparative-scale gas chromatography on the same column. The proton nmr spectrum showed bands at τ 2.83 (phenyl), τ 4.27 (terminal proton), a triplet of triplets with J = 0.95 cps for the coupling with CF_2, τ 7.01 (CH_2), a triplet of doublets with J = 0.30 cps for the coupling with CF_2. The fluorine nmr had a pair of triplets at 115 ppm relative to trichlorofluoromethane.

Anal. Calcd for $C_8H_8F_2$: C, 67.60; H, 5.67; F, 26.73. Found: C, 67.53; H, 5.73; F, 27.01.

Acid Catalysis of the Fluorination.—The preparation of *p*-chlorophenyliodosodifluoride was repeated according to directions above. The reagent solution was divided into four parts. Styrene (5 ml) in 30 ml of methylene chloride was added to the first part, and 5.0 ml of styrene in 30 ml of pyridine was added to the second part. The third and fourth parts were each treated with 5 g of magnesium oxide and filtered. Styrene (5 ml) in 30 ml of methylene chloride was added to the third part and 1.0 ml of trifluoroacetic acid and then 5.0 ml of styrene in 30 ml of methylene chloride was added to the fourth part. After 20 hr each sample was analyzed by vpc. 1,1-Difluoro-2-phenylethane was produced in 37% yield in part 1, 0% in part 2, 3% in part 3, and 32% in part 4. Samples from parts 2 and 3 released iodine with aqueous potassium iodide solution; parts 1 and 4 did not.

Acknowledgment.—The author expresses his gratitude to Dr. R. A. Henry for suggesting this research and to Donald W. Moore for nmr spectra.

(7) Wherever possible, polyethylene ware was used to avoid the decomposition of the reagent on glass surfaces.

Synthesis of Retuline

ERNEST WENKERT AND R. SKLAR[1]

Department of Chemistry, Indiana University, Bloomington, Indiana

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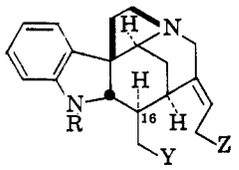
The isolation of a new alkaloid, retuline ($C_{21}H_{26}O_2N_2$), from an African *Strychnos* species was reported in 1951.[2] It was shown to lack O-methyl and N-methyl groups and its ultraviolet spectrum was reminiscent of that

(1) Public Health Service Predoctoral Fellow, 1963–1965.

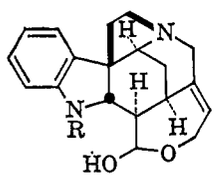
(2) J. Bosley, *J. Pharm. Belg.*, **6**, 150, 243 (1951); *Chem. Abstr.*, **46**, 2756 (1952).

of strychnine. These facts and its melting and solubility characteristics led to a later suggestion[3] of the alkaloid being tetrahydroneostrychnine.[4] However, recent proton magnetic resonance and mass spectral studies of retuline indicated structure **1a** (no stereochemistry implied) for the alkaloid.[5]



1a, R = Ac; Y = OH, Z = H
b, R = H; Y = Z = OH
c, R = Ac; Y = Z = OAc
d, R = Ac; Y = OAc, Z = H
e, R = Ac; Y = Z = OH
f, R = Y = H; Z = OH
g, R = Y = Z = H

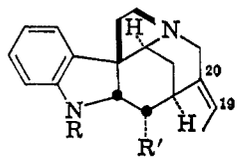
The availability of strychnoid substances from our study of the chemistry of the Wieland–Gumlich aldehyde (**2a**) prompted an investigation of the structure of retuline by synthesis. Two schemes led readily to compound **1a**. Acetylation of the aminoglycol **1b**,[6] palladium-induced hydrogenolysis of the product **1c**, and mild saponification of the resultant diacetyl derivative **1d** yielded **1a**. Alternatively, sodium borohydride reduction of diaboline (**2b**), prepared from the Wieland–Gumlich aldehyde (**2a**),[7] and hydrogenolysis[8] of the



2a, R = H
b, R = Ac

resultant amido glycol **1e** also afforded **1a**. However the synthetic amido alcohol proved to be different from retuline.

On the assumption that retuline might be the 16-epimer of **1a** this isomer was synthesized. Acetylation of the amino alcohol **3a**, prepared previously from akuamminicine[9] by zinc–acid reduction[10] and lithium aluminum hydride reduction of the dihydro product (**3b**),[11] and mild saponification of the diacyl derivative (**3c**) produced the amido alcohol **3d**. The latter was identical in all respects with retuline.[12] This establishes the stereo structure of the natural product and places the alkaloid alongside geissoschizoline (**3e**)[13] into a group of only two monomeric strychnoid bases of known 16β-hydrogen configuration.[14]



3a, R = H; R′ = CH_2OH
b, R = H; R′ = CO_2Me
c, R = Ac; R′ = CH_2OAc
d, R = Ac; R′ = CH_2OH
e, R = H; R′ = CH_2OH, 19,20-dihydro, 20α-H

Experimental Section[15]

16-Isoretuline (1a).—A solution of 342 mg of the diol **1b** and 2 ml of acetic anhydride in 5 ml of pyridine was heated on a steam bath for 1.5 hr. The solution was evaporated under vacuum and an ether solution of the oily residue filtered through a short column of basic alumina yielding 483 mg of crude **1c** as colorless gum: infrared spectrum ($CHCl_3$) C=O 5.76 (vs), 6.03 (s) μ, C=C 6.25 (w) μ. Since neither this compound nor its hydrochloride salt could be induced to crystallize, the crude salt was used directly in the next experiment.

