New Compounds: Mannich Bases from 2-Phenylindolizines II. 3-Dialkylaminomethyl Derivatives

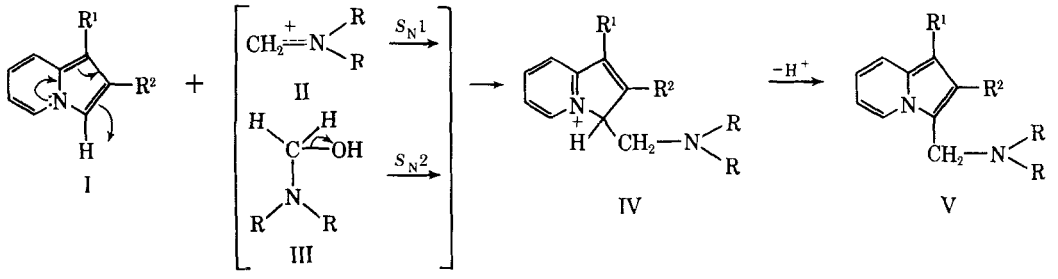
By WILLIAM B. HARRELL* and ROBERT F. DOERGE

In continuing the search for new therapeutic agents in the indolizine series, eight new Mannich bases derived from 1,2-diphenylindolizine have been synthesized. In addition, 1-(2-hydroxyethyl)-2-phenylindolizine, a new indolizine, and its 3-pyrrolidinomethyl derivative have been synthesized. The mechanism by which 1,2-disubstituted indolizines participate in the Mannich reaction has been discussed and alternate S_N1 and S_N2 routes have been proposed.

IN A PREVIOUS PAPER (1) the authors described the synthesis of a series of Mannich bases with the dialkylaminomethyl substituent at the C-1 position of the indolizine ring. The purpose of this investigation was to continue the search for useful therapeutic agents by synthesizing a series of 3-dialkylaminomethyl-1,2-diphenylindolizines. Eight new compounds were prepared in this series. In addition, a new indolizine, 1-(2-hydroxyethyl)-2-phenylindolizine, was synthesized and its 3-pyrrolidinomethyl derivative was prepared by the Mannich reaction (2). These compounds are currently being evaluated for possible activity on the central nervous system. If interesting activity is found, a study of the relationship of chemical structure with activity will be conducted.

DISCUSSION

The successful preparation of Mannich bases derived from indolizines in which the dialkylaminomethyl substituent occurs at the C-3 position has not been reported previously in the literature. In part I of this study the authors proposed a mechanism by which indolizines, based on their eneamine nature (3), participate in the Mannich reaction to form the 1-dialkylaminomethyl derivatives. Scheme I illustrates how this mechanism can be expanded to include the preparation of Mannich bases with the dialkylaminomethyl substituent occurring at the C-3 position. Alternate S_N1 and S_N2 routes are proposed.



Scheme 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. Results of pharmacological screening will be reported elsewhere.

Materials—The starting indolizines were prepared by the Chichibabin synthesis (4) which involved condensing phenacyl bromide with the appropriate 2-substituted pyridine and heating the resulting pyridinium bromide in aqueous sodium bicarbonate. The preparation of 1,2-diphenylindolizine (I) has been reported previously (5).

Preparation of Mannich Bases from 1,2-Diphenylindolizine—The following general procedure was employed in the synthesis of these compounds. A mixture containing formaldehyde (0.05 mole), the secondary amine (0.05 mole), and 20–30 ml. of *N,N*-dimethylformamide (DMF) was stirred with a magnetic stirrer at room temperature for 30 min. The indolizine (0.01 mole) was then dissolved in the mixture and stirring was continued for 2 to 3 hr. In all cases except one, the product crystallized out during the stirring process. In the case of the 3-morpholinomethyl derivative, crystallization occurred after allowing to stand at room temperature for 24 hr. The preparation of 3-diethylaminomethyl-1,2-diphenylindolizine is described in the following section and is typical of the experimental procedures employed.

