Heptamethyleneimine in the Mannich Reaction I

Substituted β-Amino Ketones and Substituted γ-Amino Alcohols

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

OVER A PERIOD of years many Mannich bases have been prepared (1–25) for pharmacological testing as antispasmodics, analgesics, local anesthetics, or chemotherapeutic agents. Such compounds are prepared easily by the Mannich reaction; this consists of the condensation of formaldehyde (paraformaldehyde) with ammonia or a primary or secondary amine and a compound containing at least one active hydrogen atom. The reaction may be illustrated as

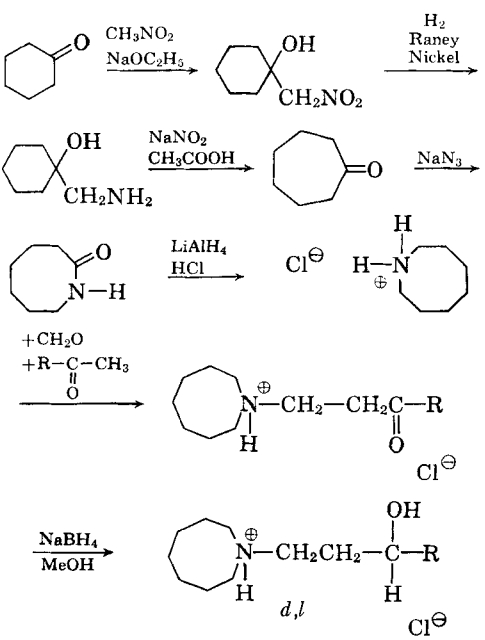
$$R{-}\overset{\overset{O}{\|}}{C}{-}CH_3 + HCHO + R_2NH\cdot HCl \rightarrow RCOCH_2CH_2NR_2\cdot HCl + H_2O$$

Most of the compounds prepared to the present have been alkylamino, dialkylamino, or 5- or 6-membered heterocyclic rings; a few large rings (amines) have been employed in this condensation. An attempt has been made to extend the Mannich reaction to larger nitrogen-containing rings and to evaluate them.

It was anticipated that the enlargement of the carbon content of the molecule would increase the lipid solubility. The method of preparing cycloheptanone was that of Boesenken and Derx (26); for heptamethyleneimine the method was that of Blicke (27). The Mannich reaction was carried out according to the original work of Tollens, in 1903 (28), and the Mannich base so obtained was reduced with sodium borohydride (29).

PHARMACOLOGY

The preliminary pharmacological results of these β-amino ketones and γ-amino alcohols (Tables I and II) are somewhat confusing, and no satisfactory SAR has been deduced. First, the *p*-nitro derivative (No. *1*) possessed an intraperitoneal LD_{50} of 175 mg./Kg. and exhibited borderline anti-inflammatory activity at 30 mg./Kg. However, when the dose was increased to 58 mg./Kg., impending toxicity precluded quantitative evaluation of true anti-inflammatory activity. The rats exhibited toxic symptoms as the dosage was increased beyond this point. The compound, therefore, appeared too toxic to warrant further investigation, and the observed anti-inflammatory activity was considered nonspecific and due to impending toxicity. No other compound exhibited anti-inflammatory activity. It would have been expected that the *p*-ethoxy compound (No. *3*, Table I) would have some local anesthetic activity since β-hexamethyleneimino-*p*-ethoxypropiophenone, "ethamine," is a very active agent (30); but no local anesthetic activity was elicited by this compound. It is noteworthy that the *p*-butoxy analog (No. 7, Table I) protected mice from electrically induced convulsions following parenteral administration of 32 mg./Kg. The intraperitoneal LD_{50} was only 95 mg./Kg.; however, the reduction of dosage to 16 mg./Kg. resulted in a loss of anticonvulsant activity.



The observation was made that the thiophene analog (No. *8*, Table I) of the Mannich base exhibited no anti-inflammatory activity following oral doses as high as 100 ml./Kg. A dosage of 150 mg./Kg., however, did produce significant analgesia. When the dose was reduced to 75 mg./Kg., all evidence of such activity disappeared. Although no toxicity was observed at 300 mg./Kg., the compound does not appear sufficiently potent for serious consideration as an analgesic agent.

