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THE ^{1}H NMR SPECTRA OF THE STRYCHNOS ALKALOIDS RETULINE ISORETULINE, AND THEIR N-DEACETYL COMPOUNDS.

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ABSTRACT.

The 300 MHz ^{1}H NMR spectra of the title compounds are discussed. The vicinal coupling constants ^{3}J H2,H16 and ^{3}J H16,H15 are about 10 Hz and 4 Hz in the iso series, and about 7 Hz and 1 Hz for 1 and 2. In isoretuline, the piperidine ring (ring D) has a chair conformation, but in retuline a boat conformation, with C21 in the tip position, prevails. This conclusion is based on the pattern of allylic and homoallylic couplings around the double bond, and rests also on comparison with the spectrum of strychnine. Evidence is presented for a hydrogen bond between the C17 hydroxymethyl and the N1-$COCH_3$ group in isoretuline.

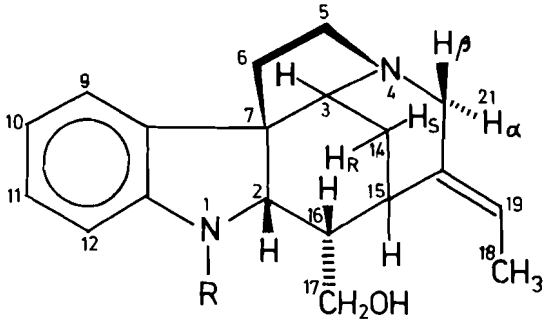
INTRODUCTION.

Retuline 1, $C_{21}H_{26}N_2O_2$, is an alkaloid of the African species Strychnos henningsii Gilg. It was first isolated by Bosly[1]. Bisset[2a] and Occolowitz[2b] deduced its structure from spectroscopic data. Wenkert, Sklar[3] and Hymon, Schmid[4] established the stereochemical details, especially the unusual 16β hydrogen configuration, by a stereospecific synthesis. More recently, two of us[5], and also French workers[6b], have demonstrated the presence of N-deacetylretuline in Strychnos variabilis De Wild. The same Strychnos species has also yielded the 16 epimer of retuline, termed isoretuline and the N-deacylated compound[7]. It now appears that retuline and isoretuline are constituent parts of dimeric alkaloids, which have lately been detected in Strychnos variabilis[8]. As part of a programme aimed at the determination of the structure of these dimeric bases, we report here on an extensive ^{1}H NMR study of retuline, isoretuline and the corresponding N-deacetyl compounds.

EXPERIMENTAL.

Retuline was available from previous research[1]. Isoretuline was prepared using the method of Wenkert, Sklar[3]. The N-acetyl group of these alkaloids was

hydrolytically removed by boiling for 4 h in 1 N hydrochloric acid. The physical constants are in agreement with literature data[6]. The ^{1}H NMR spectra were recorded on a VARIAN HR 300 MHz spectrometer, operating in the CW mode. The spectra are taken in $CDCl_3$ solution, at 18 °C. The samples were not degassed. Decoupling and INDOR experiments were performed using a SC 8525-2 unit. TMS was used as the internal standard. The chemical shifts and coupling constants were obtained by first order analysis, except for the sometimes very tightly coupled hydroxymethyl group (C17). The data are collected in the tables. Figure 1 shows the spectrum of N deacetyl retuline. The numbering of the atoms and rings is shown in the formulae. We shall occasionnally compare NMR parameters of the title compounds (1, 2, 3, 4) and of strychnine (5). For convenience, we shall apply the retuline numbering to strychnine (their conventional numberings are different). The distinct resonances of the methylene protons at C17, C4 and C6 were not completely assigned. They are denominated by the usual low field A/high field B nomenclature.



