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THE PHOTOCHEMISTRY OF PROAPORPHINES: A NEW ROUTE TO THE APORPHINES

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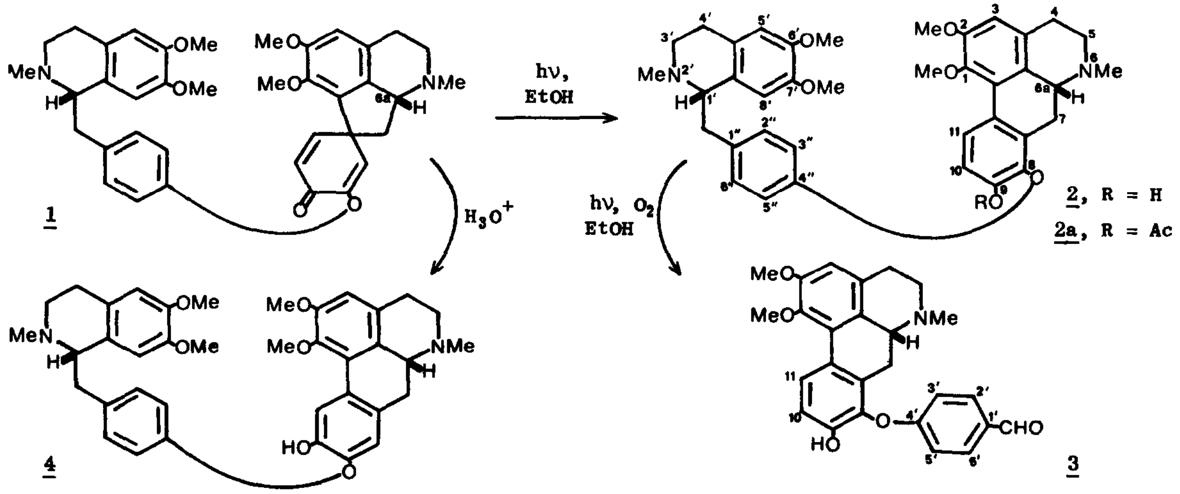
Proaporphines undergo light catalyzed rearrangement. Pakistanamine (1) is thus converted into lumipakistanine (2), while pronuciferine (7) and N-acetylnorpronuciferine (8) afford the corresponding C-9 hydroxylated aporphines 9 and 10. Possible biogenetic schemes for the formation of C-8-, C-9-, and C-8,9-substituted aporphines are presented.

Although several light catalyzed preparations of proaporphines are available, no photo reactions of proaporphines have been recorded in the literature.[3] Since it is well known that dienones undergo an interesting series of light catalyzed transformations,[4] an ethanolic solution (75 mL) of 100 mg of pure pakistanamine (1), the only known proaporphine-benzylisoquinoline alkaloid,[5] was subjected to sunlight under a nitrogen atmosphere for 48 hours.[6] Separation of the products by TLC provided 13 mg of the hitherto unknown lumipakistanine (2), $C_{38}H_{42}N_2O_6$, mp 112-114° C (ether), $[\alpha]^{25}_{D}$ +117° (c = 0.5, EtOH), λ^{EtOH}_{max} 220 sh and 282 nm (log ε 4.87 and 4.55); ms m/e 621 $(M-1)^+$, 416, 310, 206 (base) and 190. Characteristically, the nmr spectrum of 2 incorporates an H-11 doublet at δ8.20, while H-10 is evidenced by a doublet at δ6.99.[5] Unreacted 1 (72 mg) was also present, so that the yield of the lumi product based upon recovered starting material is 46%. A minor product, isolated in trace amount, is the oily new aporphinoid neolumipakistanine (3), $C_{26}H_{25}NO_5$, ms m/e 431 $(M)^+$, 416, 400 (base), 388, 357 and 312, which could also be obtained by direct sunlight irradiation of an ethanolic solution of lumipakistanine (2) (Scheme I).[6,7]

Acetic anhydride in pyridine acetylation of lumipakistanine furnished amorphous 9-O-acetyllumipakistanine (2a), $C_{40}H_{44}N_2O_7$, $\nu^{CHCl_3}_{max}$ 1760 cm^{-1}, ms m/e 663 $(M-1)^+$, 458, 416, 309, 266, 206 (base) and 190. Significantly, the H-11 absorption in the nmr spectrum of 2a is downfield at δ8.28d and H-10 is at δ7.11d.[8]

