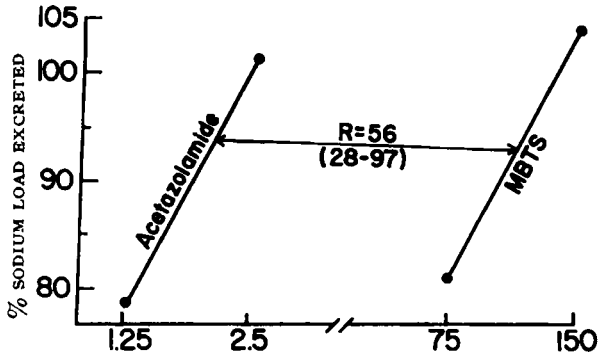


Fig. 2.—The natruretic action of MBTS compared to that of acetazolamide using a four-point parallel-line bioassay. *R* equals potency ratio with 95% confidence limits in parentheses.

ruresis. The greater kaluresis produced by BTS and MBTS when equivalent natruretic doses of these agents and acetazolamide were employed therefore suggests that these benzimidazolyl-toluenesulfonamide compounds exert a greater effect on the distally located exchange mechanism than does acetazolamide.

REFERENCES

(1) Southworth, H., *Proc. Soc. Exptl. Biol. Med.*, **36**, 58(1937).
(2) Mann, T., and Keilin, D., *Nature*, **146**, 164(1940).
(3) Maren, T. H., *Trans. N. Y. Acad. Sci.*, **15**, 53(1952).
(4) Miller, W. H., Dessert, A. M., and Roblin, R. O., Jr., *J. Am. Chem. Soc.*, **72**, 4893(1950).
(5) Hosein, E. A., Denstedt, O. F., and Griffith, H. R., *Anesthesiology*, **16**, 142(1955).
(6) Lipschitz, W. L., Hadidian, Z., and Kerpesar, A., *J. Pharmacol. Exptl. Therap.*, **79**, 97(1943).
(7) Steel, R. G. D., and Torrie, J. H., "Principles and Procedures of Statistics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 107.
(8) Finney, D. J., "Statistical Method in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952, p. 148.
(9) Höber, R., *Proc. Soc. Exptl. Biol. Med.*, **49**, 87(1942).
(10) Pitts, R. F., Gurd, R. S., Kessler, R. H., and Hierholzer, K., *Am. J. Physiol.*, **194**, 125(1958).
(11) Clapp, J. R., Watson, J. F., and Berliner, R. W., *ibid.*, **205**, 693(1963).

Use of 3-Azabicyclo[3.2.2]nonane in the Mannich Reaction IV. Additional Derived Products

By C. DEWITT BLANTON, JR., and W. LEWIS NOBLES

Additional β-amino ketones, phenol Mannich bases, allylamines, propylamines, and γ-aminoalkyl esters involving the use of 3-azabicyclo[3.2.2]nonane in the Mannich reaction are reported. Results of biological tests are cited.

ADDITIONAL MANNICH bases derived from 3-azabicyclo[3.2.2.]nonane are reported in Tables I–V. Results of biological tests are cited.

EXPERIMENTAL

The Mannich reaction was carried out as previously described (1). Preparation of the phenolic Mannich bases was achieved by the procedure of Burckhalter *et al.* (2) or by that of Bruson and MacMullen (3). The γ-amino secondary and γ-amino tertiary alcohols used as intermediates for the preparation of the compounds reported herein were prepared as described earlier (4, 5). The procedure of Pohland and Sullivan (6), Method D, was adopted as a general one for the esterification of γ-amino secondary alcohols. The method employed for the dehydration of the tertiary alcohols was patterned after that of Adamson (7). The procedure adopted as a general one for the reduction of allylamines to propylamines was patterned after that of Adamson and Billinghurst (8). For the preparation of the allylamines 7 and 10 (Table III) the tertiary alcohols, 3 - [3 - (3 - azabicyclo[3.2.2.]-nonyl)] - 1,1 - di - (2 - thienyl)propan - 1 - ol hydrochloride and 3 - [3 - (3 - azabicyclo[3.2.2]nonyl)]-1 - (4′ - propoxyphenyl) - 1 - phenylpropan - 1 - ol hydrochloride, underwent dehydration during their isolation from the Grignard reaction medium.

