of the hydrochloride with shaking after each addition). The crude amide (m.p. 126–128°) was recrystallized once from dry benzene and then melted at 126.5–128.5°. No depression in melting point was observed on admixture with *trans*-N-(*p*-nitrobenzoyl)-2-chlorocyclopentylamine.[10] As a further check on its identity, the *p*-nitrobenzamide was converted, in 92% yield, to *cis*-2-*p*-nitrophenyl-4,5-trimethyleneoxazoline.[5]

Similar attempts at ring closure using the *cis*-*p*-nitrobenzamide (IIIb) led invariably to recovery of starting material.

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Mannich Bases Derived from α-Phenoxyacetophenones

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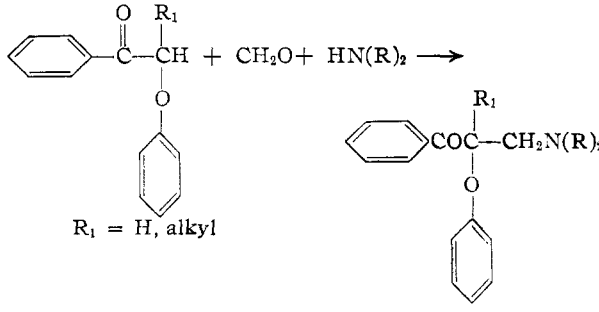
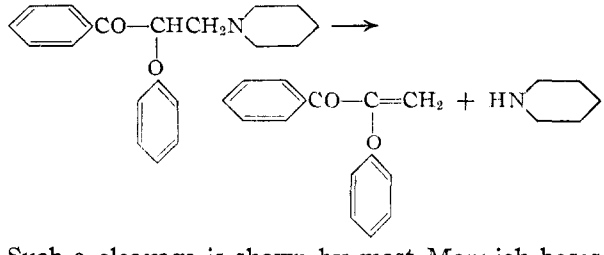
RECEIVED JULY 10, 1952

We have found that α-phenoxyacetophenones readily undergo the Mannich reaction. A survey of the literature[1,2] indicated that substituted acetophenones of this type have not been used in this reaction. The compounds used in the present work were α-phenoxyacetophenone, various ring-substituted α-phenoxyacetophenones and α-phenoxypropiophenone. The general reaction may be depicted as



The reactions were carried out by heating the ketone under reflux either with the amine hydrochloride and paraformaldehyde in the presence of a small amount of concentrated hydrochloric acid (procedure A) or with the amine and formaldehyde solution (procedure B). The compounds prepared are listed in Table I.

Attempted purification by distillation under reduced pressure of the Mannich base formed by the reaction of piperidine, α-phenoxyacetophenone and formaldehyde caused the elimination of piperidine with the resulting olefin being the only product which could be isolated.



Such a cleavage is shown by most Mannich bases when subjected to heat or distillation.[1,3]

(1) *Cf.* F. F. Blicke in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 303.

(2) H. Karbe, *Arch. Pharm.*, **283**, 48 (1950).

(3) J. H. Burckhalter and R. C. Fuson, THIS JOURNAL, **70**, 4184 (1948).

The first two amino ketones listed in Table I were reduced to the corresponding carbinols by catalytic reduction using palladium-on-charcoal as a catalyst. In each case only one diastereoisomeric form was isolated.

Experimental[4]

α-Phenoxy-*p*-(*n*-propoxy)-acetophenone.—To a stirred solution of 25.95 g. of *p*-(*n*-propoxy)-acetophenone in 100 ml. of ether at 10–15° was added dropwise 23.3 g. of bromine. After a short time a large amount of solid separated. The ether was removed *in vacuo* and a solution of 14.1 g. of phenol and 7.05 g. of sodium hydroxide in 70 ml. of water was added to the residue. The mixture was stirred and heated under reflux for 14 hours and, when cool, was extracted with ether. The ethereal extracts were washed with water, the ether removed by distillation and the residue was distilled *in vacuo* through a short Vigreux column; yield 19.1 g. (49%), b.p. 180–190° (0.6 mm.). The distillate solidified upon standing. Recrystallization from cyclohexane–petroleum ether gave colorless platelets melting at 49–50.5°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.57; H, 6.42.

α-(*p*-*n*-Propoxyphenoxy)-acetophenone.—A mixture of 19.9 g. (0.10 mole) of phenacyl bromide, 15.2 g. (0.10 mole) of *p*-*n*-propoxyphenol, 18.5 g. of anhydrous potassium carbonate and 200 ml. of acetone was heated under reflux with continuous stirring for 7 hours. The reaction mixture was cooled and then diluted with 200 ml. of water. The aqueous acetone mixture was extracted with ether. The ethereal solution after washing twice with 100-ml. portions of 10% sodium hydroxide was dried over sodium sulfate and then concentrated. The residual oil was crystallized from 2:1 ethyl alcohol–water. The cream-colored crystalline material was purified by recrystallization from 100 ml. of ethyl alcohol. The product was collected as colorless needles melting at 56.5–58°, wt. 22.5 g. (83%).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.89, 75.44; H, 7.06, 6.78.

