TABLE I—EFFECT OF SELECTED ESTER TYPE PLASTICIZERS ON THE DEHYDROHALOGENATION TRANSITION OF POLYVINYL CHLORIDE

Plasticizer	Mol. Wt.	Onset[a] Temp., °C.	Peak[b] Temp., °C.	Heat of Dehydrohalogenation cal./Gm.	Kcal./mole	Polymer Wt. Loss, %
Pure polymer		243.4	278.8	30.9		
Dimethyl phthalate	194.18	258.2	266.9	16.2	3.15	76.4
Dibutyl phthalate	278.34	262.3	271.4	13.8	3.85	75.8
Dioctyl phthalate	390.53	271.4	277.9	10.9	4.27	75.9
Ditridecyl phthalate	530.0	273.8	289.2	50.7	26.9	65.5
Dioctyl adipate	370.56	271.2	275.9	10.6	3.95	76.0
Didecyl adipate	426.67	277.3	280.7	16.0	6.85	77.4
Dibutyl suberate	286.3	260.7	269.0	15.3	4.39	75.3
Dihexyl azelate	356.0	270.2	276.1	18.4	6.57	76.0
Dioctyl azelate	412.0	275.0	282.1	17.4	7.20	75.3
Dibutyl sebacete	314.0	263.5	271.7	12.6	3.95	76.0
Dioctyl sebacate	426.0	276.1	283.3	19.1	8.18	73.0
Dibenzyl sebacate	382.0	264.2	272.2	39.6	15.6	72.5
Dibutyl dodecanedioate	342.0	267.8	273.1	11.9	4.08	75.5
Trioctyl trimellitate	546.0	272.4	292.4	37.4	20.5	75.7
Trioctyl phosphate	362.40	265.4	269.6	16.7	6.07	75.5

[a] Onset temperature at which dehydrohalogenation takes place. [b] Peak temperature at which dehydrohalogenation takes place.

greater protective effect than the lower ones and that an increase in the hydrophobic moiety of the plasticizers plays an important role in the protective mechanism afforded to the PVC.

The use of differential thermal analysis for the evaluation of a group of plasticizers in regard to their protective effects under purely thermal conditions reveals that this technique can give considerable information in a relatively short period of time which should be helpful when a new plasticizer is to be considered for a polyvinyl chloride formula.

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Application of 1-(*N*-β-Hydroxyethyl-4-piperidyl)-3-(4-piperidyl)-propane in the Mannich Reaction I

Substituted β-Aminoketones

By RAJENDRA S. VARMA and W. LEWIS NOBLES

The Mannich reaction has been successfully performed using 1-(*N*-β-hydroxyethyl-4-piperidyl)-3-(4-piperidyl)propane (4-DI-PIP-OL). A series of Mannich bases has been prepared employing 4-DI-PIP-OL and various ketones. Characteristic infrared absorption bands for OH, $\overset{+}{N}H$, $-\overset{O}{\overset{\|}{C}}-$ groups are recorded. The compounds are to be screened for possible pharmacological activity.

MANNICH BASES have been prepared (1–25) for pharmacological testing as antispasmodics, analgesics, local anesthetics, or chemotherapeutic agents. Such compounds are usually prepared by the condensation of formaldehyde (paraformaldehyde) with ammonia, a primary or secondary amine, and a compound containing at least one active hydrogen atom. The condensation reaction may be illustrated as in Scheme I.

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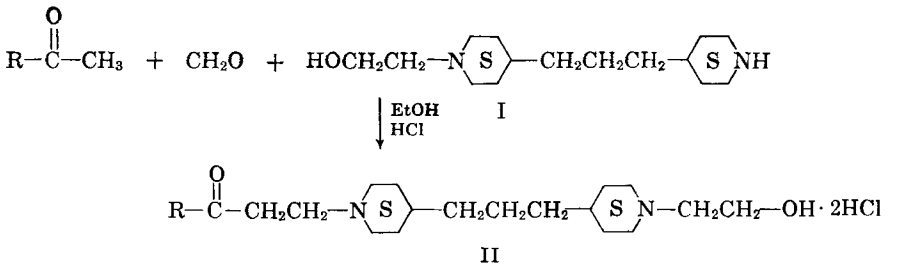
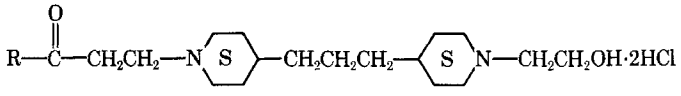


