[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF NORTH CAROLINA]

NON-PEPTIDE AMIDES OF *ALPHA* AMINO ACIDS[1]

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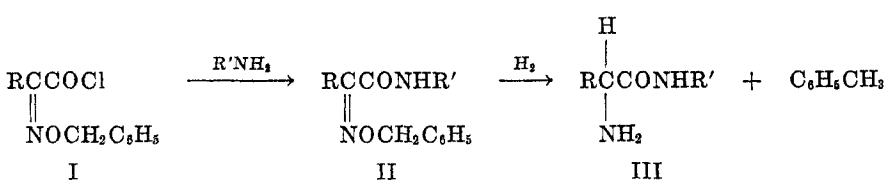
The amides of α-amino acids as they occur in proteins, that is, combined with other α-amino acids, are well known, but amides of these acids formed with physiologically active bases are practically unknown. The anilide of glycine (1) is reported to be a weaker analgesic than acetanilid and N^4-glycylsulfanilamide (2) has been found to possess weak "sulfa" activity. These compounds, chemically typical non-peptide amides of amino acids, are pharmacodynamically inadequate as representative of the amides which may be projected as derived from other acids and bases. In view of the biological specificity of the α-amino acids, particularly those considered as biologically indispensable, it would seem hazardous to suppose that the physiological behavior may be determined by the examination of a limited number of compounds. For example, not only will the pharmacological properties of the base be modified by conversion into an amide, but the amide of leucine, say, may differ significantly from the corresponding amide of tryptophan or phenylalanine.

For the synthesis of these non-peptide amides various available procedures for the synthesis of peptides may be employed, with appropriate modification. The approach selected for the present investigation was *via* the α-benzyloximino acid, since it permits the synthesis of derivatives of the natural products as well as their analogs and homologs without the necessity of first preparing the amino acid itself. The steps involved in the synthesis are as follows:



I II III

The essential steps for the preparation of compounds of Type I from the appropriate alkyl malonic esters have been described by previous workers (3–5). Modifications and improvements in experimental procedure are described below. The synthesis of the amides, Type II, presented no difficulty and the data for those prepared are summarized in Table I.

The catalytic hydrogenation studies of the amides of Type II led to interesting results. In those compounds where R′ is aliphatic, operating at room temperature, no hydrogen was taken up with palladium-charcoal catalysts in aqueous ammoniacal medium (3). Under similar conditions where R′ was aromatic one mole of hydrogen was taken up, the product being a debenzylated amide of the α-oximino acid, RCH(:NOH)CONHAr. At higher temperatures the reactions

[1] No. 15 in the amino acid series; for No. 14 see Hartung, Kramer, and Hager, in press.

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TABLE I

AMIDES OF α-BENZYLOXIMINO ACIDS

$$R{-}C(=NOCH_2C_6H_5){-}COY$$

R	Y	YIELD, %[a]	M.P.,[b] °C.	N[i]	
				Calc'd	Found
$C_6H_5CH_2$—	—NHC_6H_5	90	83–85[c]		
	—NHC_6H_4COOH-*p*	92	182–183[d]	7.21	6.96, 7.13
	—NHC_6H_4COOH-*o*	82.5	186–187	7.21	7.20, 6.99
	—$NHC_6H_4SO_2NH_2$-*p*	94	185–186	9.93	9.58, 9.72
	—$NHCH(CH_3)CHOHC_6H_5$	90	[e]	6.96	6.15, 6.14
	—$N(CH_3)CH(CH_3)CHOHC_6H_5(-)$	83	[e]	6.73	6.44, 6.54
$(CH_3)_2CHCH_2$—	—NHC_6H_5	81.5	57–58[f]		
	—NHC_6H_4COOH-*p*	95	142–143[g]	7.91	7.85, 7.81
	—NHC_6H_4COOH-*o*	94	172[h]		
	—$NHC_6H_4SO_2NH_2$-*p*	93	204	10.80	11.13, 11.08
	—$NHCH(CH_3)CHOHC_6H_5$	91	[e]	7.61	7.66, 7.61
	—$N(CH_3)CH(CH_3)CHOHC_6H_5(-)$	95	[e]	7.33	7.35, 7.60

[a] Yield based on α-benzyloximino acid. [b] Melting points are uncorrected. [c] Weaver (5) reported 78–79°. A mixture m.p. with some of his original product gave no depression. [d] Neutralization equivalent: Calc'd, 388. Found: 397, 394. [e] Viscous, non-distillable oil. [f] Weaver (5) reported 57°. [g] Neutralization equivalent: Calc'd 354. Found: 348, 351. [h] Neutralization equivalent: Calc'd, 354. Found: 351, 357. [i] All N analyses by semi-micro Kjeldahl.

with both types of amides progressed further but never to completion. Accordingly the effects of trace amounts of rhodium and of platinum (6, 7) were investigated. It was observed that the presence of rhodium (50:1 gram-atomic ratio) was altogether favorable, in some instances affording the desired amide of the amino acid at room temperature and at pressures as low as four atmospheres. However, at temperatures of about 70° and pressures ranging from 50 to 95 atmospheres the hydrogenation results with Pd-Rh-C catalysts were uniformly satisfactory.

