extracts combined, and dried over anhydrous calcium sulfate. The mixture was filtered and the ether evaporated. The residue was dissolved in a minimal amount of warm ethyl acetate, a crystal of 4-hydroxycyclohexanone oxime added, and crystallization allowed to proceed. The product was collected by filtration, m.p. 76–78°.

4 - tert - Butylcyclohexanone - $3_{(axial)}$,5,5 - d_3—This compound was obtained in 85% yield from the chromic acid oxidation of a mixture of *cis* and *trans*-4-*tert*-butylcyclohexanol-$3_{(axial)}$,5,5-d_3 (8) according to the method of Brown and Garg (33). The product was recrystallized from a water–methanol mixture, m.p. 49–50°. Ziegenbein and co-workers (34) reported a b.p. of 84–85° at 7.0 mm. and a m.p. of 49–50° for 4-*tert*-butylcyclohexanone.

4 - tert - Butylcyclohexanone - $3_{(axial)}$,5,5 - d_3-oxime—This compound was obtained in 92% yield by the slightly modified method of Ziegenbein and co-workers (34) for obtaining 4-*tert*-butylcyclohexanone oxime. To a solution of 20% ammonium hydroxide (19 ml., 0.11 mole), hydroxylamine hydrochloride (3.9 Gm., 0.056 mole), and methanol (75 ml.) was added 4-*tert*-butylcyclohexanone-$3_{(axial)}$,5,5-d_3 (5 Gm., 0.033 mole). The resulting solution was stirred for approximately 1 hr. at room temperature and then allowed to stand overnight. As the reaction progressed, the product precipitated, and after standing overnight it was collected by filtration. A second crop of product was obtained by adding water to the filtrate. The crystalline fractions were combined and recrystallized from a water–methanol mixture, m.p. 138–140°. Ziegenbein and co-workers (34) reported a m.p. of 133° for 4-*tert*-butylcyclohexanone oxime.

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Octamethyleneimine in the Mannich Reaction I

Substituted β-Amino Ketones and Substituted α-Amino Alcohols

By HEINO A. LUTS, J. F. GRATTAN, S. YANKELOWITZ*, and W. L. NOBLES†

A group of Mannich bases, utilizing octamethyleneimine as the amine component, has been prepared. Their preparation and biological activities are given.

OVER A period of years, a variety of Mannich bases has been prepared (1–26) for pharmacological testing. A typical Mannich condensation of the type discussed here may be illustrated as follows:

$$R{-}\overset{\overset{O}{\|}}{C}{-}CH_3 + HCHO + R_2NH{\cdot}HCl \rightarrow RCOCH_2CH_2NR_2{\cdot}HCl + H_2O$$

Certain substituted β-aminoketones and derivatives have been reported (2, 3, 5, 7) to show both local anesthetic and antispasmodic activity. The extensive literature dealing with

Received February 10, 1967, from Structure-Activity Research, Inc., Oxford, MS 38655, and Smith, Miller & Patch, New York, NY 10010
Accepted for publication May 23, 1967.
Presented to the Medicinal Chemistry Section, A.PH.A. Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.
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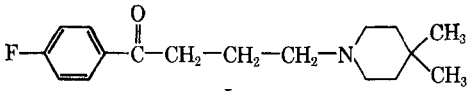
the Mannich reaction has been reviewed by Blicke (27) and later by Reichert (28).

Mannich and Lammering (2) reported that β-piperidinopropiophenone hydrochloride possesses local anesthetic activity. Denton and co-workers (7) in a series of papers described the antispasmodic activity of the Mannich bases. Under the conditions reported by these workers for determining antispasmodic activity, β-piperidinopropiophenone hydrochloride and 2-(β-piperidinopropionyl)-thiophene hydrochloride possess antispasmodic activity equal to that of β-diethylaminoethyl diphenyl acetate hydrochloride[1] and greater than that of papaverine. Burckhalter and Johnson (20) reported the antibacterial activity of certain Mannich bases derived from α,β-unsaturated ketones. Mercier and his associates indicated that the diethylamino Mannich base from acetophenone was adrenolytic, hypotensive, and ganglioplegic (10). β-Amino ketones derived from hexamethyleneimine were reported to possess CNS tranquilizing ability as well as local anesthetic activity (29, 30).

