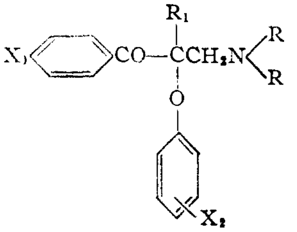
TABLE I

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]	$C_{19}H_{23}NO_2 \cdot HCl$[i]	68.35	7.25	4.20	68.31	6.97	4.58[e]
n-C_3H_7O-	H	H	Piperidine[n]	77	A	88–90[a]	$C_{23}H_{29}NO_3 \cdot HCl$[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 $\left(i.e., —N\begin{matrix} R \\ R \end{matrix} = —N\begin{matrix} CH_2—CH_2 \\ CH_2—CH_2 \end{matrix}CH\right)$.

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.

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

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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., β = 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

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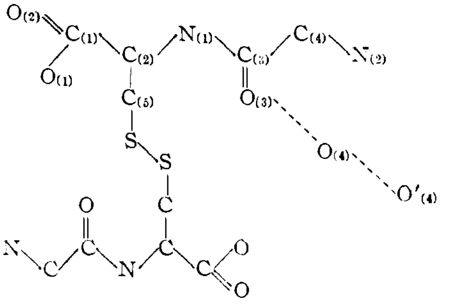
(8) Analysis of the once-distilled product, which boiled somewhat higher than the final product, indicated a mixture of Mannich base and olefin.

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

coördinates are given in the following tables. The numbering scheme used to identify the atoms in the asymmetric unit should be clear from the accompanying sketch.



BOND LENGTHS IN N,N'-DIGLYCYL-L-CYSTINE DIHYDRATE

Bond	R_{ij} Å.	Hydrogen bond	R_{ij} Å.
S–S	2.04	N_1—O_3	3.31
S–C_5	1.86	N_2—O_1	2.75
C_5–C_2	1.52	N_2—O_1'	2.89
C_2–C_1	1.55	N_2—O_2	2.75
C_1–O_1	1.24	O_4—O_4'	2.91
C_1–O_2	1.21	O_4—O_3	3.13
C_2–N_1	1.48		
N_1–C_3	1.35	Average probable error in distances is 0.02 Å.	
C_3–O_3	1.21		
C_3–C_4	1.55	O_4 refers to the oxygen atom of the water of hydration.	
C_4–N_2	1.46		

BOND ANGLES IN N,N'-DIGLYCYL-L-CYSTINE DIHYDRATE

Angle	θ, degrees	Hydrogen bond angle	θ, degrees
S–S–C_5	103	C_4–N_2—O_1'	85
S–C_5–C_2	105	C_4–N_2—O_1	129
C_5–C_2–C_1	117	C_4–N_2—O_2	112
C_5–C_2–N_1	118	C_1–O_1—N_2	143
C_1–C_2–N_1	109	C_1–O_1—N_2'	96
O_1–C_1–O_2	127	C_1–O_2—N_2	126
C_2–C_1–O_1	115	C_3–O_3—N_1	144
C_2–C_1–O_2	118	C_2–N_1—O_3	140
C_2–N_1–C_3	122	C_3–N_1—O_3	96
N_1–C_3–O_3	125	C_3–O_3—O_4	106
C_4–C_3–O_3	121	O_3—O_4—O_4'	118
N_1–C_3–C_4	113	Average probable error in angles is 1°	
C_3–C_4–N_2	109		

One of the many interesting features of this structure is the long hydrogen bond (3.31 Å.) existing between the respective amide groups of molecules related by the *b* repeat. Van der Waals repulsions between the molecules involved seem to be responsible for the unusual length. This weak bond is accompanied by a slight non-planarity of the amide group of the molecule. The non-planarity, which corresponds to a rotation of approximately 6° about the N_1–C_3 bond, introduces a strain energy calculated to be only 0.4 kcal./mole, however. The slightly long N_1–C_3 bond and the short C_3–O_3 bond may also be a consequence of the weak N_1–O_3 hydrogen bond.

The disposition of hydrogen bonds about the terminal nitrogen atom leaves no doubt concerning the zwitterion nature of this peptide. It may also be mentioned that the C_5–S–S–C_5' dihedral angle is calculated to be in 101° in good agreement with the value found in S_8.[2] A more complete description of this investigation will appear shortly.

The authors wish to thank Dr. E. J. Cohn of Harvard University who kindly made available a sample of N,N'-diglycyl-L-cystine for this work.

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(2) B. E. Warren and J. T. Burwell, *J. Chem. Phys.*, **3**, 6 (1935).

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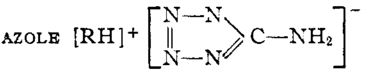
NEW COMPOUNDS

Salts of 5-Aminotetrazole

The salts listed in Table I were prepared by either of two methods: (1) Equivalent quantities of anhydrous 5-aminotetrazole and the appropriate anhydrous amine or free guanidine base were caused to react in a minimum volume of hot, absolute methanol or ethanol; if the product did not crystallize upon cooling, a small volume of diethyl ether was added. (2) Equivalent quantities of 5-aminotetrazole monohydrate and the appropriate carbonate or bicarbonate salt of the base were dissolved in a small volume of water; the solution was evaporated to dryness to give the salt. These salts were recrystallized from absolute methanol, ethanol or mixtures of ethanol and diethyl ether. All of these salts were very soluble in water and in general were also appreciably soluble in methanol or ethanol. Salts derived from very volatile bases were unstable and readily dissociated into the free base and a residue of 5-aminotetrazole. For example, methylamine could be completely removed from its salt by heating at 80 to 100° for a few hours or by evacuating continuously at room temperature for a few days. For this reason the melting points of some of these salts were rather indefinite even when the sample was sealed in a capillary.

TABLE I

SALTS OF 5-AMINOTETRAZOLE $[RH]^+$



R	Formula	M.p., °C.[a]	Nitrogen,[b] % Calcd.	Nitrogen,[b] % Found
Hydrazine[c]	CH_7N_7	124–125	[d]	[d]
Methylamine	$C_2H_8N_6$	[e]	72.38	72.51
Diethylamine	$C_5H_{14}N_6$	[f]	53.13	53.23
Ethylenediamine	$C_4H_{14}N_{12}$	166–167	73.01	74.23
Piperidine	$C_6H_{14}N_6$	176–178	49.38	49.43
Morpholine	$C_5H_{12}N_6$	126–127	48.81	48.81
Benzylamine	$C_8H_{12}N_6$	130.5–131.5	43.72	43.71
Guanidine	$C_2H_8N_8$	126–126.5	77.74	78.45
Methylguanidine	$C_3H_{10}N_8$	109–110	70.85	70.22
Phenylguanidine	$C_8H_{12}N_8$	121–121.5	50.89	50.84
Aminoguanidine	$C_2H_9N_9$	93–95	79.21	79.10
Benzalamino-guanidine	$C_9H_{13}N_9$	145.5–146.5	50.99	51.09

[a] The melting points are corrected. [b] Analyses by Margaret M. Mayfield. [c] This salt was first prepared by Howard W. Kruse, Inorganic Chemistry Branch, Chemistry Division, U. S. Naval Ordnance Test Station. [d] Calcd.: C, 10.25; H, 6.03. Found: C, 10.52; H, 6.17. [e] Melts 112–117° with preliminary softening from about 95°. [f] Melts 114–118° with preliminary softening from about 100°.

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