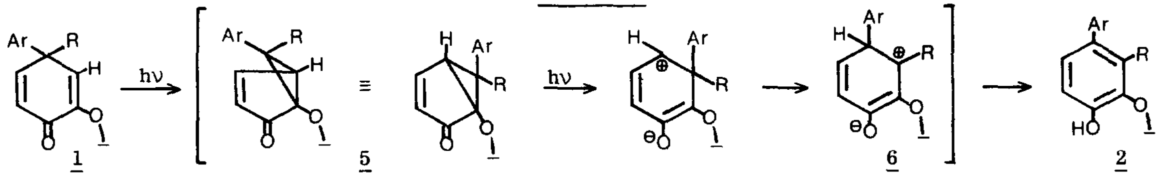
Scheme I



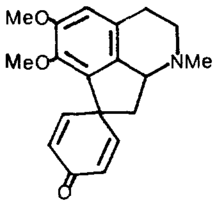
The generation of lumipakistanine (2) by photolysis of pakistanamine (1) should be compared to the known formation of 1-O-methylpakistanine (4) through acid catalyzed dienone-phenol rearrangement of 1 (Scheme I).[5] *Prima facie*, it appears, therefore, as if aryl migration occurs during the acid catalyzed process, whereas the alternate alkyl migration takes place as a result of photolysis.

The genesis of lumipakistanine (2) can actually be understood in terms of a sequence of two distinct photochemical processes. Initial formation of the bicyclo [3.1.0] hexenone 5 is followed by a second light catalyzed reaction which results in aryl migration to give 6 (Scheme II).[9-13]

Scheme II



To prove the generality of the present light catalyzed rearrangement of proaporphines, ethanolic solutions of (±)-pronuciferine (7) and (±)-N-acetylnorpronuciferine (8) were subjected to sunlight for 16 hours. Following TLC, 7 provided a 10% yield of 1,2-dimethoxy-9-hydroxyaporphine (9), $C_{19}H_{21}NO_3$, mp 220° C (MeOH), λ_{max}^{EtOH} 213, 235 sh and 280 nm (log ε 4.17, 3.91 and 3.84); while 8 produced a 10% yield of N-acetyl-1,2-dimethoxy-9-hydroxynoraporphine (10), $C_{20}H_{21}NO_4$, mp 296-297° C (MeOH), λ_{max}^{EtOH} 214, 233 sh and 283 nm (log ε 4.02, 3.71 and 3.63). Both transformations must proceed through the intermediacy of a bicyclohexenone such as 11. Light catalyzed rearrangements are thus a general feature of the reactivity of proaporphines, regardless of the state of aggregation of the molecule (monomeric or dimeric) and the degree of basicity of the nitrogen atom.



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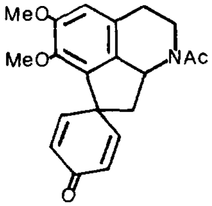

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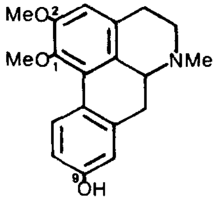

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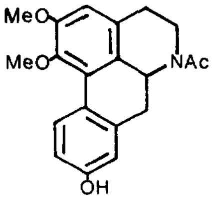