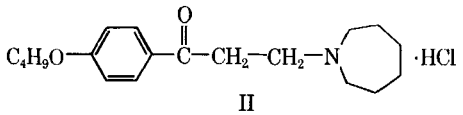
Most of the compounds prepared to the present have been alkylamino, dialkylamino, or 5- or 6-membered heterocyclic rings; only a few large ring amines have been prepared. In the last paper (26), heptamethyleneimine was used; now an attempt has been made to extend the Mannich reaction to a larger nitrogen-containing ring and to evaluate the compounds thus obtained. The authors have anticipated that the enlargement of the carbon content of the molecule would increase the lipid solubility and, because of the different shape of the amine ring (as compared to simple dialkylamines), it was felt also that these compounds might possibly exhibit different biological properties.

The demonstration that larger nitrogen-containing ring systems or highly branched amines in Mannich bases tend to elicit (26) a significant pharmacological activity which may or may not be particularly pronounced in Mannich bases containing smaller ring systems has influenced the continuation of this work. Recently, more evidence, in a degree, of this has come to our attention in the work of Simpson (31) that 4-fluoro-4-(4,4-dimethylpiperidino)butyrophenone acted as an antipsychotic agent and lowered blood cholesterol (I).



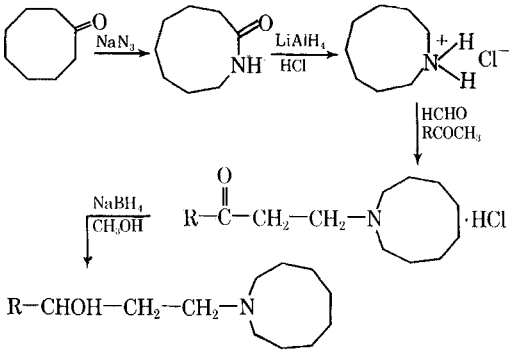
I

Zaidler and Kudrin (32) noted that 4′-butoxy-3-[hexahydro-(1*H*)azepine-1-yl]propiophenone hydrochloride has relatively high antiarrhythmic activity (II).



II

The method of preparing the octamethyleneimine was that of Blicke and associates (33). The Mannich reaction was carried out according to the original work of Tollens, in 1903 (34), and the Mannich base so obtained was reduced with sodium borohydride (35). (Scheme I.)



Scheme I

PHARMACOLOGY

The preliminary pharmacological results of these β-amino ketones and γ-amino alcohols, listed in Table I, are indicated below.

Phenylquinone Writhing Test in Mice—Good activity: 40% decrease of writhing movements as compared to untreated controls. Slight activity: 10–40% decrease of the writhing movements as compared to the untreated controls.

Hexobarbital[2] Induced Sleep in Mice—Good potentiation: 40% increase in sleeping time over the untreated controls. Slight potentiation: 10–40% increase in sleeping time over the untreated controls.

Tremorine Test in Mice—Induced tremors (T), lacrimation (L), and salivation (S). Good activity: one or more factors (T, L, S) decreased by 75–100% as compared with untreated controls. Slight activity: one or more factors (T, L, S) decreased by 50–75% as compared with untreated controls.

Compound *1* demonstrated a mild depressant effect, good activity in the phenylquinone test, possessed a transient hypotensive activity, and had an ocular anesthetic effect.

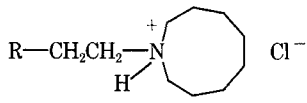
Compound *2* acted as a mild depressant and affected muscle tone. It had a good antipyretic and hypotensive activity. In the hexobarbital-induced sleep test in mice it demonstrated a good potentiation.

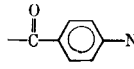
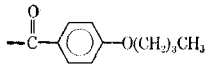
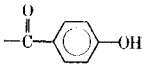
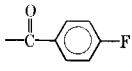
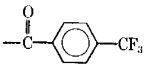
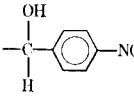
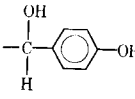
Compound *3* also exhibited a mild depressant

[1] Trademarked as Trasentin by Ciba Pharmaceutical Co., Summit, N. J.

[2] Trademarked as Evipal by Winthrop Laboratories, New York, N. Y.

TABLE I—MANNICH BASES



Compd.	R	Formula	M.p., °C.	Anal.—C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1		$C_{17}H_{25}ClN_2O_3$	190–191	59.94	59.82	7.39	7.31	8.22	8.18
2		$C_{21}H_{34}ClNO_2$	163	68.54	68.60	9.31	9.26	3.81	3.76
3		$C_{17}H_{26}ClNO_2$	160–161	65.47	65.34	8.40	8.31	4.49	4.43
4		$C_{17}H_{25}NOFCl$	138–139	65.09	65.17	8.03	7.92	4.45	4.51
5		$C_{18}H_{25}ClNOF_3$	153–154	59.41	59.56	6.95	6.82	3.85	3.97
6		$C_{15}H_{24}NSOCl$	142–143	59.68	59.55	8.01	7.89	4.67	4.56
7	 *d,l*	$C_{17}H_{27}ClN_2O_3$	182–186	59.58	59.71	8.23	8.32	8.17	8.22
8	 *d,l*	$C_{71}H_{28}ClNO_2$	144–146	65.06	65.27	8.99	8.81	4.45	4.57

effect and an effect on muscle tone. This compound demonstrated a slight sympathomimetic activity, and elicited a good phenylquinone writhing response. It also demonstrated good activity as an analgesic in the "hot plate" test method, and activity in a reversed hexobarbital test. It was also a good antipyretic.

