material was identical to the spectrum of a sample of CF_3NO prepared from CF_3I.[7]

Nitrosyl perfluorobutyrate from lead perfluorobutyrate. A 1-l. three neck flask was equipped with a stirrer, a Dry-Ice–acetone cold finger condenser, and a 250-ml. Erlenmeyer flask attached to the reaction flask via thin-walled rubber tubing so that solids could be added without exposure to atmospheric moisture. The reaction flask was cooled in Dry Ice–acetone, charged with nitrosyl chloride (176 g., 2.7 moles), and stirred while lead perfluorobutyrate (104 g., 0.164 mole) was added portionwise from the Erlenmeyer flask. After the addition was complete (approximately 10 min.) the addition assembly was replaced with a glass stopper and the reaction mixture was stirred at reflux for 4 hours. After being allowed to stand overnight in Dry Ice, the mixture was again brought to reflux and 200 ml. CCl_3F were added. The precipitate was allowed to settle and the mixture was filtered being careful to decant the bulk of the solution before the solids were poured into the funnel The filtration was performed in a sintered glass funnel under 2 to 3 lb. nitrogen pressure. The excess nitrosyl chloride and CCl_3F were removed at room temperature and the product remaining distilled under reduced pressure yielding 72 g. (90% yield) nitrosyl perfluorobutyrate, b.p. 72°/93 mm.

Anal. Calcd. for $C_4F_7NO_3$: C, 19.8; F, 54.7; N, 5.76. Found: C, 20.4; F, 55.1; N, 5.4.

The NMR $C_6H_5\phi$*[6] values for CF_3, $—CF_2—$, and $—CF_2—$ adjacent to the carbonyl were 80.71 triplet, 126.45 singlet, and 118.28 quartet, respectively, at 10% conc. by volume.

Preparation of nitrosyl trifluoroacetate from calcium trifluoroacetate and $(NO_2)S_2O_7$. Calcium trifluoroacetate (25.0 g., 0.094 mole) was triturated with $(NO)_2S_2O_7$ (25.0 g., 0.106 mole) under a stream of nitrogen. The mixture was then stirred and heated at 90° under vacuum. A yellow liquid (4 g.) was collected in a trap cooled in Dry Ice–acetone. The infrared spectrum of this material showed it to be nitrosyl trifluoroacetate plus some trifluoroacetic acid.

Preparation of Nitrosylperfluoro(β-ethoxy)propionate from silver perfluoro(β-ethoxy)propionate. A 500 ml. round bottom flask was equipped with an outlet protected by a drying tube, a magnetic stirrer, and a 125 ml. Erlenmeyer flask attached to the reaction flask via thin-walled rubber tubing so that solids could be added without exposure to atmospheric moisture. The reaction flask was flushed with dry nitrogen, cooled in Dry Ice–acetone, charged with 30 cc. (42.6 g., 0.65 mole) nitrosyl chloride and stirred while 34.5 g. (0.892 mole) silver perfluoro(β-ethoxy)propionate was added portionwise from the Erlenmeyer flask. After the addition was complete (approximately ten minutes), the addition assembly was replaced with a glass stopper and the reaction mixture was stirred at −20° to −40° for 2 hr. The mixture was then allowed to warm to room temperature while the excess nitrosyl chloride distilled into a Dry Ice trap. The residue was vacuum distilled giving 27 g. (97.7% yield) nitrosyl perfluoro(β-ethoxy)propionate, b.p. 44°C at 14 mm.

Anal. Calcd. for $C_5F_9NO_4$: C, 19.4%; N, 4.52%. Found: C, 19.3%; N, 4.5%.

Preparation of nitrosyl 3,4-dichloropentafluorobutyrate from silver 3,4-dichloropentafluorobutyrate. Silver 3,4-dichloropentafluorobutyrate (44.9 g., 0.127 mole) was allowed to react with 40 ml. (57 g., 0.87 mole) nitrosyl chloride in the same manner as described above for perfluoro (β-ethoxy)propionate. Distillation of the product gave 31 g. (88.5% yield) nitrosyl 3,4-dichloropentafluorobutyrate, b.p. 63° at 5.5 mm.

Anal. Calcd. for $C_4F_5Cl_2NO_3$: C, 17.4; F, 34.4; N, 5.1. Found: C, 17.7; F, 34.1; N, 4.5.

Preparation of nitrosyl 3,5,6-trichlorooctafluorocaproate from silver 3,5,6-trichlorooctafluorocaproate. Silver 3,5,6-trichlorooctafluorocaproate (26.8 g., 0.0570 mole) was allowed to react with 40 ml. (57 g., 0.87 mole) nitrosyl chloride in the same manner as described above for perfluoro(β-ethoxy)propionate. Distillation of the product gave 20.0 g. (89.4% yield) nitrosyl 3,5,6-trichlorooctafluorocaproate, b.p. 73° at 0.5 mm.

