EXPERIMENTAL[6,7]

3-Indolecarbonyl chloride. The 3-indoleglyoxalyl chloride obtained from the reaction of 10 g. of indole with 10 ml. of oxalyl chloride in 100 ml. of ether[1] was dissolved in 150 ml. of tetrachloroethane and the solution heated to 115–120°. After the rapid evolution of carbon monoxide had ceased, the deep brown solution was rapidly cooled to room temperature, 450 ml. of hexane added to precipitate the crude reaction product, the latter collected, washed with hexane, and dried in a stream of dry air to give *ca.* 10 g. of crude reaction product in the form of a brownish yellow powder. Analysis of a representative product gave Cl, 4.7%; calcd. for 3-indolecarbonyl chloride, 11.1%. An infrared spectrum, determined in solid KBr, exhibited two peaks of *ca.* equal intensity, one at *ca.* 1750 cm.$^{-1}$ and the other at *ca.* 1690 cm.$^{-1}$ The crude reaction product was dissolved in boiling benzene, the solution filtered, 25 ml. of hexane added to the hot solution, the dark brown precipitate which appeared on cooling discarded, an additional 5 ml. of hexane added to the filtrate, the brown precipitate again discarded, 75 ml. of hexane added to the now light yellow solution to give after collection by filtration and drying 2.5–3.5 g., (16–23% based upon indole) of 3-indolecarbonyl chloride in the form of yellow crystals.

Hydrolysis of the above acid chloride in the presence of 1*M* aqueous sodium bicarbonate gave, after acidification, 3-indolecarboxylic acid, m.p. 217–219° dec. (lit.[8] m.p. 218–220).

The crude reaction product, 10.61 g., was suspended in 60 ml. of aqueous 1*M* sodium bicarbonate, the insoluble residue collected and the solution acidified to give 1.17 g. (11%) of 3-indolecarboxylic acid, m.p. 217–219° with dec. The insoluble residue was dissolved in 60 ml. of 1*M* aqueous sodium hydroxide, the solution filtered and the filtrate acidified to give 6.17 g. (58%) of 3-indolecarboxylic acid, m.p. 214–217° dec. Hydrolysis of the crude reaction product with 1*M* aqueous sodium hydroxide under more drastic conditions gave, after acidification, *ca.* 95% of the above carboxylic acid.

To a filtered solution of 3 g. of the crude reaction product in 25 ml. of anhydrous methanol, was added 30 ml. of water. The solid product which formed was recrystallized from aqueous methanol to give *ca.* 1 g. of methyl 3-indolecarboxylate, m.p. 144–145.6° (lit.,[4] m.p. 147–148°).

The similar reaction of 3 g. of the crude reaction product with 25 ml. of absolute ethanol gave, after three recrystallizations from aqueous ethanol, *ca.* 1 g. of ethyl 3-indolecarboxylate, m.p. 119–123° (lit.,[3] m.p. 118–120°).

3-Indolecarboxanilide. Recrystallized 3-indolecarbonyl chloride was added to an excess of aniline in anhydrous ethyl acetate, the ethyl acetate solution washed with aqueous hydrochloric acid, aqueous sodium hydroxide and water and then dried. The addition of hexane to the dry ethyl acetate solution gave 3-indolecarboxanilide, m.p. 175.5–176.2° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{15}H_{12}ON_2$ (236): C, 76.3; H, 5.1; N, 11.9. Found: C, 76.4; H, 5.2; N, 11.8.

3-Indolecarbox-p-toluide. The reaction of the recrystallized acid chloride with *p*-toluidine as described above for the corresponding anilide gave 3-indolecarbox-*p*-toluide, m.p. 200.9–201.1°, after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{16}H_{14}ON_2$ (250): C, 76.8; H, 5.6; N, 11.2. Found: C, 76.9; H, 5.7; N, 10.8.

3-Indolecarbonylglycine ethyl ester. A solution of 1.55 g. of glycine ethyl ester hydrochloride in 5 ml. of water containing 3.18 g. of potassium carbonate was placed in a separatory funnel containing 60 ml. of ethyl acetate. Two grams of recrystallized 3-indolecarbonyl chloride in 30 ml. of ethyl acetate was added to the reaction mixture which was then shaken for 10 min. The ethyl acetate phase was separated, washed with water, dried, and the solvent removed to give 0.84 g. (30%) of 3-indolecarbonylglycine ethyl ester, m.p. 159–160°, after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$ (246): C, 63.4; H, 5.7; N, 11.4. Found: C, 63.5; H, 5.7; N, 11.6.

