[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Syntheses of Some Substituted 1-Phenyl-2,3-diamino-1-propanols from α-Halogen Substituted Mannich Bases

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A number of substituted 1-phenyl-2,3-diamino-1-propanols have been prepared from α-halogen substituted Mannich bases derived from acetophenone and propiophenone. α,β-Dimorpholinoisobutyrophenone has been shown to undergo hydrogenolysis to α-morpholinoisobutyrophenone. Lithium aluminum hydride has been used to reduce sterically hindered ketones where catalytic methods failed. An α-bromo substituted Mannich base hydrobromide has been prepared which brominates acetone.

The α-halogen substituted Mannich bases, derived from acetophenone and propiophenone, offer an attractive route for the preparation of substituted 1-phenyl-2,3-diamino-1-propanols. Such molecules are related structurally to those compounds possessing sympathomimetic activity, as they are derivatives of ethanolamine as well as of ethylenediamine. To avoid the side reactions resulting from the use of ammonia or methylamine in the Mannich reaction, dibenzylamine and N-methylbenzylamine, respectively, were used. The N-benzyl groups were subsequently removed by catalytic hydrogenolysis.[1]

In the one case where a primary amine was used, the reaction of benzylamine with α-bromo-β-morpholinoisobutyrophenone hydrobromide, the product could not be isolated in pure form. Reduction of the crude product, however, gave a low yield of 1-phenyl-2-benzylamino-2-methyl-3-morpholino-1-propanol.

It was found that pure products were obtained more readily by bromination of the Mannich base hydrobromides than by attempting to purify the unstable α-chloro Mannich base hydrochlorides, obtainable directly from phenacyl chloride.[2] The α-bromo Mannich base hydrobromides from acetophenone were also unstable, while those derived from propiophenone were stable over a period of several months.

Diaminoketones prepared by the action of amines on the α-halo Mannich base salts were likewise found to be stabilized by the presence of an α-methyl group.

1-Phenyl-2,3-dipiperidino-1-propanol and 1-phenyl-2,3-dimorpholino-1-propanol were prepared by catalytic hydrogenation of the corresponding ketones. α,β-Dimorpholinoisobutyrophenone could not be hydrogenated under similar conditions. Attempts to catalytically reduce this compound at 80° in acetic acid resulted in its cleavage to morpholine and α-morpholinoisobutyrophenone.[3] It was readily reduced, however, by lithium aluminum hydride to the corresponding alcohol.

Removal of the N-benzyl groups by catalytic hydrogenolysis proceeded smoothly to the corresponding primary or secondary amine in good yield.

(1) J. S. Buck and R. Baltzly, THIS JOURNAL, **63**, 1964 (1941); L. Birkofer, *Ber.*, **75**, 429 (1942).

(2) A. H. Land, C. Ziegler and J. M. Sprague, THIS JOURNAL, **69**, 127 (1947).

(3) It is possible that this reaction may have involved a simple elimination of amine from a β-amino ketone followed by reduction of the resultant double bond.

Attempts to prepare the hydrochloride of α,β-dipiperidinopropiophenone were unsuccessful. The initial white precipitate quickly changed to a sticky gum from which only piperidine hydrochloride was isolated. In order to obtain more information about this cleavage reaction, α,β-dipiperidinopropiophenone was treated with aqueous hydrogen chloride. Under these conditions acetylbenzoyl was isolated in good yields, indicating that two molecules of piperidine had been eliminated. α,β-Dimorpholinopropiophenone cleaved in a similar manner but α,β-dimorpholinoisobutyrophenone was stable under similar conditions.

An interesting reaction was noted when α-bromo-β-(N-methylbenzylamino)-propiophenone hydrobromide was treated with acetone. The acetone was brominated with quantitative regeneration of β-(N-methylbenzylamino)-propiophenone hydrobromide. Since α-bromo-β-morpholinopropiophenone hydrobromide does not brominate acetone it must be concluded that the β-(N-methylbenzylamino) group must exert an activating influence for this reaction.

