Two definite crystalline phases were observed with drocarbil. The two phases occurred from the recrystallization from alcohol. A separation of phases was not successful. Therefore, analyses could not be made.

SUMMARY

1. The optical crystallographic data are reported for thirteen N. F. X solid substances and one U. S. P. XV solid substance.

2. The data afford a rapid and specific method of identification.

3. The data can be determined on small amounts of material.

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Mercurated Amides of Alpha-Amino Acids*

By WILLIAM O. FOYE and ROBERT A. MODE†

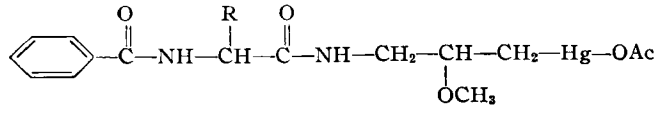
Naturally-occurring α-amino acids have been employed in the preparation of a series of mercurated allyl amides as possible diuretics with low toxic and irritant properties. Relatively stable, recrystallizable and water-soluble mercurials were isolated which showed diuretic activity either by intravenous or oral administration.

THE ORGANIC MERCURIALS have been accepted as one of the most effective types of agents for the stimulation of diuresis in the relief of edema (1), but occasional toxic reactions (2) often cardiovascular in nature, limit their usefulness. The report of Wachstein and Meisel (3) that the presence of certain α-amino acids alleviated the toxicity of mercurial diuretics in rats made promising a study of mercurated derivatives of α-amino acids themselves. Furthermore, the studies of Rowland (4) which indicated that the toxicity of mercurial diuretics was not due directly to the ionization of the mercury also suggested the use of relatively nontoxic organic components for the preparation of mercurial diuretics. A series of mercurated derivatives of α-amino acids having the following structure (I) has accordingly been prepared. These compounds are named as N-(3-acetoxymercuri-2-methoxypropyl)-alpha-substituted hippuramides in this communication.

The majority of organic mercurials which have seen clinical use are 3-substituted mercuri 2-methoxypropylamides of organic acids (which are designated as mercurated allyl amides in this discussion), since the allyl group provides a convenient seat of attachment for the mercury. Although a variety of organic acids have been employed in possible diuretics of this type, no α-amino acids have been reported for this purpose. Some closely related types which have shown good diuretic activity, however, are mercurated N-allyl urethans (5) and mercurated derivatives of N-allyl urea (6).

DISCUSSION

Attempts to prepare mercurated allyl amides of α-amino acids in which the amino group is unprotected produced only noncrystallizable, nonpurifiable oils. When the amino groups were blocked with the benzoyl group, however, the desired products were readily obtained by amide formation with



(I)

allyl isothiocyanate and mercuration with mercuric acetate in methanol. The exact structure of methoxy-mercurated allyl amides has been proved by Pearson, *et al.* (7).

The major problem encountered in this synthesis was the isolation of the mercurated product in crystalline form. The oils which resulted after re-

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TABLE I.—N-(3-ACETOXYMERCURI-2-METHOXYPROPYL)-HIPPURAMIDES (I)

Amino Acid Used	Yield, %[a]	m. p.[b]	Recrystn. Solvent	Formula	Analyses, % Calcd.	Found[c]
Glycine	30	139–142°	Methanol-ether	$C_{15}H_{20}O_5N_2Hg$	C: 35.41	35.63
					H: 3.93	4.12
Alanine	48	146–148°		$C_{16}H_{22}O_5N_2Hg$	C: 36.73	36.49
					H: 4.24	4.14
dl-Leucine	88	154–156°	Methanol-ether	$C_{19}H_{28}O_5N_2Hg$	C: 40.38	40.48
					H: 5.00	5.26
dl-Methionine	58	123–127°		$C_{18}H_{26}O_5N_2SHg$	C: 37.06	37.64
					H: 4.50	4.20
dl-Phenylalanine	77	164–166°	Acetone	$C_{22}H_{26}O_5N_2Hg$	C: 44.11	44.41
					H: 4.37	4.55

[a] Calculated from the allyl amides of the α-benzoylamino acids.
[b] All melting points are corrected.
[c] Analyses for C and H were carried out by the Clark Microanalytical Laboratory, Urbana, Ill.

fluxing the methanol solutions of the allyl amides and mercuric acetate were eventually found to crystallize from ether-methanol solutions of the correct proportion to give faint turbidity, after prolonged scratching and cooling. When the mercurials were obtained without refluxing but by prolonged standing at room temperature, lower melting products resulted which gave the same analysis after thorough drying. These products are believed to be hydrates. In either case, the mercurated amides were relatively stable, recrystallizable, and water-soluble. The physical characteristics and analytical proof of the compounds prepared are listed in Table I.

