ductivity bridge at 25°. The data from both of the analytical procedures demonstrated that there was some aggregation at 25° for each substance which had shown aggregation previously at its freezing temperature, except for pyrilamine HCl which did not aggregate at 25° in the concentration range studied. Moreover, with both the conductivity and vapor pressure methods bromodiphenhydramine HCl data showed an initial aggregation point at 0.052 *M* which agreed quite well with the freezing depression data of the initial aggregation concentration (0.058 *M*), but it did not show the second break in the curve at 0.248 *M* which was disclosed by the freezing point method. The fact that this second break was not found at 25° could mean that it was temperature dependent or resulted from some other condition not controlled in the study. This point needs further investigation.

REFERENCES

(1) Hammarlund, E. R., and Pedersen-Bjergaard, K., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 107(1958).
(2) Hammarlund, E. R., Deming, J. G., and Pedersen-Bjergaard, K., *J. Pharm. Sci.*, **54**, 160(1965).
(3) Hammarlund, E. R., and Pedersen-Bjergaard, K., *ibid.*, **50**, 24(1961).
(4) Hammarlund, E. R., and Pedersen-Bjergaard, K., *Dansk Tidsskr. Farm. Suppl. II.*, **1956**, 107.
(5) Johnson, R. D., Goyan, F. M., and Tuck, L. D., *J. Pharm. Sci.*, **54**, 1176(1965).
(6) Husa, W. J., and Adams, J. R., *J. Am. Pharm. Assoc., Sci. Ed.*, **33**, 329(1944).
(7) Grosicki, T. S., and Husa, W. J., *ibid.*, **43**, 632(1954).
(8) Hunter, F. T., *J. Clin. Invest.*, **19**, 691(1940).
(9) Farhadieh, B., "Aggregation of Certain Medicinal Amines in Aqueous Solutions of Their Salts," Thesis, University of Washington, Seattle, Wash., 1965.

Attempted Mannich Condensation with Indanedione-1,3

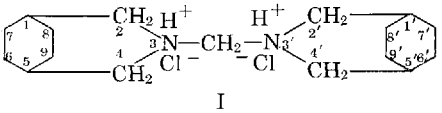
By RAJENDRA S. VARMA and W. LEWIS NOBLES

All attempts to prepare Mannich bases of indanedione failed. In every instance the end product was an amorphous solid with a high melting point and insoluble in most organic solvents. In one instance, while using 3-azabicyclo (3.2.2)nonane as the secondary amine component, a small amount of white crystalline substance was isolated from the mother liquor and identified as methylenebis-3-azabicyclo (3.2.2)nonane dihydrochloride with the help of infrared and NMR spectra. The structure of this compound was confirmed by unambiguous synthesis.

THE CONDENSATION between an amine (primary or secondary) or its salt with formaldehyde and a compound having an active hydrogen is known as the Mannich reaction.

Numerous Mannich bases are recorded in the literature (1–9); these have been prepared for pharmacological screening as antispasmodics, analgesics, chemotherapeutics, and local anesthetics.

In an effort to prepare Mannich bases of indanedione-1,3 for pharmacological testing, the condensation reaction was attempted several times utilizing dimethylamine, diethylamine, morpholine, piperidine, and 3-azabicyclo (3.2.2)nonane (AZBN) as the secondary amine component. Formaldehyde was used either as its aqueous solution or paraformaldehyde. Each synthesis resulted in a high yield of amorphous solid which was insoluble in most organic solvents. This solid material was washed several times with ether and ethanol, dried, and analyzed for elemental content. The analytical data did not correspond with the desired Mannich base. In one instance while using AZBN the mother liquor was refrigerated after adding acetone. This gave a white crystalline solid in small amounts. A pure sample was prepared after three recrystallizations from ethanol. The analytical values corresponded with methylenebis-3-azabicyclo(3.2.2)-nonane dihydrochloride (I). The infrared spectrum showed no carbonyl absorption. This ruled out the possibility of its being an indanedione Mannich base. The infrared spectrum was somewhat similar to that of AZBN.