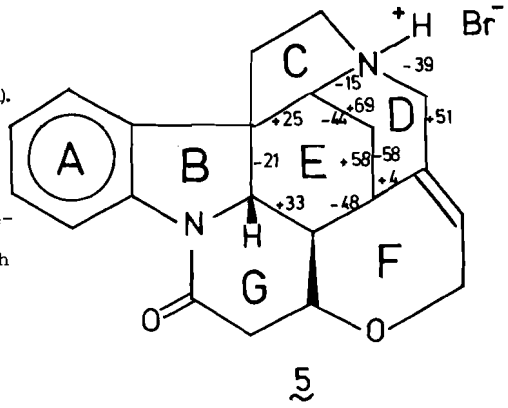
1 R = Ac Retuline

2 R = H N-deacetyl Retuline

For inverted configuration at C16

3 R = Ac Isoretuline

4 R = H N-deacetyl Isoretuline



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RESULTS and DISCUSSION.

The pentacyclic title compounds have two substituents which can assume different orientations with respect to the ring skeleton: the acetyl group on N1 and the hydroxymethyl group at C16. We shall discuss their conformation in some detail. In the polycyclic skeleton, our interest will be mainly focused on the 2-aza-bicyclo|3.3.1|system constituted by rings D and E. In general, bicyclo|3.3.1|nonane systems have a flattened double chair conformation. However, in strychnine hydrobromide - a close relative of the bases at hand - ring D oc-

curs in a boat form, as was firmly established by crystallographic methods[9].

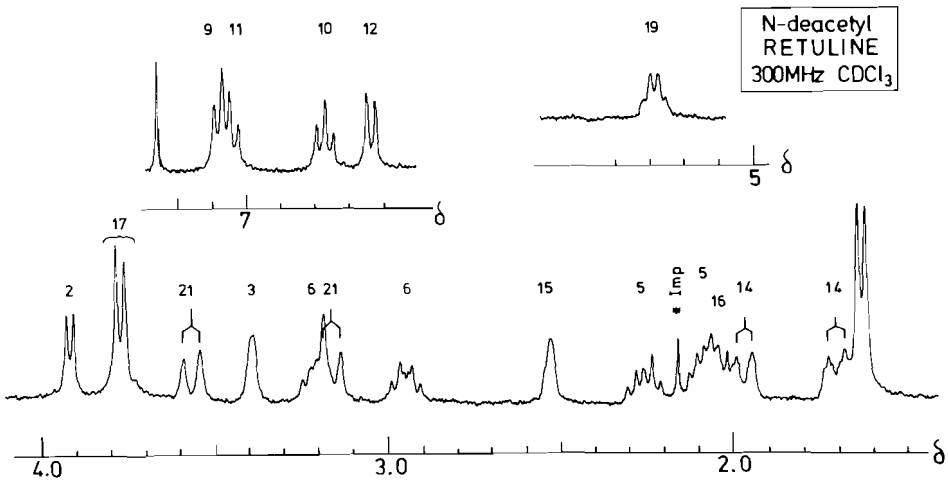
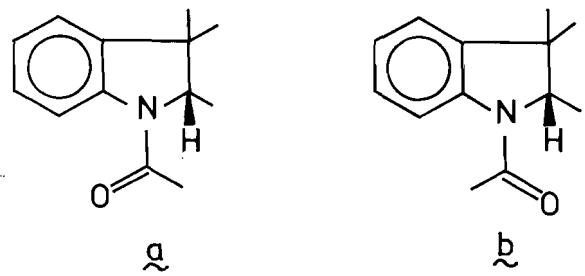


Figure 1: The ^{1}H-NMR spectrum of N-deacetyl retuline.

In 1 and 3 the restricted rotation around the N1-$COCH_3$ bond can in principle give rise to two rotamers, a, (acyl oxygen oriented towards the aromatic ring) and b. These two rotamers are easily discriminated because the amide



a b

group has a strong magnetic anisotropy[10]. The aromatic proton H12 is expected at $\delta \sim 8$ ppm in the a rotamer, and at $\delta \sim 7$ in the b rotamer. In the simple model compound N-acetyl-2,3-dihydroindole, rotamer a is the more stable one to the extent that the b form cannot even be detected by ^{1}H NMR.[11] As noted before[4], retuline exists in about 70% a and 30% b form. In contrast, isoretuline assumes almost exclusively the b conformation. There is no aromatic proton to be found around $\delta = 8$, and conversely H2 is at low field, as observed in the b

TABLE I. Chemical Shifts of N-deacetyl isoretuline (4), isoretuline (3), N-deacetyl retuline (2) and retuline (1).

