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THE INDENOBENZAZEPINE-SPIROBENZYLISOQUINOLINE REARRANGEMENT; STEREOCONTROLLED SYNTHESES OF (±)-RADDEANINE AND (±)-YENHUSOMINE

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Stereoselective rearrangement of indenobenzazepine cis ketols 2 and 5 with TFAA in pyridine produces spirobenzylisoquinolines 3 and 6, respectively. The latter product is also obtained by rearrangement of trans ketol 7. The transformation of ketols 5 and 7 must, therefore, proceed through the intermediacy of aziridinium cation 9. A similar process obtains in the transformation of 2 to 3. $NaBH_4$ reduction of 3 gives (±)-raddeanine (4). Rearrangement of diol 10 supplies 4 directly. (±)-Yenhusomine (13) is obtained from the rearrangement of either diol 11 or 12. In like fashion, diols 14 and 15 supply spirobenzylisoquinoline 17.

In the wake of the establishment of the new structure 1 for fumarofine,[3] we became interested in investigating the chemistry of this unusual indenobenzazepine ketol. A prime concern was to determine whether an aziridinium cation could be formed by taking advantage of the vicinal relationship between the nitrogen atom and the tertiary alcohol at C-14. Treatment of O-methylfumarofine (2)[3] with trifluoroacetic anhydride (TFAA) in pyridine at room temperature overnight, followed by ammonium hydroxide work-up, supplied in excellent yield (86%) spirobenzylisoquinoline 3, $C_{21}H_{21}O_6N$, mp 171-173° (EtOAc), νmax ($CHCl_3$) 1710 and 3550 cm^{-1}, whose stereochemistry at C-13 was established by virtue of the downfield nmr chemical shift (δ5.41) of H-13. Consonant with this steric assignment, sodium borohydride in methanol reduction of 3 proceeded with approach of the reagent from the less hindered syn or nitrogen side of the molecule to give rise to (±)-raddeanine (4), mp 218-220° (MeOH) (lit.[4] mp 219-220°), which occurs in Corydalis ledebouriana K. et K. (Fumariaceae).[5]

In a similar vein, TFAA treatment of the known cis ketol 5[6] supplied spirobenzylisoquinoline 6 (85%), mp 190-191° (MeOH) (lit.[7] mp 191-192°), which had previously been prepared by a non-stereospecific route from a synthetic phthalideisoquinoline.[7]

In order to gain some insight into the mechanism of this new indenobenzazepine-spirobenzylisoquinoline rearrangement, the trans fused synthetic ketol 7[6] was also treated with TFAA under identical conditions. The product, isolated in 91% yield, proved to be again the spirobenzylisoquinoline 6. Sodium borohydride reduction of this material led to spiro diol 8, $C_{21}H_{23}O_6N$, mp 187-188° (EtOAc), formed by selective hydride addition to the syn side of the molecule. It follows that the stereochemistry of the B/C annelation of the starting indenobenzazepine ketol has no direct bearing on the course of its rearrangement into a spirobenzylisoquinoline.

The transformation of indenobenzazepine ketols 5 and 7 must, therefore, proceed through the intermediacy of aziridinium cation 9. Nucleophilic attack of hydroxide anion at C-13 then results in fission of the N-7 to C-13 bond with inversion at C-13 to form spiro alcohol 6. A similar process must obtain in the transformation of O-methylfumarofine (2) into spirobenzylisoquinoline 3.

The next phase of the present investigation was to study the course of the rearrangement of indenobenzazepines hydroxylated at both C-13 and 14. For this purpose, it was necessary to have on

hand a series of indenobenzazepine diols of established stereochemistry. The cis diol 10 was available from the osmium tetroxide oxidation carried out in the course of the synthetic sequence that had led to O-methylfumarofine (2).[3] A very minor product (2%) of this same oxidation was the alternate cis diol 11, $C_{21}H_{23}O_6N$. Additionally, sodium borohydride in methanol reduction of O-methylfumarofine (2)[3] proceeded with neighboring group participation to supply amorphous trans diol 12, $C_{21}H_{23}O_6N$.

When cis diol 10 was rearranged using TFAA in pyridine, (±)-raddeanine (4) was again obtained. Significantly, however, rearrangement of either cis glycol 11 or O-methyldihydrofumarofine (12) provided amorphous (±)-yenhusomine (13), $C_{21}H_{23}O_6N$, an alkaloid known only in the dextrorotatory form and found in C. ochotensis Turcz.[5,8]

The rearrangement of diol 10 must, therefore, proceed through the intermediacy of an aziridinium cation similar to 9. The initial secondary hydroxyl group at C-13 is, of course, trifluoroacetylated by the reagent. However, during the basic work-up, facile ester hydrolysis ensues with regeneration of the free hydroxyl with retention of configuration in the resulting spirobenzylisoquinoline.