Experimental

Procedure A. β-Morpholinoisobutyrophenone Hydrobromide.—To 200 ml. of absolute alcohol were added 100.8 g. (0.6 mole) of morpholine hydrobromide, 80.8 g. (0.6 mole) of propiophenone, 27 g. of paraformaldehyde and 10 ml. of concentrated hydrobromic acid. Nine grams of paraformaldehyde was added after 5 hours of refluxing and another 9 g. after 10 hours of refluxing. After 15 hours the hot mixture was poured into 1200 ml. of acetone. After cooling to 5°, the crystals were removed by filtration and washed with three 125-ml. portions of cold acetone. The product was recrystallized from alcohol–acetone, yield 131 g., m.p. 174–174.5°.

Procedure B. α-Bromo-β-morpholinoisobutyrophenone Hydrobromide. — β-Morpholinoisobutyrophenone hydrobromide (118.3 g., 0.377 mole) was dissolved in 1000 ml. of hot glacial acetic acid. Bromine (60.2 g., 0.377 mole) was added dropwise with stirring at 100° over a period of one-half hour. The mixture was heated at 100° for an additional 2 hours. After cooling to room temperature, precipitation was completed by the addition of anhydrous ether. The product was removed and washed with five 150-ml. portions of dry ether, yield 134.6 g., m.p. 159.5–160.5°. After recrystallization from absolute alcohol, a sample melted at 160.5–161.5°.

α-Bromo-β-morpholinopropiophenone hydrobromide was prepared in a similar manner. α-Bromo-β-(N-methylbenzylamino)-propiophenone hydrobromide could not be isolated as a solid. It was isolated as an oil after removal of the acetic acid by vacuum distillation and was used in this form for further reactions.

Procedure C. α,β-Dipiperidinopropiophenone Hydrochloride.—Twenty grams (0.0695 mole) of α-chloro-β-piperidinopropiophenone (2) was dissolved in 500 ml. of water at room temperature. This solution was added dropwise, with stirring, to 17.7 g. (0.208 mole) of piperidine in

TABLE I

Mannich base hydrobromides, $C_6H_5COC(R)H—CH_2—N(R')—R''\cdot HBr$

R	R′ / N—R″	R‴ / N—R^{IV}	Yield, %[a]	M.p., °C.[b]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	Morpholino-		82	189.5–190.5[c]	52.01	6.04	4.67	52.19	6.36	4.58
CH_3	Morpholino-		70	174–174.5[c]	53.51	6.42	4.46	53.34	6.38	4.48
H	$C_6H_5CH_2N(-CH_3)-$		84	199–200[d]	61.08	6.03	4.19	61.27	6.03	4.17
	α-Bromo Mannich base hydrobromides, $C_6H_5COC(R)Br—CH_2—N(R')—R''$									
H	Morpholino		95[e]	175–176[g]	41.18	4.53	3.70	41.47	4.48	3.78
CH_3	Morpholino		91[e]	160.5–161.5[d]	42.77	4.87	3.56	42.96	4.73	3.58
H	$C_6H_5CH_2N(-CH_3)-$		[f]							
	α-Amino Mannich bases, $C_6H_5COC(R)—CH_2—N(R')—R''$ with $R''—N—R^{IV}$									
H	Piperidino-	Piperidino-	67	73.5–74[d]	75.96	9.40	9.33	75.99	9.26	9.35
H	Morpholino-	Morpholino-	50	77.5–78.5[h]	67.08	7.95	9.20	67.00	7.95	9.17
CH_3	Morpholino-	Morpholino-	96	84–84.6[i]	67.90	8.23	8.80	68.02	8.34	8.61
CH_3	Morpholino-	$C_6H_5CH_2NH-$	[f]							
H	Morpholino-	$(C_6H_5CH_2)N-$	[f]							
CH_3	Morpholino	$(C_6H_5CH_2)_2N-$	84	130.5–131.5[i]	78.47	7.53	6.54	78.60	7.69	6.52
H	$C_6H_5CH_2N(-CH_3)-$	Morpholino	[f]							

[a] Yields of pure products. [b] Cor. m.p. [c] Recryst. from alcohol–acetone. [d] Recryst. from alcohol. [e] Crude yields. [f] Not isolated in pure form. [g] Recryst. from acetone. [h] Recryst. from alcohol–water. [i] Recryst. from ether.

