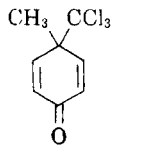
# Communications TO THE EDITOR

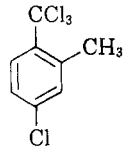
## A New Rearrangement Involving a Trichloromethyl Group

*Sir:*

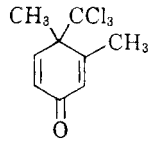
The rearrangement of 4-methyl-4-trichloromethyl-2,5-cyclohexadienone (I) to 3-methyl-4-trichloromethylchlorobenzene (II) on treatment with phosphorus pentachloride has been reported.[1] In an attempt to make 3,5-dimethyl-4-trichloromethyl chlorobenzene by a similar rearrangement, we prepared 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadienone (III).[2] When treated with phosphorus pentachloride, III underwent a new rearrangement to yield 3-(β,β,β-trichloroethyl)-4-methylchlorobenzene (IV) in 88% yield. No trace of a benzotrichloride product was detectable.



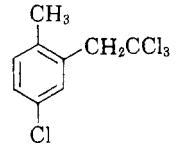

I




II




III




IV

The structure of IV was established by the following facts. Oxidation with alkaline permanganate yielded 4-chlorophthalic acid. Oxidation with a theoretical amount of chromic acid yielded 2-(β,β,β-trichloroethyl)-4-chlorobenzoic acid. Treatment of IV with sodium ethoxide readily afforded 3-(β,β-dichlorovinyl)-4-methyl chlorobenzene (V) which in turn yielded 2-methyl-5-chlorobenzoic acid on oxidation.

3,4-Dimethyl-4-trichloromethyl-2,5-cyclohexadienone (III) was prepared by the reaction of 61.1 g. of 3,4-dimethylphenol, 400 ml. of carbon tetrachloride, and 166 g. of anhydrous aluminum chloride at 5–20° for 2.5 hr. The yield was 92.1 g. (76.6%) of III, m.p. 60.0–61.0°. (*Anal.* Calcd. for $C_9H_9OCl_3$: C, 45.0; H, 3.8; Cl, 44.5. Found: C, 45.1; H, 3.6; Cl, 44.5.) The spontaneous exothermic reaction of 24 g. of III with 21 g. of phosphorus pentachloride yielded 22.8 g. (88.5%) of 3-(β,β,β-trichloroethyl)-4-methylchlorobenzene (IV), b.p. 121.0–128.0° at 4 mm., m.p. 35.0–36.1°. (*Anal.* Calcd. for $C_9H_8Cl_4$: C, 41.9; H, 3.1; Cl, 55.0. Found: C, 41.5; H, 3.2; Cl, 55.0.) The oxidation of 1.3 g. of IV with 1.3 g. of sodium dichromate dihydrate in a mixture of 60 ml. of glacial acetic acid and 2 ml. of concentrated sulfuric acid for 12 hr. on a steam bath yielded 1.34 g. (93.0%) of 2-(β,β,β-trichloroethyl)-4-chlorobenzoic acid, m.p. 168.0–169.5°. (*Anal.* Calcd. for $C_9H_6Cl_4O_2$: C, 37.8; H, 2.1; Cl, 49.0. Found: C, 37.7; H, 2.2; Cl, 49.0.)

The slow addition of an ethanolic solution of 10 g. of sodium ethoxide to an ethanolic solution of 38.5 g. of IV yielded 13.5 g. (40.8%) of 3-(β,β-dichlorovinyl)-4-methylchlorobenzene (V) as the major product, b.p. 114.5–115.5° at 16 mm. (*Anal.* Calcd. for $C_9H_7Cl_3$: C, 48.9; H, 3.2; Cl, 48.1. Found: C, 49.0; H, 3.3; Cl, 47.8.) The oxidation of 2.2 g. of V with 3.2 g. of potassium permanganate in a 4 to 1 pyridine-water mixture was completed in 10 min. at 25° to yield 1.05 g. (62.0%) of 5-chloro-2-methylbenzoic acid, m.p. 169.5–171.0°. A mixed m.p. with authentic 5-chloro-2-methylbenzoic acid[1] was unchanged.

