tion. Furthermore, the zinc chloride has to be removed with scrupulous and time-consuming aqueous washing in order to avoid decomposition of the products on distillation. It was found that much of the tedium of these preparations can be avoided by the use of a procedure which is in essence that of Cambron.[2] With elimination of the zinc chloride the usually troublesome emulsion formation on washing is avoided, the necessity for close temperature control is eliminated and the yields on reacted hydrocarbon are ample for most purposes. The following examples illustrate the procedure.

Experimental

p-Ethylbenzyl Chloride.—238 g. of ethylbenzene, 90 g. of paraformaldehyde, 250 g. of glacial acetic acid, 280 cc. of concentrated hydrochloric acid and 135 cc. of 85% phosphoric acid were agitated at 100° (steam-bath) for four and one-half hours. On cooling the organic layer was separated, washed three times with cold water and distilled to yield 114 g. of recovered ethylbenzene, b. p. 42° at 28 mm., and 132 g. of *p*-ethylbenzyl chloride, b. p. 111° at 26 mm., $n^{25}D$ 1.5290, for 38% conversion and 73% yield.

p-Butylbenzyl Chloride.—96 g. of *n*-butylbenzene, 29 g. of paraformaldehyde, 79 g. of glacial acetic acid, 88 cc. of concentrated hydrochloric acid and 43 cc. of 85% phosphoric acid were stirred under reflux for sixteen hours. On cooling, the organic layer was separated and washed three times with cold water. On distillation there was obtained 69.5 g. of recovered *n*-butylbenzene and 24 g. of *p*-butylbenzyl chloride, b. p. 142–146° at 27 mm., $n^{26}D$ 1.5159, for 27.5% conversion and 67% yield.

(2) Cambron, *Can. J. Research*, **17B**, 10 (1939).

MONSANTO CHEMICAL COMPANY
CENTRAL RESEARCH DEPARTMENT
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RECEIVED APRIL 4, 1946

The Toxicity of 3-Fluoro-*d*(+)- and *l*(−)-tyrosine

BY CARL NIEMANN AND M. M. RAPPORT

The toxicity and physiological action of 3-fluoro-*dl*-tyrosine have been the subject of numerous investigations[1] and in view of the interest shown in this substance it appeared desirable to compare the toxicity of the *d*- and *l*-isomers with that of the *dl*-mixture.[2] The *d*- and *l*-isomers were obtained from the *dl*-mixture by adoption of the method of enzymatic resolution originally developed by Bergmann and co-workers.[3]

In the rat the toxicity of each antipode was found to be identical with that of the *dl*-mixture and one may conclude that antipodal specificity with reference to the amino side chain is not a critical factor in the toxic action of 3-fluorotyrosine. One cannot conclude that the amino acid side chain is without effect, as *o*-fluorophenol is much less toxic than is 3-fluorotyrosine.[4] It appears that the presence of the amino acid side chain denies to 3-fluorotyrosine the detoxification routes ordinarily available to phenols with the result that the rat is forced to metabolize 3-fluorotyrosine with the concomitant formation of toxic end products other than fluoride ion.[1a] It appears from the work of Niedner[1b] that 3-fluorotyrosine behaves similarly in the mouse, for the LD_{50} for the mouse is apparently equal to that for the rat.

Experimental

N-Benzoyl-3-fluoro-*dl*-tyrosine.—3-Fluoro-*dl*-tyrosine[2] (20 g.) was benzoylated following the procedure of Carter and Stevens[5] to give 20.1 g. (66%) of N-benzoyl-3-fluoro-*dl*-tyrosine, m. p. 178–179° after recrystallization from a mixture of ethyl acetate and ligroin.

Anal. Calcd. for $C_{16}H_{14}O_4NF$ (303); C, 63.4; H, 4.7; N, 4.6. Found: C, 63.5; H, 4.4; N, 4.5.

