former and *Pseudomonas* sp. for the latter. The sampling plan of MIL-STD-105-D is used for the statistical evaluation of the membranes for acceptance or rejection.

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Mannich Bases from 2-Phenylindolizines I

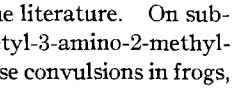
3-Alkyl-1-dialkylaminomethyl Derivatives

By WILLIAM B. HARRELL* and ROBERT F. DOERGE

In a search for new therapeutic agents, a series of Mannich derivatives of 3-methyl-2-phenylindolizine and 3-ethyl-2-phenylindolizine has been prepared. The mechanism by which 2,3-disubstituted indolizines participate in the Mannich reaction has been examined and alternate S_N1 and S_N2 routes have been proposed. 1-Diethylaminomethyl-3-methyl-2-phenylindolizine has been tested and found to have central nervous system depressant activity.

MANY PHYSIOLOGICALLY active compounds have the indole nucleus in their structure. The similarity between the indole and indolizine nuclei has prompted speculation that indolizine analogs of biologically important indoles could conceivably have potent physiological activity (1–3). It is this concept, coupled with the observation that only a few such investigations had been reported in this area, that encouraged the consideration of the indolizine nucleus for the present investigation.

Reports on the biological activity of indolizines are indeed very scarce in the literature. On subcutaneous injection 1-acetyl-3-amino-2-methylindolizine was shown to cause convulsions in frogs, mice, and rabbits (4). β-(1-Indolizinyl)-α-aminopropionic acid, the indolizine analog of the amino acid tryptophane, has been prepared (2) and shown to inhibit indole formation by an indole-accumulating mutant of *Salmonella typhimurium* (5). A series of arylindolizines was synthesized by Venturella for pharmacological testing (3, 6, 7), but to date no report on the activity of these compounds has appeared in the literature.

Having decided upon the indolizine structure, attention was focused on the various possibilities of chemical modification which might logically be expected to produce physiologically active compounds. Among the biologically active indoles, many are aminoalkyl derivatives such as serotonin, bufotenine, psilocin, reserpine, and lysergic acid diethylamide, all of which are known to have pronounced activity on the central nervous system. It was noted that in all of these compounds, the indole nitrogen and the extra-indole nitrogen are separated by four carbon atoms  , a spatial arrangement which might be a contributing factor in determining their activities. It was therefore reasoned that certain aminoalkylindolizines with the same carbon spread between the nitrogens might also possess activity on the central nervous system. After considering several possible chemical modifications, the Mannich reaction was chosen because the resulting dialkylaminomethyl substituent, when introduced at the C-1 position, would give the desired intramolecular spread. A comparison between bufotenine (I) and the Mannich bases (II) obtained by the reaction of 2,3-disubstituted indolizines with formaldehyde and dimethylamine illustrates this similarity.

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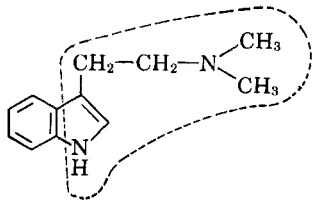
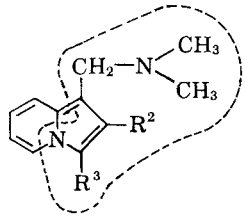
* Fellow of the American Foundation for Pharmaceutical Education, 1963–1964 and 1965–1966. National Science Foundation Science Faculty Fellow, 1964–1965. Present address: Department of Pharmaceutical Chemistry, School of Pharmacy, Texas Southern University, Houston.



I



II

The purpose of this investigation was to synthesize several 1-substituted Mannich bases derived from selected 2-phenylindolizines to be evaluated for possible activity on the central nervous system. If interesting activity was found, a study of the relationship of chemical structure with activity would be conducted.