Details of this and related work will be reported later.

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(1) K. Von Auwers and W. Julicher, *Ber.*, **55**, 2180 (1922).

(2) Compare Th. Zincke and R. Suhl, *Ber.*, **39**, 4152 (1906).

## Favorable Effect of Imidazole on Peptide Synthesis by the Tetraethylpyrophosphite Method

*Sir:*

It has been proposed that the imidazole group of histidine is an active site on enzyme molecules, and imidazole has been shown to be a catalyst for the hydrolysis of esters.[1,2] Acyl imidazoles are known to be highly reactive, and in fact peptide derivatives have been synthesized *via* *N*-acylation of the imidazole ring of methyl *N*-benzoyl-L-histidinate.[3] It was, therefore, of interest to study the effect of added imidazole on the synthesis of peptides by several of the commonly used procedures.

No improvement of yields was found in preliminary experiments using the isobutyl chlorocarbonate

(1) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652 (1957).

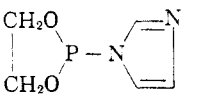
(2) T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **79**, 1663 (1957).

(3) T. Wieland and G. Schneider, *Ann.*, **580**, 159 (1953).

and azide procedures. In contrast, yields were consistently improved when imidazole was used in peptide syntheses by the tetraethylpyrophosphite procedure. For example, the reaction of carbobenzoxyglycine with ethyl L-tyrosinate gave crude yields of 60–70% of ethyl carbobenzoxyglycyl-L-tyrosinate[4,5] by the standard tetraethylpyrophosphite procedure,[5] and 85–90% when an equivalent of imidazole was present; recrystallized yields were in proportion. Several experiments showed that the rate of peptide formation was approximately doubled. For example, the reaction of carbobenzoxyglycine with ethyl DL-phenylalaninate hydrobromide in diethyl phosphite with trimethyl phosphite as HBr acceptor and tetraethyl pyrophosphite as reagent by the standard procedure[5] was timed so that the reaction was incomplete: heating for 180 seconds on a steam bath gave a 41% yield of ethyl carbobenzoxyglycyl-DL-phenylalaninate when no imidazole was present, and 75% when an equivalent of imidazole was present.

Maximum yields are obtained when imidazole is used in molar equivalence to the amino acid or peptide reactants. Also, best results are obtained when the imidazole is mixed with tetraethylpyrophosphite before addition of the latter to the peptide-forming reactants.

An attempt to isolate a possible intermediate, diethyl 1-imidazolephosphite, from reaction of tetraethyl pyrophosphite with imidazole was unsuccessful. However, the reaction of ethylene chlorophosphite with imidazole in benzene in the presence of triethylamine gave cyclic ethylene 1-imidazolephosphite [2-(1-imidazolyl)-1,3,2-dioxaphospholane] (I) as a very hygroscopic, crystalline solid, m.p. about 35°.



(I)

*Anal:* Calcd.: C, 37.98%; H, 4.46%. Found: C, 38.59; 37.94%; H, 4.85, 4.72%. A sample quickly weighed out was used in place of tetraethylpyrophosphite to prepare ethyl carbobenzoxyglycyl-L-tyrosinate by the standard procedure, giving a 91% crude yield, m.p. 122–125°. Recrystallization from ethanol-water gave an over-all yield of 77% with m.p. 125.5–127°. Thus cyclic ethylene 1-imidazolephosphite is an excellent peptide-forming reagent, but its hygroscopicity might limit its utility.

The effects of substituted imidazoles and related heterocycles are under investigation and will be reported at a later date.

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(4) J. R. Vaughan, Jr. and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

(5) G. W. Anderson, J. Blodinger, and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5309 (1952).