The above stereochemical conclusions were further reinforced by the rearrangement of diol 14, $C_{21}H_{23}O_6N$, mp 148-150° (EtOAc), formed by sodium borohydride reduction of the known ketol 5,[6] and thus a stereochemical analog of O-methyldihydrofumarofine (12);[3] and diol 15, $C_{21}H_{23}O_6N$, mp 201-202° (EtOAc), obtained from the sodium borohydride reduction of the known bridged compound 16.[6] These two diols differ only at C-14, so that their rearrangement should lead to the identical material. Indeed, this was found to be the case when amorphous spirobenzylisoquinoline 17, $C_{21}H_{23}O_6N$, was the only product isolated.

A singular feature of naturally occurring spirobenzylisoquinolines is that in all cases where a hydroxyl group is located at C-13, this function lies on the anti side of the molecule, i.e. on the side opposite the nitrogen atom.[5] The present indenobenzazepine rearrangement also leads without exception to spirobenzylisoquinolines possessing an anti C-13 hydroxyl group. There is thus a possibility that the rearrangement of indenobenzazepines may be relevant to spirobenzylisoquinoline biogenesis, and may be responsible for the stereospecific formation of C-13 hydroxylated alkaloids in the latter series. In such a sequence, a spirobenzylisoquinoline bearing a ketone at C-8 (e.g. parfumine, parfumidine or fumariline) would undergo oxidative rearrangement[3] to an indenobenzazepine ketol which could then be reduced non-stereospecifically to a diol. Rearrangement of the diol as delineated above would supply a spirobenzylisoquinoline hydroxylated at C-8 (syn or anti) and at C-13 (anti), such as raddeanine (4), yenhusomine (8), or ochrobirine.[9] Selective oxidation at the less hindered hydroxyl would then provide spirobenzylisoquinolines incorporating a ketone at C-13 and a hydroxyl at C-8. An alternate and equally plausible hypothesis for the formation of C-8 and C-13 dioxygenated spirobenzylisoquinolines is that they originate from an intermediate such as 18 which can undergo intramolecular aldol condensation to produce spirobenzylisoquinoline 19. Such a species could then undergo reduction from the less hindered syn side to supply an alkaloid bearing an anti hydroxyl at C-13.

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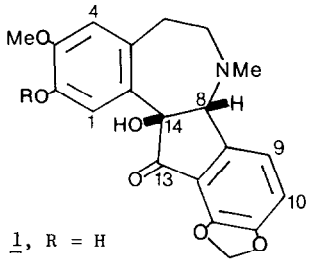

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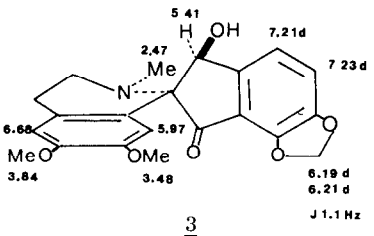
2, R = Me



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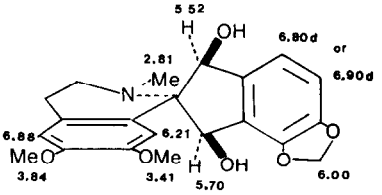

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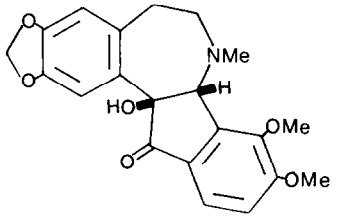

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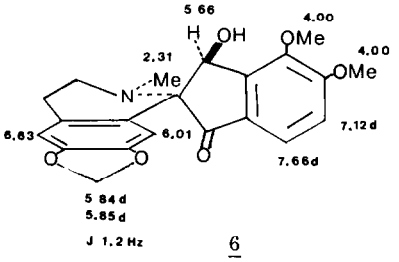

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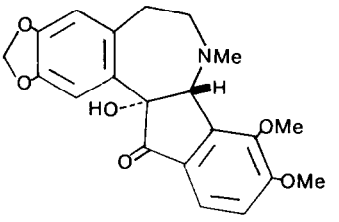

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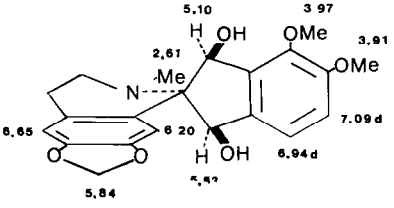

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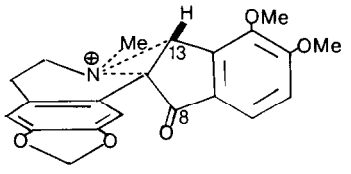

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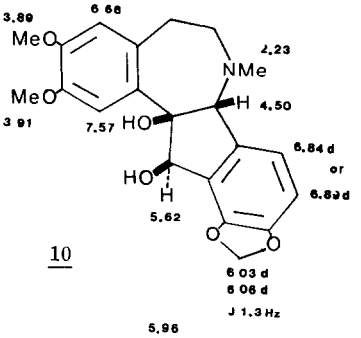