	H19	H2	H3	H17A	H17B	H15	H21α	H21β	Me18	H14S	H14R	H16	H5A	H5B	H6A	H6B	NAc	H12	H10	H11	H9
4	5.47	3.46	3.48	3.67	3.52	2.70	3.43	3.03	1.57	1.94	1.72	1.78	3.15	2.81	2.53	1.84		6.63	6.75	7.04	7.05
3 rot. b	5.51	4.73	3.52	3.64	3.58	2.80	3.52	3.21	1.66	1.96	1.62	1.66	3.21	2.79	2.43	1.81	2.43	a	a	a	a
2	5.30	3.93	3.37	3.80	3.79	2.54	3.56	3.16	1.67	1.71	1.97	2.07	3.18	2.95	2.25	2.09		6.65	6.78	7.05	7.08
1 rot. a	5.44	4.12	3.85	3.38	3.12	3.05	3.76	∿2.80	1.72	∿1.60	1.93	∿2.80	3.21	∿2.80	∿1.98	∿1.58	2.30	8.08	a	7.22	a
1 rot. b	5.40	4.59	3.77	3.35	3.05	3.05	3.71	∿2.80	1.70	∿1.60	∿1.92	∿2.92					2.39	a	a	a	a

(a) between 7.05 and 7.25 δ

TABLE II. Coupling Constants (Hz) in N-deacetyl isoretuline (4), isoretuline (3), N-deacetyl retuline (2) and retuline (1).

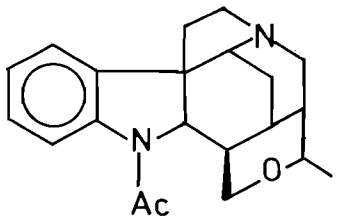
	4	3	2	1 [a]		4	3	2	1
^3J(H12,H11)	7.8		7.8	—	^4J(H15,H19)	*	*	∿0.5	**
^3J(H18,H19)	6.8	6.8	6.8	∿6.8 [b]	^2J(14S,14R)	-13.2	-13.2	-14.4	—
^3J(H2,H16)	9.5	10.4	6	7.2 [b]	^3J(14S,H15) ^3J(14S,H3)	3.3	3.3	3.0	—
^3J(H15,H16)	∿4	∿4	<1	—	^3J(14R,H15) ^3J(14R,H3)	2.7	2.7	2.5	—
^2J(17A,17B)	-10.2	-12.2	∿-11	-11 [b]	^2J(5A,5B)	-12	-12.5	-11	—
^3J(17A,H16)	5.0	4.2	∿5	5.5 [b]	^2J(6A,6B)	-13.5	-13.2	-13	—
^3J(17B,H16)	9.0	5.2	∿10	9 [b]	^3J(5A,6A)	∿8	∿7	∿7	—
^2J(21α,21β)	-13.6	-13.4	-14.6	—	^3J(5A,6B)	∿10	∿10	∿7	—
^5J(21α,H18)	0	0	∿0.5	1.5	^3J(5B,6A)	∿8	∿9	∿7	—
^5J(21β,H18)	2.0	2.0	∿0.3	∿0	^3J(5B,6B)	∿6	∿4	∿7	—
^5J(H15,H18)	0	0	*	**	ΣJ(5A)	30	29.5	∿23	—
^4J(21α,H19)	*	*	∿0.5	0	ΣJ(5B)	24.5	25	∿25	—
					ΣJ(6A)	30	30	∿28	—
^4J(21β,H19)	1.8	1.8	∿0.5	*	ΣJ(6B)	27.5	—	—	—

[a] The few coupling constants which could be obtained for 1b are within experimental error identical to those of 1a. They are not reported separately, but are identified in the table by a superscript **b**.