A different situation was observed with the *p*-chloro compound (No. *6*, Table I); the ketone had no analgesic activity, but the alcohol (No. *14*) ex-

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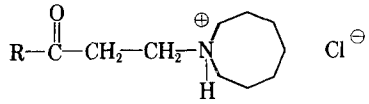
TABLE I.—MANNICH BASES



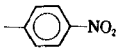
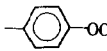
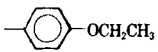
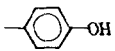
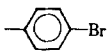
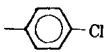
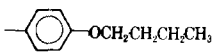
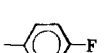
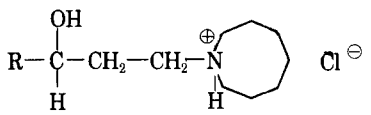
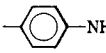
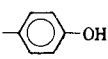
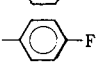
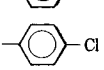
No.	R	Yield	Mol. Wt.	M.p., °C.	Formula	Anal. C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1		49	326.84	153–156	$C_{16}H_{23}ClN_2O_3$	58.92	58.81	7.05	7.01	8.59	8.61
2		50	311.87	140–141	$C_{17}H_{26}ClNO_2$	65.54	65.49	8.41	8.44	4.49	4.43
3		53	325.89	156–159	$C_{18}H_{28}ClNO_2$	61.93	62.01	8.85	8.81	4.30	4.28
4		65	297.84	161–162	$C_{16}H_{24}ClNO_2$	64.65	64.52	8.11	8.17	4.17	4.21
5		52	360.74	158–159	$C_{16}H_{23}ClNOBr$	53.38	53.36	6.41	6.49	3.88	4.79
6		45	316.25	152–153	$C_{16}H_{23}Cl_2NO$	60.77	60.63	7.33	7.28	4.46	4.76
7		70	353.90	164–165	$C_{20}H_{32}NO_2Cl$	67.87	67.74	9.11	9.04	3.93	3.98
8		24	287.84	154–155	$C_{14}H_{22}ONSCl$	58.91	58.74	7.70	7.79	4.86	4.89
9		43	299.79	128–129	$C_{16}H_{23}NOFCl$	64.09	64.10	7.73	7.69	4.66	4.79
10		30	297.84	123–124	$C_{16}H_{24}ClNO_2$	64.52	64.44	8.11	8.13	4.17	4.10

TABLE II.—SECONDARY γ-AMINOALCOHOLS



No.	R	Yield	Mol. Wt.	M.p., °C.	Empirical Formula	Anal. C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
11		76	298.81	174	$C_{16}H_{27}N_2OCl$	64.31	64.26	9.10	8.96	9.40	9.32
12		78	299.85	120–121	$C_{16}H_{26}ClNO_2$	64.09	63.91	8.77	8.65	4.49	4.69
13		67	301.80	82–83	$C_{16}H_{25}NOFCl$	63.66	63.54	8.38	8.29	4.63	4.58
14		78	318.26	117–118	$C_{16}H_{25}NOCl_2$	60.36	60.28	7.95	7.86	4.39	4.37
15		84	289.84	120–121	$C_{14}H_{24}NOSCl$	58.01	57.92	8.36	8.27	4.80	4.63

hibited remarkable analgesic activity following parenteral administration of doses as low as 32 mg./Kg. The intraperitoneal LD_{50} was in the range of 150 to 200 mg./Kg. However, no significant activity could be demonstrated following oral administration of doses as high as 120 mg./Kg.