3 - Diethylaminomethyl - 1,2 - diphenylindolizine—To a 125-ml. conical flask equipped with a Teflon coated magnetic stirrer was added 4 ml. of 37% aqueous formaldehyde (0.05 mole), 3.7 Gm. diethylamine (0.05 mole), and 20 ml. DMF, and the mixture was stirred at room temperature for 30 min. To the mixture was added 2.7 Gm. 1,2-diphenylindolizine (0.01 mole) and stirring was continued for 3 hr. The product began to crystallize about 1 hr. after the addition of the indolizine.

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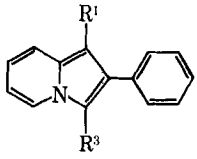
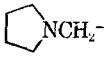
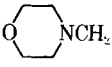
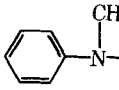
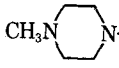
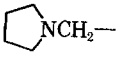
TABLE I—MANNICH BASES PREPARED



No.	Empirical Formula	R¹	R³	M.p., °C.	Yield, %	Recrystn. Solvent	Anal., % Calcd.	Found
I*a*	$C_{23}H_{22}N_2$		$(CH_3)_2NCH_2$—	140–141	95	Ethanol	C, 84.63 H, 6.79 N, 8.58	84.09 7.45 8.58
I*b*	$C_{25}H_{26}N_2$		$(C_2H_5)_2NCH_2$—	114.5–115.5	87.5	Acetone–water	C, 84.71 H, 7.39 N, 7.90	84.32 7.35 7.82
I*c*	$C_{27}H_{30}N_2$		$[(CH_3)_2CH]_2NCH_2$—	123–124	58	Acetone–water	C, 84.77 H, 7.90 N, 7.32	84.43 7.85 7.22
I*d*	$C_{25}H_{24}N_2$			143–144	85	Acetone–water	C, 85.19 H, 6.86 N, 7.95	85.81 6.92 6.81
I*e*	$C_{26}H_{26}N_2$			128–129	90	Acetone–water	C, 85.21 H, 7.15 N, 7.64	85.18 7.17 7.55
I*f*	$C_{25}H_{24}N_2O$			141–142	78.5	Acetone–water	C, 81.49 H, 6.57 N, 7.60	81.20 6.54 7.45
I*g*	$C_{28}H_{24}N_2$			162–163	85	DMF–water	C, 86.56 H, 6.23 N, 7.21	85.80 6.25 7.98
I*h*	$C_{26}H_{27}N_3$			36–137	84	Ethyl acetate	C, 81.85 H, 7.13 N, 11.01	82.00 7.09 10.70
II*a*	$C_{21}H_{24}N_2O$	$HOCH_2CH_2$—		122–124	62	DMF–water	C, 78.72 H, 7.55 N, 8.74	78.65 7.54 8.72

Upon completion of the crystallization, the flask was placed in the refrigerator overnight. The product was filtered, washed with 25% ethanol, recrystallized from hot ethanol, and yielded 3.1 Gm. (87.5%), m.p. 114.5–115.5°.

Anal.—Calcd. for $C_{25}H_{26}N_2$: C, 84.71; H, 7.39; N, 7.90. Found: C, 84.32; H, 7.35; N, 7.82.

2 - (3 - Hydroxypropyl) - 1 - phenacylpyridinium Bromide—To a 1-L. conical flask, equipped with a magnetic stirrer and cooled in an ice bath was added 99.5 Gm. phenacyl bromide (0.5 mole) dissolved in 300 ml. ether. To the well-stirred ethereal solution was added dropwise 110 Gm. (0.8 mole) of 3-(2-pyridyl)-1-propanol over a 10-min. period. The temperature of the surrounding ice water bath was allowed to rise gradually to room temperature and stirring was continued for an additional 10 to 12 hr. The crystalline product was collected and washed with ether. Recrystallization from ethanol yielded 131 Gm. (78%), m.p. 138–140°. The identity of this new intermediate was confirmed by the successful ring closure to 1-(2-hydroxyethyl)-2-phenylindolizine in the Chichibabin reaction.