A solution of **1c** hydrochloride (from 483 mg of crude **1c**) and 200 mg of 10% palladium–charcoal was hydrogenated at atmospheric pressure and room temperature for 1 hr at which time 1.1 moles of hydrogen had been absorbed and the gas uptake had slowed considerably. The catalyst was filtered and the solvent removed under vacuum yielding 431 mg of oily 16-isoretuline acetate (**1d**): spectra: infrared ($CHCl_3$) C=O 5.76 (s), 6.03 (vs) μ, C=C 6.25 (m) μ; pmr three-proton singlets 1.96, 2.36 ppm (acetyl Me), two-proton pair of doublets 1.57 and 1.59 ppm (J = 7 cps) (ethylidene Me), four-proton broad singlet 7.16 ppm (aromatic H). The product could not be induced to crystallize and was saponified directly.

A solution of 431 mg of **1d** in 5 ml of ethanol was made basic with 10% aqueous sodium hydroxide and then concentrated under vacuum on a steam bath until a precipitate started forming. The mixture was extracted with chloroform and the extract dried over magnesium sulfate and evaporated. Crystallization of the residue from ethyl acetate yielded 332 mg of solid, mp 175–190°. Recrystallization and sublimation afforded 16-isoretuline (**1a**): mp 197–204°; $[\alpha]D$ +128° (c 0.9, MeOH); spectra: infrared (Nujol) OH 3.15 (m) μ, C=O 6.03 (s) μ, C=C 6.23 (m) μ; pmr three-proton singlet 2.40 ppm (acetyl Me), three-proton broad doublet 1.66 ppm (J = 7 cps) (ethylidene Me), four-proton broad singlet 7.18 ppm (aromatic Hs).

Anal. Calcd for $C_{21}H_{26}O_2N_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.47; H, 7.65; N, 8.38.

A solution of crude diaboline (**2b**), prepared from 500 mg of **2a**,[7] in 25 ml of 8:2 methanol–water was treated with excess sodium borohydride. After stirring for 1.5 hr at room temperature the solution was concentrated to a small volume under vacuum and extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated and the residue, 467 mg, crystallized from ethanol–ethyl acetate. Sublimation of the crystalline solid, 310 mg, mp 244–250°, yielded **1e**: mp 248–251°; $[\alpha]D$ +145° (c 1.0, MeOH); infrared spectrum (Nujol) OH 3.04, 3.09 (w) μ, C=O 6.03 (s) μ, C=C 6.25 (m) μ.

Anal. Calcd for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.39. Found: C, 71.04; H, 7.48.

Active palladium–charcoal catalyst,[8] 150 mg, and then 5 drops of 70% perchloric acid were added to a solution of 150 mg of **1e** in 15 ml of 5:3 water–acetic acid; the mixture was hydrogenated at room temperature and atmospheric pressure for 1 hr.

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(4) O. Achmatowicz, G. R. Clemo, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 767 (1932).
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(7) J. A. Deyrup, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **45**, 2266 (1962).
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(11) M.-M. Janot, J. LeMen, A. LeHir, J. Levy, and F. Puisieux, *Compt. Rend.*, **250**, 4383 (1960).
(12) The authors are indebted to Dr. N. G. Bisset for a gift of the alkaloid.
(13) M.-M. Janot, *Tetrahedron*, **14**, 113 (1961), and references therein.
(14) Part of our study of the chemistry of the Wieland–Gumlich aldehyde (**2a**), its two-step conversion to the fully deoxygenated derivative **1g**, is included in the Experimental Section.
(15) All melting points are uncorrected. Infrared spectra were obtained on Perkin-Elmer spectrophotometers, models 21 or 137B. Proton magnetic resonance (pmr) spectra were taken on dilute deuteriochloroform solutions containing tetramethylsilane as internal standard on a Varian Associates A-60 spectrometer.

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

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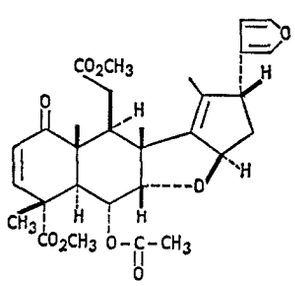
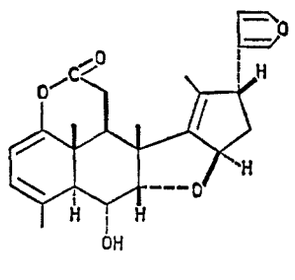
The structure and relative configuration of the bitter principle nimbin (I) have recently been elucidated.[1,2]



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

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(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.