(13). While the capillary method was employed, the tubes were uncoated and the animals were unanesthetized which, if anything, would be expected to mask the effect of epinephrine rather than to increase the sensitivity.

Combined Nicotine-Epinephrine Effects.—The results obtained by combining 0.01 mg./Kg. of nicotine with either 0.04 or 0.06 mg./Kg. of epinephrine are shown in Fig. 2 and Table I. Changes in both instances were in the direction of an increased time to coagulate, although both drugs individually had depressed the coagulation time. It is perhaps worthy of note that the combined nicotine-epinephrine, while not inducing a significant increase in the coagulation time as measured by the *t*-test, apparently prolonged the duration of the response. Further, the direction of the change is what would be anticipated if nicotine exerts its action through catecholamine release.

Modification of Nicotine and Epinephrine Responses by Piperoxan.—The injection of piperoxan alone in a dose of 0.25 mg./Kg. caused a minimal and nonsignificant increase in the rate of coagulation (Table I and Fig. 3). Administration of this dose 10 minutes prior to either 0.01 mg./Kg. of epinephrine or nicotine resulted in coagulation times which varied no more than did repeated control determinations. This blockade of the nicotine effect is consistent with the results of Takatsuki (3), demonstrating that nicotine exerts its characteristic action on the coagulation time through the release of catecholamines. As the actions of nicotine and epinephrine are both apparently mediated through the latter agent, and as the response to their combined administration indicates an additive effect, it is likely that the combination of smaller doses of each would result in a shorter coagulation time. Although the experimental evidence does not directly support the contention, it is further likely that the amounts of nicotine absorbed during smoking would increase rather than decrease the rate of coagulation, even in the presence of systemic catecholamine release. In man, Johnston has reported that 0.08 to 0.13 mg. of nicotine intravenously produces effects similar to those induced by one deep inhalation of cigarette smoke (15).

REFERENCES

(1) Wenzel, D. G., Kamal, J. S., and Turner, J. A., *N. Y. Acad. Sci.*, **90**, 302(1960).
(2) Wenzel, D. G., Turner, J. A., Jordan, S. W., and Singh, J., *Circulation Research*, **9**, 694(1961).
(3) Takatsuki, S., *Japan. J. Med. Sci. IV*, **5**, 71(1931).
(4) Kanowoka, S., *Tôhoku J. Exptl. Med.*, **24**, 307(1934).
(5) Grassi, B., and Caltabiano, S., *Rass. fisiopatol. clin. e terap.*, **28**, 755(1956).
(6) Eisen, M. E., *Am. J. Surgery*, **95**, 438(1958).
(7) Blackburn, H., Jr., Orma, E., Härtel, G., and Punsar, S., *Am. J. Med. Sci.*, **238**, 448(1959).
(8) Vosburgh, C. H., and Richards, A. N., *Am. J. Physiol.*, **9**, 36(1903).
(9) Wiggers, C. J., *Arch. intern. med. exptl.*, **3**, 139(1909).
(10) Van den Velden, R., *Münch. med. Wochschr.*, **58**, 184 (1911).
(11) Cannon, W. B., and Gray, H., *Am. J. Physiol.*, **34**, 232(1914).
(12) Cannon, W. B., and Mendenhall, W. L., *ibid.*, **34**, 251(1914).
(13) Forwell, G. D., and Ingram, G. I. G., *J. Physiol.*, **135**, 371(1957).
(14) Härtel, G., *J. Appl. Physiol.*, **15**, 605(1960).
(15) Johnston, L. M., *Lancet*, **243**, 742(1942).

Use of 3-Azabicyclo[3.2.2.]nonane in the Mannich Reaction I

Substituted β-Amino Ketones

By C. DeWITT BLANTON, Jr., and W. LEWIS NOBLES

A group of Mannich bases, indicated as types I, II, and III, have been prepared utilizing 3-azabicyclo[3.2.2.]nonane as the amine component. These β-aminoketones are to be screened for possible pharmacodynamic activity.

