REACTIONS OF HARMALINE AND ITS DERIVATIVES, VII, SYNTHESIS OF 11-METHOXY INDOLOQUINOLIZIDINES BY PHOTOCHEMICAL CYCLIZATION OF ENAMINE INTERMEDIATES

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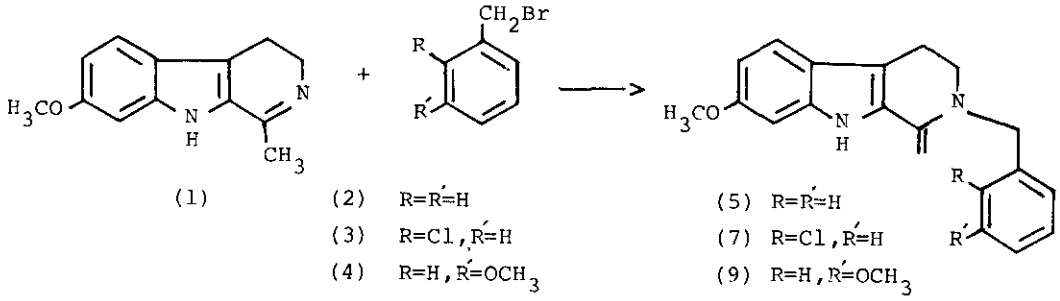
Abstract — Reactions of harmaline with benzyl halide and their ring substituted analogues affords enamine intermediates, photocyclization of which results in the formation of reserpine analogues in high yields. The procedure thus provides a synthetic approach to pharmacologically interesting substances from readily accessible precursors.

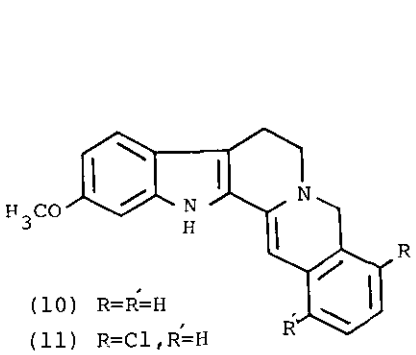
We have previously demonstrated the existence of an imine-enamine equilibrium in harmaline (1),[1-3] a major indole alkaloid from the seeds of Peganum harmala,[4-5] and used it for the synthesis of indoloquinolizidines and derivatives of indole alkaloids of medicinal repute.[1-3,6-10] Due to a rapid tautomeric equilibrium of the olefinic bond both N- and C-alkylations were found to occur.

In continuation of these studies, harmaline was allowed to react with excess of benzyl bromide (2), o-chlorobenzyl bromide (3) and 3-methoxybenzyl bromide (4) in refluxing 1:1 methanol-benzene. After several hours harmaline was found to be converted into two faster moving products, possessing a green flourescence. The products were isolated from the reaction mixture by column chromatography and their respective spectral data identified them as the monoalkylated products (5), (7) and (9) obtained in 50-55% yields and the dialkylated products (6), obtained in 15-20% yield, and (8) which was formed in low yields.

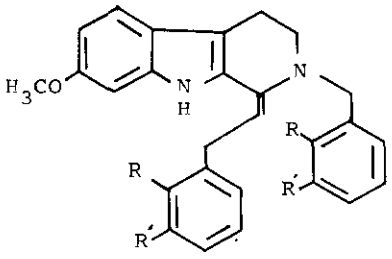
The enamine intermediates (5),(6),(7) and (9) when irradiated in dichloromethane, for 1-7 hours with a medium pressure mercury lamp afforded the corresponding cyclized products (10),(11),(12) and (13) in good yields (80-85%). The spectral data of all the products is tabulated in Table 1.