3-Indolecarbonyl-L-phenylalanine methyl ester. The reaction of 2 g. of 3-indolecarbonyl chloride, 3.2 g. of L-phenylalanine methyl ester hydrochloride and 4.18 g. of potassium carbonate was conducted as described for the glycine analog. The oily product recovered from the ethyl acetate phase was dissolved in methanol and this solution was brought to the cloud point by the addition of water. After standing for 20 hr. at 4°, the product was collected and recrystallized from aqueous methanol to give 1.08 g. (30%) of 3-indolecarbonyl-L-phenylalanine methyl ester, m.p. 133–134°.

Anal. Calcd. for $C_{19}H_{18}O_3N_2$ (322): C, 70.8; H, 5.6; N, 8.7. Found: C, 70.8; H, 5.6; N, 8.7.

This investigation was supported in part by a grant from the National Institutes of Health, U. S. Public Health Service.

CONTRIBUTION NO. 2222 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY
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(6) All melting points are corrected.

(7) Microanalyses by Dr. A. Elek.

Glycolamide Esters of Acylated α-Amino Acids

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Received August 5, 1957

It is common knowledge that a number of acylated α-amino acid alkyl esters are hydrolyzed in the presence of the pancreatic proteases. However, their use as specific substrates in studies with the above enzymes frequently is limited by their relatively low solubility in water.

In the course of a search for a class of neutral water soluble acylated α-amino acid esters capable of functioning as specific substrates for α-chymotrypsin, it was observed that benzoylglycolamide, prepared by the condensation of sodium benzoate and chloracetamide, was sufficiently soluble in water to permit the preparation of 0.1 *M* solutions. While the very water soluble acetyl-DL-phenylalanine glycolamide ester could be prepared in an analogous manner, it was clear that a more satisfactory synthesis was required.

When acetyl-DL and L-phenylalanine were employed as representative examples, it was found that reaction of the corresponding cyanomethyl esters[1] with an excess of hydrogen chloride and one mole equivalent of methanol in benzene, followed by removal of the benzene by distillation at atmospheric pressure, gave the desired acetyl-DL- and L-phenylalanine glycolamide esters in good yields. McElvain and Nelson[2] have noted that imidoes-

(1) R. Schwyzer, M. Feurer, B. Iselin, and H. Kagi, *Helv. Chim. Acta*, **38**, 80 (1955).

(2) S. M. McElvain and J. N. Nelson, *J. Am. Chem. Soc.*, **64**, 1825 (1942).

ter hydrochlorides when heated to 60–80° give the corresponding amides and alkyl halides.

When examined in aqueous solutions at 25° and *p*H 7.9, acetyl-L-phenylalanine glycolamide ester was rapidly hydrolyzed, to acetyl-L-phenylalanine and glycolamide, by α-chymotrypsin.

EXPERIMENTAL[3,4]

Acetyl-DL-phenylalanine cyanomethyl ester. The reaction of 14.4 g. of acetyl-DL-phenylalanine with 9.08 g. of redistilled chloracetonitrile in the presence of triethylamine according to the procedure of Schwyzer *et al.*[1] gave 11.0 g. (64%) of crude cyanomethyl ester. The crude ester was recrystallized twice from a mixture of anhydrous ethanol and hexane to give acetyl-DL-phenylalanine cyanomethyl ester, colorless needles, m.p. 94–95°.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$ (246): C, 63.4; H, 5.7; N, 11.4. Found: C, 63.5; H, 5.7; N, 11.4.

Reaction of the cyanomethyl ester with benzylamine[1] gave acetyl-DL-phenylalaninebenzylamide, m.p. 161.5–162.9°.

Anal. Calcd. for $C_{17}H_{18}O_2N_2$ (282): N, 9.5. Found: N, 9.5.

Acetyl-DL-phenylalanine glycolamide ester. A solution of 2.46 g. of acetyl-DL-phenylanine cyanomethyl ester in 75 ml. of benzene and 3.3 ml. of 3 *M* methanol in benzene was saturated with dry hydrogen chloride. The solution was allowed to stand at room temperature for 15 min., the benzene removed by distillation at atmospheric pressure, and the colorless residue dissolved in 350 ml. of hot ethyl acetate. This solution was cooled to give 1.69 g. (64%) of the glycolamide ester which was recrystallized from ethyl acetate to give acetyl-DL-phenylalanine glycolamide ester, m.p. 160.5–161.5°.

