Use of *N*-Methyltetrahydrofurfurylamine in the Mannich Reaction

By CHARLOTTE H. BRUENING, CHARLES M. DARLING, ROBERT A. MAGARIAN, and W. LEWIS NOBLES

Mannich bases have been prepared using *N*-methyltetrahydrofurfurylamine as the amine component. The preparation and pharmacodynamic activity of the β-aminoketones are given.

THE LITERATURE is replete with examples of the Mannich reaction (1–25) which is basically the condensation of an active hydrogen component with a basic component and formaldehyde or paraformaldehyde. The Mannich reaction has been reviewed by Blicke (26), Karbe (27), Merz (28), Reichert (29), Hellmann and Opitz (30), and more recently by Nobles (31) and Ogata and Kawasaki (32). The application of this reaction to the preparation of β-aminoketones utilizes an appropriate ketone as the active hydrogen component. Such compounds are easily prepared by the Mannich reaction and are of interest as antispasmodics, analgesics, local anesthetics, and chemotherapeutic agents (1–24). The condensation reactions, performed under the conditions reported here, may be illustrated as in Scheme I. Many compounds prepared heretofore have an alkylamino, dialkylamino, and azabicyclic amine as the amine moiety as well as nitrogen heterocycles of various sizes. In this paper the Mannich reaction has been extended to include an α-substituted dialkylamino component in which the substituent is a ring possessing a heteroatom other than nitrogen in order to determine its physiological activity. Furan has been compared with pyrrole derivatives in classes of compounds where activity is more dependent on the presence of such groups than the total structure, *e.g.*, many local anesthetics are known to be aryl esters having the structure, $ArCOO(CH_2)_2NR_2$, where the aryl group can be phenyl, 2-pyrryl, 2-thienyl, and 2-furyl (33). Even though the activity of furan derivatives is weaker, in many cases, than that of the corresponding thiophene and benzene compounds, it still exhibits bio-isosteric effects (34). The pharmacological properties of a series of furan derivatives were determined by La Barre *et al.* (35). The compounds tested exhibited an antispasmodic effect on isolated intestine and coronary dilation.

Clarke and co-workers (36–38) studied the tetrahydrofurfuryl group as the moiety in α-benzyltetrahydrofurfurylamine derivatives which demonstrated psychomotor stimulant activity.

The occurrence of the furan ring system in a number of medicinals as well as the widespread appearance of Mannich bases in medicinal agents makes it particularly attractive to combine both features in a single structural unit.

PHARMACOLOGY

The initial pharmacologic profile of the compounds in Table I was determined by the administration of the drugs over a dosage range of 50–2000 mg./Kg. in mice *via* the oral route. Under these conditions compound I produced nonspecific stimulation followed by depressant effects, and was moderately toxic. Compound II demonstrated convulsant and nonspecific effects to 1000 mg./Kg. and slight CNS depressant effects at 500 mg./Kg. It exhibited no significant activity. Mannich base III possessed toxic properties and produced significant effects only following lethal doses. Compound IV had no significant activity orally or intraperitoneally. The aminoketone V evoked slight CNS and sympathetic stimulant effects. The increased spontaneous motor activity, piloerection, and exophthalmic effect were not significant. Compounds VI and VII provided no significant activity at nonlethal doses; however, the latter exhibited weak CNS depressant effects.

There were no apparent effects for the compounds at 50 mg./Kg.; however, there were similarities at 2000 mg./Kg. Compounds I, II, III, and V produced marked ataxia, opisthotonus, straub tail, and prostration; I and II elicited muscle weakness, no clonic seizures, and no marked exophthalmos effect as did II and V while only II had "popcorn" effects. Mannich bases I and II exhibited slight and moderate salivation, while only compounds II and III exhibited slight lachrymal properties. The aminoketone IV was observed to elicit a slight increase in SMA, slight and moderate ataxia; one-half of the animals tested were hypersensitive to sound and touch. Mice treated with compound VI exhibited marked ataxia, belly drag, asphyxial-like seizure, prostration, and grasping. Mannich base III brought about a slight reduction in motor activity, marked ataxia, belly drag, grasping, slight salivation, and slight lachrymation, myoclonic jerking, prostration, and muscle weakness. The righting-placing-reflex was negative for compounds I, II, III, and VIII. The pinnal, corneal, and grasp-pain reflexes were negative for compounds I, III, and VIII.