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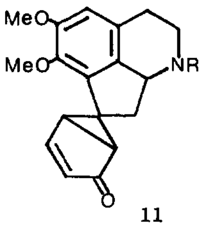
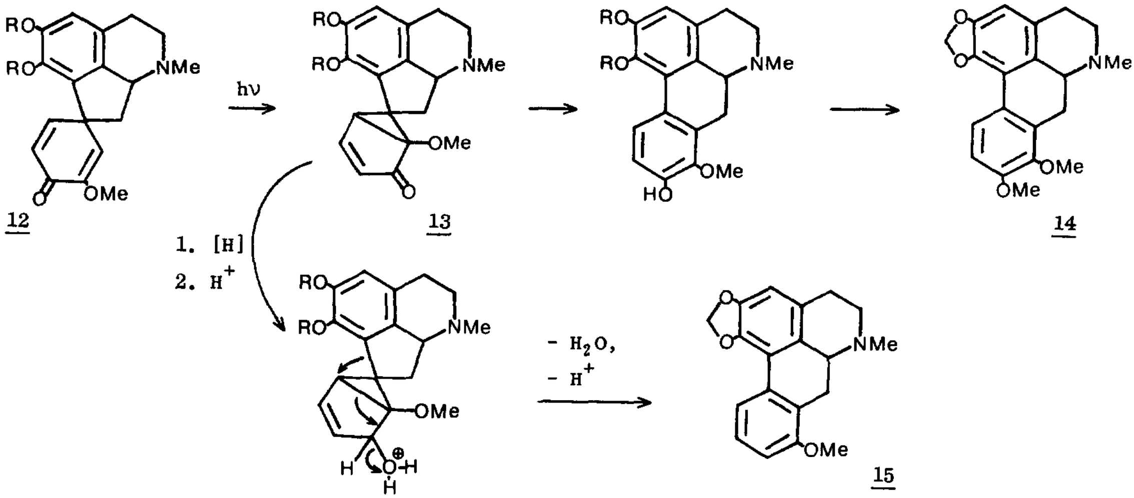


11

The biogenesis of aporphines substituted in ring D only at C-9, such as anolobine, roemeroline, xylopine and isolaureline has never been adequately explained previously since their formation via a classical type acid catalyzed dienone-phenol rearrangement of a simple proaporphine would entail alkyl rather than the usually preferred aryl migration.[14] It is possible that at least some of these alkaloids may be formed by a light catalyzed rearrangement of a simple proaporphine with subsequent aryl migration, as exemplified by the above conversion of pronuciferine (7) to aporphine 9.

It can thus be stated that the substitution pattern of an aporphine in ring D is an indication of the specific biogenetic route which applies. An 8,9-substituted aporphine such as crebanine (14) is most likely formed in nature by photo rearrangement of proaporphine 12 to afford bicyclohexenone 13, followed by aryl migration and then O-methylation.[15] On the other hand, stephanine (15), which is substituted only at C-8, could be generated by reduction of the carbonyl of 13, succeeded by aryl migration with concomitant loss of water, and finally aromatization as shown in Scheme III.

Scheme III



NMR Data at 200 MHz (FT) in $CDCl_3$ with TMS as Internal Standard

Compound 2: δ2.29s and 2.49s (2x3H, N-6 and N-2' CH_3, respectively), 3.63s, 3.70s, 3.83s and 3.88s (4x3H, C-7', C-1, C-6' and C-2 CH_3O, respectively), 6.78d and 6.98d (2x2H, H-3" and 5", and H-2" and 6", J = 8.8 Hz), 6.10s, 6.55s and 6.59s (3x1H, H-8', H-5' and H-3, respectively), 6.99d and 8.20d (2x1H, H-10 and 11, respectively, J = 8.8 Hz).

Compound 2a: δ2.09s (3H, CH_3CO), 2.35s and 2.54s (2x3H, N-6 and N-2' CH_3, respectively), 3.62s, 3.71s, 3.83s and 3.89s (4x3H, C-7', C-1, C-6' and C-2 CH_3O, respectively), 6.75d and 7.00d (2x2H, H-3" and 5", and H-2" and 6", J = 8.7 Hz), 6.08s, 6.56s and 6.65s (3x1H, H-8', H-5' and H-3, respectively), 7.11d and 8.28d (2x1H, H-10 and 11, respectively, J = 8.5 Hz).

Compound 3: δ2.23s (3H, NCH_3), 3.72s and 3.89s (2x1H, C-1 and C-2 CH_3O, respectively), 6.61s (1H, H-3), 7.05d and 7.86d (2x2H, H-3' and 5', and H-2' and 6', J = 8.8 Hz), 7.04d and 8.26d (2x1H, H-10 and H-11, respectively, J = 8.8 Hz).

Compound 9: δ2.55s (3H, NCH_3), 3.64s and 3.88s (2x3H, C-1 and C-2 CH_3O, respectively), 6.59s (1H, H-3), 6.74-6.80m (2H, H-8 and 10), and 8.26d (1H, H-11, $J_{10,11}$ = 8.1 Hz).