The negative sign of geminal coupling constants is assumed.

* Line narrowing is observed upon double irradiation, but the magnitude of the coupling constant could not be determined.

isomer of retuline. This can be attributed to a destabilization of form a by a steric inaction between the methyl of N-$COCH_3$ and the 16β-hydroxymethyl group. This is probably only part of the explanation. We find that in dimethyl sulfoxide (DMS) solvent isoretuline assumes mainly the a form. In O-acetyl isoretuline, rotamer a is present in about 10%. In other alkaloids of similar stereochemistry, such as strychnospermine (6)[10b, 12] the two rotamers are present in comparable amounts.



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We think that in isoretuline the b rotamer is stabilized by hydrogen bonding N-$C(CH_3)$=O··· HO-CH_2.

In isoretuline the coupling constants ^3J(H16,H17A) ≃ ^3J(H16,H17B) ≃ 4.5 Hz are both small. This implies that both H17A and H17B are in a gauche relation to H16, and in consequence the C17-O bond is antiperiplanar to C16-H16. The O-H bond must be near gauche to the C16-C17 bond. Indeed, ^2J(17A,17B) is -12.2 Hz. The dependency of ^2J in -CH_2OH on the rotation around the C-O bond is well researched, both theoretically and empirically[13]. The highly negative value of -12.2 Hz indicates that at most only one oxygen p lobe is parallel to a C-H bond ("parallelity effect"[13c]), the second one must bisect the H-C-H angle. Hence the O-H bond is gauche to C16-C17. Thus the sequence of torsion angles in the H16-C16-C17-O-H bonds brings the hydroxylic hydrogen close to the amide oxygen atom in 3b, and ready for participation in a hydrogen bond. The reader will have noticed a flaw in this reasoning. The magnitude of ^2J(17A,17B) establishes that the O-H and C16-C17 are gauche related. However the hydroxyl group may be oriented towards and involved in a hydrogen bond with the C19-C20 double bond. Such hydrogen bonds are well established, yet we do not think there exists one in isoretuline, because the vinylic hydrogen atoms of a double bond participating in a hydrogen bond suffer a downfield shift of about +0.2 ppm[14] which we do not observe. The chemical shifts of H19 in 1, 3 and 2, 4 are nearly

constant; yet a close approach of OH and the π bond is geometrically not possible in retuline.

In deacetyl isoretuline, a quite expected hydrogen bonding in the 1,3-aminoalcohol moiety HN1-C2-C16-C17-OH is straight forwardly deduced from the data. There is a large and a small vicinal coupling constant J(16,17)(∿9 and ∿5 Hz) indicating a gauche orientation of the bonds C17-O and C15-C16. Moreover, the low negative value of $^{2}J(17A,17B) = -10.2$ Hz shows that there must be[13] substantial eclipsing of the oxygen lone pairs with the C17 methylene. The torsion angles in the aminoalcohol moiety are such that they bring the oxygen and the nitrogen atom closely together. Using similar arguments, Bernstein and co-workers[15] have deduced hydrogen bonding in 1,3-aminoalcohols. Thus we find that in isoretuline and deacetyl isoretuline the conformation of the hydroxymethyl group is basically the same. Consonant with this conclusion is the observation that the chemical shifts in both compounds are rather similar, except of course for H2, which is strongly deshielded by the amide group in rotamer $\underset{\sim}{b}$.