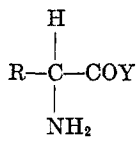
The data for the amides of α-amino acids prepared thus far are summarized in Table II.

EXPERIMENTAL

The α-oximino acids were prepared essentially by methods previously described (4, 5). It was found, however, that an increase in the time of hydrolysis of the nitrosated alkylmalonic ester yielded a purer product.

TABLE II

AMIDES OF α-AMINO ACIDS



R	Y	YIELD, %	M.P.[a], °C.	N	
				Calc'd	Found
$C_6H_5CH_2$—	—NHC_6H_5	92	78–80[b]		
	—NHC_6H_4COOH-*p*	92	260–261d.	9.85	9.57, 9.64
	—NHC_6H_4COOH-*o*	97	145	9.85	9.65, 9.81
	—$NHC_6H_4SO_2NH_2$-*p*	87	212–213d.	13.16	13.00, 13.11
	—$NHCHCHOHC_6H_5$ | CH_3	74	134–135	9.43	9.29, 9.21
$(CH_3)_2CHCH_2$—	—NHC_6H_5	83	62	13.59	13.22, 13.52
	—NHC_6H_4COOH-*p*	95	232–233	11.20	10.78, 10.79
	—NHC_6H_4COOH-*o*	88	155–157	11.20	10.97, 10.92
	—$NHC_6H_4SO_2NH_2$-*p*	81	172–174	14.74	14.89, 14.91
	—$NHCHCHOHC_6H_5$ | CH_3	57	107–110[c]	9.30[c]	9.09, 9.14

[a] The melting points are uncorrected. [b] Beilstein, Vol. 14, Suppl. 2, p. 301 reports 80.5° as the corrected m.p. [c] As the hydrochloride.

Benzylation. The following modification, as described for the preparation of β-phenyl-α-benzyloximinopropionic acid, is an improvement over procedures previously given.

In a 1-liter, 3-neck, round-bottom flask equipped with a mercury-seal stirrer and a condenser closed by a drying tube was placed 500 ml. of commercial absolute alcohol in which was dissolved 11.5 g. of sodium (0.5 mole). This was followed by 45 g. (0.25 mole) of β-phenyl-α-oximinopropionic acid, and then by 64 g. (0.5 mole) of benzyl chloride, which was added rapidly. The solution was refluxed until it became neutral (2–3 hours). Then 100 ml. of 20% ethanolic KOH was added. The condenser was set for downward distillation and practically all of the alcohol was removed. To the viscous tan mass remaining was added 800 ml. of water. The solution was transferred to a separatory-funnel and extracted with several portions of ether. The water solution was then decolorized with several portions of Nuchar (carbon), cooled in an ice-salt bath, and neutralized with 15% HCl. The gray product, after drying, weighed 57.5 g., yield 86%, melting at 65–69°. After recrystallization 52.3 g., yield 76%, of colorless crystals were obtained, m.p. 70–71°. Waters and Weaver report a melting point of 79–80°. After recrystallization and drying *in vacuo* over P_2O_5 the melting point was raised to the reported value.

Anal. Neutr. equiv. (m.p. 70–71°). Calc'd for $C_{15}H_{14}NO$—COOH: 269. Found: 274, 276.

Acid chlorides. The method of Weaver was employed except that the acid chloride was not isolated and purified by distillation. The impurities and the reagents which boil at a temperature considerably lower than that of the acid chloride were removed under reduced pressure, leaving essentially pure acid chloride.

Amide intermediates. Two equivalents of the amine were used to one equivalent of acid chloride. The amine hydrochloride could be recovered and the amine reclaimed. Yields were calculated on the basis of the benzyloximino acid used in the preparation of the acid chloride since the acid chloride was used immediately after preparation.

The preparation of *N^4-(β-phenyl-α-benzyloximinopropionyl)sulfanilamide* which follows is an example in this group.