3-Fluoro-*l*(−)-tyrosine.—N-Benzoyl-3-fluoro-*dl*-tyrosine (8.75 g.) was dissolved in 35 ml. of *N* sodium hydroxide and 44 ml. of 2 *M* sodium acetate and the solution filtered prior to the addition of 88 ml. of 0.1 *M* citrate buffer (*p*H 5.0), 0.65 g. of cysteine hydrochloride, 5.25 ml. of aniline, 88 ml. of a filtered papain solution prepared by dissolving 0.9 g. of purified papain[3a] in 100 ml. of 0.05 *M* citrate buffer (*p*H 5.0) and 170 ml. of water. After the addition of 1 ml. of 50% acetic acid the solution (*p*H 5.8) was incubated at 40° for seven days adding 1 ml. of 50% acetic acid on the second and third days. The precipitate was collected, washed with cold water and 50% aqueous ethanol and dried to give 3.25 g. of crude N-benzoyl-3-fluoro-*l*(−)-tyrosylanilide, m. p. 194–197° dec. The filtrate obtained after the removal of the precipitated anilide was adjusted to *p*H 5.5 with 50% acetic acid and incubated at 40° for another week. A second crop of 1.70 g. of anilide, m. p. 192–196°, was obtained to give a total yield of 4.95 g. or 91% of the theoretical quantity. A suspension of 4.95 g. of the above anilide in 200 ml. of 10% hydrochloric acid was refluxed for eighteen hours, the hydrolysate cooled to 25°, filtered and the filtrate extracted with ether. The aqueous phase was concentrated *in vacuo* to 50 ml. and neutralized by the addition of sodium acetate. The addition of ether to the solution induced crystallization whereupon the ethereal phase was decanted, the product collected and recrystallized twice from water to give 1.2 g. (48%) of 3-fluoro-*l*(−)-tyrosine, m. p. 278–279° with decomposition starting at 265° when heated at the rate of 5°/min.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199): C, 54.3; H, 5.1; N, 7.0. Found: C, 54.5; H, 5.2; N, 6.9: $[\alpha]^{26}D = \frac{-0.29 \times 1.95}{1 \times 0.100} = -5.7°$ (in 4% hydrochloric acid).

3-Fluoro-*d*(+)-tyrosine.—The filtrate remaining after the removal of the second crop of N-benzoyl-3-fluoro-*l*(−)-tyrosylanilide was acidified with concd. hydrochloric acid to *p*H 1–2 and exhaustively extracted with ethyl acetate. The ethyl acetate phase was dried over sodium sulfate, the solvent removed and the residual oil refluxed with 200 ml. of 10% hydrochloric acid for eighteen hours. The hydrolysate was treated as described above and 2.2 g. of a mixture of 25% of 3-fluoro-*l*(−)-tyrosine and 75% of 3-fluoro-*d*(+)-tyrosine was obtained. This product was dissolved in the minimum quantity of hot water, the solution cooled, the precipitate discarded and the filtrate evaporated to dryness. The residue was recrystallized from water to give 0.9 g. of 3-fluoro-*d*(+)-tyrosine, m. p. 279–

(1) See for example (a) P. Boyer, R. Evans and P. Phillips, *J. Pharmacol. Exptl. Therap.*, **73**, 176 (1941); (b) K. Niedner, *Z. Krebsforsch.*, **51**, 159 (1941).

(2) C. Niemann, A. A. Benson and J. F. Mead, THIS JOURNAL, **63**, 2204 (1941).

(3) (a) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937); (b) C. Niemann and P. L. Nichols, Jr., *ibid.*, **143**, 191 (1942).

(4) Unpublished experiments have shown that the LD_{50} of *o*-fluorophenol in the rat is greater than 100 mg./kg. when administered subcutaneously.

(5) H. E. Carter and C. M. Stevens, *J. Biol. Chem.*, **138**, 628 (1941).

280° with decomposition starting at 265° when heated at the rate of 5°/min.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199): C, 54.3; H, 5.1; N, 7.0. Found: C, 54.3; H, 5.1; N, 6.9: $[\alpha]^{26}D = \frac{0.29 \times 1.95}{1 \times 0.100} = 5.7°$ (in 4% hydrochloric acid).

Toxicity Determinations.—The procedure employed was that described by Phillips, *et al.*,[1a] *i. e.*, single subcutaneous injections of solutions of the hydrochloride in both mature (150–300 g.) and immature (80–150 g.) rats. The toxic symptoms were identical with those reported[1a] and most of the deaths occurred during the first twenty-four hours although the period of observation was taken as forty-eight hours.

TABLE I

TOXICITY DATA

Substance	Moles/kg. × 10⁵[a]	Mortality per group Immature rat	Mature rat
3-Fluoro-*l*(−)-tyrosine	4.5	0/6	
	5.0	0/4	
	6.3	5/10	0/8
	7.5	4/4	4/8
3-Fluoro-*d*(+)-tyrosine	6.3	2/6	0/8
	7.5		4/8
3-Fluoro-*dl*-tyrosine	6.3	2/6	0/8
	7.5		6/8

[a] Mg./kg. = moles/kg. × 2 × 10⁵.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIF. RECEIVED MAY 20, 1946

Synthesis of 2,4-Dichloropropiophenone

BY JOHN T. SHEEHAN[1]

According to the available literature,[2,3] the Friedel–Crafts condensation of acyl halides with dihalogenated benzene derivatives proceeds with the formation of negligible or vanishing yields. Consequently it seemed worth while to note the present exception to this observed behavior, which was encountered in the course of another investigation. In this instance, the yield was found equal to that obtained in the usual Friedel–Crafts condensation between acyl halides and aromatic hydrocarbons, albeit a longer period of heating and a greater amount of anhydrous aluminum chloride than usual were employed.