I

The NMR spectrum was consistent with the proposed structure (I). Bands at δ = 1.95 (16H, singlet) are due to methylene protons at 6,7,8,9,-6′,7′,8′,9′ and those at δ = 2.17 (6H, multiplet) correspond to protons at 1,5,1′,5′ and the methylene group between the two nitrogens. Bands at δ = 3.36 (8H, triplet) may be assigned to protons at 2,4 and 2′,4′. Bands at δ = 7.47 (2H, singlet) represent protons at 3 and 3′. When D_2O was added, the peak at δ = 7.47 disappeared due to the exchange of the protons on the nitrogen atoms.

Methylenebis-3-azabicyclo(3.2.2)nonane dihydrochloride was synthesized by utilizing another route. The melting point and infrared spectrum of the resulting product were identical in every respect to those relative to the Mannich (AZBN) mother liquor product. The mixed melting point showed no depression. On the basis of the above evidence the structure (I) of methylenebis-3-azabicyclo(3.2.2)-nonane dihydrochloride is assigned to the product isolated from the mother liquor. Isolation of similar types of by-products are recorded in the literature (10, 11). Thus *N,N′*-tetraethylmethylenediamine (10) and methylenedipiperidine (11) have been obtained when using diethylamine and piperidine, respectively.

The mechanism of the Mannich reaction has been investigated by Hellmann and Opitz (12) and Cummings and Shelton (13). It is proposed (14) that the reaction is initiated by a condensation between the amine and formaldehyde to yield an amino-

Received May 26, 1966, from the Department of Pharmaceutical Chemistry, University of Mississippi, University.
Accepted for publication August 5, 1966.
This project was supported in part by funds provided under grant AI 04701 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

methanol. The attack of a proton on the oxygen atom of the amino-methanol followed by expulsion of water leads to a resonance established carbonium-immonium ion. This electrophilic carbonium ion then reacts with a nucleophile which, under Mannich conditions, is usually the carbanion resulting from the ionization of the active hydrogen containing compound. It appears that under Mannich conditions AZBN acts as the nucleophile as well as condensing with the formaldehyde.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were charted on a Perkin Elmer model 137 spectrophotometer in Nujol mull. The NMR spectrum was recorded with a Varian A-60 spectrometer in $CDCl_3$, using tetramethylsilane as the internal standard.

Attempted Mannich Condensation of Indanedione-1,3 with AZBN.—AZBN (12.51 Gm., 0.10 mole) dissolved in 50 ml. of ethanol was acidified to pH 4 by dropwise addition of concentrated hydrochloric acid. Indanedione (14.6 Gm., 0.10 mole) was added followed by 4.5 Gm. (0.15 mole) of paraformaldehyde. The reaction mixture was heated on a water bath for 4 hr. The reaction mixture was cooled and filtered. This gave a product weighing 11.5 Gm. which could not be recrystallized because of its insolubility in most organic solvents. The mother liquor was diluted with 100 ml. of acetone and refrigerated overnight. A crystalline solid (6.5 Gm.) was obtained; this was recrystallized from ethanol, m.p. 301° dec. NMR data, δ = 1.95 (16H, singlet); 2.17 (6H, multiplet); 3.36 (8H, triplet); 7.47 (2H, singlet).

Anal.—Calcd. for $C_{17}H_{32}Cl_2N_2$: C, 60.90; H, 9.59; Cl, 21.74; N, 8.35. Found: C, 60.13; H, 9.77; Cl, 21.81; N, 8.55.

Methylenebis-3-azabicyclo(3.2.2)nonane Dihydrochloride (I).—AZBN (6.25 Gm., 0.05 mole) dissolved in 25 ml. of ethanol was acidified with concentrated hydrochloric acid to pH 4. Paraformaldehyde (1.11 Gm., 0.037 mole) was added and the reaction mixture refluxed on a boiling water bath for 3 hr. At the end of this period the contents were cooled and 100 ml. of acetone was added. The solution was refrigerated overnight. The desired product which was obtained as white needles, was recrystallized from ethanol or ethanol–acetone, m.p. 301° dec. Yield, 5.5 Gm. (65%). The mixed melting point obtained with the product isolated from the Mannich condensation (AZBN) showed no depression. Infrared spectra of both products were identical.