To 10.3 g. (0.06 mole) of sulfanilamide dissolved in 50 ml. of acetone was added slowly, with stirring, the acid chloride prepared from 8.1 g. (0.03 mole) of β-phenyl-α-benzyloximinopropionic acid. Heat was evolved as a precipitate formed. After standing covered for an hour the acetone was allowed to evaporate in the hood. To the semi-solid remaining was added 150 ml. of water. The crude product was filtered out, sucked dry, and recrystallized from 95% alcohol. Yield, 12 g., 94%, of colorless crystals, m.p. 185–186°.

The properties of the various amides are given in Table I.

Amides of α-oximino acids. These compounds were prepared during reduction studies on the α-benzyloximino amides described above. The reductions were carried out in a Parr hydrogenator at an initial pressure of approximately 60 p.s.i.g. Various catalysts were investigated.

The preparation of *β-phenyl-α-oximinopropionyl-p-aminobenzoic acid* is typical for those in this group.

To 3.44 g. (0.009 mole) of N-(β-phenyl-α-benzyloximinopropionyl)-*p*-aminobenzoic acid dissolved in 100 ml. of water and 5 ml. of concentrated NH_4OH was added 1 g. of a palladium-Norit catalyst which contained 200 mg. of palladium chloride. After 18 minutes of shaking 1 molar-equivalent of hydrogen was absorbed. Longer shaking and heating to 50° did not cause the uptake of additional hydrogen. After 2 hours the shaking was stopped and the catalyst was filtered out. The clear solution was acidified and a white flocculent precipitate formed. This product melted with decomposition 270–277°; yield, 2 g., 76%.

Anal. Neutr. equiv. Calc'd for the dibasic acid $C_{15}H_{12}NO\begin{cases}COOH\\=NOH\end{cases}$: 298. Found: 304, 305.

In a similar manner were obtained:[3] *β-phenyl-α-oximinopropionanilide*, m.p. 164–165°.

Anal. Calc'd for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.83, 10.65. and *N^4-(β-phenyl-α-oximinopropionyl)sulfanilamide*, m.p. 233°.

Anal. Calc'd for $C_{15}H_{15}N_3O_2S$: N, 12.6. Found: N, 12.2, 12.3.

Amides of α-amino acids. All reductions at high pressures were carried out in an Aminco apparatus. The initial pressures were varied from 50–75 atmospheres of hydrogen, the lower pressure being sufficient for most reductions. The palladium-rhodium[4] catalyst was prepared by depositing the metals on the Norit from a solution of palladium chloride and rhodium chloride in sodium acetate (7). In every instance reported a catalyst containing 300 mg. of palladium chloride and 7.06 mg. of rhodium chloride (50 to 1 atomic ratio of Pd to Rh) deposited on 1 gram of Norit was employed.

The preparation of *N-phenylalanyl-p-aminobenzoic acid* is typical of the hydrogenation procedure found most satisfactory.

To 3.88 g. (0.01 mole) of N-(β-phenyl-α-benzyloximinopropionyl)-*p*-aminobenzoic acid dissolved in 100 ml. of commercial absolute alcohol and 6 ml. of concentrated NH_4OH was added the Pd-Rh Norit catalyst. The mixture was allowed to rock for ½ hour and then was heated to 75°. The heater was turned off and the mixture was allowed to rock overnight. After a total of 17 hours the machine was stopped, the catalyst was filtered off, and the solution was evaporated to dryness on a steam-bath. The white acid-soluble residue was washed with alcohol and dried *in vacuo* over P_2O_5. There was collected 2.6 g. (92%).

The properties of the various amides are summarized in Table II.

The amides of the α-amino acids and also the amides of the intermediate benzyloximino acids are being examined for their biological properties. It is hoped that the results of these studies will be available in connection with other work.

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[3] Isolated in analogous manner, but in low yields, was a compound, presumably α-oximinoisocaproanilide, m.p. 138–139°. The yield was insufficient to allow for purification to maximum purity.

[4] We are grateful to the American Platinum Works, Newark, N. J., for supplying palladium, rhodium, and platinum for the preparation of all catalysts.

SUMMARY

1. Amides of α-amino acids with physiologically active bases may be prepared by the catalytic hydrogenation of the corresponding amides of α-benzyloximino acids. The synthesis of 10 compounds and their intermediates is described.

2. Palladium-on-charcoal catalysts effect hydrogenolysis of the benzyloximino grouping, affording the amides of the corresponding α-oximino acids. The addition of rhodium to the catalyst, in the ratio of Rh:Pd::1:50, provides a catalyst which under conditions of higher pressure and temperature will reduce the benzyloximino grouping to the corresponding primary amine.

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