Experimental

2,4-Dichloropropiophenone.—Forty grams (0.27 mole) of *m*-dichlorobenzene and 48 g. (0.50 mole) of propionyl chloride were dissolved in 300 cc. of carbon disulfide. The solution was refluxed on a steam-bath while stirring, and to it was added, over a period of ten minutes, 160 g. (1.20 moles) of anhydrous aluminum chloride. The heating and stirring were continued for twenty-four hours, during which time the evolution of hydrogen chloride was noticeable but never vigorous. The carbon disulfide was then distilled off and the residue poured into 300 cc. of 6 *N* hydrochloric acid in ice. The oily layer which separated was extracted with four 125-cc. portions of benzene. The combined benzene extract was washed twice with 300 cc. of water, once with 350 cc. of 10% sodium hydroxide, and finally three times with 300 cc. of water. It was then dried over anhydrous calcium chloride. The latter was filtered off, the solvent evaporated and the residue distilled. The main fraction boiled at 118–120° at 5 mm. On redistillation it boiled at 121–123° at 6.5–7 mm. The yield was 48.5 g. (89%). At 19 mm. the boiling point is 138–140°; $n^{25}D$ 1.5510 and d^{25} 1.2871.

Anal. Calcd. for $C_9H_8OCl_2$: C, 53.20; H, 3.95; Cl, 34.97. Found: C, 53.10; H, 3.89; Cl, 34.96.

On oxidation with potassium permanganate, the above compound yielded only one product, and that in almost quantitative yield. After recrystallization from water it melted at 158°. A mixed melting point with an authentic sample of 2,4-dichlorobenzoic acid gave no depression.

Anal. Calcd. for $C_7H_4O_2Cl_2$: C, 43.97; H, 2.09; Cl, 37.12. Found: C, 44.15; H, 2.30; Cl, 37.09.

WINTHROP CHEMICAL COMPANY, INC.
RENSSELAER, NEW YORK RECEIVED MAY 2, 1946

(1) Present address: Squibb Institute for Medical Research, New Brunswick, N. J.

(2) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," A. C. S. Monograph 87, Reinhold Publishing Corp., New York, N. Y., 1941, pp. 226–228.

(3) Roberts and Turner, *J. Chem. Soc.*, 1832 (1927).

Carbonyl Chlorofluoride[1]

BY J. H. SIMONS, D. F. HERMAN AND W. H. PEARLSON

We have found that carbonyl chlorofluoride can be prepared readily by shaking a mixture of hydrogen fluoride and phosgene in a copper bomb at approximately 80° and 280 pounds per square inch pressure. Some fluorophosgene is simultaneously produced but as hydrogen chloride is one of the products and as this boils too close to fluorophosgene for separation by distillation, no significant amounts of fluorophosgene were prepared from these preparations.

The apparatus consisted of a heavy-wall copper bomb of about 250-cc. capacity which was connected to a copper condenser cooled by tap water. The condenser was fitted with a pressure gage and a valve through which the gaseous products could be removed. The bomb was placed in an electrically heated furnace located in a shaking machine. Hydrogen fluoride was removed from the exit gases by means of anhydrous sodium fluoride. After passage through a sulfuric acid bubbler the gases were condensed in traps cooled with liquid air. The procedure consisted of adding to the cooled bomb a charge of about 100 g. of phosgene and 200 g. of hydrogen fluoride. The apparatus was then assembled and heating and shaking begun. When the pressure reached the desired value, between 250 and 300 pounds per square inch, the exit gases were bled off at a rate to maintain the pressure constant. The rate of the reaction was usually negligible below 50° but increased rapidly with temperature so that at 70 to 90° a satisfactory rate of production could be maintained.

Phosgene from different sources gave different rates of production. A sample made by the method of Grignard and Urbain[2] and purified

(1) This paper is based on work done for the Office of Scientific Research and Development under Contract No. NDCrc-167 with Pennsylvania State College.

(2) Grignard and Urbain, *Compt. rend.*, **169**, 17 (1919).