$$\underset{\text{I}}{CCl_3P(O)(OEt)_2} + KF \longrightarrow K^+ + \underset{\text{II}}{[CCl_3]^-} + \underset{\text{III}}{FP(O)(OEt)_2} \quad (1)$$

fluoridate (III) (see eq 1). In the presence of the water of hydration, the trichloromethide ion (II) would immediately be hydrolyzed to chloroform[9] (eq 2),

$$\underset{\text{II}}{[CCl_3]^-} + H_2O \longrightarrow OH^- + CHCl_3 \quad (2)$$

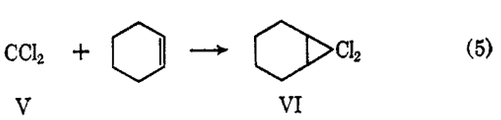
and the diethyl phosphorofluoridate (III) would be hydrolyzed with the formation of diethyl hydrogen phosphate (IV)[10] (eq 3).

$$\underset{\text{III}}{FP(O)(OEt)_2} + H_2O \longrightarrow \underset{\text{IV}}{HOP(O)(OEt)_2} + HF \quad (3)$$

The procedure was repeated using anhydrous potassium fluoride. Upon warming diethyl trichloromethylphosphonate with anhydrous potassium fluoride a good yield of diethyl phosphorofluoridate (III) was obtained. Apparently, under mild conditions, and in the absence of water, carbon–phosphorus bond scission had again occurred. It was not clear what the other product(s) of the reaction might be because, from the stoichiometry of the reaction, the other products are the potassium ion and the trichloromethide ion (II).

It has been shown that dichlorocarbene (V) is produced from the trichloromethide ion in several other reactions by the loss of chloride ion[11] (eq 4). Dichlorocarbene (V) adds readily to olefins to form cyclopropane derivatives;[11] so the reaction was repeated in the presence of cyclohexene and 7,7-dichlorobicyclo[4.1.0]heptane (dichloronorcarane) (VI) was isolated in 40% yield (eq 5).

$$\underset{\text{II}}{[CCl_3]^-} \longrightarrow Cl^- + \underset{\text{V}}{CCl_2} \quad (4)$$



V VI (5)

Anhydrous sodium fluoride is almost completely ineffective in promoting the cleavage. Lithium fluoride and calcium fluoride are completely ineffective. Ammonium fluoride works as well, if not better, than potassium fluoride in effecting the scission. Antimony trifluoride apparently is somewhat active and silver monofluoride produces a rather exothermic reaction with diethyl trichloromethylphosphonate resulting in carbon–phosphorus bond scission. The carbon–phosphorus bonds in diethyl dichloromethylphosphonate, diethyl chloromethylphosphonate, and diethyl methylphosphonate are unaffected by warming with anhydrous potassium fluoride.

If methanol is used as a solvent to increase the solubility of the potassium fluoride in diethyl trichloromethylphosphonate (I) the reaction proceeds quite exothermically at room temperature to give diethyl methyl phosphate (VII) (eq 6).

$$\underset{\text{I}}{CCl_3P(O)(OEt)_2} + KF + MeOH \longrightarrow \underset{\text{VII}}{MeOP(O)(OEt)_2} \quad (6)$$

The mechanism and synthetic applications of this cleavage are presently under investigation.

(9) J. Hine and A. M. Dowell, Jr., *J. Amer. Chem. Soc.*, **76**, 2688 (1954).
(10) N. B. Chapman and B. C. Saunders, *J. Chem. Soc.*, 1010 (1948).
(11) W. von E. Doering and A. K. Hoffman, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

Experimental Section

Reaction with Potassium Fluoride Dihydrate.—After heating a mixture of 51.1 g (0.2 mol) of diethyl trichloromethylphosphonate and 46.4 g (0.49 mol) of potassium fluoride dihydrate at reflux (71°) for 30 min, 20 g (84%) of chloroform (bp 58–60 (740 mm), $n^{25}D$ 1.4437) was distilled from the reaction mixture.