TABLE II

1-PHENYL-2,3-DIAMINO-1-PROPANOLS $C_6H_5CHOH—C(R)—CH_2—N(R')—R''$ with $R''—N—R^{IV}$

R	R′ / N—R″	R‴ / N—R^{IV}	Method of preparation	Yield,[a] %	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	Piperidino-	Piperidino-	E	68	105.5–106[b]	75.46	10.00	9.27	75.55	9.81	9.29
H	Morpholino-	Morpholino-	DE	67	107–108[c]	66.64	8.55	9.14	66.84	8.68	8.97
CH_3	Morpholino-	Morpholino-	F	87	126–130[c]	67.47	8.81	8.74	67.64	8.90	8.79
CH_3	Morpholino-	$C_6H_5CH_2NH-$	DF	10	131–131.5[b]	74.25	8.31	8.25	74.20	8.20	8.19
H	Morpholino-	$(C_6H_5CH_2)_2N-$	DF	71	134.5–135[b]	77.85	7.74	6.73	78.08	7.83	6.66
H	Morpholino-	H_2N-	G	77	91–92[d]	66.07	8.53	11.86	66.12	8.39	11.82
CH_3	Morpholino-	$(C_6H_5CH_2)_2N-$	F	73	113.5–114.5[b]	78.10	7.96	6.51	78.25	7.91	6.37
H	$C_6H_5CH_2N(CH_3)—$	Morpholino-	B, D, F	38	101–101.5[c]	74.25	8.31	8.25	74.07	8.49	8.02
H	CH_3NH-	Morpholino-	G	78	96.4–96.8[d]	67.17	8.86	11.19	67.20	9.04	11.20

[a] Yields of pure products. [b] Recryst. from acetone–water. [c] Recryst. from alcohol–water. [d] Recryst. from hexane.

200 ml. of water. The temperature was maintained below 10°. The yellow product which separated was removed and washed thoroughly with cold water. The product was vacuum dried at room temperature, yield 14 g. Since this compound loses piperidine rapidly when warmed, it was necessary to employ low temperature recrystallization. The crude product was dissolved in 150 ml. of dry alcohol at room temperature. A small amount of orange residue was removed and water added dropwise until precipitation was imminent. The solution was then cooled in a Dry Ice–acetone-bath for a short time and the product removed by filtration, m.p. 73.5–74°. Attempts to prepare the hydrochloride of α,β-dipiperidinopropiophenone, by treating an ether solution of the latter with dry hydrogen chloride at low temperature, gave a white solid which rapidly changed to a sticky gum. Ether–alcohol extraction of this material gave only piperidine hydrochloride. In order to obtain more information concerning this reaction, the free base was treated with hydrochloric acid.

Acid Hydrolysis of α,β-Dipiperidinopropiophene.—Sixty-three grams of the base was dissolved in hydrochloric acid (52.5 ml. of concd. HCl + 300 ml. of H_2O). The resulting solution was diluted to 650 ml. and allowed to stand for 5 days. The oil which separated was extracted with ether and dried over anhydrous magnesium sulfate. Fractional distillation gave 18.90 g. (61% yield) of acetylbenzoyl, b.p. 223°, m.p. of osazone 142.5–144.5°.[4]

Procedure D. α,β-Dimorpholinopropiophenone.—Ten grams (0.0264 mole) of powdered α-bromo-β-morpholinopropiophenone was added with stirring over a period of 15 minutes to 6.9 g. (0.079 mole) of morpholine in dry alcohol. The temperature was kept below 30°. The mixture was stirred for an additional 15 minutes. Anhydrous ether (250 ml.) was added and after standing for a short time the morpholine hydrobromide was removed by filtration. After removing the ether from the filtrate, water was added until precipitation was about to occur. The solution was cooled to 0° and after standing for a short time the product was removed, washed and dried, m.p. 77.5–78.5°. This compound similar to α,β-dipiperidinopropiophenone failed to give a stable hydrochloride when treated in dry ether solution with dry hydrogen chloride.

The other α-amino Mannich bases were prepared by this procedure, but α-benzylamino-β-morpholinoisobutyrophenone, α-dibenzylamino-β-morpholinopropiophenone and α-morpholino-β-(N-methylbenzylamino)-propiophenone were obtained only as unstable oils. They were used in this form for the preparation of the corresponding alcohols.