The diuretic activity of these compounds, determined at the Lilly Research Laboratories by Drs. K. K. Chen and E. B. Robbins, was in general described as good, although the leucine and phenylalanine derivatives had a weak effect. The results of intravenous administration in dogs is summarized in Table II. The glycine derivative, the most promising of these diuretics, also produced diuresis in oral doses of 2 mg./Kg. in one of four dogs without signs of gastric distress. Oral doses of 4 mg./Kg. caused diuresis in three of four dogs and gastric distress in two of four. No gastric distress was observed from the intravenous doses. The acute oral toxicity of the glycine derivative in 1% solution was approximately 350 mg./Kg. in the mouse.

TABLE II.—DIURETIC ACTIVITY OF THE MERCURATED AMIDES

Mercurated Amide	Dose,[a] mg./Kg.	Diuresis Obs./No. of Dogs	Dose,[a] mg./Kg.	Diuresis Obs./No. of Dogs
Glycine	0.5	2/6	1.0	6/6
Alanine	0.5	3/6	1.0	4/6
Methionine	0.5	3/6	1.0	3/6
Leucine	0.5	1/2	1.0	1/2
Phenylalanine	0.5	0/2	1.0	2/2

[a] The compounds were dissolved in dimethylformamide and administered intravenously.

EXPERIMENTAL

α-Benzoylamino Acids.—Benzoylation of the *dl* α-amino acids was carried out by the general procedure of Ingersoll and Babcock (8) for hippuric acid, except that the reaction mixtures were shaken, instead of being stirred, until the odor of benzoyl chloride had disappeared. The following yields and melting points were obtained after recrystallization from aqueous alcohol: N-benzoyl alanine, 89%, 165–167°; N-benzoyl leucine, 86%, 141–143°; N-benzoyl methionine, 79%, 152.5–154°; N-benzoyl phenylalanine, 92%, 186–187.5°. Several of these melting points are higher than those previously reported.

N-Allyl Hippuramides.—The general procedure of Diels and Beccard (9) was used. In a 200-cc. flask equipped with a reflux condenser and a gas collecting attachment were placed 50 Gm. (0.28 mole) of hippuric acid and 30 Gm. (0.30 mole) of freshly distilled allyl isothiocyanate (b. p. 150.7°). The mixture was heated at 130° until no more gas, carbon oxysulfide, was evolved (generally two hours were required). After cooling to room temperature, the impure product was dissolved in boiling acetone and precipitated by petroleum ether. After several such precipitations and recrystallization from aqueous alcohol, 36.8 Gm. (60%) of white, crystalline N-allylhippuramide was obtained; m. p. 133–135° (Lit., m. p. 138.5°).

N-allyl-α-methylhippuramide, after recrystallization from acetone, was obtained in 50% yield as white, mossy needles; m. p. 139–140.5°.

Anal.—Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94. Found: C, 67.33; H, 7.04.

N-Allyl-α-isobutylhippuramide, recrystallized from acetone, was obtained in 60% yield as glistening, white crystals; m. p. 154–155°.

Anal.—Calcd. for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08. Found: C, 70.07; H, 8.14.

N - Allyl - α - (β' - methylmercaptoethyl) - hippuramide, recrystallized from acetone, was obtained in 58% yield as white needles; m. p. 136.5–138°.

Anal.—Calcd. for $C_{15}H_{20}O_2N_2S$: C, 61.61; H, 6.89. Found: C, 61.38; H, 7.07.

N-Allyl-α-benzylhippuramide, white needles, was obtained in 62% yield after recrystallization from acetone; m. p. 164–166°.