RECORDED in the literature (1–11) are numerous ketonic Mannich bases, prepared for pharmacological testing as antispasmodics, analgesics, chemotherapeutic agents, and local anesthetics. Such compounds may, in general, be prepared easily by means of the Mannich reaction which utilizes the appropriate ketone, formaldehyde, or paraformaldehyde, and the desired amine. This may be illustrated as follows

$$RCOCH_3 + HCHO + R'_2NH \cdot HCl \rightarrow RCOCH_2CH_2NR'_2 \cdot HCl + H_2O$$

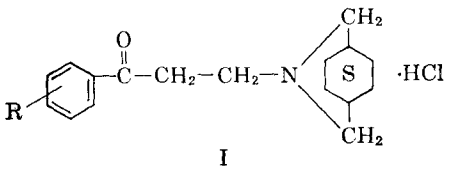
Received October 23, 1961, from the School of Pharmacy, The University of Mississippi, University.
Accepted for publication November 24, 1961.

The rather extensive literature dealing with this reaction has been reviewed by Blicke (12), Karbe (13), Reichert (14), and more recently by Hellmann and Opitz (15).

The great versatility of these ketonic Mannich bases prompted us to prepare a number of Mannich bases of types I, II, and III, in which the amine moiety is 3-azabicyclo[3.2.2.]nonane. In addition, the concept of vinylogous substances, as set forth by Fuson (16), has led us to prepare several vinylogs of types I and II. (See Tables I–III.)

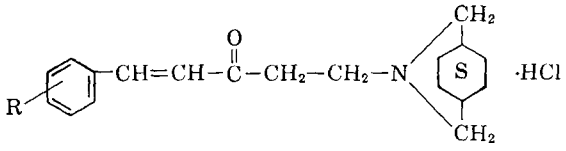
To study more fully the effect of structural variants, Mannich bases have been prepared of

TABLE I.—MANNICH BASES TYPE I



I

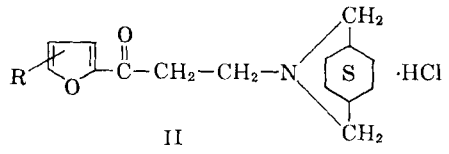
No.[a]	R	Yield, %	M.p.,[b] °C.	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	Hydrogen[d]	66.0	199–200	$C_{17}H_{23}NO \cdot HCl$	67.47	66.83	8.33	8.38	4.77	4.77
2	*p*-Nitro[d]	41.4	202–203	$C_{17}H_{22}N_2O_3 \cdot HCl$	58.70	58.26	6.95	6.94	8.05	8.06
3	*p*-Chloro[d]	45.7	207–208	$C_{17}H_{22}ClNO \cdot HCl$	60.54	60.53	7.17	7.16	4.15	4.17
4	*p*-Methoxy	51.6	213–214	$C_{18}H_{25}NO_2 \cdot HCl$	66.76	66.78	8.04	8.25	4.33	3.98
5	*p*-Ethoxy	50.2	201–201	$C_{19}H_{27}NO_2 \cdot HCl$	67.54	67.64	8.35	8.41	4.15	4.45
6	*o*-Hydroxy	36.5	196–197	$C_{17}H_{23}NO_2 \cdot HCl$	65.91	65.21	7.75	7.68	4.52	4.56
7	*p*-Methyl	54.5	220–221	$C_{18}H_{25}NO \cdot HCl$	70.22	69.88	8.51	8.52	4.45	4.48
8	*p*-Fluoro[d]	35.4	203–204	$C_{17}H_{22}FNO \cdot HCl$	63.62	63.67	7.53	7.69	4.36	4.53
9	*p*-Bromo	33.2	211–212	$C_{17}H_{22}BrNO \cdot HCl$	54.78	53.67	6.22	5.99	3.76	3.77
10	*p*-Hydroxy	38.4	226–228	$C_{17}H_{23}NO_2 \cdot HCl$	65.90	65.65	7.81	7.99	4.52	4.59
11	*p*-Phenyl	53.7	211–212	$C_{23}H_{27}NO \cdot HCl$	74.69	74.53	7.58	7.56	3.78	3.95
12	*m*-Nitro	21.3	230–231	$C_{17}H_{22}N_2O_3 \cdot HCl$	60.26	60.29	6.84	7.18	8.27	8.48
13	*p*-Ethyl	53.4	211–213	$C_{19}H_{27}NO \cdot HCl$	70.89	71.01	8.77	8.35	4.35	4.44
14	*m*-Bromo	32.7	217–218	$C_{17}H_{22}NO \cdot HCl$	54.65	54.39	6.17	5.94	3.76	3.66
15	*m*-Hydroxy	48.0	210–212	$C_{17}H_{23}NO_2 \cdot HCl$	65.90	65.88	7.81	7.83	4.52	4.66
16	*p*-Amino	49.5	99–100	$C_{17}H_{24}N_2O$	75.00	74.69	8.82	9.08	10.29	10.45