In retuline and deacetyl retuline the four bond sequence H16·C16-C17-O·H must have a gauche,gauche conformation, as is shown by the magnitude of the interproton couplings of H16,H17A,H17B. Again, it is not possible to discriminate the two possible gauche conformations from the NMR data. However it seems a safe assumption that in deacetyl retuline there exists also a hydrogen bond in the 1,3 aminoalcohol part of the molecule. Now in retuline the chemical shift of H15, for both conformers $\underset{\sim}{a}$ and $\underset{\sim}{b}$, is about 0.5 ppm downfield from H15 in deacetyl retuline. This very large effect cannot be due to the too remote amide group. It is however readily explained by assuming that the C15-H15 and C17-O bond are parallel, - or otherwise stated, that H-15 is pseudo syndiaxial with the oxygen atom - in the acetylated but not in the deacylated compound. It is indeed well established that the above mentioned pseudo 1,3-diaxial relation hydrogen-oxygen induces a downfield displacement of the hydrogen atom by about +0.5 ppm[16]. The conclusion is then that gauche relations of H16·C16-C17·O in deacetyl retuline and in retuline have an opposite sign: in the free base the oxygen atom is oriented towards the nitrogen, in the amide it is oriented towards H15. This completes the description of the conformational behaviour of the mobile substituents $NCOCH_3$ and CH_2OH on the perimeter of the title compounds.

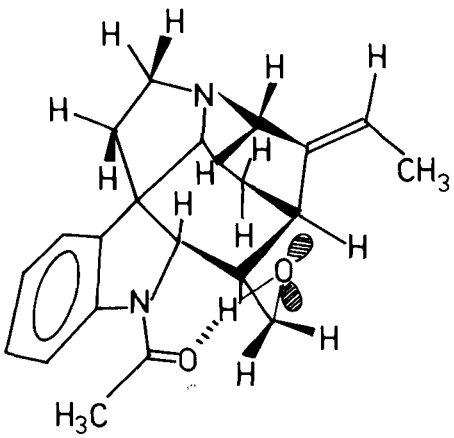
We now turn to the unsaturated aza bicyclo[3.3.1]system of rings D and E. For comparison we have calculated from the crystallographic data[9a] the ring tor-

sion angles in strychnine hydrobromide. These torsion angles are shown in formula 5. The vicinal coupling constant J(H2,H16) in retuline and isoretuline is 7.2 and 10.4 Hz respectively. Kopple[17] has developed an accurate torsion angle versus coupling constant relation for an Acyl-N-CH-CH unit. The application of the Kopple relation to J(H2,H16) yields H2-C2-C16-H16 torsion angles of 34° (retuline) and 154° (isoretuline). By assuming a trigonal projection symmetry, the torsion angle C7·C2-C16·C15 is then 34° in both alkaloids. This is precisely the angle found in crystalline strychnine hydrobromide. The J(H2,H16) in 5 amounts also to 10.47 Hz[21]. Undoubtedly the mutual agreement of the three torsion angles is partly fortuitous, but the conclusion must be that the conformation of ring E is the same in the three alkaloids. However, in the deacetyl compounds J(H2,H16) is smaller than in the N acetyl bases by about 1 Hz. This might be the result of a somewhat different torsion angle versus J relation in NH-CH-CH and in AcN-CH-CH units - we are unaware of definite data on this point - or the changes are indeed simply the result of changes in torsion angles. The latter assumption implies that deacetyl retuline would be more puckered in the C2-C16 bond than retuline, but that deacetyl isoretuline would be more flattened than isoretuline. The changes in torsion angle would be in both cases of the order of 8°. J(H16,H15) is the second vicinal coupling involving the centre (C16) where isoretuline and retuline are epimeric. This coupling constant is indeed very different for deacetyl isoretuline (about 4 Hz) and for retuline (not directly observed, 1 Hz or less). The data are consistent with C16-C15 torsion angle of 48°, as observed in strychnine.

