pound, m.p. 105–113°. This substituted oxazole when recrystallized from hot dilute alcohol was obtained as a white flaky compound which melted at 120–120.5° after drying at room temperature *in vacuo* for 2 hours.

Anal.[3] Calcd. for $C_8H_5N_2OF_3$: C, 47.53; H, 2.49; N, 13.86. Found: C, 47.80, 47.80; H, 2.76, 2.53; N, 13.16, 13.35.

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RECEIVED JULY 20, 1950

Some *dl*-Alanyl-l-tyrosine Derivatives

N-Carbobenzoxy-*dl*-alanyl-l-tyrosine Ethyl Ester.—Two grams of N-carbobenzoxy-*dl*-alanine was suspended in 20 ml. of dry ether in a two-neck flask fitted with a mercury-seal stirrer and a calcium chloride drying tube. To the chilled suspension was added with stirring, 2.1 g. of phosphorus pentachloride. After one-half hour the solution was filtered into an ice-cold solution of 1.99 g. of *l*-tyrosine ethyl ester in 15 ml. of ethyl acetate. Saturated potassium bicarbonate, 20 ml., was added. After stirring for one-half hour in the cold and one hour at room temperature, the solution was transferred to a separatory funnel and was extracted with 1 *N* hydrochloric acid, half-saturated potassium bicarbonate and aqueous sodium chloride. The ether layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was dissolved in ethyl acetate and petroleum ether was added to an incipient turbidity. On cooling to −30° a precipitate was obtained; it was filtered and placed in a desiccator overnight. The product was dissolved in warm absolute methanol and ether was added until the solution was turbid. It was placed in the ice-box; crystallization occurred overnight. Recrystallization was effected by dissolving the crystals in a minimum amount of absolute methanol and adding petroleum ether. The product (930 mg.) melted at 132–134°.

Anal. Calcd. for $C_{22}H_{26}O_6N_2$: C, 63.75; H, 6.32. Found: C, 63.42; H, 6.51.

N-Carbobenzoxy-*dl*-alanyl-l-tyrosineamide.—One gram of the ester was dissolved in 20 ml. of absolute methanol previously saturated with dry ammonia. After standing for one week in the refrigerator, the solvent was removed under reduced pressure. The residual oil crystallized on standing in a desiccator over sulfuric acid. The amide, recrystallized from aqueous methanol, 300 mg., melted at 208–209° with decomposition.

Anal. Calcd. for $C_{20}H_{23}O_5N_3$: C, 62.32; H, 6.01; N, 11.18. Found: C, 62.42; H, 6.58; N, 10.90.

N-Carbobenzoxy-*dl*-alanyl-l-tyrosinehydrazide.—To 100 mg. of the ester, dissolved in about 1.0 ml. of absolute methanol there was added ten drops of 100% hydrazine hydrate. The solution, after standing for two hours, became a crystalline mass. The precipitate was filtered, washed with ice-cold methanol and dried. The yield, 60 mg., melted at 214–215°. On recrystallization from absolute ethanol the melting point rose to 216–217°.

Anal. Calcd. for $C_{20}H_{24}O_5N_4$: C, 59.99; H, 6.04; N, 14.01. Found: C, 59.57; H, 6.21; N, 13.46.

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COMMUNICATIONS TO THE EDITOR

DIETHYL CHLOROPHOSPHITE AS A REAGENT FOR PEPTIDE SYNTHESES

Sir:

The general methods of peptide synthesis in use involve lengthening the chain by the reaction of carboxy derivatives (halides, azides, anhydrides) with an amino group. We have found diethyl chlorophosphite to be a unique reagent in forming both reactive amides and anhydrides, thus allowing addition of aminoacid units to either end of a peptide chain.

The amides, $(C_2H_5O)_2PNHCH(R)COOR'$, are oils, at least some of which are distillable. They react with carbobenzoxyaminoacids in inert solvents to form carbobenzoxypeptide esters. The anhydrides, $(C_2H_5O)_2POCOCH(R)NHR'$, prepared in inert anhydrous solvents, are conveniently treated *in situ* with aminoacid esters. In both reactions, the by-product is presumably diethylphosphite.

Diethyl DL-α-carbethoxy-β-phenylethylaminophosphite was obtained by the reaction of DL-phenylalanine ethyl ester hydrochloride with diethyl chlorophosphite[1] and two equivalents of triethylamine in absolute ether, filtering the triethylamine hydrochloride and distilling; yield 48%, b.p. 148–151° at 0.25 mm., $n^{25}D$ 1.4908, d^{25} 1.071 (*Anal.* Calcd. for $C_{15}H_{24}NO_4P$: P, 9.88. Found: P, 9.86, 9.59.) Refluxing in toluene with carbobenzoxyglycine for one-half to two hours gave yields of 58 to 65% of carbobenzoxyglycyl-DL-phenylalanine ethyl ester[2] after recrystallization from ethanol–water, m.p. 88–90°. The phosphite derivative of glycylglycine ester reacted as an undistilled oil with carbobenzoxyglycine to give carbobenzoxydiglycylglycine ethyl ester,[3] 34% yield after recrystallization, m.p. 166–167°.

Carbobenzoxyglycine anilide (m.p. 147–148°) and carbobenzoxy-L-phenylalanine anilide (m.p. 170°), $[\alpha]^{24}D$ − 5.4° (*c*, 3; chloroform)[4] were made in good yields by the reaction of diethyl anilinophosphite[1] with the acids.

Phosphate anhydrides of carbobenzoxy- and phthalylglycine have been used for peptide syntheses.[5,6] We have found that the anhydrides of diethyl phosphite are more conveniently prepared. These are readily obtained by the reaction of diethyl chlorophosphite with carbobenzoxy- or phthalylaminoacids or peptides and triethylamine in solvents such as toluene or dioxane. Following filtration of triethylamine hydrochloride, the anhydride is treated in solution with an equivalent of an aminoacid ester at reflux for one to two hours;

(1) H. G. Cook, *et al.*, *J. Chem. Soc.*, 2921 (1949).

(2) H. Neurath, *et al.*, *J. Biol. Chem.*, **170**, 222 (1947).

(3) J. S. Fruton, *et al.*, *ibid.*, **173**, 467 (1948).

(4) The possibility of partial racemization is being investigated.

(5) H. Chantrenne, *Biochim. et Biophys. Acta*, **4**, 484 (1950).

(6) J. C. Sheehan and V. S. Frank, THIS JOURNAL, **72**, 1312 (1950).