Procedure E. 1-Phenyl-2,3-dipiperidino-1-propanol.—α,β-Dipiperidinopropiophenone, 14.65 g. (0.0488 mole) in 135 ml. of dry alcohol was hydrogenated using a platinum oxide catalyst. After removing the catalyst, the solution was heated to boiling and water added to the point of incipient precipitation. On cooling to 0° the alcohol separated in crystalline form. It was recrystallized from acetone–water, yield 93%, m.p. 107–108°.

Procedure F. 1-Phenyl-2-methyl-2,3-dimorpholino-1-propanol.—To 1.70 g. (0.0450 mole) of lithium aluminum hydride in 80 ml. of ether, was added a solution of 22.55 g. (0.0709 mole) of α,β-dimorpholinoisobutyrophenone in 80

(4) H. Muller and H. von Pechmann, *Ber.*, **22**, 2128 (1889).

ml. of dry ether. The rate of addition permitted slow refluxing. Stirring was continued for 15 minutes after the addition was complete. Water was then added with stirring until no more hydrogen was evolved. The solution was cooled to 0° and sulfuric acid (18.6 ml. concd. acid in 100 ml. of water) added. Stirring was continued for an additional hour and the mixture allowed to stand overnight. The ether was discarded and the aqueous layer was added gradually to a solution of 63.2 g. of sodium hydroxide in 200 ml. of water with stirring. The temperature was kept below 10°. The white precipitate was removed and washed with 200 ml. of water. The residue was refluxed with 100 ml. of alcohol and the insoluble material was removed by filtration. While the filtrate was refluxed, 200 ml. of water was slowly added. On cooling the resulting solution to 5°, the alcohol crystallized. The product was recrystallized by this same procedure, yield 90%, m.p. 126–130°. Further recrystallization did not alter the melting point.

Procedure G. 1-Phenyl-2-morpholino-3-methylamino-1-propanol.—α-Morpholino-β-(N-methylbenzylamino)-propiophenone, 13.28 g., in 150 ml. of alcohol was hydrogenated at 75° using a palladium-on-carbon catalyst. The reaction was complete in 1.5 hours. After removing the catalyst, the alcohol was removed by vacuum distillation leaving a glassy residue. The latter was dissolved in 250 ml. of hexane, filtered and the filtrate cooled to 0°. The product separated as white needles, m.p. 96–96.5°. Another recrystallization from hexane gave an 80% yield, m.p. 96.4–96.8°.

Hydrogenolysis of α,β-Dimorpholinoisobutyrophenone to α-Morpholinoisobutyrophenone.—The dimorpholino compound was hydrogenated in glacial acetic acid solution at 80° in the presence of a palladium–carbon catalyst. When hydrogenation was complete, the solution was diluted and filtered. The filtrate was added dropwise to a sodium hydroxide solution kept at 0–5°. The mixture was then extracted with ether. The ether solution was dried and the product precipitated as its hydrobromide. The latter was recrystallized from dry ethanol, yield 80%, m.p. 235–236°.

Anal. Calcd. for $C_{14}H_{19}NO_2 \cdot HBr$: C, 52.01; H, 6.10; N, 4.67. Found: C, 52.30; H, 6.41; N, 4.51.

A sample of the free base was made by adding a cold dilute solution of sodium hydroxide to an aqueous solution of the hydrobromide. The precipitated base after washing with water and drying in vacuum melted at 43.1–43.4°.

Preparation of 1-Phenyl-2-morpholino-2-methyl-1-propanol.—Twelve grams of crude α-morpholinoisobutyrophenone was dissolved in 60 ml. of dry ether and reduced with 1.45 g. of lithium aluminum hydride in 60 ml. of dry ether. Water was then added to decompose the excess reducing agent and the resulting solids dissolved with 8 ml. of sulfuric acid in 50 ml. of water. This solution was added gradually to a solution of 36 g. of sodium hydroxide in 150 ml. of water with stirring and cooling. The ether layer was removed and the aqueous layer again extracted with ether. After removing the ether, the residual oil was dried in a vacuum desiccator over sodium hydroxide. The oil was then dissolved in dry ether and the hydrochloride precipitated with dry hydrogen chloride. Recrystallization from dry alcohol gave a pure product, yield 50%, m.p. 231.3–231.8° dec. The free base was obtained by addition of dilute sodium hydroxide solution to an aqueous solution of the hydrochloride. It was recrystallized from 50% alcohol, m.p. 73.8–74.2°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.32; H, 8.95; N, 6.08.

