New Compounds: Amino Acid Derivatives of Nicotinic Acid

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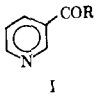
Abstract □ The azide method was adapted to the synthesis of monopeptides of nicotinic acid. Using this method, nicotinoyl-*dl*-α-alanine, nicotinoyl-L-alanine, nicotinoyl-*dl*-valine, nicotinoyl-L-leucine, and nicotinoyl-*dl*-phenylalanine were prepared.

Keyphrases □ Nicotinic acid—synthesis of amino acid derivatives, azide method □ Amino acid derivatives of nicotinic acid—synthesis □ Peptides, mono—synthesis of amino acid derivatives of nicotinic acid

The interesting pharmacological properties of the complex heteroaroyl polypeptide, actinomycin (1), suggested the possibility of potential activity of simple heteroaroylamino acids. The potent pharmacological activity of nicotinic acid and its derivatives led to the choice of this heteroaroyl function for initial investigation. This paper describes the synthesis of some amino acid amide derivatives of nicotinic acid (I).

To prepare the peptides from nicotinic acid, the acid chloride was first investigated as an intermediate. It was reported (2), without experimental details, that the Schotten–Baumann reaction between the acid chloride and the amino acid afforded the desired peptide. It was found that the nicotinoyl chloride hydrochloride could be formed readily by the reaction of the nicotinic acid with thionyl chloride; however, this acid chloride hydrochloride was hydrolyzed with base more rapidly



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than it underwent reaction with an amino acid under Schotten–Baumann conditions, and the reactants were not soluble in nonpolar solvents. Although one preparation was reported (3) for the acid chloride without the formation of the hydrochloride, the product is troublesome to purify, and on exposure to the air the acid chloride soon solidified to nicotinic acid hydrochloride.

It was decided, therefore, to use the azide procedure and, in particular, the modified Curtius reaction of Fox and Field (4). The reaction of nicotinoyl azide with various amino acids was carried out at room temperature. A 40–50% yield of analytically pure product was obtained. The amides prepared in this series are listed in Table I. Each of the nicotinoyl amino acid amides has the characteristic absorption of the IR spectrum at 3400 (—NH), 1730 (—carboxyl), and 1640 cm.$^{-1}$ (—amide). The UV absorption showed maxima at 256 and 262 nm. in absolute ethanol, characteristic of the nicotinoyl chromophore (Table II).

Except for nicotinoyl-*dl*-α-alanine (I*a*), the amino acid derivatives showed no overt activity in mice on oral administration; I*a* exhibited a mild, transient hy-

Table I—Nicotinoyl Amino Acids

Compound	R	Melting Point	Yield, %	Empirical Formula	Analyses, % Calc.	Found
I*a*	*dl*-α-Alanine	201–202°	46	$C_9H_{10}N_2O_3$	C 55.66 H 5.19 N 14.43	55.60 5.01 14.29
I*b*	L-Alanine	206–207°	47	$C_9H_{10}N_2O_3$	C 55.66 H 5.19 N —	55.97 5.20 —
I*c*	*dl*-Valine (5)	216–217°	46	$C_{11}H_{14}N_2O_3$	C 59.45 H 6.35 N 12.60	59.68 6.51 12.64
I*d*	L-Leucine (5)	185–186.5°	40	$C_{12}H_{16}N_2O_3$	C 61.00 H 6.83 N 11.86	60.96 6.95 11.69
I*e*	*dl*-Phenylalanine	224–226°	50	$C_{15}H_{14}N_2O_3$	C 66.65 H 5.22 N —	66.34 5.95 —

Table II—Spectra Data and Optical Rotation for Nicotinoyl Amino Acids

I*a* IR $\nu_{max.}$: 3400, 1720, and 1640 cm.$^{-1}$; UV $\lambda_{max.}$: 256 nm. (ϵ = 4100) and 262 nm. (ϵ = 4000)
I*b* $[\alpha]_D^{27}$ = −28° (c = 0.5 in absolute ethanol); IR $\nu_{max.}$: 3400, 1720, and 1650 cm.$^{-1}$; UV $\lambda_{max.}$: 256 nm. (ϵ = 3400) and 262 nm. (ϵ = 3400)
I*c* IR $\nu_{max.}$: 3400, 1720, and 1650 cm.$^{-1}$; UV $\lambda_{max.}$: 256 nm. (ϵ = 5300) and 261 nm. (ϵ = 5300)
I*d* $[\alpha]_D^{28}$ = −36° (c = 0.5 in absolute ethanol); IR $\nu_{max.}$: 3400, 1720, and 1650 cm.$^{-1}$; UV $\lambda_{max.}$: 256 nm. (ϵ = 4800) and 262 nm. (ϵ = 4900)
I*e* IR $\nu_{max.}$: 3400, 1720, and 1650 cm.$^{-1}$; UV $\lambda_{max.}$: 256 nm. (ϵ = 3000) and 262 nm. (ϵ = 2800)

potonia. Intravenous administration of Ia, Id, and Ie caused a mild decrease in activity of the mice.