Scheme I

Mannich and Lammering (2) reported that β-piperidinopropiophenone hydrochloride possessed local anesthetic activity. Blicke and Blake (3) found that the corresponding Mannich base from 2-acetylpyrrole possessed marked activity of this type. Levvy and Nisbet (5) indicated that both piperidino and dimethylamino Mannich bases derived from 2-acetylthiophene demonstrated local anesthetic activity. Denton and his associates (6, 7) described the preparation and pharmacological evaluation of various β-dialkylaminopropiophenones and their derivatives. Many of these proved to be effective antispasmodics. Certain Mannich bases derived from α,β-unsaturated ketones have exhibited antibacterial activity (20). Many compounds prepared heretofore have possessed an alkylamino, dialkylamino, or azabicyclo amine as the amine moiety as well as a number of nitrogen heterocycles of various sizes. In this communication the Mannich reaction has been extended to include 4-DI-PIP-OL, a novel secondary amine. Recently it has been reported (26) that 1-(4-pyridyl)-3-(piperidyl)propane derivatives demonstrate anticonvulsant, antiparkinsonian, and antidepressant properties. In view of this and the multiplicity of pharmacological effects elicited by numerous ketonic Mannich bases, we have prepared a number of β-aminoketones of general structure II.

In a preliminary screening, compound *21* (Table I) has shown activity against both Gram-positive and Gram-negative bacteria. The detailed screening results will be published at a later date.

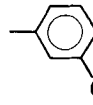
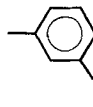
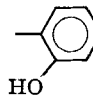
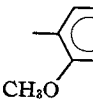
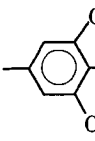
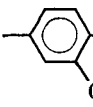
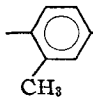
TABLE I—MANNICH BASE DIHYDROCHLORIDES



Compd.	R	M. p., °C.	Yield, %	Mol. Formula	Anal., %[d] Calcd.	Found
1	—[a]	208–210	55	$C_{24}H_{40}Cl_2N_2O_2 \cdot {}^1/_2H_2O$	C, 61.51 H, 8.82 N, 5.98	61.57 8.87 6.14
2	—CH_3 [a]	205–207	42	$C_{25}H_{42}Cl_2N_2O_2 \cdot {}^1/_2H_2O$	C, 62.23 H, 8.98 N, 5.81	62.32 8.66 6.12
3	—NO_2 [a]	210–211	49	$C_{24}H_{39}Cl_2N_3O_4$	C, 57.14 H, 7.79 N, 8.33	57.26 8.25 7.98
4	—F [a]	209–211	63	$C_{24}H_{39}Cl_2FN_2O_2$	C, 60.35 H, 8.23 N, 5.87	60.34 8.62 5.96
5	—[a] (NO_2)	190–192	50	$C_{24}H_{39}Cl_2N_3O_4$	C, 57.14 H, 7.79 N, 8.33	56.95 8.15 7.88
6	—[a] (OCH_3)	155–157	61	$C_{25}H_{42}Cl_2N_2O_3$	C, 60.77 H, 8.67 N, 5.67	60.70 8.82 6.02

(*Continued on next page.*)

TABLE I—(*Continued.*)

Compd.	R	M. p., °C.	Yield, %	Mol. Formula	Anal., %[d] Calcd.	Found
7	 [a]	194–196	63	$C_{24}H_{40}Cl_2N_2O_3$	C, 60.60 H, 8.67 N, 5.89	60.36 8.77 5.96
8	 [a]	182–183	53	$C_{25}H_{42}Cl_2N_2O_3 \cdot {}^1/_4H_2O$	C, 62.80 H, 8.96 N, 5.86	62.43 8.88 6.24
9	 [a]	201–203	58	$C_{24}H_{40}Cl_2N_2O_3$	C, 60.60 H, 8.67 N, 5.89	60.58 8.82 5.61
10	 [a]	125	30	$C_{25}H_{42}Cl_2N_2O_3 \cdot H_2O$	C, 59.15 H, 8.74	58.98 8.91
11	 [c]	222–224	73	$C_{24}H_{39}Cl_3N_2O_2$	C, 58.35 H, 7.96 N, 5.67	58.25 7.76 5.86
12	 [a]	227–229	48	$C_{24}H_{39}BrCl_2N_2O_2$	C, 53.52 H, 7.30 N, 5.20	53.39 7.31 5.03
13	 [a]	193–194	52	$C_{30}H_{44}Cl_2N_2O_2 \cdot H_2O$	C, 65.07 H, 8.38 N, 5.06	65.05 8.53 5.20
14	 [a]	189–192	49	$C_{26}H_{44}Cl_2N_2O_3$	C, 62.01 H, 8.81 N, 5.56	61.95 8.74 5.77
15	 [a]	195–196	65	$C_{24}H_{44}Cl_2N_2O_3$	C, 60.60 H, 8.67 N, 5.89	60.46 8.54 5.93
16	 [a]	184–185	36	$C_{27}H_{46}Cl_2N_2O_5 \cdot {}^1/_2H_2O$	C, 58.07 H, 8.48 N, 5.02	58.00 8.92 5.34
17	 [a]	182–185	37	$C_{25}H_{39}Cl_2F_3N_2O_2 \cdot {}^1/_2H_2O$	C, 55.95 H, 7.51 N, 5.22	55.55 7.77 5.89
18	 [a]	166–170	50	$C_{25}H_{42}Cl_2N_2O_3$	C, 61.33 H, 8.65 N, 5.72	61.21 8.79 5.91
19	 [a]	218–220	50	$C_{25}H_{42}Cl_2N_2O_3$	C, 61.33 H, 8.65 N, 5.72	61.52 8.82 5.80
20	 [a]	178–180	30	$C_{25}H_{42}Cl_2N_2O_3$	C, 61.33 H, 8.65 N, 5.72	61.40 8.81 5.84
21	 [b]	197–199	53	$C_{22}H_{38}Cl_2N_2O_2S$	C, 56.78 H, 8.23 N, 6.02	56.59 8.43 5.85

