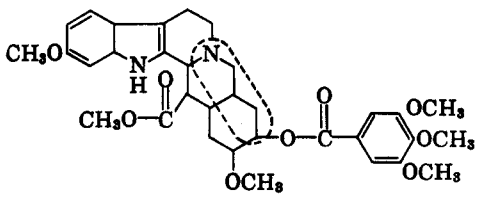
Synthetic Relatives of Reserpine

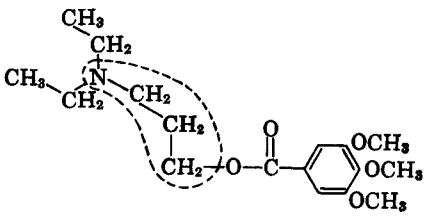
By CHARLOTTE H. BRUENING and W. LEWIS NOBLES

A group of Mannich bases, containing the 3,4,5-trimethoxyphenyl moiety as in reserpine, has been synthesized. Preliminary pharmacological screening suggests that one of the group, the morpholine Mannich base from 3,4,5-trimethoxybenzalacetone, demonstrated certain CNS depressant effects in mice, indicating that it might be considered as a tranquilizing agent for further studies.

MILLER AND WEINBERG (1) reported that 3-(*N,N* - diethylamino)propyl - 3,4,5 - trimethoxybenzoate (II) possessed approximately one-third of the tranquilizing action of reserpine (I). The structural analogy between these compounds



I



II

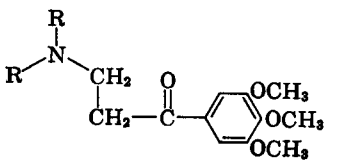
would indicate that some tranquilizing activity resides in a relatively small portion of the reserpine molecule. Since this report there have been several hundred publications dealing with the biological activity of compounds containing the trimethoxybenzoyl moiety of the parent molecule. Many of the aspects of this work have been reviewed by Schlager (2).

Recorded in the literature (3–11) are numerous ketonic Mannich bases, prepared for pharmacological testing as antispasmodics, analgesics, chemotherapeutic agents, and local anesthetics. Such compounds may in general be prepared readily by means of the Mannich reaction which utilizes the appropriate ketone, formaldehyde, or paraformaldehyde and the desired amine. This may be illustrated as follows:

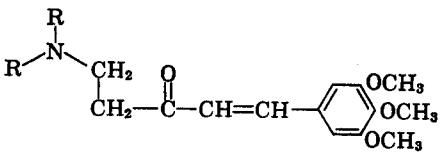
$$RCOCH_3 + HCHO + R'_2NH \cdot HCl \rightarrow RCOCH_2CH_2NR'_2 \cdot HCl + H_2O$$

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

In an effort to prepare synthetic relatives of reserpine utilizing the Mannich reaction, Mannich bases were prepared from 3,4,5-trimethoxyacetophenone and 3,4,5-trimethoxybenzalacetone. The structural analogy, albeit limited, can be easily seen from an inspection of the following structures (III and IV) and a comparison of them with the parent structure (I) above.



III



IV

PHARMACOLOGICAL RESULTS

The three Mannich bases (*A–C*) obtained from trimethoxyacetophenone were subjected to a study of preliminary dose effects, pernicious preening, and maximal electric shock seizure utilizing Swiss-Webster mice.

With compound *A*, the oral administration of 250–2000 mg./Kg. produced asphyxial-like convulsions, cyanosis, and death within 4–10 min. The administration of 500–2000 mg./Kg. of compound *B* elicited ataxia, muscle weakness, asphyxial convulsions, cyanosis, and death. Dosages in the range of 250–2000 mg./Kg. of compound *C* elicited tonic-clonic seizures, motor deficits, followed by increased activity, tremors, cyanosis, asphyxial seizures, and death. Lower doses (100 mg./Kg.) produced CNS stimulant effects. Hypothermia followed doses of 500 mg./Kg. or greater of compound *C*. Compound *C* demonstrated enough activity to warrant further testing for analeptic activity.

Oral or intraperitoneal administration of 500 and 2000 mg./Kg., respectively, elicited no significant overt effects. Oral administration of 2000 mg./Kg. of compound *E* produced slight reduction in motor activity, lachrymation, muscle weakness, tremors, marked hypothermia, champing, and asphyxial seizures, terminating in death. Lower doses to 500 mg./Kg. were marked by slight lachrymation and motor disturbances.

Because of the particularly interesting activity demonstrated by 3,4,5-trimethoxybenzoyl morpholide in the work of Vargha (15), the Mannich base prepared from morpholine and the trimethoxybenzalacetone was subjected to intensive screening by Hazleton Laboratories, Inc.[1] For this compound, the estimated LD_{50} was found to be 112 mg./Kg. Analysis of the rat pharmacodynamic record showed that this compound elicited a transient

Received February 18, 1965, from the Department of Pharmaceutical Chemistry, School of Pharmacy, University of Mississippi, University.

Accepted for publication March 16, 1965.

This investigation was supported in part by research grant MY-03232 from the U. S. Public Health Service, Bethesda, Md.

