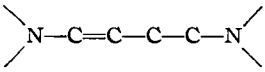
Mannich Bases from 2-Phenylindolizines III. 1,3-Bis(dialkylaminomethyl)-2-phenylindolizines

By WILLIAM B. HARRELL* and ROBERT F. DOERGE

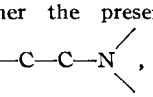
In seeking new therapeutic agents derived from indolizines, four new Mannich bases derived from 2-phenylindolizine have been synthesized. Preliminary pharmacological screening of 3-diethylaminomethyl-1,2-diphenylindolizine, a compound previously reported in these studies, has been carried out and the results are given.

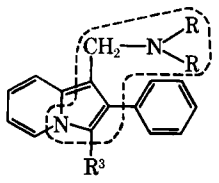
THE STRUCTURAL ANALOGY between indolizines with dialkylaminomethyl side chains and certain biologically interesting indoles has been pointed out in previous publications by the authors (1, 2). It is suggested that compounds such as reserpine, lysergic acid diethylamide, and psilocin might owe their activity in part to the presence of a certain spatial arrangement between the indole nitrogen and the extraindole nitrogen:



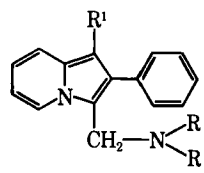
In Part I of this study the preparation of a series of Mannich bases derived from 2,3-disubstituted indolizines was reported. One compound in the series, 1-diethylaminomethyl-3-methyl-2-phenylindolizine, was tested and found to exhibit central nervous system depressant activity.

In these studies the Mannich reaction (3) has been employed because it is a convenient way to introduce dialkylaminomethyl side chains at the C-1 or C-3 positions of the indolizine nucleus. The primary purpose of this study was to synthesize a number of Mannich bases derived from selected 2-phenylindolizines and to evaluate them for possible activity on the central nervous system. If significant activity was observed, an attempt to correlate chemical structure with activity would be made.

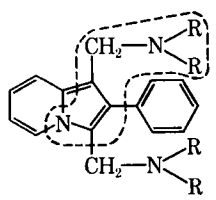
To date three types of Mannich bases derived from 2-phenylindolizines have been synthesized. These compounds have the general structures represented below. The structural analogy between Types I and III with lysergic acid diethylamide (IV) is also shown; thus it will be of interest to determine whether the presence of the grouping,  , has any influence on the activity of these compounds.



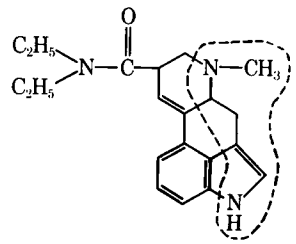
I



II

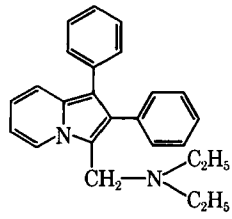


III



IV

The syntheses of Types I and II have been reported in previous publications by the authors (1, 2). In addition to the activity previously reported for 1-diethylaminomethyl-3-methyl-2-phenylindolizine, a compound of Type I, the following preliminary pharmacological data have been obtained for 3-diethylaminomethyl-1,2-diphenylindolizine (V), a compound of Type II:



V

When injected intraperitoneally in mice as a solution in propylene glycol, the compound, in doses of 10 mg./kg. body weight, exerted a pronounced central nervous system depressant effect. The animals did not appear to sleep and were easily aroused. Spontaneous motor activity was measured through the use of a photoelectric cell activity cage and was found to be decreased in mice. Rats, when given the compound intraperitoneally in propylene glycol exhibited a loss of aggressiveness. The compound

Received May 22, 1968, from the School of Pharmacy, Oregon State University, Corvallis, OR 97331
Accepted for publication June 25, 1968.
Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.
Abstracted in part from a thesis submitted by William B. Harrell to the Graduate School, Oregon State University, in partial fulfillment of Doctor of Philosophy degree requirements.

* 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, TX 77004

showed no significant anticonvulsant activity by the supramaximal electroshock method using mice. The LD_{50} was found to be 215 mg./kg. body weight using mice.

A more extensive biological evaluation of these compounds and others prepared in this study is currently being carried out and the results will be reported elsewhere.