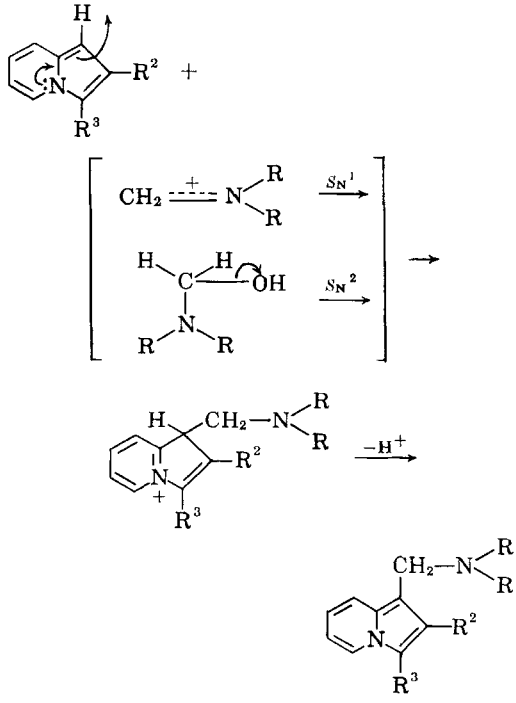
Preliminary pharmacological data were obtained for 1-diethylaminomethyl-3-ethyl-2-phenylindolizine (IV*b*). When injected in mice as a suspension in gum acacia, the compound exerted a depressant action on the central nervous system. The approximate LD_{50} was determined and found to be in the range of 70–100 mg./Kg. These compounds will be investigated more extensively and the results reported elsewhere.

DISCUSSION

The indolizines employed in this investigation were 3-methyl-2-phenylindolizine (III) and 3-ethyl-2-phenylindolizine (IV). These compounds were prepared by the Chichibabin synthesis (8) which involves condensing α-picoline with the appropriate phenacyl bromide and heating the resulting picolinium bromide in aqueous sodium bicarbonate.

There have been only two reports in the literature on the synthesis of Mannich bases from indolizines. Rossiter and Saxton obtained 2,3-dimethyl-1-dimethylaminomethylindolizine as an unstable oil using glacial acetic acid as the solvent (9). Carbon and Brehm (2), employing the same reaction conditions, prepared 3-acetyl-1-dimethylaminomethylindolizine. The present investigators, however, found that the acid conditions employed by these two groups gave undesirable results when applied to 2-phenylindolizines. Before proceeding further, it was considered advisable to examine more closely the mechanics of the Mannich reaction (10) with the hope that a set of reaction conditions could be devised that would be more favorable than those previously described in the literature.

The mechanism by which indolizines participate in the Mannich reaction has not been previously discussed in the literature, although several mechanisms have been proposed for the participation of ketones and other active hydrogen compounds (11–18). While most of the more prominent theories propose that the reaction results from a nucleophilic attack on a species of the type $(R_2N{=}CH_2)^+$ or $R_2N{-}CH_2OH$, the nature of the attacking nucleophile has not been clearly defined. According to Cummings and Shelton (14), two possibilities exist with ketones: attack by a carbanion of the type $R{-}\overset{O}{\overset{\|}{C}}{-}CH_2^-$, enhanced by running the reaction in basic medium, and attack by the enol form $R{-}\overset{:OH}{\overset{|}{C}}{=}CH_2$, which seems to be favored in acid medium. The present authors observed that ionization of indolizines in the presence of base is not likely to occur at the C-1 or C-3 position, the positions which are involved in the Mannich reaction, because of the high electron density at these positions (19, 20). It was also observed that, if such a carbanion should exist, it would be highly unstable due to the lack of resonance-stabilization. Since the enamine nature of indolizines has been observed (21) and because the similarity of enamines to enols is well established, the authors propose that indolizines participate in the Mannich reaction either by an S_N1 or S_N2 mechanism. (Scheme I.)



Scheme I

An important side reaction which can cause interference if conditions are not carefully controlled is the condensation of the indolizine with formaldehyde to form bis(indolizinyl)methanes. As a further means of control, the authors prepared bis(3-ethyl-2-phenyl-1-indolizinyl)methane (VI) and bis(3-methyl-2-phenyl-1-indolizinyl)methane (V) by reacting the corresponding indolizine with formalde-

hyde in the absence of a secondary amine. These are new compounds and the methods of synthesis are reported under *Experimental*. The compounds and their pertinent analytical data are given in Table I.