[1] The preliminary biological data on compound *F* were provided by the Hazleton Laboratories, Inc., under the supervision of the Scientific Staff, Psychopharmacology Service Center, and was supported under contract PH 43-63-555 from the National Institute of Mental Health, U. S. Public Health Service, Bethesda, Md.

TABLE I.

Compd.	Amine	M.p., °C.	Yield, %	Formula	Anal. Calcd.	Anal. Found
Mannich Base Hydrochlorides of 3,4,5-Trimethoxyacetophenone						
A	Hexamethyleneimine	178–179	45	$C_{18}H_{28}ClNO_4$	C, 60.41	60.57
					H, 7.89	7.77
					N, 3.91	4.28
B	Piperidine	201–202	69	$C_{17}H_{26}ClNO_4$	C, 59.38	59.46
					H, 7.62	7.47
					N, 4.07	4.32
C	3-Azabicyclo (3,2,2)nonane	221–222	72	$C_{20}H_{30}ClNO_4$	C, 62.57	62.87
					H, 7.88	7.77
					N, 3.65	3.90
Mannich Base Hydrochlorides of 3,4,5-Trimethoxybenzalacetone						
D	Pyrrolidine	181–182	41	$C_{18}H_{26}ClNO_4$	C, 60.75	61.05
					H, 7.36	7.50
					N, 3.94	3.98
E	Piperidine	192–193	42	$C_{19}H_{28}ClNO_4$	C, 61.70	61.39
					H, 7.63	7.90
					N, 3.79	3.78
F	Morpholine	195–196	60	$C_{18}H_{26}ClNO_5$	C, 58.14	58.17
					H, 7.05	6.99
					N, 3.77	3.80

hypotensive effect at all dosage levels tested. Hexobarbital sleeping time was prolonged significantly at dosages of 11.2 and 33.6 mg./Kg. Analysis of the hotplate analgesia test data revealed that this compound possessed no analgesic properties, and the electroshock studies likewise indicated a lack of anticonvulsant properties. Analysis of the actophotometer data showed that this compound decreased spontaneous motor activity at all dosages tested (3.36–33.6 mg./Kg.). This compound interfered with conditioned avoidance responses in a dose related manner. No pathological changes were observed upon gross necropsy. A summary conclusion provided by Hazleton Laboratories indicated that this agent showed certain CNS depressant effects in mice, indicating that it could be considered as a tranquilizing agent for further studies. The compound, like many CNS depressants, elicited a hypotensive effect in the rat.

EXPERIMENTAL

Basic data indicating the structure, yield, melting point, and other such items for the six compounds presented in this study are indicated in Table I. 3,4,5-Trimethoxybenzalacetone was prepared according to the method of Burckhalter and Johnson (16) for 2,3-dimethoxybenzalacetone in a yield of 55%. The Mannich bases were prepared as follows.

In a 50-ml. flask containing 25 ml. of absolute ethanol was added 0.05 mole of the respective amine, and the pH was adjusted to 3–4 with concentrated HCl. To this was added 0.05 mole of the appropriate ketone and 2.3 Gm. of paraformaldehyde. The reaction mixture was allowed to reflux for approximately 3 hr. and was then poured into 100 ml. of dry acetone. After cooling in the refrigerator overnight, the precipitate was collected and recrystallized from an ethanol–acetone mixture.

REFERENCES

(1) Miller, F. M., and Weinberg, M. S., *Chem. Eng. News*, **34**, 4760(1956).
(2) Schlager, L. H., *Arzneimittel-Forsch.*, **13**, 226(1963).
(3) Mannich, C., and Lammering, D., *Ber.*, **55**, 3510 (1922).
(4) Blicke, F. F., and Blake, E. S., *J. Am. Chem. Soc.*, **52**, 235(1930).
(5) Levvy, G. A., and Nisbet, H. B., *J. Chem. Soc.*, **1938**, 1053.
(6) Denton, J. J., *et al.*, *J. Am. Chem. Soc.*, **71**, 2048, 2050, 2053, 2054(1949); **72**, 3279, 3792(1950).
(7) Fry, E. M., and Everette, L. M., *J. Org. Chem.*, **24**, 116(1959).
(8) Burckhalter, J. H., and Johnson, S. H., *J. Am. Chem. Soc.*, **73**, 4835(1951).
(9) Nobles, W. L., *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.* **43**, 641, 644(1954); **44**, 273, 717(1955); **47**, 77(1958).
(10) Mercier, F., *et al.*, *J. Physiol. Paris*, **45**, 186(1953).
(11) Hayes, K., U. S. pat. 2,663,710; through *Chem. Abstr.*, **48**, 12809(1954).
(12) Blicke, F. F., "Organic Reactions," vol. 1, John Wiley & Sons, Inc., New York, N. Y., 1942, p. 303.
(13) Reichert, B., "Die Mannich-Reaktion," Springer-Verlag, Berlin, Germany, 1959.
(14) Hellmann, H., and Opitz, G., "α-Aminoalkylierung," Verlag Chemie, Weinheim, Germany, 1960.
(15) Vargha, L., *et al.*, *Biochem. Pharmacol.*, **11**, 639(1962).
(16) Burckhalter, J. H., and Johnson, S. H., *J. Am. Chem. Soc.*, **73**, 4835(1951).