The Mannich bases were also studied for cardiovascular, somatic, and visceral effects in dogs anesthetized with pentobarbital. Intravenous injections of 1 and 10 mg./Kg. were administered with the following results.

Compound I demonstrated a slight hypotensive effect with reduction in heart rate and produced a slight transient relaxation of the ileum.

Compound II produced a slight relaxation of ileum and a transient inhibition of linguo-mandibular reflex, but had no significant effect on blood pressure or heart rate.

Compound III was found to be inactive and IV had only a slight hypotensive effect.

Compound V possessed slight to moderate hypotensive effect at 10 mg./Kg. but was found to be inactive at 1 mg./Kg. It also had weak smooth muscle relaxant properties.

Compounds VI and VII were found to be inactive.

EXPERIMENTAL

Mannich Bases (Table I).—The keto bases were prepared generally by the conditions set forth by Nobles and his associates (23) in *Procedure B*. This method was utilized to obtain the amine as the

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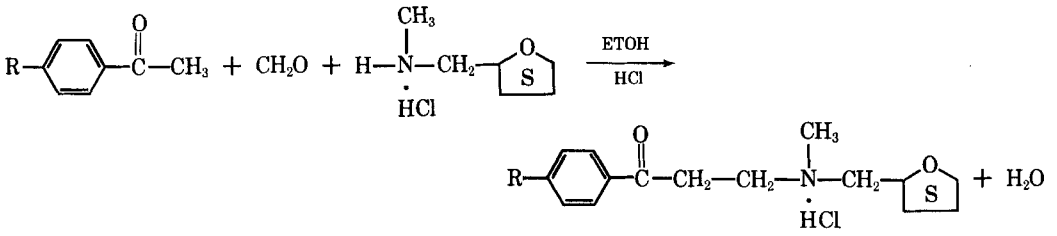
The ketones used in this study were commercially available and the amine, *N*-methyltetrahydrofurfurylamine, was supplied through the courtesy of Miles Chemical Co.



Scheme I

crystalline hydrochloride. The secondary amine (0.1 mole) was dissolved in 25 ml. of alcohol, and this solution was adjusted to pH 3–4 by the dropwise addition of concentrated hydrochloric acid.

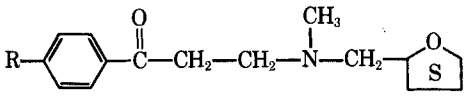
To the alcoholic solution was added 0.1 mole of ketone and 4.5 Gm. of paraformaldehyde; this mixture was allowed to reflux for 2.5 hr. It proved necessary to add one-half the quantity of paraformaldehyde at the beginning of reflux and the remainder after 0.5 hr. to insure depolymerization of the unchanged paraformaldehyde and bring it into solution. The paraformaldehyde is used in excess since part of it reacts with ethanol to form methylene diethyl ether (39).

Although the condensations in the Mannich reaction proceed much faster in the higher-boiling solvents, and the formation of certain by-products, obtained by prolonged heating in ethanol, is avoided (26), it is believed that the condensation is less subject to side reactions associated with the instability of the aminoketone salts at the higher temperatures (40). A higher boiling alcohol was tried without success in an effort to attempt to provide a better yield of product.

The time required for a Mannich reaction depends, among other things, upon the nature of the ketone and the amine salt and upon the boiling point of the solvent (26); it was found that these reactions in ethanolic solution yielded products after the mixtures had been refluxed for 2.5 hr. An increase in reflux time was of no avail in producing better yields.

At the end of 2.5 hr., the solution was poured into 100 ml. of acetone to aid in the precipitation of the

TABLE I.—MANNICH BASES



Compd.[a]	R	Formula	M.p.,[b] °C.	Yield, %	Anal.[c] Calcd.	Found
I	Hydrogen	$C_{15}H_{21}NO_2 \cdot HCl$	115–117[d]	76.8	C, 63.48 H, 7.82 N, 4.94	63.03 7.63 4.99
II	*p*-Phenyl	$C_{21}H_{25}NO_2 \cdot HCl$	132–134	47.7	C, 70.08 H, 7.28 N, 3.89	70.17 7.17 3.80
III	*p*-Hydroxy	$C_{15}H_{21}NO_3 \cdot HCl$	155.5–156.5	54.0	C, 60.09 H, 7.40 N, 4.67	60.13 7.55 4.54
IV	*p*-Nitro	$C_{15}H_{20}N_2O_4 \cdot HCl$	156.5–157.5	32.1	C, 54.79 H, 6.44 N, 8.52	54.91 6.31 8.53
V	*p*-Bromo	$C_{15}H_{20}BrNO_2 \cdot HCl$	159–161	38.8	C, 49.67 H, 5.84 N, 3.86	49.67 5.89 3.84
VI	Methoxy	$C_{18}H_{27}NO_5 \cdot HCl$	144.5–146.5	35.2	C, 57.36 H, 8.29 N, 3.72	57.65 7.97 3.72
VII	Hydrogen	$C_{17}H_{23}NO_2 \cdot HCl$	146–148	48.1	C, 65.91 H, 7.81 N, 4.52	65.91 7.81 4.49