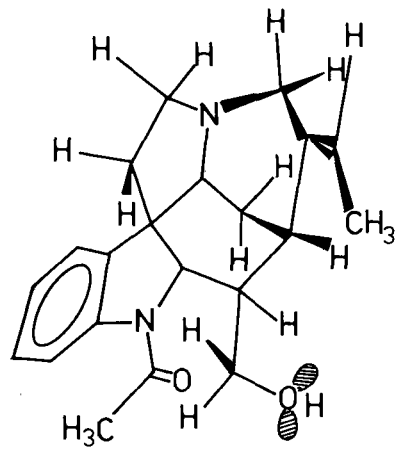
In the C15-C21-C20-C19-C18 region - the double bond and its α substituents - we have in principle at our disposal two parameters to assess the conformation (a) the stringent geometric requirements for allylic and homoallylic couplings[18] (b) the orientation dependent influence of a double bond on the geminal coupling of an α methylene[13,19]. In isoretuline and deacetyl isoretuline the upfield C21 methylene proton is the only one which is involved in substantial allylic (with H19) and homoallylic (with Me18) coupling, about 2 Hz in each case. The allylic couplings of the low field C21 methylene proton, and also of H15, are small, and homoallylic couplings could not be detected. The C-H bond of the upfield C21 methylene must be perpendicular to the plane of the double bond, the two other α C-H bonds must lie in that plane. As a consequence, the upfield C21 methylene proton is assignable as H21β. The interpretation of these coupling constants in conformational terms can only be that ring D has a chair form. Here

then the conformation of strychnine and isoretuline is different, although the configuration of the chiral centers is the same. The occurrence of a boat form in strychnine hydrobromide is a consequence of the geometric constraints imposed by the formation of ring F.

In retuline and, to a certain extent also in deacetyl retuline the long range coupling constants across the double bond are quite different from those in isoretuline. The Me(C18) resonance is a rather broad doublet. There are homoallylic couplings with H15, with the downfield resonance of the C21 methylene, and a less pronounced one with the upfield C21 methylene proton. In the Me(C18) resonance a doublet of doublet structure (J ∿ 6.8 & 1.5 Hz) becomes apparent upon irradiation of H15 (the latter feature is not observed in deacetyl retuline). Moreover, in contrast with isoretuline, there are (small) allylic couplings of H19, not only with the two C21 methylene protons, but also a substantial one with H15. The data show that the torsion angle H15-C20-C19···H19 must be fairly large. The conclusion is forced upon us that in retuline ring D



isoretuline 3b



retuline 1b

has a boat conformation. We are aware of the numerous cases in the literature where some "abnormal" or "unexpected" NMR parameters were assumed to arise from unspecified "boat" forms. It is therefore with reluctance that we make the same step, especially as there is no immediately obvious explanation why ring D should have a boat conformation. We have therefore sought corroboratory evidence. The geminal coupling in the C21 methylene in retuline is somewhat more negative (-14.8 Hz) than in isoretuline (-13.5 Hz). The coupling is influenced by the orientation of (a) the double bond (b) the nitrogen lone pair[20]. We as-

sume as a first approximation that these influences are additive (but see e.g. ref. 13a and b). Summing up these influences for the conformational change: ring D in chair form to ring D in boat form (the torsion angles C3-N4 and C15-C20 becoming zero) one finds that negative contributions from the double bond are compensated by positive shifts from the nitrogen. The C21 methylene geminal coupling is therefore not very sensitive to the described conformational change.* The more negative value of $^{2}J(C21)$ in retuline is certainly in the right trend for ring D having a boat conformation.

Recently a ^{1}H NMR study of strychnine base was published by Carter and coworkers[21]. With the restriction that in strychnine C18 is not a freely rotating methyl group, but a $-CH_2OR$ function fixed by incorporation into ring F, the pattern of long range couplings in strychnine and retuline is very similar. There are homoallylic couplings between the upfield C18 methylene proton and (a) H15 and (b) the downfield C21 methylene proton of about 2 Hz.** Allylic couplings are found between H19 and (a) the downfield C21 methylene proton (a weak one) (b) H15 (about 2 Hz)**. In addition, the downfield C21 methylene proton shows a ^{4}J long range interaction with H5B, a proton of ring C. This last coupling was assumed to arise from a W coupling path. Carter and coworkers have not discussed the conformation of ring D. The coupling data make the conclusion unescapable that it has a boat form. For, assuming a chair form of ring D how could the axial C21 methylene proton - its axial character a logical deduction from the allylic and homoallylic couplings - also show W coupling with H5 ? Therefore strychnine bromide and the free base must have ring D in essentially the same boat conformation. This is quite acceptable if one considers the formation of ring F to entail necessarily that geometry of ring D.