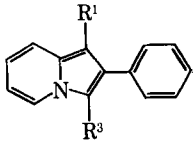
EXPERIMENTAL

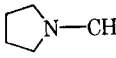
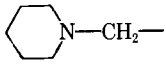
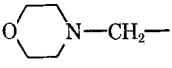
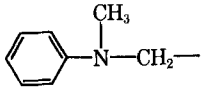
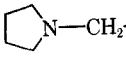
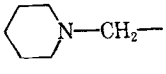
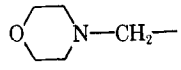
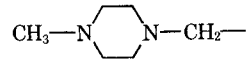
All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were provided by Weiler and Strauss Microanalytical Laboratory, Oxford, England. Preliminary pharmacological screening was performed by Dr. Robert Brummett, Department of Pharmacology, University of Oregon Medical School, Portland, Oreg.

Materials.—The preparation of 3 - methyl - 2 - phenylindolizine and 3-ethyl-2-phenylindolizine has been previously reported in the literature (22, 23).

Preparation of Mannich Bases.—The following general procedure was employed in the synthesis of these compounds. The formaldehyde (0.05 mole) and the secondary amine (0.05 mole) were combined and allowed to stand at room temperature for 15 min. The mixture was then added to a solution containing the indolizine (0.01 mole) dissolved in 30

TABLE I.—MANNICH BASES PREPARED



Compd.	Empirical Formula	R^1	R^3	M.p.	Yield, %	Recrystn. Solvent	Anal., % Calcd.	Found
III*a*	$C_{18}H_{20}N_2$	$(CH_3)_2NCH_2$-	CH_3-	66–67°	86	Acetone–water	C, 81.78 H, 7.63 N, 10.60	C, 81.72 H, 7.71 N, 10.65
III*b*	$C_{20}H_{24}N_2$	$(C_2H_5)_2NCH_2$-	CH_3-	81–82°	89	Dioxane–water	C, 82.15 H, 8.27 N, 9.58	C, 82.36 H, 8.42 N, 9.34
III*c*	$C_{20}H_{22}N_2$		CH_3-	102–104°	89	Dioxane–water	C, 82.72 H, 7.64 N, 9.65	C, 82.45 H, 7.49 N, 9.40
III*d*	$C_{21}H_{24}N_2$		CH_3-	104.5–106.5°	90.5	Dioxane–water	C, 82.85 H, 7.95 N, 9.20	C, 82.79 H, 8.08 N, 9.05
III*e*	$C_{20}H_{22}N_2O$		CH_3-	133–134°	78	Dioxane–water	C, 78.40 H, 7.24 N, 9.14	C, 78.14 H, 7.31 N, 8.97
III*f*	$C_{23}H_{22}N_2$		CH_3-	131–132°	82.8	Acetone	C, 84.63 H, 6.79 N, 8.58	C, 84.60 H, 6.90 N, 8.47
IV*a*	$C_{19}H_{22}N_2$	$(CH_3)_2NCH_2$-	C_2H_5-	65.5–66.0°	87	Acetone–water	C, 81.97 H, 7.97 N, 10.06	C, 82.02 H 8.02 N, 10.15
IV*b*	$C_{21}H_{26}N_2$	$(C_2H_5)_2NCH_2$-	C_2H_5-	56–57°	80	Ethanol	C, 82.31 H, 8.55 N, 9.14	C, 82.16 H, 8.65 N, 9.21
IV*c*	$C_{21}H_{24}N_2$		C_2H_5-	78–79°	76	Ethanol	C, 82.85 H, 7.95 N, 9.20	C, 82.89 H, 8.04 N, 9.13
IV*d*	$C_{22}H_{26}N_2$		C_2H_5-	101–102°	79	Ethanol	C, 82.97 H, 8.23 N, 8.80	C, 83.07 H, 8.38 N, 8.80
IV*e*	$C_{21}H_{24}N_2O$		C_2H_5-	78–79°	75	Ethanol	C, 78.72 H, 7.55 N, 8.74	C, 78.88 H, 7.55 N, 8.81
IV*f*	$C_{22}H_{27}N_3$		C_2H_5-	117–118°	76	Acetone–water	C, 79.24 H, 8.16 N, 12.60	C, 79.05 H, 8.24 N, 11.96