α-(*p*-Chlorophenoxy)-acetophenone was prepared by the method described above for α-(*p*-*n*-propoxyphenoxy)-acetophenone using the corresponding amount of *p*-chlorophenol. The yield of crude product, melting at 96–97.5°, was 90%. Recrystallization from 3-A alcohol[5] gave large glistening plates melting at 98–99°.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.16; H, 4.50; Cl, 14.37. Found: C, 68.25; H, 4.57; Cl, 14.66.

β-(Diethylamino)-α-phenoxypropiophenone Hydrochloride (Procedure A).—The procedure used was essentially that of Mannich and Lammering.[6] A mixture of 2.19 g. (0.02 mole) of diethylamine hydrochloride, 1 drop of concentrated hydrochloric acid, 0.9 g. (0.03 mole) of paraformaldehyde, 4.24 g. (0.02 mole) of α-phenoxyacetophenone[7] and 6 ml. of absolute ethanol was heated under reflux on a steam-bath. After a short time a homogeneous solution was obtained and refluxing was continued for 1 hour. Two additional 0.6-g. (0.02 mole) portions of paraformaldehyde were added and refluxing continued for an additional 2 hours after each portion had been added. After standing overnight the yellow solution was poured into 30 ml. of water and the resulting mixture extracted with ether and the ether extracts discarded. The aqueous layer was made alkaline with ammonium hydroxide and the resulting mixture extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate and the hydrochloride prepared by the addition of an ethereal hydrogen chloride solution. The yield was 4.50 g. (68%), m.p. 128–129°. One recrystallization from methyl ethyl ketone–ethyl acetate (1:1) gave material melting at 128.5–129°.

β-(Dimethylamino)-α-(*p*-*n*-propoxyphenoxy)-propiophenone Hydrochloride (Procedure B).—Ten milliliters of 37% formaldehyde solution was added dropwise at 0° to a well-stirred solution of dimethylamine (slight excess) in 150 ml. of

(4) All melting points are corrected for stem exposure, unless otherwise indicated.

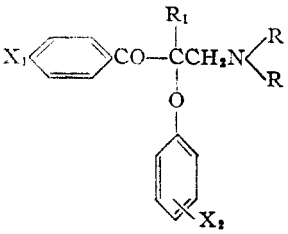
(5) Commercially denatured ethanol containing 5% methanol.

(6) C. Mannich and D. Lammering, *Ber.*, **55**, 3510 (1922).

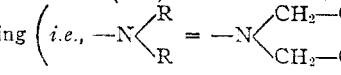
(7) R. Mohlau, *ibid.*, **15**, 2498 (1882).

TABLE I

MANNICH BASES FROM α-PHENOXYACETOPHENONES



X_1	X_2	R_1	R	Yield, %	Procedure	Hydrochloride m.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	H	CH_3	78	A	153–154[a,b]	$C_{17}H_{19}NO_2 \cdot HCl$[h]	66.77	6.59	4.58	66.40[d]	6.52	4.49
H	H	H	C_2H_5	68	A	128.5–129.0[a]	$C_{18}H_{21}NO_2 \cdot HCl$[i]	68.35	7.25	4.20	68.31	6.97	4.58[e]
n-C_3H_7O-	H	H	Piperidiue[n]	77	A	88–90[a]	$C_{23}H_{29}NO_2 \cdot HCl$[h]	68.38	7.49	3.47	68.48	7.77	3.38
H	*p*-Cl	H	C_2H_5	73	A	104.5–105.5[a]	$C_{19}H_{22}NClO_2 \cdot HCl$[j]	61.96	6.29	3.80	61.96	6.24	3.95
H	*p*-*n*-C_3H_7O	H	CH_3	58	B	152.5–154[c]	$C_{20}H_{25}NO_3 \cdot HCl$[k]	66.01	7.20	[f]	66.36	7.19	[f]
H	H	CH_3	CH_3	62	B[m]	188–189.5[c]	$C_{18}H_{21}NO_2 \cdot HCl$[l]	67.59	6.94	[g]	67.75	6.87	[g]

[a] Corrected for stem exposure. [b] The free base melted at 56.5–57.5°. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.11; H, 7.11; N, 5.48. [c] Determined on a Fischer–Johns melting-point block, uncorrected for stem exposure. [d] Calcd. for Cl, 11.59; found, 11.39. [e] Calcd. for Cl, 10.62; found, 10.52. [f] Calcd. for Cl, 9.74; found, 9.90. [g] Calcd. for Cl, 11.09; found, 11.06. [h] Recrystallized from methyl ethyl ketone. [i] Recrystallized from methyl ethyl ketone–ethyl acetate (1:1). [j] Recrystallized from ethyl acetate. [k] Recrystallized from ethyl alcohol–ether (1:2). [l] Recrystallized from ethyl alcohol–ether (1:1). [m] The reflux time was increased from 4 to 17 hours. [n] The R groups are incorporated into a piperidine ring (*i.e.*, ).