Stimulated by Carter's observations we have looked for and indeed detected a small long range coupling between H5B and the downfield H21 methylene proton in deacetyl retuline. In conclusion the long range coupling parameters of strychnine confirm that ring D of retuline has a boat form. The upfield C21 methylene proton can now confidently be assigned as ß.

One cannot resist speculating as to why ring D should have a chair conformation in isoretuline and a boat form in retuline. We hypothesise that the chair

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* For other boat forms, where the nitrogen atom is the top atom, a large negative shift is however observed, see the discussion of the spectrum of vallesamine in ref. 13b.

** This coupling is not reported by Carter[21], but was established by us using double irradiation techniques.

form in isoretuline is primarily the result of a destabilization of the boat form due to interaction between the C17 hydroxymethyl group and the double bond C20-C19. In this connection it would be interesting to examine the compound with a hydrogen atom instead of a hydroxymethyl group at C16. It might well have a boat conformation of ring D.

Let us now consider C14. The geminal coupling J14 is more negative in deacetyl retuline (-14.4 Hz) than in (deacetyl)isoretuline (-13.2 Hz). Not unexpectedly anymore, the values of $^{2}J(14)$ in strychnine and in retuline are identical despite the fact that C16 has the opposite configuration in the two compounds. The more negative value of $^{2}J(14)$ in retuline in comparison to isoretuline can be interpreted as the result of a smaller H-C-H angle[22] due to steric compression in the former from the C21 methylene and/or the C17 hydroxymethyl group. The assignment of the C14 methylene hydrogens is fairly straightforward. Each of these atoms is gauche to H15 and H3. The vicinal couplings constants are therefore small. However, one of the C14 methylene protons, which we denominate S*, is gauche to N4 and to H3, and as such should show an enhanced vicinal coupling constant $^{3}J(H3,H14)$[23]. Due to overlap, the individual values of J(H3,H14) and J(H15,H14) are not easy to measure. Their sum can easily be determined, and must be greater for the H14 S proton. On this basis, it is the downfield C14 methylene of isoretuline and deacetyl isoretuline, and the upfield one in retuline, which must be assigned as H14 S.
This shift inversion is due to the effect of the axial C-17 hydroxymethyl group in retuline, which displaces the γ synaxial H14 hydrogen to lower field, and simultaneously shifts the γ equatorial one upfield by about the same amount[24]. In strychnine[21] H14 S is the downfield C14 methylene proton, which fits perfectly in the above discussed situation.

It now remains to discuss briefly the pyrrolidine ring C. We have not attempted to assign the resonances. Carter and coworkers have reported, without comment, a geminal coupling of 0.02 Hz between H6A and H6B. This is erroneous. H6A and H6B are just very tightly coupled. The weak outer lines of H6A and H6B were ignored in the analysis, although two of them are clearly visible in the published spectrum[21]. We have run the spectrum of strychnine in pyridine. The shift difference of the C6 methylene becomes larger, and the weak outer lines

* The α,β nomenclature cannot be used for the C14 methylene hydrogens. In a sense, both are α. We have employed the IUPAC nomenclature for prochiral atoms to denominate them, using for brevity R and S instead of pro-R and pro-S.

are now stronger. We measured a quite unexceptional geminal coupling constant of -12.8 Hz, in good agreement with the approximate data for the title compounds.

Note added in proof: When this work was finished there appeared a report[25] on the NMR parameters (^{1}H and mainly ^{13}C) of isoretuline (not of retuline). The conclusions of the authors in regard to the conformation of ring D are consonant with ours. However, they sometimes write retuline when isoretuline is meant. Confusion is the result.

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