Reports in the literature on the utilization of the Mannich reaction with indolizines have been very scarce and the scope of such investigations has been limited. Rossiter and Saxton (4) prepared 1-dimethylaminomethyl - 2,3 - dimethylindolizine by treating 2,3-dimethylindolizine with formaldehyde and dimethylamine. Carbon and Brehm (5), following the method of Rossiter and Saxton, reported the synthesis of 3-acetyl-1-dimethylaminomethylindolizine. To date no other Mannich bases derived from indolizines have been reported in the literature, except those previously described by the present authors. In these studies the syntheses of Mannich bases which involved the C-1 position have been described, the C-3 position, and both the C-1 and C-3 positions of the indolizine nucleus. A mechanism by which indolizines participate in the Mannich reaction in forming Mannich bases at these two positions (1, 2) has been proposed. In continuing medicinal chemical investigation of indolizines, further studies involving the Mannich reaction are planned.

EXPERIMENTAL

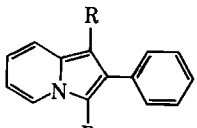
All melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were provided by Weiler and Strauss Microanalytical Laboratory, Oxford, England. Preliminary pharmacological screening of V was carried out with the assistance of Dr. Edward J. Eugere at Texas Southern University.

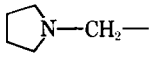
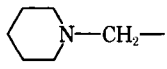
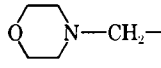
Materials—The parent indolizine employed in the syntheses of the Mannich bases in this series was 2-phenylindolizine (Table I). This compound was prepared by the Chichibabin synthesis (6) and has been previously reported in the literature (7).

1,3-Bis(dimethylaminomethyl)-2-phenylindolizine (VI)—A mixture containing 20 ml. dimethylamine (0.11 mole), 6 ml. of 37% aqueous formaldehyde (0.075 mole), and 0.1 ml. of 50% sodium hydroxide was allowed to stand in an ice bath for 20 min. The mixture was added slowly with shaking to a flask containing 2 g. 2-phenylindolizine (0.01 mole) dissolved in 50 ml. *N,N*-dimethylformamide. The flask was stoppered and allowed to stand at room temperature for 72 hr. Water was added in excess very slowly to the reaction mixture and the product precipitated as a heavy oil. Excessive shaking was avoided during the addition of water to prevent the formation of an emulsion. After allowing to stand overnight, the aqueous layer was carefully decanted. The semisolid residue was dissolved with heating in a minimum amount of hot ethanol. Water, equivalent to about 10% of the volume of the alcoholic solution, was added while the solution was still hot. After allowing to cool to room temperature, the clear solution was placed in the freezing compartment of the refrigerator. The product crystallized after 2 days in the refrigerator. The product was removed by filtration and washed with 50% ethanol. The yield was 2.7 g. (88%). Upon recrystallization from hot ethanol the compound gave m.p. 68.5–69.5°.

1,3 - Bis(pyrrolidinomethyl) - 2 - phenylindolizine (VII)—A mixture containing 10 ml. dioxane, 1.8 g. pyrrolidine (0.025 mole), and 1.8 ml. 37% aqueous formaldehyde (0.023 mole) was allowed to stand at room temperature for 15 min. To this mixture was added 0.97 g. 2-phenylindolizine (0.005 mole) and, after swirling occasionally for about 1 hr. to dissolve the indolizine, the resulting solution was allowed to stand for 48 hr. at room temperature. The mixture was poured into an evaporating dish and cold air was blown over the surface to remove the solvent. When evaporation was nearly complete, the oily residue was washed with water and dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration, washed with 5–7 ml. ether, and the filtrate placed in the freezer compartment of the refrigerator. After 3 days, the inside of the flask was scratched with a glass stirring rod and returned to the freezer. Crystals appeared within 1 hr. The mixture was allowed to remain in the freezer for 4 hr. longer to allow crystallization to be completed. The product was removed by suction, washed with cold ethanol, and recrystallized from

TABLE I—MANNICH BASES PREPARED



Compd.	Empirical Formula	R	M.p., °C.	Yield, %	Recrystn. Solvent		Anal., % Calcd.	Found
VI	$C_{20}H_{25}N_3$	$(CH_3)_2NCH_2$—	68.5–69.5	88	Ethanol	C	78.14	78.05
						H	8.20	8.09
						N	13.67	13.86
VII	$C_{24}H_{29}N_3$		106–107	70	Acetone–water	C	80.18	80.24
						H	8.13	8.24
						N	11.69	11.68
VIII	$C_{26}H_{33}N_3$		98.5–99.5	85	Ethanol	C	80.58	80.53
						H	8.58	8.57
						N	10.84	10.74
IX	$C_{24}H_{29}N_3O_2$		156–157	81	Ethanol	C	73.63	73.75
						H	7.47	7.56
						N	10.73	10.84

cold acetone–water. The yield was 1.2 g. (70%), m.p. 106–107°.