Compound *4* acted as a mild depressant, with some effect on muscle tone, by increasing tonus. A slight phenylquinone writhing effect and a good antipyretic effect were demonstrated. There was only transient hypotensive activity.

Compound *5* acted as a mild depressant, possessing also a slight to good phenylquinone writhing effect. Good antipyretic effect was demonstrated.

Compound *6* possessed a transient hypotensive activity with a slight anti-parkinsonism effect.

Compound *7* decreased spontaneous motor activity and demonstrated some sympathomimetic activity. It had only a slight phenylquinone writhing effect. A slight analgesic effect was elicited with the "hot plate" test. Good potentiation of hexobarbital-induced sleep was noted; only slight ocular anesthetic activity was demonstrated.

Compound *8* acted as a mild depressant but showed a slight phenylquinone writhing effect. However, good activity in hexobarbital-induced sleep potentiation was noted.

EXPERIMENTAL[3]

β-Amino Ketones—The preparation of the β-amino ketones was accomplished by the following general procedure. A solution of 0.05 mole of the appropriate acetophenone, 0.05 mole of octamethyleneimine hydrochloride, 1.5 Gm. of paraformaldehyde, and 140 ml. of absolute ethanol was refluxed for 1 hr. Three-hundred milligrams of paraformaldehyde was added, and the solution was refluxed for another hour. The ethanol was then boiled off until only 25 ml. of solution remained. After cooling to room temperature, 100 ml. of acetone and 100 ml. of anhydrous ether were added. The mixture was cooled and filtered. The crystals were twice washed with 30 ml. of anhydrous ether and recrystallized from ethanol–ether.

γ-Amino Secondary Alcohols—The preparation of the γ-amino secondary alcohols was patterned after the method of Chaikin and Brown (35). The γ-amino ketone (0.05 mole) was suspended in 100 ml. of methanol and to this was added 0.1 mole of sodium borohydride. The addition was conducted at a rate such as to maintain the temperature between 20–40°. After the evolution of hydrogen had subsided, the methanol was removed first by

[3] Microanalysis was performed by Mr. G. Roberts, Jr., Florham Park, N. J. All melting points are uncorrected.

distilling, later under vacuum. The residue was suspended in 100 ml. of distilled water and extracted with three 100-ml. portions of ether. The ether was then removed under diminished pressure and the alcohol recrystallized to analytical purity from an ethanol solution.

SUMMARY

The compounds evaluated indicate that the larger ring amine components in Mannich bases show pharmacological potentialities and should be included as amine components in series. More extensive work is in progress.

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Acetylation of Acetaminophen in Tablet Formulations Containing Aspirin

By K. T. KOSHY*, A. E. TROUP, R. N. DUVALL, R. C. CONWELL, and L. L. SHANKLE

The degradation of aspirin in commercial products containing acetaminophen was found to be accompanied by the formation of diacetyl-*p*-aminophenol (DAPAP) or *p*-acetoxyacetanilid. This reaction product was not detectable using conventional acetaminophen analytical procedures, but was detected qualitatively by means of thin-layer chromatography. A procedure utilizing partition–column chromatography and gas–liquid chromatography was developed for the determination of DAPAP in products containing aspirin, acetaminophen, and caffeine. Commercial products were found to contain various levels of DAPAP up to 4 mg./tablet. Magnesium stearate was found to accelerate the reaction markedly.

THE STABILITY of aspirin *per se* in pharmaceutical dosage forms has received considerable attention and the problem is widely recognized. However, reports of the interaction of aspirin with other drugs, such as amines and phenols, have only recently begun to appear in the literature. Troup and Mitchner (1) reported that phenylephrine underwent acetylation in tablets containing aspirin. Under accelerated conditions, the mono-, di-, and triacetylated products were formed. Even at 24° the secondary amine group

Received April 11, 1967, from the Pharmaceutical Research and Development Laboratory, Consumer Products Division, Miles Laboratories, Inc., Elkhart, IN 46514
Accepted for publication June 2, 1967.
Presented to the Drug Standards, Analysis and Control Section, A.PH.A. Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.
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