Reaction of α-Bromo-β-(N-methylbenzylamino)-propiophenone Hydrobromide with Acetone.—Fourteen grams of the oil obtained from the bromination of β-(N-methylbenzylamino)-propiophenone hydrobromide was dissolved by shaking with 200 ml. of acetone. Just as the last of the oil dissolved, colorless crystals began to appear. After standing overnight, the mixture was cooled to 0° and filtered. The filtrate had strong lachrymatory properties. The crystals, after washing with acetone and drying, melted at 198–199° and no depression was noted when mixed with β-(N-methylbenzylamino)-propiophenone. Recovery was quantitative.

The possibility that the brominated β-(N-methylbenzylamino)-propiophenone was a perbromide was considered but was thought to be improbable for several reasons. The yields of the crude oil, 60–70%, were not high enough to warrant the assumption that more than one bromine atom was present. When the β-(N-methylbenzylamino)-propiophenone was treated with 1 mole of bromine, the latter was almost completely decolorized, large amounts of hydrogen bromide were evolved and the resulting bromo compound coupled normally with 2 moles of morpholine to give excellent yields of morpholine hydrobromide and α-morpholino-β-(N-methylbenzylamino)-propiophenone.

PHILADELPHIA 4, PENNSYLVANIA

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Identification of "β-Dihydroxanthopterin" as 2,4-Diamino-6-hydroxy-*p*-oxazino(2,3-d)pyrimidine

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The "β-dihydroxanthopterin," previously obtained by the cyclization of 5-chloroacetamido-2,4-diamino-6-hydroxypyrimidine, and assigned the 7,8-dihydroxanthopterin structure, has now been identified as 2,4-diamino-6-hydroxy-*p*-oxoazino(2,3-d)pyrimidine. Proof of structure rests on the identification of the hydrolytic cleavage product as 6-carboxymethoxy-2,4,5-triaminopyrimidine, rather than 2,5-diamino-6-hydroxypyrimidyl-4-aminoacetic acid as previously supposed. This identification follows from the reaction of the acid with glyoxal to give 2-amino-4-carboxymethoxypteridine, and synthesis of its ethyl ester from 2,4-diamino-6-chloropyrimidine *via* 5-*p*-chlorobenzeneazo-2,4-diamino-6-carbethoxymethoxypyrimidine. Cyclization of the 6-carbethoxymethoxy-2,4,5-triaminopyrimidine occurs spontaneously in alkaline solution to give a product identical with that obtained from the 5-chloroacetamidopyrimidine.

Several years ago the preparation was reported of a compound believed to be 7,8-dihydroxanthopterin (V) on the basis of its synthesis from 5-chloroacetamido-2,4-diamino-6-hydroxypyrimidine (VI).[1] This compound was designated as "β-dihydroxanthopterin" since it was found to differ in its physical and chemical properties from the "α-dihydroxanthopterin" obtained by the catalytic reduction of xanthopterin,[2] the sodium–amalgam reduction of leucopterin,[3,4] or the decarboxylation of dihydroxanthopterincarboxylic acid.[5] The outstanding chemical difference between the α- and β-isomers was the ease with which the α-isomer could be

(1) G. H. Hitchings and G. B. Elion, THIS JOURNAL, **71**, 467 (1949).

(2) B. L. O'Dell, J. M. Vandenbelt, E. S. Bloom and J. J. Pfiffner, *ibid.*, **69**, 250 (1947).

(3) J. R. Totter, *J. Biol. Chem.*, **154**, 105 (1944).

(4) G. B. Elion, A. E. Light and G. H. Hitchings, THIS JOURNAL, **71**, 741 (1949).

(5) R. Purrmann, *Ann.*, **548**, 284 (1941).