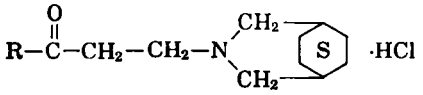
BIOLOGICAL TEST RESULTS[1]

During the preliminary screening program, compounds reported in this series of papers exhibited a broad spectrum of antimicrobial activity against such organisms as *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Candida albicans, Trichophyton mentagrophytes,* and *Trichomonas foetus.* The activity is particularly pronounced against *Trichophyton* and *Trichomonas;* in this regard, the compound β-3-(3-azabicyclo [3.2.2.] nonyl) - 2,5 - dimethyl-

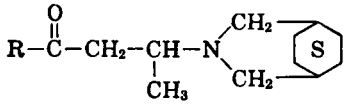
Received October 22, 1963, from the School of Pharmacy, University of Mississippi, University.
Accepted for publication January 20, 1964.

[1] Pharmacological results were supplied by Dr. Paul N. Craig of Smith Kline and French Laboratories, Philadelphia, Pa.

TABLE I.—ADDITIONAL β-AMINO KETONES



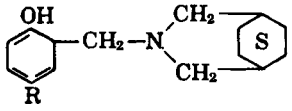
No.[a]	R	Yield, %	M.p.,[b] °C.	Formula	Analyses[c] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	*p*-Propoxyphenyl	62.1	199–201	$C_{20}H_{29}NO_2 \cdot HCl$	68.28	68.50	8.53	8.77	3.98	3.79
2	*o*-Butoxyphenyl	45.0	172–173	$C_{21}H_{29}NO_2 \cdot HCl$	68.92	69.05	8.81	8.86	3.87	4.12
3	3,4-Dimethylphenyl	52.6	216–216.5	$C_{16}H_{21}NO \cdot HCl$	70.92	71.03	8.71	8.75	4.35	4.39
4	2,5-Dimethylphenyl	36.1	210–211	$C_{16}H_{21}NO \cdot HCl$	70.92	71.25	8.71	8.81	4.35	4.36
5	2,4-Dimethylphenyl	78.3	204–206[d]	$C_{16}H_{21}NO \cdot HCl$	70.92	70.88	8.71	8.73	4.35	4.45
6	2,4,6-Trimethylphenyl	44.8	203–205[d]	$C_{26}H_{23}NO \cdot HCl$	71.51	71.37	9.00	8.89	4.17	4.22
7	*o*-Fluorophenyl	37.4	187–190[d]	$C_{17}H_{18}FNO \cdot HCl$	65.48	65.83	7.43	7.75	4.49	4.53
8	*o*-Trifluoromethylphenyl	35.6	195–200[d]	$C_{18}H_{18}F_3NO \cdot HCl$	59.75	59.94	6.41	6.69	3.87	4.07
9	*p*-Trifluoromethylphenyl	48.8	203–205[d]	$C_{18}H_{18}F_3NO \cdot HCl$	59.75	59.74	6.41	6.63	3.87	3.92



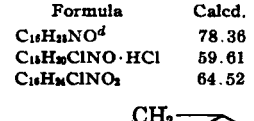
10	5-Chloro-2-thienyl	62.9	202–204	$C_{16}H_{22}ClNOS \cdot HCl$	55.17	55.28	6.66	6.49	4.03	4.01

[a] All Mannich bases in this table were recrystallized from an ethanol–acetone, ethanol, or ethanol–water solution. [b] Melting points, which are uncorrected, were taken on a Fisher-Johns melting point apparatus. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul N. Craig, Smith Kline and French Laboratories, Philadelphia, Pa. [d] Compound sublimed and melting points were taken by the sealed capillary method.