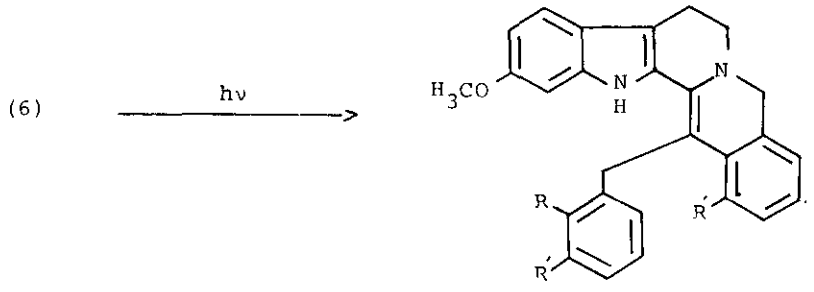
(1) (2) R=R′=H (3) R=Cl, R′=H (4) R=H, R′=OCH_3 (5) R=R′=H (7) R=Cl, R′=H (9) R=H, R′=OCH_3



(10) R=R′=H (11) R=Cl, R′=H (12) R=H, R′=OCH_3



(6) R=R′=H (8) R=Cl, R′=H



(13) R=R′=H

Table-1. Melting Points and Spectral Data

No.	M.P. (°C)	IR (KBr) $\nu_{max.}$ (cm^{-1})	U.V. (MeOH) (i) $\lambda_{max.}$ nm (ii) $\lambda_{min.}$ nm	N.M.R. (δ)	M.S. (70 ev) M/e relative intensity
5.	110	1630(C=C) 3440(N-H)	(i)215,288,314,327 (ii)275,299,322	($CDCl_3$) 3.05(m,4H,CH_2CH_2N-) 3.80(s,3H,OCH_3) 5.11 (broad s,2H,=CH_2)	304.1593 (M^+,$C_{20}H_{20}N_2O$),291, 213,200,187,170,169,156,144, 143,106,96,91,77
6.	106-110	1630(C=C)	(i)217,262,404 (ii)247,300	(d_6-DMSO) 3.95(s,3H,OCH_3) 5.98(broad s,1H,=CH)	394.2042(M^+,$C_{27}H_{26}N_2O$),303, 291,210,96,94,91,82,80,77,65
7.	112-114	1630(C=C) 3420(N-H) 810(C-Cl)	(i)220,262,400 (ii)245,295	($CDCl_3$) 3.85(s,5H,OCH_3,ϕ-CH_2N) 5.2(s,2H,=CH_2)	338.1184(M^+,$C_{20}H_{19}N_2OCl$),327, 325,303,227,214,212,200, 197,125
8.*	226	1630(C=C) 800(C-Cl)	(i)221,262,406 (ii)248,300	-	427.1562(M^+,Cl,$C_{27}H_{24}N_2O_2$), 337,325,303,301
9.	90	1640(C=C)	(i)220,263,398 (ii)245,294	($CDCl_3$) 3.09(m,4H,CH_2CH_2N-) 3.85(s,6H,2OCH_3) 3.88(m,2H,ϕCH_2N) 5.1(broad s,2H,=CH_2)	334.1682(M^+,$C_{21}H_{22}N_2O_2$),332, 321,213,199,187,172,121,91, 801,65
10.	150-152	1635(C=C) 3420(N-H)	(i)214,255,335 (ii)227,291	(d_6-DMSO) 3.9(s,3H,-OCH_3) 5.95(s,1H,=CH)	302.1442(M^+,$C_{20}H_{18}N_2O$),213, 206,169,143,126,103,91,77, 69,60
11.	178	3400(N-H) 800(C-Cl)	(i)212,255,337 (ii)231,292	(d_6-DMSO) 3.5(s,3H,OCH_3) 6.06(s,1H,=CH)	336.1024(M^+,$C_{20}H_{17}N_2OCl$),212, 197,169,160,127,125,106,99, 91,89,69,63
12.	98	1640(C=C)	(i)212,227,255,336 (ii)219,236,294	($CDCl_3$) 3.76(s,3H,OCH_3) 5.0(s,1H,=CH)	332.1527(M^+,$C_{21}H_{20}N_2O_2$),212, 169,168,122,121,104,91,77,69
13.	234-238	1630(C=C) 3400(N-H)	(i)213,257,338 (ii)233,295	(d_6-DMSO) 3.95(s,3H,OCH_3)	392.1895(M^+,$C_{27}H_{24}N_2O$),302, 301,205,211

Compound (8) was obtained in very low yields, so an n.m.r. could not be recorded

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