Reaction with Anhydrous Potassium Fluoride.—In a flask fitted with a reflux condenser protected by a calcium chloride tube 206 g (0.81 mol) of diethyl trichloromethylphosphonate and 188 g (3.24 mol) of anhydrous potassium fluoride were stirred over a steam bath for 60 hr. Distillation from the reaction flask gave 108.5 g (86%) of diethyl phosphorofluoridate: bp 80–80.5 (32 mm); $n^{27}D$ 1.3710; d^{27}_4 1.1399.

Anal. Calcd for $C_4H_{10}FO_3P$: C, 30.78; H, 6.46; F, 12.17; P, 19.85. Found: C, 30.78, 30.83; H, 6.23, 6.24; F, 12.15, 12.20; P, 19.97, 19.81.

Note: Phosphorofluoridates are known to be extremely toxic. At lower concentration their vapors have a myotic effect (pupil constriction) on the eye and at higher concentrations they can cause respiratory collapse.[12]

Reaction in Cyclohexene.—In a flask fitted with a reflux condenser protected by a calcium chloride tube 112 g (0.5 mol) of diethyl trichloromethylphosphonate, 58 g (1.0 mol) of anhydrous potassium fluoride, and 82 g (0.5 mol) of cyclohexene were stirred while heated in an oil bath at 110° for 24 hr. After filtering, the precipitate was washed with two 50-ml portions of dry ether. The filtrate and washings were combined and the ether and unreacted cyclohexene were distilled out. The residue was stirred with 100 ml of water for 4 hr at 60°. The hydrolysate was extracted with two 50-ml portions of petroleum ether. After drying over magnesium sulfate the petroleum ether was removed from the combined extracts at 20 mm on a rotary evaporator. Distillation of the residue gave 33.0 g (40.0%) of dichloronorcarane, bp 84–85° (17 mm), $n^{24}D$ 1.5010.

Anal. Calcd for $C_7H_{10}Cl_2$: C, 50.93; H. 6.11; Cl, 42.96. Found: C, 50.83, 50.93; H, 6.11, 6.04; Cl, 43.01, 42.90.

Reaction in Methanol.—Diethyl trichloromethylphosphonate (25.6 g, 0.1 mol) was added, dropwise at first, to 11.6 g (0.2 mol) of anhydrous potassium fluoride, with stirring. When there was no apparent evidence of reaction the remainder of the ester was run into the flask. In about 2 min the temperature began to rise so rapidly that the flask had to be cooled with an ice bath to keep the methanol from refluxing at a rate that exceeded the capacity of the condenser. When the reaction had subsided heat was applied to keep the methanol refluxing for 24 hr. After cooling, 50 ml of ether was added, the solids were filtered, and distillation of the filtrate gave 13.5 g (80%) of diethyl methyl phosphate, bp 104–105° (21 mm), $n^{21}D$ 1.4031.

Registry No.—I, 866-23-9; III, 358-74-7; V, 1605-72-7; VI, 823-69-8; VII, 867-17-4.

(12) B. C. Saunders, "Some Aspects of the Chemistry of Organic Compounds Containing Phosphorus and Fluorine," Cambridge University Press, London, 1957, p 1.

3,5-Dichlorotyrosines. Preparation of D and L Forms[1]

KENNETH R. BRODY AND RICHARD P. SPENCER

Department of Radiology, Yale University School of Medicine, New Haven, Connecticut

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A number of references to 3,5-dichloro-L-tyrosine have been reported[2–4] which are based on a synthesis

(1) Supported by U. S. Public Health Service Grants CA06519 and AM09429.
(2) F. K. Beilstein, "Handbuch der organische Chemie," Vol. 14, 2nd ed, Part I, Springer-Verlag, Berlin, 1951, p 670; Part II, pp 377, 382.
(3) S. Bouchilloux, *Bull. Soc. Chim. Biol.*, **37**, 255 (1955).
(4) Houben-Weyl's, "Methoden der organischen Chemie," Vol. 5, Part 3, Georg Thieme Verlag, Stuttgart, Germany, 1962, p 685.

described by Zeynek.[5] The product obtained had been variously described as gray, yellow, or brown and as the mono- and dihydrate. A reexamination of the procedure was undertaken and we found that the products formed by this method varied in both composition and color.