Compound 10: δ2.29s (3H, CH_3CO), 3.67s and 3.90s (2x3H, C-1 and C-2 CH_3O), 5.10dd (1H, H-6a, $J_{6a,7cis}$ = 4 Hz, and $J_{6a,7trans}$ = 14 Hz), 6.61s (1H, H-3), 6.82dd (1H, H-10, $J_{8,10}$ = 2.7 Hz and $J_{10,11}$ = 8.5 Hz), 6.90d (1H, H-8, $J_{8,10}$ = 2.7 Hz) and 8.31d (1H, H-11, $J_{10,11}$ = 8.5 Hz).

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References and Notes

1. Permanent address: PCSIR Laboratories, Peshawar, Pakistan.
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3. For a review of the photolytic routes to proaporphines, see M. Shamma and J.L. Moniot, *Isoquinoline Alkaloids Research, 1972-1977*, Plenum Press, N.Y. (1978), pp. 118-119.
4. The photochemistry of dienones has been the subject of annual reviews by W.M. Horspool in *Specialist Periodical Reports*, *Photochemistry*, The Chemical Society, London.
5. M. Shamma, J.L. Moniot, S.Y. Yao, G.A. Miana and M. Ikram, *J. Am. Chem. Soc.*, **95**, 5742 (1973).
6. The pakistanamine (**1**) used in the present study was isolated from the roots of *Berberis calliobotrys* Bienert, ex Aitch. (Berberidaceae), in which it is one of the major alkaloids. The plant was collected in the Chitral region of Pakistan. Pakistanamine is best purified by applying an acetone solution of the crude picrate salt directly on a TLC plate, and eluting with benzene-chloroform-diethylamine (5:4:1). The main alkaloidal band, R_f 0.44, is extracted with methanol, and the solvent gently removed *in vacuo*. The residue is taken up in ether, and the ether evaporated again *in vacuo*, with the minimum application of heat, to furnish for the first time the alkaloid in a crystalline state, mp 93-94° C. The yield of lumipakistanine (**2**) falls drastically when even slightly impure pakistanamine (**1**) is used in the photolysis. The R_f value for lumipakistanine in the same solvent system is 0.24, and that for neolumipakistanine (**3**) is 0.11. All TLC was on Merck F-254 silica gel plates. The nitrogen gas used in the photolysis was not deoxygenated.
7. Photolytic oxidation of tetrahydrobenzylisoquinolines is known to result in cleavage of the C-1 to C-α bond with formation of a substituted benzaldehyde from ring C; see I.R.C. Bick, J.B. Bremner and P. Wiriyachitra, *Tetrahedron Lett.*, 4795 (1971).
8. The corresponding downfield shift for H-11 upon O-acetylation of 1-O-methylpakistanine (**4**) to 1-O-methyl-10-O-acetylpakistanine is 0.11 ppm; see Reference 5 above.
9. According to the Woodward-Hoffmann rules, the initial photochemical process leading to bicyclohexenone **5** would be classified as a ($\sigma^2 a + \pi^2 a$) Class A cycloaddition, see R.B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim (1970), pp. 89-92.
10. An alternate mechanism has been offered to explain the formation of the bicyclohexenone intermediate; see H.E. Zimmerman, *Angew. Chem., Internat. Edit.*, **8**, 1 (1969).
11. The photochemistry of dienones has been extensively studied; see D.I. Schuster, G.C. Barile and K.-c. Lin, *J. Am. Chem. Soc.*, **97**, 4441 (1975), and references cited therein.
12. Another case of the generation of a phenol from photolysis of a dienone is that offered by Z. Horii, M. Aoi, Y. Hayashi and C. Iwata, *Chem. Commun.*, 210 (1972).
13. Since no bicyclohexenone **5** was isolated, the exact steric course of the photo reaction leading to this intermediate cannot be determined, and the stereochemistry of pakistanamine (**1**) about the spiro center cannot be deduced from the chemistry described here.
14. For a complete listing of aporphines, see H. Guinaudeau, M. Leboeuf and A. Cavé, *J. Natural Products*, **42**, 325 (1979), and references cited therein.
15. The rearrangement of a bicyclohexenone intermediate with aryl migration to supply an aporphine may proceed in nature by either a photochemical or an acid catalyzed pathway.

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