Anal.—Calcd. for $C_{17}H_{32}Cl_2N_2$: N, 8.35; Found: N, 8.53.

REFERENCES

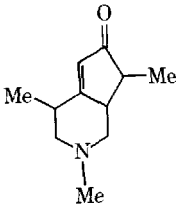
(1) Mannich, C., and Lammering, D., *Ber.*, **55**, 3510 (1922).
(2) Blicke, F. F., and Blake, E. S., *J. Am. Chem. Soc.*, **52**, 235(1930).
(3) Levvy, G. A., and Nisbet, H. B., *J. Chem. Soc.*, **1938**, 1053.
(4) Denton, J. J., *et al.*, *J. Am. Chem. Soc.*, **71**, 2048, 2050, 2053, 2054(1949); **72**, 3279, 3792(1950).
(5) Fry, E. M., and Everette, L. M., *J. Org. Chem.*, **24**, 116(1959).
(6) Burckhalter, J. H., and Johnson, S. H., *J. Am. Chem. Soc.*, **73**, 4835(1951).
(7) Nobles, W. L., *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 641, 644(1954); **44**, 273, 717(1955); **47**, 77(1958).
(8) Mercier, F., *et al.*, *J. Physiol. Paris*, **45**, 186(1953).
(9) Hayes, K., U. S. pat. 2,663,710; through *Chem. Abstr.*, **48**, 12809(1954).
(10) Mannich, C., and Ritsert, C., *Ber.*, **57**, 1116(1924).
(11) Mannich, C., and Curtaz, R., *Arch. Pharm.*, **264**, 741(1926).
(12) Hellmann, H., and Opitz, G., *Angew. Chem.*, **68**, 265(1959); *Chem. Ber.*, **89**, 81(1956); **90**, 8, 15(1957); Hellman, H., and Opitz, G., *Ann.*, **604**, 214(1957); **605**, 141(1957).
(13) Cummings, T. F., and Shelton, J. R., *J. Org. Chem.*, **25**, 419(1960).
(14) Nobles, W. L., and Thompson, B. B., *J. Pharm. Sci.*, **53**, 1554(1964).

Antidiabetic Effect of Tecomine and Tecostanine

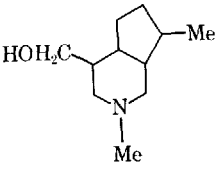
By YOUSSEF HAMMOUDA and M. SAMIR AMER*

The hypoglycemic properties of tecomine citrate and tecostanine hydrochloride on fasting blood sugar, glucose tolerance, depancreatized, and alloxan-diabetic rabbits is described. The two drugs proved to be effective antidiabetic agents only in the presence of the pancreas.

TECOMINE (I) and tecostanine (II) are two alkaloids isolated by Hammouda and Motawi (1) and Hammouda *et al.* (2) from the leaves of *Tecoma stans* (Juss.). The leaves of the various species of *Tecoma* have long been used by the natives in Mexico for the control of diabetes (3, 4). Since the structure of the two alkaloids isolated therefrom was elucidated (5–7), it was of interest to determine whether the two alkaloids are responsible for the long known antidiabetic properties of the leaves. The present study was initiated to determine the hypoglycemic properties of the two alkaloids and to determine the possible mechanism by which they produce this effect. A short note was previously published on this subject (8).



I



II

Received June 1, 1966, from the Department of Pharmaceutics and the Department of Pharmacology, Faculty of Pharmacy, University of Alexandria, Alexandria, U.A.R.
Accepted for publication August 15, 1966.
* Present address: Department of Pharmacology, College of Medicine, University of Illinois, Chicago.