In general CD_3 as initially formed possesses sufficient energy to make the reaction go on the first collision if steric requirements are met. (d) If the reaction does not go on the first collision, CD_3 is sufficiently deactivated so that the reaction occurs with very low probability on a succeeding collision.

We can then write

$$p_r \propto 2CD_3H$$
$$p_m \propto CD_4\text{-}CD_3H$$

Thus, we have for the ratio p_r/p_m for the photolysis of CD_3CDO

λ, Å.	>3000	~2537
p_r/p_m	25	1.4

This result is in reasonably good agreement with that of Blacet, *et al.*, when we note the slight differences in wave length of light employed and the fact that our data are for the d_4 compound. The assumptions employed in arrival at this estimate are rough. More careful consideration might include note of the fact that $E_4 < E_3$[8]; such more precise considerations would lead to the conclusion that our estimates of p_r/p_m tends to be high. The details of a more reliable calculation are not readily apparent.

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[8] Data given in reference 6 indicate that the CD_4/CD_3H ratio at 140-200°, where the chain reaction overwhelmingly predominates, is 0.62. Thus, E_4 is ~0.4 kcal./mole less than E_3.

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RECEIVED AUGUST 23, 1950

NEW COMPOUNDS

Some Derivatives of Biphenyl

4-Ethoxy-2'-nitrobiphenyl was prepared by a crossed Ullmann synthesis.[1] A mixture of 92 g. of *o*-iodonitrobenzene and 65 g. of commercial copper-bronze powder was added slowly with stirring to a mixture of 92 g. of *p*-iodophenetole and 50 g. of sand, while the temperature was maintained at 220-235°. After 15 minutes, an additional 65 g. of copper-bronze was added, and heating and stirring were continued for 2.5 hours. The desired product was isolated from the reaction mixture by successive ether extraction, vacuum distillation, chromatographic separation on alumina, recrystallization from alcohol and vacuum sublimation. The yield was 12 g. (13%) of yellow solid, m.p. 52-52.5°. *Anal.*[2] Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39. Found: C, 69.32; H, 5.16.

2-Amino-4'-ethoxybiphenyl was obtained in 76% yield by the reduction of 3 g. of 4-ethoxy-2'-nitrobiphenyl with tin and hydrochloric acid.[3] After three vacuum sublimations, the product was a white solid which darkened on standing and melted at 54-55°. *Anal.* Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.81; H, 7.00.

4-Ethoxy-2'-hydroxybiphenyl.—A solution of 1.0 g. of 2-amino-4'-ethoxybiphenyl in 200 ml. of dilute sulfuric acid was diazotized at −5° with 0.4 g. of sodium nitrite. After standing for three days at room temperature the solution was extracted with ether. Evaporation of the ether and vacuum sublimation of the remaining tar gave 0.7 g. (70% yield) of an oil which later solidified. After three further vacuum sublimations and a recrystallization from petroleum ether, the product was obtained as a white solid which melted at 53.5-54.5°. A mixture of equal amounts of 2-amino-4'-ethoxybiphenyl and 4-ethoxy-2'-hydroxybiphenyl melted at 43-47°. *Anal.* Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.43; H, 6.67.

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RECEIVED AUGUST 24, 1950

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[1] For a review of the Ullman synthesis of biaryls see P. E. Fanta, *Chem. Revs.*, **38**, 139 (1946).

[2] All analyses by Micro-Tech Laboratories, Skokie, Illinois.

[3] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 144.

Preparation of 2-Pyrroyltrifluoroacetone[1]

To 0.3 mole of sodium ethoxide suspended in 150 ml. of anhydrous ether in a three-necked flask fitted with a stirrer, reflux condenser and separatory funnel, 43 g. (0.3 mole) of ethyl trifluoroacetate was added slowly with stirring. To the resulting clear, light brown, solution, 32.7 g. (0.3 mole) of 2-acetylpyrrole,[2] m.p. 89-91°, dissolved in 350 ml. of anhydrous ether was added. When approximately one-half of the solution had been added, a precipitate appeared which redissolved as more of the ketone was added to give a clear yellowish-brown solution. The reaction mixture then was stirred for about 5 hours and allowed to stand overnight. Five hundred ml. of a copper acetate solution (0.23 mole of copper) was added and the mixture stirred for 3 hours more. On standing, two layers separated, a bluish-green ether layer containing most of the copper chelate, and a bluish aqueous layer containing some suspended copper chelate. The ether was then stripped and the precipitated copper chelate filtered and air-dried. The yield was 68 g., 95% of the theoretical amount. When some of the copper chelate was steam distilled to remove any unreacted 2-acetylpyrrole, no unreacted ketone was recovered. A solution containing 31 g. of the copper chelate in 800 ml. of ether, in a 2000-ml. erlenmeyer flask, was treated under pressure with dry hydrogen sulfide. Two 30-minute treatments were required before all the blue color of the copper compound had disappeared. The precipitated copper sulfide was filtered after each treatment with the aid of Filter Cel. The resulting clear, brown solution when stripped of the ether gave a pasty brown product. The crude product was distilled twice, under vacuum, with the fraction between 112-117° (5 mm.) collected. The distillate was a dark yellow liquid which solidified as it came in contact with the receiving flask. The yield was 14 g. The melting point range 59-69° indicated that the diketone was still impure, thus it was recrystallized, twice, from petroleum ether (60-68° fraction) to give long light yellow needles. The yield was 8.7 g. of the purified material. The melting point, after drying in a vacuum at room temperature for three hours, was 68.5-70.0°.

Anal.[3] Calcd. for $C_8H_6NO_2F_3$: C, 46.83; H, 2.95; N, 6.83. Found: C, 47.06, 47.20; H, 2.90, 2.95; N, 7.41, 7.22.

Further identification was provided by the metal analysis of bis-(1,1,1-trifluoro-4-(2-pyrryl)-2,4-butanediono)-copper. For analysis, the copper chelate, prepared as above, was recrystallized from hot 95% ethyl alcohol and dried at 110° for 24 hours after a preliminary drying for 12 hours at room temperature *in vacuo*, m.p. (dec.) 160°.

Anal. Calcd. for $CuC_{16}H_{10}N_2O_6F_6$: Cu, 13.47. Found: Cu, 13.43.

The isoxazole was produced by placing 1.33 g. of 2-pyrroyltrifluoroacetone in 15 ml. of 0.5 *N* HCl and adding enough ethyl alcohol to effect solution. Then a solution, containing 0.9 g. of hydroxylamine hydrochloride in 5 ml. of water, was added and the solution allowed to stand overnight. The solution was heated on a steam-bath until a precipitate appeared, at which time the heating was stopped and the mixture cooled in a water-ice mixture. The product was filtered and air-dried giving a yellow colored com-

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[1] Based on research carried out under Task Order 4 of Contract N 7onr-28504 between the Office of Naval Research and the University of Wisconsin.

[2] A. A. Berlin, *J. Gen. Chem.* (*U. S. S. R.*), **14**, 438-46 (1944); *C. A.*, **39**, 4606[8].

[3] Analysis by Clark Microanalytical Laboratory, Urbana, Illinois.

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-1-tyrosine Derivatives

N-Carbobenzoxy-*dl*-alanyl-1-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-1-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-1-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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RECEIVED JULY 21, 1950

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;

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[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).