Anal.—Calcd. for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54. Found: C, 73.98; H, 6.14.

Mercuration of the Allyl Amides.—The preparation of the glycine derivative is representative of this procedure. To a hot solution of 10 Gm. (0.046 mole) of N-allylhippuramide in 200 ml. of absolute methanol was added a hot solution of 14.5 Gm. (0.045 mole) of mercuric acetate in 200 ml. of absolute methanol. The mixture was warmed gently for ten minutes and then allowed to cool to room temperature, when a small quantity of flaky precipitate appeared. After filtration, the solution

was allowed to stand overnight. It was then refluxed for two to three hours, when another small amount of gray precipitate formed and was removed. The resulting solution was concentrated at 30° (40 mm. pressure) to a viscous oil which was dried at room temperature under vacuum (1 mm.) to remove any remaining acetic acid. The product was dissolved in hot methanol, and anhydrous ether was added to the point of lasting turbidity. After prolonged cooling (generally over two days) and scratching, white crystals (7.3 Gm., 30%) were obtained which could be recrystallized from methanol-ether solution. The melting point was 139–142°. When the refluxing period was shortened or omitted and the oil was not dried, a melting point of 116–122° was obtained.

SUMMARY

1. A series of mercurated allyl amides of α-amino acids has been prepared for evaluation of diuretic activity.

2. The following new compounds have been characterized: N-(3-acetoxy-mercuri-2-methoxypropyl)-hippuramide, N-allyl-α-methylhippuramide, N-(3-acetoxymercuri-2-methoxypropyl)-α-methylhippuramide, N-allyl-α-isobutylhippuramide, N-(3-acetoxymercuri-2-methoxypropyl)-α-isobutyl-hippuramide, N-allyl-α-(β′-methylmercaptoethyl) - hippuramide, N-(3-acetoxymercuri-2-methoxypropyl)-α-(β′-methylmercaptoethyl) - hippuramide, N - allyl - α - benzylhippuramide, and N-(3-acetoxymercuri-2-methoxypropyl)-α-benzylhippuramide.

3. These compounds showed good diuretic activity and low toxic and irritant properties by intravenous administration in dogs. The mercurated glycine amide also showed good diuretic activity by oral administration.

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The Synthesis of Some New Alkyl *p*-N-Alkyl Amidinobenzoates*

By ROBERT BOBLITT† and OLE GISVOLD‡

The following compounds have been prepared and reported: the *n*-amyl, iso-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, and cyclohexyl derivatives of the benzyl, hexahydrobenzyl, and cyclohexyl esters of *p*-carboxybenzamidine. If possible, these compounds will be screened for anesthetic and antibiotic properties and the results reported later.

PREVIOUS publications (1, 2) have described the synthesis of some esters of some N-alkyl *p*-carboxybenzamidines. Prolonged surface and infiltration anesthesia, approximately four hundred minutes, was obtained by certain esters when the alcohol portion was benzyl, hexahydrobenzyl, or cyclohexyl.

Following an initial drop in activity by N-methylation or N-ethylation, there is a uniform increase in the duration of activity with an increase in the size of the N-alkyl substituent. The largest alkyl group that was introduced was an *n*-butyl group. These N-alkyl derivatives exhibited maximum activity. It was therefore of interest to determine the size and nature of the N-alkyl groups that would lead to maximum surface and intracutaneous activities.

EXPERIMENTAL

The preparation of the intermediates such as *p*-cyanobenzoic acid, *p*-cyanobenzoyl chloride, alkyl-*p*-cyanobenzoates, alkyl-*p*-carbethoxyiminobenzoates and amidines were prepared essentially according to previously described procedures. However, some improvements and variations are reported as follows.

Alkyl-*p*-cyanobenzoates.—Improved yields, almost quantitative, of these intermediates were obtained when two equivalents of the alcohol and one equivalent of *p*-cyanobenzoyl chloride were refluxed in benzene.

Alkyl-*p*-carbethoxyiminobenzoates.—It should be recorded here that the use of anhydrous ether, as in Pinner's original method, gave considerably greater yields of the imidic esters than when anhy-

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