1,3 - Bis(piperidinomethyl) - 2 - phenylindolizine (VIII)—Six milliliters of 37% aqueous formaldehyde (0.075 mole) and 8.4 g. piperidine (0.10 mole) were combined with 75 ml. dioxane. One-tenth milliliter of 50% sodium hydroxide was added and the mixture was allowed to stand for 15 min. at room temperature. Two grams 2-phenylindolizine (0.01 mole) was dissolved in the mixture which was then allowed to stand at room temperature for 48 hr. The reaction mixture was transferred to an evaporating dish and cold air was blown across the surface. Evaporation was accompanied by vigorous scratching with a glass rod. The crystalline product which was obtained during the evaporation process was removed by filtration and washed with 50% ethanol. The yield was 3.3 g. (85%). On recrystallization from hot ethanol the compound gave m.p. 98.5–99.5°.

1,3 - Bis(morpholinomethyl) - 2 - phenylindolizine (IX)—Six milliliters of 37% aqueous formaldehyde (0.075 mole) and 8.7 g. morpholine (0.10 mole) were combined with 75 ml. dioxane. One-tenth milliliter of 50% sodium hydroxide solution was added and the mixture was allowed to stand for 15 min. at room temperature. Two grams 2-phenylindolizine (0.01 mole) was added and the flask swirled to achieve solution. The reaction mixture was allowed to stand at room temperature for 48 hr. and then transferred to an evaporating dish. Evaporation was carried out by blowing cold air across the surface accompanied by vigorous scratching with a glass rod. The crystalline product obtained was removed by filtration and washed with 50% ethanol. The yield was 3.2 g. (81%). The product was recrystallized from ethanol and gave m.p. 156–157°.

REFERENCES

(1) Harrell, W. B., and Doerge, R. F., *J. Pharm. Sci.*, **56**, 225(1967).
(2) *Ibid.*, **56**, 1200(1967).
(3) Mannich, C., and Krösche, W., *Arch. Pharm.*, **250**, 647 (1912).
(4) Rossiter, E. D., and Saxton, J. E., *J. Chem. Soc.*, **1953**, 3654.
(5) Carbon, J. A., and Brehm, S., *J. Org. Chem.*, **26**, 3376 (1961).
(6) Chichibabin, A. E., *Chem. Ber.*, **60**, 1607(1927).
(7) Borrows, E. T., Holland, D. O., and Kenya, J., *J. Chem. Soc.*, **1946**, 1069.

Keyphrases

Mannich bases—synthesis
2-Phenylindolizine derivatives—Mannich bases
3-Diethylaminomethyl-1,2-diphenylindolizine—pharmacological screening

Effect of Perfusion Rate and Distribution Factors on Drug Elimination Kinetics in a Perfused Organ System

By RENPEI NAGASHIMA and GERHARD LEVY*

The effects of flow rate and volume of perfusate on the elimination of a drug from a perfusion fluid by an organ or tissue such as the liver, kidney, or intestine are examined. It is shown that the volume of perfusate (or the apparent volume of distribution of a drug) has a pronounced effect on the rate constant for the decline of drug concentration in the perfusate, but that perfusion rate has an effect only if the concentration of drug in the perfusate leaving the organ is appreciably lower than the concentration in the fluid entering the organ.

MANY KINETIC studies of drug absorption or metabolism are carried out by perfusing a segment of intestine, or an organ such as the liver, and determining the change in the concentration of the drug in the perfusate as a function of time. Two important variables in such experiments are the volume of perfusate and its rate of flow through the organ. These variables are encountered also *in vivo* since blood flow rate can be affected by shock, in certain disease conditions, and by some drugs, and since the apparent volume of distribution of drugs (which is analogous in certain respects to the perfusate volume in *in vitro* studies) differs as a function of plasma protein concentration, type and concentration of drug, and other factors. The pharmacokinetic analysis to be presented here will deal specifically with the isolated perfused liver system, but the principles which will be outlined apply equally to the other systems mentioned above.

The liver is viewed as a tissue with numerous parallel channels through which perfusate flows. The concentration of drug in the perfusate leaving the liver is lower than the drug concentration in the fluid entering the liver, due to biotransformation of the drug in that tissue. This decrease in the drug concentration is a function of the activity of the biotransformation process (assuming that drug transfer from perfusate to liver is not rate limiting), and the contact time of a given increment of perfusate with liver tissue (1). If the elimination is a zero-order process, the drug concentration in the

Received May 3, 1968, from the Biopharmaceutics Laboratory, Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214
Accepted for publication July 2, 1968.
* To whom requests for reprints should be directed.