TABLE II.—PHENOL MANNICH BASES



No.[a]	R	Yield, %	M.p.,[b] °C.	Formula	Analyses[c] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	*p*-Methyl	78.0	107–108	$C_{16}H_{21}NO$[d]	78.36	78.29	9.39	9.23	5.72	5.75
2	*p*-Chloro	31.6	244–246	$C_{15}H_{19}ClNO \cdot HCl$	59.61	59.49	7.00	7.05	4.63	4.69
3	*p*-Methoxy	63.2	153–155	$C_{16}H_{21}ClNO_2$	64.52	64.20	8.12	8.18	4.70	4.46



4	2-(α-Naphthol)	51.7	195–196	$C_{19}H_{21}NO \cdot HCl$	71.79	71.37	7.61	7.62	4.41	4.29
5	1-(β-Naphthol)	88.3	155–157	$C_{19}H_{21}NO$	81.09	80.93	8.24	8.14	4.98	4.86

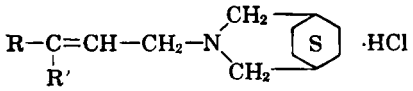
[a] All Mannich bases in this table were recrystallized from an ethanol–acetone, ethanol, or ethanol–water solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul N. Craig, Smith Kline and French Laboratories, Philadelphia, Pa. [d] This was reported earlier (1) erroneously as the disubstituted product.

propiophenone hydrochloride (Table I, Compound 4) was especially interesting.

For determining the antimicrobial activity, filter paper disks (6.3 mm.) are dipped in a 20 mg./ml. suspension of the test compound and tested for activity by the agar diffusion method. A Petri dish of 90-mm. diameter is employed, and the activity is determined by the zone of inhibition. For compound 4 (Table I), this zone of inhibition is greater than 90 mm. for *Trichophyton* and *Trichomonas* by the above method.

The benzenoid and heterocyclic ketonic Mannich bases displayed similar antimicrobial activity and toxicities, although activity of the heterocyclic compounds was not so pronounced. 3-Azabicyclo-[3.2.2.]nonane was observed to exhibit no activity as an antimicrobial agent. The amino alcohols, allylamines, and propylamines have not shown this marked antimicrobial activity, but are pharmacological agents having central nervous system activity. It is anticipated that future publications will be presented concerning these compounds as more details of the biological screening program become available.

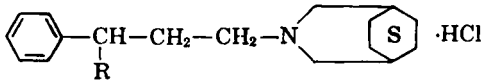
TABLE III.—ALLYLAMINES (HYDROCHLORIDE SALTS)



No.[a]	R	R′	Yield, %	M.p.,[b] °C.	Formula	Analyses[c] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	Phenyl	Phenyl	43.8	219–220	$C_{23}H_{28}ClN$	78.05	77.63	7.97	7.85	3.96	4.01
2	Phenyl	*p*-Fluorophenyl[d]	51.0	225–227	$C_{23}H_{27}FClN$	73.32	73.22	7.31	7.29	3.72	3.75
3	Phenyl	*p*-Chlorophenyl	73.6	225–230[d]	$C_{23}H_{27}Cl_2N$	71.13	71.48	6.96	7.24	3.61	3.76
4	Phenyl	*p*-Methylphenyl	46.4	220–225	$C_{24}H_{30}ClN$	78.34	78.22	8.22	8.24	3.81	4.03
5	Phenyl	*p*-Methoxyphenyl[e]	69.5	170–175	$C_{24}H_{30}ClNO$	73.30	73.39	7.89	7.80	3.56	3.54
6	Phenyl	*p*-Ethoxyphenyl	60.3	193–195	$C_{25}H_{32}ClNO$	75.44	75.20	8.10	8.08	3.52	3.52
7	Phenyl	*p*-Propoxyphenyl	49.0	205–207	$C_{26}H_{34}ClNO$	75.70	75.44	8.25	8.22	3.39	3.45
8	Phenyl	*p*-Butoxyphenyl	88.9	175–177	$C_{27}H_{36}ClNO$	76.12	75.93	8.52	8.31	3.29	3.20
9	Phenyl	2-Thienyl	66.9	180–183	$C_{21}H_{26}ClNS$	70.06	69.39	7.28	7.27	3.89	3.98
10	2-Thienyl	2-Thienyl	71.8	195–200	$C_{19}H_{24}ClNS_2$	62.35	61.78	6.61	6.71	3.83	3.65

[a] All allylamines in this table were recrystallized from an ethanol–acetone or ethanol–ether solution. [b] Melting points are uncorrected. [c] Carbon, hydrogen, and nitrogen analyses are through the courtesy of Dr. Paul N. Craig, Smith Kline and French Laboratories, Philadelphia, Pa. [d] Calculated for 0.25 mole of water. [e] Calculated for 0.50 mole of water.