[a] All Mannich bases in this table were recrystallized from ethanol. [b] Melting points are corrected. [c] Microanalyses were performed by A. Bernhardt, Mülheim (Ruhr), West Germany. [d] Softens at 100°.

hydrochloride. The mixture was cooled to room temperature; it was then refrigerated until the product precipitated. In most cases a semisolid or oily residue appeared only after the addition of ether. Crystallization was facilitated when the residues were separated and further treated with ether and the sides of the vessel were scratched. The solid thus obtained was removed by filtration and recrystallized to analytical purity from ethanol.

The reactions proceeded with some facility; however, the yields were relatively low for most of the products obtained. Low yields may be attributed to the complexity of the products which arise in the Mannich reaction from the type of by-product formation mentioned earlier. An attempt was made to minimize this by-product formation as described above.

REFERENCES

(1) Mannich, C., and Kresche, W., *Arch. Pharm.*, **250**, 647(1912); through *Chem. Abstr.*, **7**, 2746(1913).
(2) Mannich, C., and Lammering, D., *Ber.*, **55**, 3510 (1922).
(3) Blicke, F. F., and Blake, E. S., *J. Am. Chem. Soc.*, **52**, 235(1930).
(4) Nisbet, H. B., and Gray, C. G., *J. Chem. Soc.*, **1933**, 839.
(5) Levvy, G. A., and Nisbet, H. B., *ibid.*, **1938**, 1053.
(6) Wilson, W., and Kyi, Z. Y., *ibid.*, **1952**, 1321.
(7) Denton, J. J., *et al.*, *J. Am. Chem. Soc.*, **71**, 2048, 2050 2053, 2054(1949); **72**, 3279, 3792(1950).
(8) Weijlard, J., *et al.*, *ibid.*, **78**, 2342(1956).
(9) Mercier, F., Mercier, J., and Sectier, M. R. *J. Physiol. Paris*, **45**, 186(1953); through *Chem. Abstr.*, **47**, 11527(1953).
(10) Issekutz, B., *et al.*, *Acta Physiol. Acad. Sci. Hung.*, **6**, 95(1954); through *Chem. Abstr.*, **49**, 3394(1955).
(11) DaRe, R., *et al.*, *J. Org. Chem.*, **25**, 1097(1960).
(12) Bockstahler, E. R., and Wright, D. L., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 542(1957).
(13) Florestano, H. J., and Bahler, M. E., *ibid.*, **45**, 320 (1956).
(14) Profit, E., *Chem. Tech. Berlin*, **3**, 210(1951); through *Chem. Abstr.*, **46**, 688(1952).
(15) Profit, E., *Chem. Tech. Berlin*, **4**, 241(1952); through *Chem. Abstr.*, **47**, 10532(1953).
(16) Profit, E., *Chem. Tech. Berlin*, **5**, 13(1953); through *Chem. Abstr.*, **48**, 7608(1954).
(17) Fry, E. M., and Everette, L. M., *J. Org. Chem.*, **24**, 116(1959).
(18) Fuson, R. C., *Chem. Rev.*, **16**, 1(1935).
(19) Burckhalter, J. H., and Johnson, S. H., *J. Am. Chem. Soc.*, **73**, 4835(1951).
(20) Levvy, G. A., and Nisbet, H. B., *J. Pharmacol. Exptl. Therap.*, **65**, 129(1939); through *Chem. Abstr.*, **33**, 2985(1939).
(21) Burckhalter, J. H., *et al.*, *J. Am. Chem. Soc.*, **68**, 1894(1946); **70**, 1363(1948).
(22) Hayes, K., *Chem. Abstr.*, **48**, 12809(1954); U. S. pat. 2,663,710.
(23) Nobles, W. L., Britton, S. B., and Caldwell, H. C., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 641, 644(1954); Nobles, W. L., and Caldwell, H. C., *ibid.*, **44**, 273(1955); Nobles, W. L., and Britton, S. B., *ibid.*, **44**, 717(1955); Nobles, W. L., and Burckhalter, J. H., *ibid.*, **47**, 77(1958).