A reproducible synthetic method for 3,5-dichlorotyrosine has been developed. Significant was the ease of preparation, coupled with consistent formation of a white solid of definite composition. The compound formed only as the monohydrate and when prepared from L-tyrosine was dextrorotary.

Experimental Section

A 200-ml, three-necked, standard-taper flask was fitted with a glass thermometer, a motor-driven glass stirrer in a Teflon-sealed, gas-tight stopper in the center neck, and a "T" glass standard-taper connection in the remaining neck. One of the "T" openings connected to a chlorine gas supply tank was fitted with a pressure regulator. The remaining "T" opening was connected to a "U" type manometer containing light mineral oil.

A bath containing salt–ice–water was agitated by a magnetic stirrer, and completely surrounded the reaction flask up to the center neck. A 5-g sample of L-tyrosine powder (J. T. Baker Chemical Co.) and 125 ml of propionic acid were well mixed in the flask to obtain a fine dispersion. Both the bath fluid and the reaction mixture were stirred continuously throughout the run.

The bath temperature was dropped to −10°. Chlorine was added to flush out air in the system; this was done by raising the thermometer slightly, thus creating an exit vent, for 30 sec. The thermometer was replaced in position to again make a gas-tight system, and the chlorine regulated to give a manometer reading of about 1 cm of mineral oil. In a period of 18 min, the flask temperature rose to +1°. At this point the bath mixture was adjusted to obtain a flask temperature of 0–5° for a period of 2 hr. After about 8 min from the beginning of chlorination, the flask contents almost cleared to a single phase; only a few crystals remained. Soon thereafter crystals appeared in quantity and the mass thickened, but remained sufficiently fluid for agitation. After about 10 min from the beginning of chlorination, the manometer pressure gradually increased as the chlorine absorption rate diminished. About 3 min later, the chlorine pressure reached a maximum or constant value. The chlorine pressure in the system was kept at a positive value at all times to eliminate the possibility of air or moisture entry through leakage.

Following the 2-hr chlorination period, the "T" connection was quickly removed and replaced with a single-stem standard taper reducer. This was coupled to a large, dry glass trap in series with a water aspirator. Agitation was continued while the system was under vacuum (30 mm). When the volatiles and free chlorine were being removed, the temperature dropped and then rose again to 5°.

After agitation for one more hour at 5°, the dispersion became white in color. The flask contents were then filtered by suction, using a fritted glass, Buchner-type, jacketed, filter funnel through which ice water circulated. The residue was pressed dry to remove additional mother liquor. Filtration was continued until no more solvent was removed. The residue was washed with two 5-ml portions of propionic acid at 0° and again suction was applied until no more filtrate appeared. The filter cake weighed 12.4 g and contained an appreciable amount of mother liquor and propionic acid.

A. Salting-Out Process.—One-half of this crude residue (6.2 g) was dissolved in 62 ml of water at 15° and the small amount of insoluble material was filtered off. To the filtrate, with agitation, was added 13 ml of an aqueous solution containing 3.3 g of sodium acetate trihydrate. After stirring for 10 min, the mixture was refrigerated to 10°, and filtered through a cold fritted glass funnel. The residue was washed three times by dispersing well each time in an equal volume of water at 0°. The residue was sucked dry for 2 hr or more at room temperature to constant weight. The pure product obtained weighed 2.5 g (67.6% yield). *Anal.* Calcd for $C_9H_9NCl_2O_3 \cdot H_2O$: C, 40.30; H, 4.10; N, 5.23; Cl, 26.40. Found: C, 40.35; H, 4.16; N, 5.27; Cl, 26.34.