EXPERIMENTAL[1]

4′-Nitrophenyl-β-(1 - heptamethylenimino) - ethyl Ketone Hydrochloride.—A mixture of 8.26 Gm. (0.05 mole) of *p*-nitroacetophenone, 7.48 Gm. (0.05 mole) of heptamethyleneimine hydrochloride, 1.5 Gm. of paraformaldehyde, and 50 ml. of absolute ethanol were refluxed for 32 hours. After refluxing, the ethanol was distilled until 25 ml. of solution remained. This solution was cooled in the refrigerator for 6 hours; yield, 8.1 Gm. of product (49%). The product was precipitated by adding 7 ml. of anhydrous acetone and 500 ml. of anhydrous ether to this cold solution. Recrystallization from ethanol–ether yielded 6.2 Gm. of a compound which melted in the range of 154–156°.

4′ - Hydroxyphenyl - β - (1 - heptamethylenimino)-ethyl Ketone Hydrochloride.—A mixture of 6.8 Gm. (0.05 mole) of *p*-hydroxyacetophenone, 7.48 Gm. (0.05 mole) of heptamethyleneimine hydrochloride, and 1.5 Gm. of paraformaldehyde in 50 ml. of ethanolic solution was refluxed for 3 hours. The alcohol was distilled off until 25 ml. of solution remained. The solution was then cooled for 6 hours in the refrigerator. Seven milliliters of anhydrous acetone and 500 ml. of anhydrous ether were added to this cold solution; yield, 9.7 Gm. (65%) of a compound which melted in the range of 161–162°.

2′ - Hydroxyphenyl-β - (1- heptamethylenimino)-ethyl Ketone Hydrochloride.—A solution of 6.81 Gm. (0.05 mole) of *o*-hydroxyacetophenone, 7.48 Gm. (0.05 mole) of heptamethyleneimine hydrochloride, 1.5 Gm. of paraformaldehyde, and 100 ml. of absolute ethanol was refluxed for 2 hours. An orange-red solid formed in the flask as the mixture refluxed. After cooling to room temperature, the mixture was filtered and the product washed twice with 50 ml. of ether. After recrystallization from ethanol–ether, the solid weighed 4.4 Gm. (30%) and melted in the range of 164–166°.

4′ - Methoxyphenyl-β- (1 - heptamethylenimino)-ethyl Ketone Hydrochloride.—A mixture of 7.51 Gm. (0.05 mole) of *p*-methoxyacetophenone, 7.48 Gm. (0.05 mole) of heptamethyleneimine hydrochloride, 1.5 Gm. of paraformaldehyde, and 40 ml. of absolute ethanol was heated until a solution was obtained. This solution was refluxed for 27 hours; the ethanol evaporated until 25 ml. of solution remained, and 7 ml. of anhydrous acetone and 400 ml. of anhydrous ether were added. The mixture was filtered and the solid was twice washed with 50 ml. of anhydrous ether. Recrystallization from ethanol–ether yielded 7.9 Gm. (51%) of a compound which melted in the range of 140–141°.

4′ - Bromophenyl - β - (1 - heptamethylenimino)-ethyl Ketone Hydrochloride.—An ethanolic solution of 9.95 Gm. (0.05 mole) of *p*-bromoacetophenone, 7.48 Gm. (0.05 mole) of heptamethyleneimine hydrochloride, 1.5 Gm. of paraformaldehyde, and 40 ml. of ethanol was refluxed for 3 hours. Ethanol was evaporated until 25 ml. of solution remained. This solution was cooled in the refrigerator for 6 hours; subsequently, 7 ml. of anhydrous acetone and 400 ml. of anhydrous ether were added. The resulting precipitate was filtered out of the mixture and washed twice with 50 ml. of anhydrous ether. This gave 9.5 Gm. (53%) of a compound which melted in the range of 156–159°. One recrystallization from ethanol–ether yielded 4.8 Gm. of product which melted in the range of 158–159°.