1 - (2 - Hydroxyethyl)-2-phenylindolizine—In a 2-L. beaker was placed 79 Gm. (0.24 moles) of 2 - (3 - hydroxypropyl) - 1 - phenacylpyridinium bromide and 1200 ml. of water. The beaker was placed in a water bath on a magnetic stirrer hot plate. The temperature of the reaction mixture was raised to about 60°, and 120 Gm. sodium bicarbonate was then added in small portions over a 10-min. period. After the addition, the temperature of the reaction mixture was gradually raised and maintained in the range of 80–85° with constant stirring for 2 hr. Foaming occurred during the reaction and was controlled by supplemental manual stirring with a glass rod. At the end of the reaction period, the crystalline product was filtered off while

hot by suction and washed with warm water. The air-dried product was immediately recrystallized from hot ethanol and yielded 51 Gm. (92%), m.p. 101.5–102.5°.

Anal.—Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.10; H, 6.40; N, 5.81.

1 - (2 - Hydroxyethyl) - 2 - phenyl - 3 - pyrrolidinomethylindolizine—Six milliliters of 37% aqueous formaldehyde (0.075 mole) and 5.34 Gm. of pyrrolidine (0.075 mole) were combined with 30 ml. of dioxane and allowed to stand for 15 min. at room temperature. 1-(2-Hydroxyethyl)-2-phenylindolizine, 3.57 Gm. (0.015 mole), was dissolved in the mixture which was then allowed to stand at room temperature for 24 hr. The reaction mixture was transferred to an evaporating dish and the solvent was removed by blowing cold air over the surface. Scratching with a glass rod during evaporation failed to induce crystallization and a viscous oil was obtained. The oil was transferred to a 50-ml. conical flask with the aid of about 3 ml. of ethanol and placed in the freezer compartment of the refrigerator. The product crystallized after 1 week in the refrigerator. The crystals were removed by filtration, washed with 50% ethanol, and recrystallized from hot DMF–water. The yield was 2.9 Gm. (62%), m.p. 122–124°.

Anal.—Calcd. for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55; N, 8.74. Found: C, 78.65; H, 7.54; N, 8.72.

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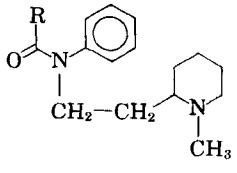
New Compounds: Amides Derived from 2-(2-Pyridyl)ethylamines

By JOSEPH SAM*

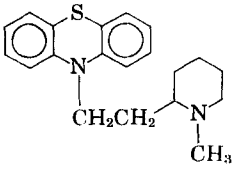
Basic amides containing the pyridylethyl- and piperidylethylamino groups have been prepared either from 2-vinylpyridines, 2-(2-aminoethyl)pyridines, or from substituted 2-(2-aminoethyl)piperidines. The amides possess some of the structural characteristics of the phenothiazine tranquilizers.

Amides, in general, exhibit a depressant effect on the central nervous system. Phenacetin, an analgesic amide, and barbital, an hypnotic amide derivative, were forerunners of many other biologically active amides (1).

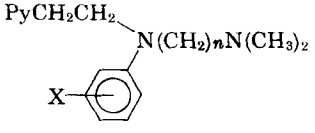
Based on (*a*) the general CNS depressant properties of amides, (*b*) the presence of the 1,3-propylenediamine entity in many biologically active compounds, and (*c*) the similarity of the reactions of the NH of the phenothiazine ring to the NH of amides, it was of interest to prepare some amides (I) possessing structural characteristics of the phenothiazine tranquilizers (II).



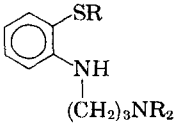
I



II



III



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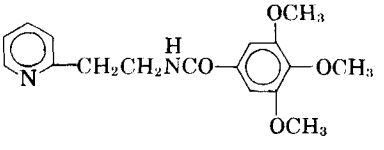
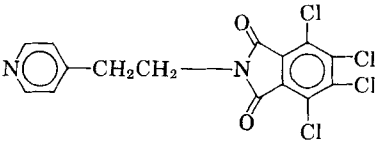


V



VI

Shapiro and associates (2) prepared some similar compounds (III) which were related to the antihistamine, tripelennamine [*N*-benzyl-*N'*,*N'*-dimethyl-*N*-(2-pyridyl)ethylenediamine] and to the phenothiazine tranquilizers. Nieforth (3) prepared

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