17	Hydrogen	61.8	203–204	$C_{19}H_{25}NO \cdot HCl$	71.34	70.78	8.19	8.16	4.38	4.37
18	*p*-Chloro	...	217–218	$C_{19}H_{24}ClNO \cdot HCl$	64.41	64.69	7.11	7.03	3.95	3.84
19	*p*-Methoxy	43.3	212–213	$C_{20}H_{27}NO_2 \cdot HCl$	68.65	68.65	8.07	8.17	4.00	4.31

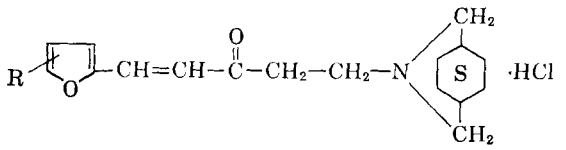
[a] All Mannich bases in this table were recrystallized from an ethanol-acetone solution, ethanol, or ethanol-water solution. Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul Craig Smith Kline & French Laboratories, Philadelphia, Pa. [d] Calculated for one-half mole of water.

TABLE II.—MANNICH BASES TYPE II



II

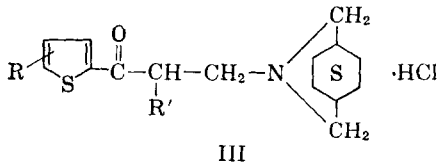
No.[a]	R	Yield, %	M.p.,[b] °C.	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	5-Nitro	30.5	212–214	$C_{15}H_{20}N_2O_4 \cdot HCl$	54.80	54.58	6.40	6.59	8.50	8.56



2	Hydrogen[d]	12.6	198–199	$C_{17}H_{23}NO_2 \cdot HCl$	64.96	64.80	7.86	8.20	4.46	4.50
3	5-Nitro	22.6	185–188	$C_{17}H_{22}N_2O_4 \cdot HCl$	57.54	57.67	6.49	6.63	7.89	7.97

[a] All Mannich bases in this table were recrystallized from an ethanol-acetone, ethanol, or ethanol-water solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul Craig, Smith Kline & French Laboratories, Philadelphia, Pa. [d] Calculated for one-fourth mole of water.

TABLE III.—MANNICH BASES TYPE III

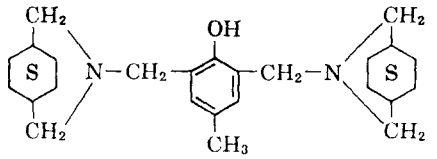
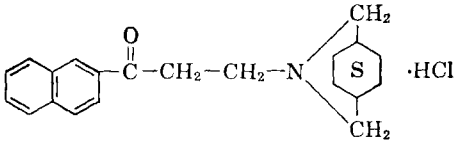


III

No.[a]	R	R′	Yield, %	M.p.,[b] °C.	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	Hydrogen	Hydrogen	58.5	203–204	$C_{15}H_{21}NOS \cdot HCl$	60.10	59.94	7.34	7.44	4.67	4.61
2	Hydrogen	Methyl	37.9	200–201	$C_{16}H_{23}NOS \cdot HCl$	61.21	60.91	7.66	7.49	4.46	4.12
3	5-Bromo	Methyl	39.4	200–201	$C_{16}H_{22}BrNOS \cdot HCl$	48.92	48.87	5.90	5.83	3.57	3.33

[a] All Mannich bases in this table were recrystallized from an ethanol-acetone, ethanol, or ethanol-water solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul Craig, Smith Kline & French Laboratories, Philadelphia, Pa.

