# Mannich Bases from 1,2-Diphenylindolizine: Ephedrine and Methamphetamine as Amine Components

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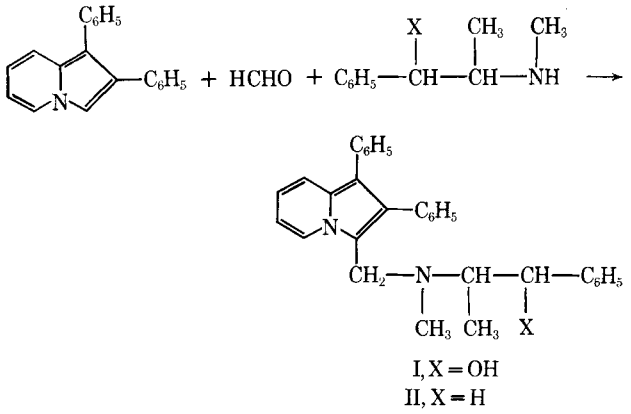
**Abstract** □ Two unique Mannich bases derived from 1,2-diphenylindolizine have been synthesized. Ephedrine and methamphetamine were employed as the secondary amine components in the syntheses. Both products showed an initial marked CNS depression. The activity of the methamphetamine derivative was reversed after 1.5 hr. to a pronounced CNS stimulation.

**Keyphrases** □ Mannich bases—synthesis □ 1,2-Diphenylindolizine—Mannich bases, synthesis □ Ephedrine, methamphetamine—amine components, Mannich reaction □ CNS activity—1,2-diphenylindolizine derivatives

It has been established in these laboratories, as a result of a continuing search for indolizines with useful biological activity, that certain 3-dialkylaminomethyl derivatives of 1,2-diphenylindolizine were potent CNS depressants (1). It was a natural curiousity that prompted the consideration of compounds with established CNS stimulant activity as secondary amine components in the synthesis of Mannich bases of this type. 1,2-Diphenyl-3-[*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylaminomethyl]indolizine (I) and 1,2-diphenyl-3-[*N*-(1-methyl-2-phenylethyl)-*N*-methylaminomethyl]indolizine (II) were synthesized from 1,2-diphenylindolizine using ephedrine and methamphetamine, respectively, as the secondary amine components in the Mannich reaction (2) (Scheme I).



I, X = OH
II, X = H

*Scheme I*

## EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analysis of I was provided by Weiler and Strauss Microanalytical Laboratory, Oxford, England. The analysis of II was performed by Galbraith Laboratories, Knoxville, Tenn. The parent indolizine employed in the synthesis of the Mannich bases was 1,2-diphenylindolizine (3, 4).

**Spontaneous Motor Activity**—A preliminary evaluation of the activity of these compounds on the CNS was carried out in the following manner. The compounds were dissolved in one part *N,N*-dimethylacetamide, diluted with nine parts water, and injected intraperitoneally in mice (Swiss white, random bred, 20–30 g.) in dosages of 5 mg./kg. body weight. Spontaneous motor activity was measured in a photoelectric cell activity cage and run against controls injected with solvent only. Both I and II showed strong CNS depressant activity. However, the animals were easily aroused and did not lose their righting reflex during this period. After approximately 1.5 hr., II showed a marked reversal of activity. The spontaneous motor activity increased significantly above that of the controls. This stimulation is presumably due to the metabolic release of the methamphetamine moiety. No significant stimulation was observed with I after 4 hr. A more extensive pharmacological study of these compounds will be carried out and the results will be reported.

**1,2-Diphenyl-3-[*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylaminomethyl]indolizine (I)**—To a 125-ml. conical flask was added 0.75 ml. of 40% aqueous formaldehyde (0.01 mole), 2.48 g. of L-ephedrine (0.015 mole), and 30 ml. of *N,N*-dimethylformamide. The mixture was allowed to stand at −5° for 48 hr. At this point 1.35 g. of 1,2-diphenylindolizine (0.005 mole) was added to the flask and the mixture stirred at room temperature for 72 hr. The reaction solution was nearly saturated with water and stirring was continued for 24 hr., during which the product crystallized out. The yield was 1.7 g. (76%). On recrystallization from acetone–water the compound gave m.p. 157–158°. The compound gave a negative color test with *p*-dimethylaminobenzaldehyde indicating that substitution had occurred at the C-3 position (5).

*Anal.*—Calcd. for $C_{31}H_{30}N_2O$: C, 83.37; H, 6.77; N, 6.27. Found: C, 83.29; H, 6.61; N, 6.15.

**1,2-Diphenyl-3-[*N*-(1-methyl-2-phenylethyl)-*N*-methylaminomethyl]indolizine (II)**—Methamphetamine hydrochloride, 6.2 g. (0.033 mole), was converted to the free base and transferred to a 250-ml. conical flask. To the flask was added 1.5 ml. of 40% aqueous formaldehyde (0.02 mole) and 70 ml. of *N,N*-dimethylformamide. The flask was stoppered and allowed to stand at −5° for 48 hr. To the mixture was added 2.7 g. of 1,2-diphenylindolizine (0.01 mole). The reaction mixture was refrigerated for 96 hr. with occasional agitation. The product crystallized out on saturation with water. The yield was 3.6 g. (83%) of fluorescent yellow crystals. Upon recrystallization from acetone–water the product gave m.p. 141–142°. The compound gave a negative color test with *p*-dimethylaminobenzaldehyde.

*Anal.*—Calcd. for $C_{31}H_{30}N_2$: C, 86.47; H, 7.02; N, 6.51. Found: C, 86.20, H, 7.02; N, 6.49.

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