ml. dioxane. The reaction flask was stoppered and allowed to stand at room temperature for 24 hr. In most instances the product crystallized on evaporation of the solvent under a stream of cold air accompanied by vigorous scratching with a glass rod. In cases where no crystallization occurred on evaporation, the residual oil was taken up in a minimum quantity of alcohol or acetone and placed in the freezing compartment of the refrigerator. The product crystallized after remaining in the refrigerator for periods ranging from 5 days to 3 weeks. The preparation of 3-ethyl-2-phenyl-1-pyrrolidinomethylindolizine is described in the following section and is typical of the experimental procedures employed.

3-Ethyl-2-phenyl-1-pyrrolidinomethylindolizine (IVc).—To 30 ml. *p*-dioxane was added 5.34 Gm. pyrrolidine (0.075 mole) and 6 ml. of 37% aqueous formaldehyde (0.075) mole and the resulting solution allowed to stand at room temperature for 15 min. To this mixture 3.3 Gm. 3-ethyl-2-phenylindolizine (0.015 mole) was added, and the flask was swirled until a clear solution was obtained. The reaction mixture was then set aside at room temperature for 24 hr. The clear solution containing the product was poured into an evaporating dish and cold air was blown across the surface to remove the solvent. Crystallization of the product occurred upon scratching the walls of the container with a glass rod during the evaporation process. The product was removed by filtration, recrystallized from ethanol, and yielded 3.5 Gm. (76%), m.p. 78–79°.

Bis(3 - methyl - 2 - phenyl - 1 - indolizinyl)methane (V).—Ten milliliters of 37% aqueous formaldehyde (0.125 mole) and 3 Gm. 3-methyl-2-phenylindolizine (0.015 mole) were dissolved in 30 ml. dioxane and the mixture was allowed to stand at room temperature for 48 hr. Crystallization of the product commenced after the first 24 hr. At the end of the 48-hr. period, 20 ml. of water was added in 5-ml. portions over a 2-hr. interval to complete crystallization. Rapid addition of the water tended to cause precipitation of an oil. The flask was allowed to stand an additional 24 hr. in the refrigerator. The crystalline product was then filtered and washed with 50% ethanol. The yield was 2.7 Gm. (87%), m.p. 162–163° dec. The product was recrystallized from hot acetone–water.

Anal.—Calcd. for $C_{31}H_{26}N_2$: C, 87.29; H, 6.14; N, 6.57. Found: C, 86.84; H, 6.14; N, 6.65.

Bis(3-ethyl-2-phenyl-1-indolizinyl)methane (VI).—Three milliliters of 37% aqueous formaldehyde (0.037 mole) and 1 Gm. 3-ethyl-2-phenylindolizine (0.0045 mole) were dissolved in 10 ml. of glacial acetic acid and the mixture was allowed to stand at room temperature for 48 hr. An equal volume of water was then added and the solution was made slightly basic with ammonium hydroxide. The gritty precipitate was filtered, washed with distilled water, and air dried. The product was dissolved in a minimum amount of hot ethyl acetate and, after cooling, was placed in the freezer compartment of the refrigerator. Crystallization occurred after 2 days in the refrigerator. The yield was 0.71 Gm. (70%), m.p. 106–107°.

Anal.—Calcd. for $C_{33}H_{30}N_2$: C, 87.19; H, 6.65; N, 6.16. Found: C, 87.29; H, 6.70; N, 6.20.

SUMMARY

Twelve new Mannich bases and two new bis-(indolizinyl)methanes derived from two indolizines have been synthesized. One of the compounds, 1 - diethylaminomethyl-3-methyl-2-phenylindolizine, has been tested and found to have CNS depressant activity.

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