(24) Nobles, W. L., and Blanton, C. D., *J. Pharm. Sci.*, **51**, 878(1962); Nobles, W. L., and Luts, H. A., *ibid.*, **51**, 273(1962); **54**, 67(1965).
(25) Nobles, W. L., and Blanton, C. D., *ibid.*, **52**, 46(1963); **53**, 521(1964); **53**, 1130(1964); Nobles, W. L., and Thompson, B. B., *ibid.*, **53**, 1554(1964); **54**, 576(1965); **54**, 709(1965).
(26) Blicke, F. F., "Organic Reactions," vol. 1, John Wiley & Sons, New York, N. Y., 1942, p. 303.
(27) Karbe, H., *Arch. Pharm.*, **283**, 48(1950).
(28) Merz, K. W., *Pharmazie*, **11**, 505(1956).
(29) Reichert, B., "Die Mannich-Reaktion," Springer Verlag, Berlin, Germany, 1959.
(30) Hellmann, H., and Opitz, G., "α-Aminoalkylierung," Verlag Chemie, Weinheim, Germany, 1960.
(31) Nobles, W. L., *Pharm. Sci. 4th Ann. Visiting Lecture Ser. Coll. Pharm., Univ. Texas*, Austin, 1961, p. 149; through *Chem. Abstr.*, **58**, 409(1963).
(32) Ogata, Y., and Kawasaki, A., *Yuki Gosei Kagaku Kyakai Shi*, **21**, 79(1963); through *Chem. Abstr.*, **59**, 2625 (1963).
(33) Gilman, H., and Pickens, R. M., *J. Am. Chem. Soc.*, **47**, 245(1925).
(34) Biel, J. H., *ibid.*, **71**, 1306(1949).
(35) LaBarre, J., *et al.*, *Arch. Intern. Pharmacodyn.*, **147**, (No. 3–4) 497(1964); through *Chem. Abstr.*, **60**, 9793(1964).
(36) Clarke, R. L., and Harris, L. S., *J. Med. Pharm. Chem.*, **5**, 77(1962).
(37) *Ibid.*, **5**, 362(1962).
(38) Harris, L. S., Clarke, R. L., and Dembinski, J. R., *Arch. Intern. Pharmacodyn.*, **146**, (No. 3–4) 392(1963); through *Chem. Abstr.*, **60**, 9793(1964).
(39) Mannich, C., and Schütz, M., *Arch. Pharm.*, **265**, 684(1927).
(40) Ruberg, L., and Small, L., *J. Am. Chem. Soc.*, **63**, 736(1941).

Antagonism of Uridine Diphosphate with 3-Methylisoquinoline Compounds

By THOMAS J. HALEY and H. DIX CHRISTENSEN

The ability of four 3-methylisoquinoline compounds to antagonize the spasmogenic effect of uridine diphosphate on goldfish intestine was determined. While there was no significant difference in potency, one compound, 6-ethoxy-7-methoxy-1-(3′,4′-diethoxybenzyl)-3-methyl-isoquinoline, had a lesser effect on acetylcholine contractions and thus may be useful in the differential analysis of tissue extracts containing both uridine diphosphate and acetylcholine.

GADDUM and Szerb (1) showed that the goldfish intestine could be used to estimate the substance P content of tissue extracts. Haley *et al.* (2) adapted the procedure for the determination of acetylcholine. However, both groups observed that tissue extracts contained a substance which stimulated the intestine even in the presence of dichloroisoprenaline, hyoscine, mepyramine, and methysergide. Gaddum and Smith (3) and Gaddum (4) showed that this unknown substance was actually uridine diphosphate. Levy and Michel-Ber (5) pointed out that the spasmogenic effect of uridine triphosphate could be blocked by papaverine. Inasmuch as other naturally occurring substances are blocked by antagonists added to the bathing solution and because such procedures are often better than laborious separations, the authors have studied the antagonism of uridine diphosphate with four synthetic 3-methylisoquinoline derivatives (6).

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