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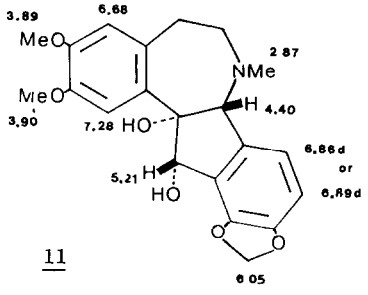

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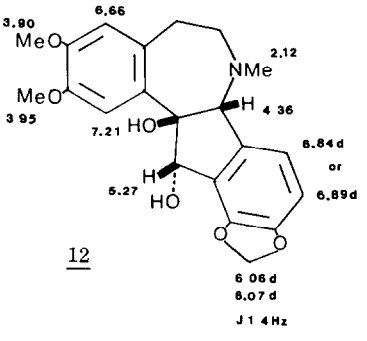

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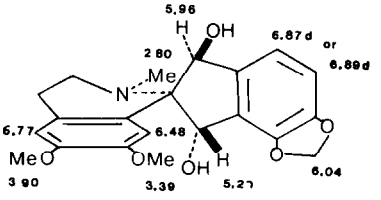

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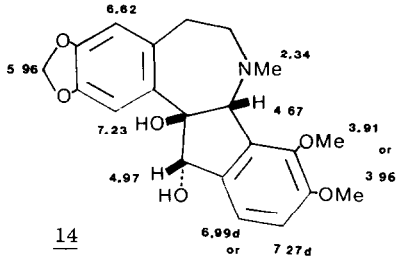

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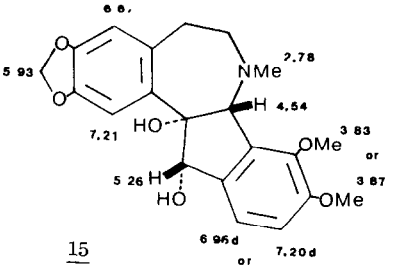

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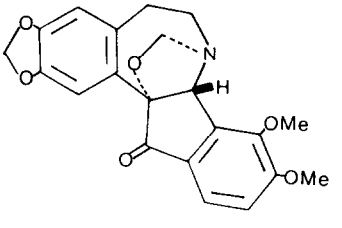

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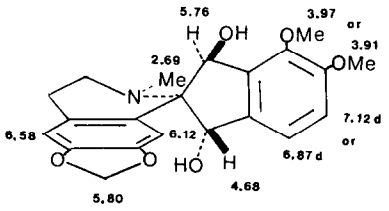

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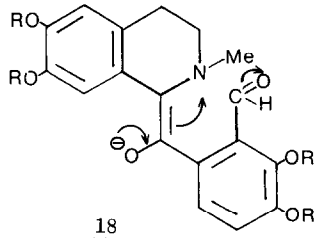

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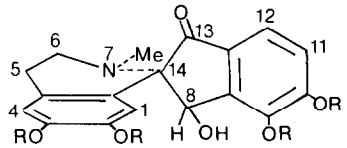

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References and Footnotes[10,11]

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2. Permanent address: Faculty of Pharmacy, University of Ankara, Ankara, Turkey.
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10. Thin layer chromatography on Merck Silica Gel F-254 glass plates in CH_2Cl_2-MeOH (80:20 v/v) showed the following R_f values: 3, 0.72; 4, 0.28; 8, 0.33; 10, 0.66; 11, 0.55; 12, 0.47; 13, 0.18; 14, 0.63; 15, 0.37; and 17, 0.27. Ultraviolet spectroscopy is not of particular significance since all indenobenzazepine diols and spirobenzylisoquinoline diols in question in methanol solution show a peak of medium intensity between 284-288 nm, a shoulder at 225-232 nm, and terminal absorption near 210 nm. All nmr spectra are at 360 MHz (FT) in $CDCl_3$. The relevant chemical shifts are shown on the structural diagrams. Unless otherwise indicated, all absorptions are singlets. The coupling constants for the ortho protons in ring D of the indenobenzazepines and spirobenzylisoquinolines in question are in the range of 8.0 to 8.5 Hz. It is important to point out that in the case of such highly polar spiro diols as 4 and 8, which are subject to hydrogen bonding, the chemical shifts for H-8 and H-13 are concentration dependent, so that values recorded in the literature[4,8] at 60 MHz do not correspond with those presently obtained at high dilution using a 360 MHz (FT) spectrometer. For the sake of uniformity, the numbering system for the reduced indenobenzazepines follows that adopted for the aromatic indenobenzazepines lahorine and lahoramine, see G. Blaskó, S.F. Hussain, A.J. Freyer and M. Shamma, Tetrahedron Lett., in press.
11. All compounds are racemates.

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