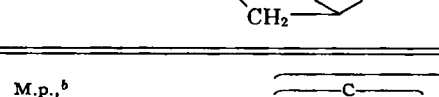
TABLE IV.—PROPYLAMINES (HYDROCHLORIDE SALTS)



No.[a]	R	Yield, %	M.p.,[b] °C.	Formula	Analyses[c] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	Phenyl	75.5	280–284	$C_{23}H_{30}ClN$	77.64	77.91	8.44	8.64	3.94	4.16
2	*p*-Fluorophenyl	45.4	257–260	$C_{23}H_{29}ClFN$	73.87	73.57	7.82	7.90	3.75	3.94
3	*p*-Chlorophenyl	57.6	263–268	$C_{23}H_{29}Cl_2N$	70.76	70.74	7.49	7.61	3.59	3.61
4	*p*-Methylphenyl	46.3	270–280	$C_{24}H_{32}ClN$	77.91	77.54	8.72	8.56	3.79	3.84
5	*p*-Methoxyphenyl	52.5	240–246	$C_{24}H_{32}ClNO$	74.68	74.82	8.36	8.24	3.63	3.75
6	*p*-Ethoxyphenyl	91.3	238–245	$C_{25}H_{34}ClNO$	75.06	75.13	8.57	8.66	3.50	3.64
7	*p*-Butoxyphenyl	87.2	215–219	$C_{27}H_{38}ClNO$	75.76	75.85	8.95	9.03	3.27	3.50

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

TABLE V.—γ-AMINOALKYL ESTERS



No.[a]	R	Yield, %	M.p.,[b] °C.	Formula	Analyses[c] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	Phenyl	93.0	228–230	$C_{19}H_{28}ClNO$	67.56	67.67	8.29	8.57	4.15	4.16
2	*p*-Chlorophenyl	95.2	220–223	$C_{19}H_{27}Cl_2NO_2$	61.26	61.81	7.53	7.46	3.76	3.94
3	*p*-Methoxyphenyl	98.1	205–207	$C_{20}H_{30}ClNO_3$	65.32	65.32	8.22	8.44	3.81	4.07
4	*p*-Methylphenyl	79.4	237–238	$C_{20}H_{30}ClNO_2$	68.26	68.19	8.59	8.85	3.98	4.12
5	*p*-Nitrophenyl	84.9	212–215	$C_{19}H_{27}ClN_2O_4$	59.61	59.20	7.11	7.23	7.32	7.82

[a] All γ-aminoalkyl esters were recrystallized from a methanol-ether solution. [b] Melting points are uncorrected. [c] Carbon hydrogen, and nitrogen analyses are through the courtesy of Dr, Paul N, Craig, Smith Kline and French Laboratories, Philadelphia, Pa.

REFERENCES

(1) Blanton, C. D., and Nobles, W. L., THIS JOURNAL, **51**, 878(1962).

(2) Burckhalter, J. H., Tendick, F. H., Jones, E. M., Holcomb, W. I., and Rawlins, A. L., *J. Am. Chem. Soc.*, **68**, 1894(1946).

(3) Bruson, H. A., and MacMullen, C. W., *ibid.*, **63**, 270 (1941).

(4) Blanton, C. D., and Nobles, W. L., THIS JOURNAL, **52**, 46(1963).

(5) *Ibid.*, **53**, 521(1964).

(6) Pohland, A., and Sullivan, J. R., *J. Am. Chem. Soc.*, **75**, 4458 (1953).

(7) Adamson, D. W., *J. Chem. Soc.*, 1949, S144.

(8) Adamson, D. W., and Billinghurst, J., *ibid.*, 1950, 1039.