[a] Obtained by procedure *B*. [b] Obtained by procedure *A*. [c] Obtained by procedure *C*. [d] Microanalyses by Dr. A. Bernhardt, Mulheim (Ruhr), W. Germany.

EXPERIMENTAL

Melting points were taken in capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 137 spectrophotometer using a Nujol mull.

1 - (N - β - Hydroxyethyl - 4 - piperidyl) - 3 - (4-piperidyl)propane Dihydrochloride—4-DI-PIP-OL, 25.4 Gm. (0.1 mole), was suspended in 25 ml. of ethanol. Concentrated hydrochloric acid (21 ml.) was added to it in small portions with cooling and shaking. After the additions were completed, some ethanol was distilled off under vacuum and 100 ml. of acetone was added to it. On refrigeration, there was obtained the desired dihydrochloride in nearly quantitative yield, which was recrystallized to analytical purity from ethanol–acetone, m.p. 205°.

Anal.—Calcd. for $C_{15}H_{32}Cl_2N_2O$: C, 55.04; H, 9.86; N, 8.56. Found: C, 54.76; H, 9.73; N, 8.58.

N,N′ - Methylenebis[1 - (N - β - hydroxyethyl-4 - piperidyl) - 3 - (4 - piperidyl)propane] Tetrahydrochloride—To a mixture of 10.16 Gm. of 4-DI-PIP-OL, 20 ml. of ethanol, and 8.4 ml. of concentrated hydrochloric acid was added 1.2 Gm. of paraformaldehyde and the resulting reaction mixture was heated under reflux for 4 hr. At the end of this period, the reaction mixture was cooled and poured into 100 ml. of acetone. The entire mass, on refrigeration overnight, gave a viscous liquid on decantation of the upper layer of solvents. This liquid was dissolved in 20 ml. of ethanol; 50 ml. of acetone was then added. This treatment gave a white solid which was subsequently recrystallized to analytical purity from ethanol–acetone, m.p. 181–185° (softens at 75°); yield, 9.5 Gm. (71%).

Anal.—Calcd. for $C_{31}H_{64}Cl_4N_4O_2$: C, 55.84; H, 9.68; N, 8.40. Found: C, 55.49, 55.61; H, 10.25, 10.15; N, 8.32.

Mol. wt. (Rast method)—Calcd. for $C_{31}H_{64}Cl_4N_4O_2$: 666.69. Found: 692.

Mannich Base Dihydrochlorides—Three general methods were employed to synthesize these compounds.

Procedure A—The aminoketones were prepared by the general procedure of refluxing 0.1 mole of the ketone with 0.1 mole of 4-DI-PIP-OL dihydrochloride and 4.5 Gm. of paraformaldehyde in 25 ml. of absolute ethanol containing 1 or 2 drops of concentrated hydrochloric acid for 15 min. Another 1.5 Gm. of paraformaldehyde was added and refluxing continued for 2 hr. At the end of this time the warm solution was poured into 50 ml. of acetone and the contents refrigerated overnight. The solid thus obtained was recrystallized from ethanol–acetone.