TABLE IV.—MISCELLANEOUS MANNICH BASES

No.[a]		Yield, %	M.p.,[b] °C.	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
										
1	...	89.9	95–100	$C_{25}H_{38}N_2O$	78.48	78.09	10.01	9.60	...	...
										
2	2-Naphthyl	42.0	221–222	$C_{21}H_{25}NO \cdot HCl$	73.34	73.32	7.62	7.53	4.07	4.23

[a] All Mannich bases in this table were recrystallized from an ethanol-acetone solution, ethanol, or ethanol-water solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul Craig, Smith Kline & French Laboratories, Philadelphia, Pa.

2-acetonaphthone and phenolic compounds, *viz.*, the disubstituted product of *p*-cresol (see Table IV). The change in activity with variation in chemical structure in other chemical series led us to study additional transformations. Denton and his co-workers (4) indicated that the reduction of the piperidino Mannich bases to the corresponding aminoalcohols led to a marked increase in antispasmodic activity in all cases except those involving a thiophene derivative. Also, many of the tertiary alcohols, prepared by these workers by the addition of a Grignard reagent to the Mannich base, exhibited increased activity over that of the parent ketone. Certain of these suggested modifications have been incorporated into the structures presented here and these studies, along with the results of pharmacological screening, will be reported in subsequent publications. Preliminary evaluation of compound No. 1 from Table II has been obtained.[1] Oral administration of 300 mg./Kg. of this compound to a rat (Pratt) failed to produce any overt activity.

EXPERIMENTAL

Experimental Results.—β-[3-(3-Azabicyclo-[3.2.2.]nonyl)]-4-aminopropiophenone was prepared according to the method of Wright and Freifelder (17). *p*-Chlorobenzalacetone was synthesized according to the method previously outlined (18). 2,6-di-[3-(3-Azabicyclo[3.2.2.]nonyl)-methyl]-*p*-cresol was prepared according to the method of Bruson and MacMullen (19). 2-Propionylthiophene was synthesized by the procedure of Kosak and Hartough (20), employing propionic anhydride rather than acetic anhydride. 2-Propionyl-5-bromothiophene was prepared according to the method of Hartough and Conley (21). This procedure was

[1] The authors wish to thank Dr. Paul Craig of Smith Kline & French Laboratories for arranging for the pharmacological testing.

modified by substituting 2-bromothiophene for 2-chlorothiophene and propionic anhydride for acetic anhydride. 3-Azabicyclo[3.2.2.]nonane was supplied through the courtesy of Eastman Chemical Products, Inc. All other ketones in this study were commercially available.

The Mannich reaction was carried out as previously described (8), utilizing procedure B. A solid usually appeared within 30–90 minutes and acetone was added to complete precipitation. It was observed that some of these compounds were only slightly soluble in ethanol, especially the ones of more complex structure. In such cases a few drops of water were added to help facilitate solution in the recrystallization processes. In general, the reactions proceeded smoothly to yield the expected product. It may be noted, however, that excellent yields are seldom obtained in the Mannich reaction due to the complexity of the products obtained which may be occasioned by by-product formation. The furan derivatives consistently produced low yields.