Anal. Calcd. for $C_{13}H_{16}O_4N_2$ (264): C, 59.1; H, 6.1; N, 10.6. Found: C, 59.1; H, 6.1; N, 10.7.

Acetyl-L-phenylalanine cyanomethyl ester. Acetyl-L-phenylalanine, 7.2 g., when treated with 4.5 g. of redistilled chloracetonitrile, as described for the DL-compound, gave 4.4 g. (52%) of crude cyanomethyl ester. Recrystallization of the crude ester from a mixture of anhydrous ethanol and hexane gave acetyl-L-phenylalanine cyanomethyl ester, colorless needles, m.p. 124.5–125.5°, $[\alpha]_D^{25.3}$ −11.2 ± 0.4 (c, 3.0% in acetone).

Anal. Calcd. for $C_{13}H_{14}O_3N_2$ (246): C, 63.4; H, 5.7; N, 11.4. Found: C, 63.6; H, 5.8; N, 11.4.

Acetyl-L-phenylalanine glycolamide ester. The reaction of 2.46 g. of acetyl-L-phenylalanine cyanomethyl ester with methanol and hydrogen chloride, under the conditions employed for the DL-compound, gave 1.6 g. (61%) of crude glycolamide ester. Recrystallization of the crude ester from a mixture of anhydrous ethanol and hexane gave acetyl-L-phenylalanine glycolamide ester, colorless needles, m.p. alanine glycolamide ester, colorless needles, m.p. 120.5–121.5°, $[\alpha]_D^{25.3}$ +2.2 ± 0.2° (c, 2.3% in absolute ethanol).

Anal. Calcd. for $C_{13}H_{16}O_4N_2$ (264): C, 59.1; H, 6.1; N, 10.6. Found: C, 59.1; H, 6.1; N, 10.6.

A mixture of the above compound and the DL-compound, m.p. 160.5–161.5 melted at 132–162°.

Acknowledgment. This investigation was supported in part by a grant from the National Institutes of Health, U. S. Public Health Service.

CONTRIBUTION NO. 2232 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY
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(3) Melting points are corrected.
(4) Microanalyses by Dr. A. Elek.

Improved Preparation of 1-Iodo-2,4-dinitrobenzene[1]

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Received July 25, 1957

Bennett and Vernon[2] prepared 2,4-dinitroiodobenzene in 30% yield by heating 2,4-dinitrochlorobenzene with five mole proportions of sodium iodide at reflux in ethylene glycol for 30 minutes. We have found that the yield can be raised to 70% by conducting the reaction in dimethylformamide solution. The procedure is simple, and this is now to be regarded as the method of choice for preparing this compound. Experiments which led to the development of optimum conditions are summarized in Table I, and our best procedure is described in the Experimental section.

TABLE I

PREPARATION OF 2,4-DINITROIODOBENZENE FROM 2,4-DINITROCHLOROBENZENE

Solvent[a]	Mole Ratio, NaI:$C_6H_3(NO_2)_2Cl$	Reflux Time, min.	Yield, %
Ethylene Glycol	5:1	60	37
DMF[b]	5:1	*ca.* 90	0[c]
DMF	5:1	30	49[d]
DMF	5:1	15	70
DMF	3:1	15	66
DMF	5:1[e]	15	71

[a] DMF stands for dimethylformamide. [b] In this experiment, technical DMF was used without being redistilled. [c] A dark tar was obtained when the reaction mixture was poured into water and no effort was made to isolate a pure product from it. [d] The crude product was recrystallized from ethanol and then from petroleum ether (b.p. 90–100°). [e] One mole of 2,4-dinitrochlorobenzene (5 times the usual amount) was used in this run.

The reaction was tried once in dimethyl sulfoxide solution. From the dark sludge obtained by pouring the reaction mixture into water, only 2,4-dinitrophenyl methyl sulfide, in 5% yield, was isolated. Presumably this compound arose from the following sequence of reactions: reduction of dimethyl sulfoxide to dimethyl sulfide by iodide ion, condensation of dimethyl sulfide with 2,4-dinitrochlorobenzene to form a sulfonium salt, and demethylation of the sulfonium salt by S_N2 attack of iodide ion on one of its methyl groups. It is interesting to note that Finger and Kruse[3] obtained small amounts of nitrophenyl methyl sulfides as by-products in the preparation of *o*- and *p*-fluoronitrobenzenes by reactions of the corresponding chloro

(1) Work supported in part by the Office of Ordnance Research, U. S. Army.

(2) G. M. Bennett and I. H. Vernon, *J. Chem. Soc.*, 1783 (1938).

(3) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956).