Procedure B—To a suspension of 0.1 mole of 4-DI-PIP-OL in 25 ml. of ethanol was added 21 ml. of concentrated hydrochloric acid in small portions with cooling and shaking. Four and five tenths grams of paraformaldehyde was then introduced into the reaction vessel followed by the appropriate ketone. The resulting reaction mixture was refluxed for 3–5 hr. During this time the entire mixture went into solution. In a few cases, an amorphous solid product separated out at the end of this period. The contents were then poured into 50 ml. of acetone and refrigerated overnight or until a solid product separated. The product was removed by filtration and recrystallized from ethanol–acetone.

Procedure C—This method is similar to that of *B* except that aqueous 37% formaldehyde solution is used in place of paraformaldehyde.

Attempted Mannich Condensation Using Methylenebis-1-(N-β-Hydroxyethyl-4-piperidyl)-3-(4-piperidyl)propane Tetrahydrochloride—Equimolar proportions of *p*-chloroacetophenone and methylenebis amine salt were refluxed in 25 ml. of ethanol for 4 hr. Working up the reaction mixture gave only unreacted methylenebis amine salt.

Infrared Spectra of the β-Aminoketone Dihydrochlorides—Spectra of these compounds have been run in Nujol mull. In Table II are recorded absorption bands for OH, $\overset{+}{N}H$, and $-\overset{O}{\overset{\|}{C}}-$ groups. Thompson and associates (27) have reported absorption spectra of a number of tertiary amine salts and our observations are in agreement with them. Mannich bases may be regarded as tertiary amine salts and they do give bands due to $\overset{+}{N}H$. The $\overset{+}{N}H$ peak is usually broad and falls in the range of 2700–2326 cm.$^{-1}$.

TABLE II—INFRARED ABSORPTION BANDS OF β-AMINOKETONE DIHYDROCHLORIDES

	cm.$^{-1}$		
Compd.[a]	OH	$\overset{+}{N}H$	$-\overset{O}{\overset{\|}{C}}-$
1	3226	2500	1695
2	3247	2564	1667
3	3226	2445	1684
4	3236	2469	1681
5	3226	2500	1689
6	3175	2632 (w)	1664
7	3333	2632 (w)	1667
8	3247	2494	1667
9	3226	2439	1639
10	3125	2632 (w)	1660
11	3226	2500	1689
12	3226	2506	1689
13	3175	2632 (w)	1672
14	3257	2469	1669
15	3380, 3140	2600	1667
16	3226	2564 (w)	1689
17	3333	2469	1669
18	3333	2667 (w)	1660
19	3279	2464	1684
20	3340	2600	1660
21	3236	2564	1669

[a] As in Table I.

DISCUSSION

4-DI-PIP-OL was converted to the dihydrochloride salt and condensed with various substituted ketones and formaldehyde. The source of formaldehyde was either paraformaldehyde or 37% aqueous formaldehyde solution. Attempts to prepare the Mannich bases using sym-trioxane were not successful. In most cases the condensation reaction was successful, and the products were easily isolated. In few cases, however, difficulty was encountered in

obtaining a pure sample. It was observed that some of the β-aminoketone hydrochlorides were very hygroscopic in the crude state, but this characteristic diminishes when the product is pure. All compounds were purified by crystallization from ethanol–acetone; some Mannich bases were not very soluble in ethanol; therefore, a few drops of water were added to facilitate dissolution. The yields were relatively low for most of the products obtained. Low yields may be attributed to the complexity of the products which arise in the Mannich reaction. Attempts to prepare Mannich bases using 3-acetylindole, 2-acetylpyridine, and 3-acetylpyridine were not successful.

It has been shown by Henry (28) that the reaction of two equivalents of an aliphatic amine with one equivalent of formaldehyde produces the methylenediamine. The work by Ingwalson (29) in attempts to prepare the Mannich base with *N*-phenylpiperazine, formaldehyde, and 2-nitropropane led to the conclusion that the only product of the reaction was bis-(*N*-phenylpiperazyl)-methane, as the properties of the product correspond with those reported by Prelog and Blazek (30). In our hands while attempting to prepare Mannich base from indanedione, formaldehyde, and 3-azabicyclononane hydrochloride, methylenebis (azabicyclononane) dihydrochloride was isolated and the expected Mannich base did not form (31). It is known (32–34) that methylenebis amines react with compounds possessing active hydrogens to produce normal Mannich bases. The authors have prepared the methylenebis amine salt of 4-DI-PIP-OL and attempted the condensation of it with 4-chloroacetophenone, but without success.

SUMMARY

Twenty-one β-aminoketone dihydrochlorides have been synthesized utilizing 4-DI-PIP-OL as a secondary amine and several substituted ketones as active hydrogen components under Mannich conditions for biological screening. Characteristic infrared absorption bands for OH, $\overset{+}{N}H$, and carbonyl groups are described.

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