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., Turner, R. J., Neier, W. B., Lawson, V. A., and Schedl, H. P., *J. Am. Chem. Soc.*, **71**, 2048, 2050, 2053, 2054 (1949); **72**, 3279, 3792(1950).
(5) Weijlard, J., *et al.*, *ibid.*, **78**, 2342(1956).
(6) Fry, E. M., and Everette, L. M., *J. Org. Chem.*, **24**, 116(1959).
(7) Burckhalter, J. H., and Johnson, S. H., *J. Am. Chem. Soc.*, **73**, 4835(1951).
(8) Nobles, W. L., *et al.*, This Journal, **43**, 641(1954); **43**, 644(1954); **44**, 273(1955); **44**, 717(1955); **47**, 77(1958).
(9) Mercier, F., *et al.*, *J. physiol. Paris*, **45**, 186(1953).
(10) Da Re, P., *et al.*, *J. Org. Chem.*, **25**, 1097(1960).
(11) Hayes, K., *Chem. Abstr.*, **48**, 12809(1954); U. S. pat. 2,663,710.
(12) Blicke, F. F., "Organic Reactions," Vol. 1, John Wiley & Sons, New York, N. Y., 1942, p. 303.
(13) Karbe, H., *Arch. Pharm.*, **283**, 48(1950).
(14) Reichert, B., "Die Mannich-Reaktion," Springer-Verlag, Germany, 1959.
(15) Hellmann, H., and Opitz, G., "α-Aminoalkylierung," Verlag Chemie, Weinheim, Germany, 1960.
(16) Fuson, R. C., *Chem. Revs.*, **16**, 1(1935).
(17) Wright, H. B., and Freifelder, M., *J. Am. Chem. Soc.*, **71**, 1513(1949).
(18) Dodgen, D., and Nobles, W. L., This Journal, **46**, 437(1957).
(19) Bruson, H. A., and MacMullen, C. W., *J. Am. Chem. Soc.*, **63**, 270(1941).
(20) Kosak, A. I., and Hartough, H. D., "Organic Synthesis," Coll. Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1955, p. 14.
(21) Hartough, H. D., and Conley, L. G., *J. Am. Chem. Soc.*, **69**, 3096(1947).

Sympathetic Nervous System Blocking Agents

Investigation of Ethyl-, Hydroxyethyl-, Vinyloxyethyl-, and Propargyl-benzyldimethylammonium Halides and Related Compounds

By JAMES H. SHORT and URSULA BIERMACHER

A series of quaternary benzylamine derivatives has been prepared. They were examined for their ability to block the sympathetic nervous system without also blocking the parasympathetic system. The most active compounds were derivatives of benzyl(vinyloxyethyl)dimethylammonium halide. The *o*-bromo analog has activity of the same order of magnitude as bretylium. Pharmacological results and structure-activity relationships are discussed.

THROUGH routine screening of compounds for cardiovascular effects, it was observed that benzyl(vinyloxyethyl)dimethylammonium bromide (Table I, No. 1) had a blocking effect on the sympathetic nervous system, but apparently had little or no effect on the parasympathetic system. It appeared, therefore, to have activity of the same type as bretylium, which has recently been investigated in the clinic as an antihypertensive agent (1).

Interest in this type of pharmacological activity led us to synthesize a series of quaternary salts in order to investigate structure-activity relationships. Some of these compounds were prepared by the reaction of a benzyl halide with a tertiary amine. For those desired compounds which were not accessible by this route, the alternative procedure, reaction of an N,N-dimethylbenzylamine with an alkyl halide was employed.

The required intermediate amines and halides were prepared by standard methods and are described in the experimental section.

PHARMACOLOGICAL RESULTS[1]

The effectiveness of these compounds as sympathetic blocking agents was determined in unanesthetized cats. The candidate drugs were administered orally, and the degree and duration of the prolapse of the nictitating membrane were the criteria used to determine whether or not the desired activity was present. Since parasympatho-

Received August 14, 1961, from the Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Ill.
Accepted for publication December 8, 1961.

[1] The pharmacological activity of these compounds was investigated by Dr. John L. Schmidt, Mr. Charles Shannon, and Mr. Leo Wiemeler of the Division of Experimental Therapy, Abbott Laboratories. We are grateful to them for permission to use their data.