(5) R. Zeynek, *Z. Physiol. Chem.*, **114**, 275 (1921).

B. Neutralization Process.—The remaining half of the crude residue (6.2 g) was dissolved in 25 ml of water at 15° and filtered. The filtrate was diluted with 200 ml of water, and then kept at 5° during subsequent operations. The solution was neutralized to pH 8 with 1 *N* NaOH with good agitation and again filtered, and the filtrate was brought to pH 3 with 1 *N* hydrochloric acid. Following filtration, the residue was washed by dispersal three times in equal volumes of water and sucked dry. Suction was continued at ambient temperature to constant weight. A white product (2.3 g) was obtained (62.3% yield). *Anal.* Found: C, 40.32; H, 4.13; N, 5.21; Cl, 26.39.

Of the two general processes, the salting-out procedure with sodium acetate solution gave slightly higher yields.

The product had a melting point of 225–228° with decomposition (Nalge microscope-type, polarized melting point apparatus). Ascending chromatography on Whatman No. 1 paper revealed a single ninhydrin-reacting spot at R_f 0.59 in 4:1:1 (v/v/v) 1-butanol–acetic acid–water and at R_f 0.70 in 130:33:40 (v/v/v) 2-propanol–concentrated HCl–water. There was an ultraviolet absorbance peak at 305 mμ. A sample of 3,5-dichlorotyrosine monohydrate allowed to stand under high vacuum at normal temperature in the presence of concentrated H_2SO_4 for 33 days showed weight loss corresponding to 1 H_2O (calcd: 6.7%; found: 6.6%). The compound synthesized from L-tyrosine was dextrorotary, $[\alpha]^{25}D$ +1.16 (*c* 5, 1 *N* HCl), whereas that synthesized from D-tyrosine was levorotary $[\alpha]^{25}D$ −1.13. To confirm the purity of the optical isomers, an enzyme system was used.[6] The large change in optical density at 332 mμ in borate buffer, in the presence of L-amino acid oxidase (*Crotalus adamanteus* venom) and catalase, with the 3,5-dichlorotyrosine prepared from L-tyrosine, was indicative of the L form. The compound synthesized from D-tyrosine, under identical test conditions, was not reactive.

In place of the propionic acid, glacial acetic acid has also been used as an alternative solvent at 20° maximum temperature (care must be taken to prevent solidification of the reaction mixture by keeping the temperature above 16°). The yield and purity of compounds formed using both solvents were identical. The keys to a successful preparation are rigid temperature control and the thorough removal of excess chlorine following halogenation.

Registry No.—3,5-Dichloro-D-tyrosine, 15924-16-0; 3,5-dichloro-L-tyrosine, 15106-62-4.

Acknowledgment.—The authors are grateful to Dr. George Delpierre for the polarimetry measurements.

(6) R. P. Spencer and D. Brock, *Endocrinology*, **70**, 750 (1962).

On the Reaction of 1-Phenylcyclopentanecarbonitrile with Methylmagnesium Iodide. Formation of Bis(1-phenylcyclopentyl) Ketone[1]

JAMES W. WILT, BROTHER HERBERT PHILIP, F.S.C., AND DAVID G. SCHULTENOVER, S. J.

Department of Chemistry, Loyola University, Chicago, Illinois 60626

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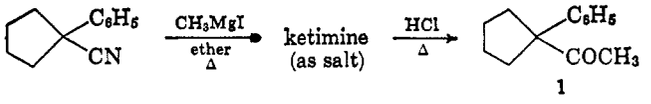
Some years ago, in connection with another problem, we had occasion to prepare 1-phenylcyclopentyl methyl ketone (**1**). We chose the method of Smith and



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(1) This reaction was first noticed during the doctoral research of Herbert Philip, and is described in his Dissertation, pp 108–109, Loyola University (1959). No structural assignment was made at that time.