EXPERIMENTAL[1]

The general procedure for the preparation of the compounds was as follows. Nicotinoyl azide (0.025 mole) was added in small portions, with vigorous stirring, to a solution of 0.025 mole of an amino acid in 25 ml. of 1 *N* NaOH at room temperature. The reaction was allowed to stand overnight at room temperature, and additional 25-ml. portions of 1 *N* NaOH were added from time to time to keep the mixture alkaline. The solution was then evaporated to dryness under reduced pressure on a steam bath. The residue was acidified by adding 12.5 ml. of 2 *N* HCl while cooling in an ice bath. The acidified solution was allowed to stand in a refrigerator to crystallize. The product was removed by filtration and recrystallized from water or ethanol.

[1] All melting points are uncorrected. Analyses were obtained from Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. UV spectra were obtained with a Perkin-Elmer spectrophotometer in absolute ethanol solution. IR spectra were obtained on a Perkin-Elmer IR spectrophotometer and determined as mulls in series 11–14 Halocarbon oil from 4000 to 1300 cm.$^{-1}$ and in mineral oil from 650 to 1300 cm.$^{-1}$.

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COMMUNICATIONS

Thermodynamic Aspects of Solubility of Small Particles

Keyphrases ☐ Solubility of small particles—thermodynamic aspects, surface enthalpy and surface entropy ☐ Particle solubility—thermodynamic aspects for small particles, surface enthalpy and surface entropy

Sir:

The dependence of vapor pressures and solubilities on the particle size for small droplets and particles is intimately involved with nucleation and crystallization phenomena and many other theoretical and practical problems of interest (1, 2). The basic theory derives from the classical Kelvin equation (1), which, when adapted to the solubility of a nonionic solid, assumed to behave ideally in solution, reads as follows:

$$-\Delta(\Delta G) = RT \ln \frac{S}{S_0} = \frac{2\gamma \bar{V}}{r} \qquad \text{(Eq. 1)}$$

where S is the solubility of spherical particles of radius r, S_0 is the corresponding solubility of large crystals ($r \rightarrow \infty$), $\Delta(\Delta G)$ is the difference in the free energy of solution of small and large crystals, γ is the interfacial tension, $\bar{V}$ is the partial molal volume of the solid in solution, R is the molar gas constant, and T is the absolute temperature.

The uncertainties in the practical application of this equation to solids, or in even a reasonable confirmation of this equation for a model system, are many. They arise in part from the difficulty of ascertaining r, the variability of γ for different crystal faces and edges so that only some poorly defined average quantity can be used, the great difficulty of determining γ for solids from independent measurements, and the fact that the surfaces of finely divided solids may be less regularly crystalline and more amorphous than well-grown crystals (1, 2). Nevertheless, the fundamental principles seem to be well established, particularly in analogy with similar principles involved in the vapor pressures of small drops of liquids and nucleation phenomena in vapors.

Smolen and Kildsig (3, 4) recently suggested that the increased solubility of small particles arises entirely from an entropy effect associated with the solution of "microparticles" from the surface. According to Eq. 1, when other pertinent variables are held constant, the solubility increase reflected in the ratio S/S_0 is *entirely* controlled by the interfacial tension, γ. This interfacial tension, γ (dynes/cm.), is well known (1, 2) to be an interfacial free energy per square centimeter, G^s (ergs/cm.^{2}), which can be expressed as:

$$G^s = H^s - TS^s \qquad \text{(Eq. 2)}$$

where H^s is the interfacial enthalpy per square centimeter, and S^s the interfacial entropy per square centimeter.

The relative contribution of the H^s and the TS^s terms to G^s depends on the interfacial system. For organic liquids, the interfacial tensions against water usually decrease with increasing temperature, so that S^s is positive (1, 2). Therefore, the surface entropy, by itself, makes a negative contribution to G^s and, therefore, γ and leads to a *decrease* in the solubility of small droplets. For solids, the difficulties of quantitative