95% ethanol. The colorless solution was allowed to warm to room temperature and then 27 g. (0.10 mole) of α-(*p*-*n*-propoxyphenoxy)-acetophenone was added. After heating under reflux for 4 hours the reaction mixture was diluted with 250 ml. of water and then extracted with ether. The ethereal extract was extracted with dilute hydrochloric acid solution, the acid extract basified with dilute sodium hydroxide solution and the resulting mixture extracted with ether. Concentration of the ethereal solution gave a brown oil. To this oil was added ethanolic hydrogen chloride solution and then ether. The resulting oily hydrochloride upon recrystallization from anhydrous ethanol–ether gave 18.0 g. (58%) of product melting at 152.5–154° (uncor.).

α-Phenoxyacrylophenone.—When the crude Mannich base obtained from piperidine hydrochloride, paraformaldehyde and α-phenoxyacetophenone (procedure A) was distilled twice[8] *in vacuo* through a 6″ Vigreux column there was obtained a nitrogen-free, golden yellow oil boiling at 147° (1.2 mm.). Upon standing, it very quickly set to a glassy solid. The over-all yield from α-phenoxyacetophenone was 65%.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.40. Found: C, 80.49; H, 5.62.

3-Diethylamino-2-phenoxy-1-phenylpropanol-1.—A mixture of 16.92 g. (0.0507 mole) of β-diethylamino-α-phenoxypropiophenone hydrochloride in 125 ml. of 95% ethanol was reduced at approximately three atmospheres pressure using 0.5 g. of 10% palladium-on-charcoal as catalyst. After the absorption of hydrogen was complete (*ca.* 8 hours) the catalyst was removed by filtration and the alcoholic solution was concentrated to dryness, the last traces of solvent being removed *in vacuo*. The colorless sirup crystallized on standing; wt. 17.0 g. (100%), m.p. 147.5–148.5°. One recrystallization from methyl ethyl ketone gave colorless rectangular prisms, melting at 149.5–150.5; wt. 14.51 g. (85%).

Anal. Calcd. for $C_{19}H_{25}NO_2 \cdot HCl$: C, 67.94; H, 7.80; N, 4.17; Cl, 10.56. Found: C, 67.89; H, 7.59; N, 4.26; Cl, 10.66.

3-Dimethylamino-2-phenoxy-1-phenylpropanol-1 was prepared in an analogous way from β-dimethylamino-α-phenoxyacetophenone hydrochloride except that the hydrogenation was carried out in an alcohol–water (2:1) solution. The crude product was recrystallized from a methyl ethyl ketone–absolute ethanol mixture (15:1) to give fine colorless needles melting at 160–160.5°; yield 71%.

Anal. Calcd. for $C_{17}H_{21}NO_2 \cdot HCl$: C, 66.33; H, 7.21; N, 4.55; Cl, 11.52. Found: C, 66.85; H, 7.13; N, 4.63; Cl, 11.59.

(8) Analysis of the once-distilled product, which boiled somewhat higher than the final product, indicated a mixture of Mannich base and olefin.

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The Structure of N,N′-Diglycyl-L-cystine Dihydrate

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RECEIVED JULY 3, 1952

In the course of our investigations of peptide structures we have determined the complete crystal structure of N,N′-diglycyl-L-cystine dihydrate[1] by X-ray methods.

Single crystal oscillation and Weissenberg photographs showed that the crystals are monoclinic with the unit cell dimensions $a = 12.26$ Å., $b = 4.84$ Å., $c = 17.17$ Å., $\beta = 124°24'$. The experimentally determined crystal density, 1.56 g./cm.^{3}, indicated that there are two (calculated as 2.02) peptide molecules per cell. The X-ray diffraction data showed Laue symmetry 2/m, and A centering, giving A2, Am or A2/m as possible space groups for the crystal. However the general positions of these space groups are at least fourfold whereas the density and unit cell dimensions showed only two molecules per cell. Therefore in any one of the possible space groups the peptide molecules would have to lie in special positions. As it seemed unlikely that the molecules could have symmetry m or 2/m, but might have symmetry 2, the A2 space group was selected as being most probably correct. A sketch of the molecules, viewed along its twofold axis, appears below.

A trial structure was deduced from Patterson projections and sections and refined by Fourier and least squares methods. Three dimensional data were used in the refinement process. The bond lengths and angles calculated from the final atomic

(1) J. Greenstein, *J. Biol. Chem.*, **128**, 241 (1939).