4′ - Ethoxyphenyl - β - (1 - heptamethylenimino)-ethyl Ketone Hydrochloride.—A mixture of 8.21 Gm. (0.05 mole) of *p*-ethoxyacetophenone, 7.48 Gm. (0.05 mole) of heptamethyleneimine hydrochloride, and 1.5 Gm. of paraformaldehyde in 40 ml. of absolute ethanol was refluxed for 3 hours. Ethanol was

[1] Microanalysis was performed by Mr. G. Roberts, Florham Park, N. Y. All melting points are uncorrected.

evaporated until 25 ml. of solution remained. This solution was cooled in the refrigerator for 6 hours; then 7 ml. of anhydrous acetone and 400 ml. of anhydrous ether were added. The resulting precipitate was filtered out of the mixture and washed twice with 50 ml. of anhydrous ether. This gave 9.5 Gm. (53%) of a compound which melted in the range of 156–159°. One recrystallization from ethanol–ether yielded 4.8 Gm. of product which melted in the range of 158–159°.

4′ - Chlorophenyl - β - (1 - heptamethylenimino)-ethyl Ketone Hydrochloride.—A solution of 8.7 Gm. (0.05 mole) of *p*-chloroacetophenone, 7.48 Gm. (0.05 mole) of heptamethyleneimine hydrochloride, 1.5 Gm. of paraformaldehyde, and 140 ml. of ethanol was refluxed for 1 hour. Three-hundred milligrams of paraformaldehyde was added, and the solution was refluxed for another hour. The ethanol was then boiled off until 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. Recrystallization from ethanol–ether yielded 7.2 Gm. (45%) of a compound which melted in the range of 152–153°.

4′ - Butoxyphenyl - β - (1 - heptamethylenimino)-ethyl Ketone Hydrochloride.—Seventy-five milliliters of an ethanolic solution of 9.4 Gm. (0.05 mole) of *p*-butoxyacetophenone, 7.48 Gm. (0.05 mole) of heptamethyleneimine hydrochloride, 1.4 Gm. of paraformaldehyde, and 3 drops of hydrochloric acid was refluxed for 7.5 hours, then reduced to 25 ml. This solution was cooled to room temperature, and 100 ml. of acetone and 150 ml. of ether were then added. After cooling, the mixture was filtered and the product washed twice with 50 ml. of anhydrous ether. One recrystallization from ethanol–ether yielded 12.5 Gm. (70%) of compound which melted in the range of 164–165°.

4′ - Fluorophenyl - β - (1 - heptamethylenimino)-ethyl Ketone Hydrochloride.—A mixture of 7.0 Gm. of *p*-fluoroacetophenone, 6.5 Gm. of heptamethyleneimine hydrochloride, 1.5 Gm. of paraformaldehyde, and 2 drops of hydrochloric acid was dissolved in 100 ml. of ethanol; the solution was refluxed for 7 hours. Ethanol was boiled off until 25 ml. of solution remained. After cooling to room temperature, 100 ml. of acetone and 150 ml. of ether were added; the mixture was cooled in the refrigerator and then filtered. The product was washed twice with 50 ml. of anhydrous ether. One recrystallization yielded a compound which weighed 5.8 Gm. (43%) and melted in the range of 128–129°.

2 - Thienyl - β - (1 - heptamethylenimino)-ethyl Ketone Hydrochloride.—A mixture of 5.67 Gm. (0.045 mole) of methyl-2-thienyl-ketone, 6.6 Gm. (0.045 mole) of heptamethyleneimine hydrochloride, 1.5 Gm. of paraformaldehyde, 2 drops of hydrochloric acid, and 100 ml. of absolute ethanol was refluxed for 8 hours. The volume of solution was reduced to 25 ml. After cooling to room temperature, 50 ml. of acetone and 75 ml. of dry ether were added. The product which precipitated was removed by filtration and washed with ether; yield, 2.8 Gm. (24%), m.p. 154–155°.

γ-AMINO SECONDARY ALCOHOLS

The preparation of the γ-amino secondary alcohols was patterned after the method of Chaikin and Brown (29). The secondary alcohols were all prepared by the following procedure. The β-amino ketone (0.05 mole) was suspended in 100 ml. of methanol, and the solution was placed in a 300-ml. three-necked flask fitted with a stirrer, thermometer, and reflux condenser. 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 somewhat, the methanol was removed 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–water solution or taken up again in anhydrous ether and acidified with anhydrous hydrogen chloride. The resulting hydrochloride was recrystallized to analytical purity from an ethanol–acetone solution.

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