Anal. Calcd. for $C_6F_8Cl_3NO_3$: C, 18.4; F, 38.7; N, 3.56. Found: C, 18.6; F, 38.4; N, 3.4.

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The Amidomethylation of 2-Chlorobenzoic Acid[1]

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Received August 10, 1961

The amidomethylation of 2-chlorobenzoic acid was undertaken in order to study the effect of the chlorine and carboxy substituents on the orientation of the entering amidomethyl group and to utilize the product in preparing derivatives to be tested for physiological activity.

The use of *N*-hydroxymethylchloroacetamide in concentrated sulfuric acid as reported by Tscherniac[3] and other workers[4–7] to amidomethylate benzoic acid was utilized in this work. It was noted in our study that if the ratio of sulfuric acid to 2-chlorobenzoic acid was doubled, the yield of product was increased from 40 to 65%. This product was shown to be 2-chloro-5-(chloroacetylaminomethyl)benzoic acid (I).

Hydrolysis of I by means of concentrated hydrochloric acid gave 3-carboxy-4-chlorobenzylamine hydrochloride (II).

The action of formaldehyde and sodium bicarbonate on II followed by hydrogenation with a palladium-charcoal catalyst gave *m*-toluic acid (III), which was identified by melting point and infrared spectra.

3-Carboxy-4-chlorobenzylamine hydrochloride was decarboxylated with soda-lime to yield 4-chlorobenzylamine, which was identified as the benzoyl derivative.

Vigorous oxidation of III with potassium dichromate and sulfuric acid gave 4-chloroisophthalic acid (IV).

(1) This work was supported in part by a grant (CY-3908) from the National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare, Bethesda, Md., and a Parke, Davis and Company Research Grant.

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Thus, the entering amidomethyl group was found to be *para* to the chlorine and *meta* to the carboxyl group.

A number of derivatives of the 2-chloro-5-aminomethylbenzoic acid were prepared by conventional means and are reported in the Experimental without comment.

EXPERIMENTAL

Condensation of 2-chlorobenzoic acid with N-hydroxymethylacetamide. A mixture of 277.8 g. (1.76 moles) of 2-chlorobenzoic acid and 700 ml. of concd. sulfuric acid was stirred and cooled to 20°. Powdered *N*-hydromethylchloroacetamide[4] (202 g., 1.8 moles) was added over a 30-min. period at 20°. After the reaction mixture was stirred overnight, the solution was poured over ice and allowed to stand for 2 days. The solid was removed, washed with water, dried, and triturated with ether. The solid was removed, m.p. 126–135°. Recrystallization from ethanol gave 300 g. (65%) of 2-chloro-5-(chloroacetylaminomethyl)benzoic acid (I), m.p. 144–146°. Recrystallization from dioxane and then from dimethylformamide raised the melting point to 147–148°.

Anal. Calcd. for $C_{10}H_9Cl_2NO_3$: Cl, 27.06; N, 5.34. Found: Cl, 27.18; N, 5.26.

3-Carboxy-4-chlorobenzylamine hydrochloride (II). A mixture of 118.0 g. (0.45 mole) of 2-chloro-5-(chloroacetylaminomethyl)benzoic acid (I) and 400 ml. of concd. hydrochloric acid was refluxed for 4 hr. After refrigerating overnight, the white solid was collected by filtration, washed with a mixture of ether and acetone, and dried. The 3-carboxy-4-chlorobenzylamine hydrochloride (II) (yield 91 g., 92%) thus obtained melted at 243–244°.

Anal. Calcd. for $C_8H_9Cl_2NO_2$: Cl, 31.93; N, 6.31. Found: Cl, 32.14; N, 6.21.

The free acid was obtained by neutralization with sodium acetate, m.p. 295–297° dec.

Anal. Calcd. for $C_8H_8ClNO_2$: Cl, 19.11; N, 7.54. Found: Cl, 19.41; N, 7.68.

Proof of structure of 5-aminomethyl-2-chlorobenzoic acid. Method A. A mixture of 2.22 g. (0.01 mole) of II from above, 1 g. of sodium bicarbonate, 4 ml. of 40% aqueous formaldehyde and 50 ml. of ethanol was allowed to stand for 1 hr. A 1-g. sample of 5% palladium-on-charcoal was added, and the mixture was hydrogenated at 50° and 35 p.s.i. of hydrogen. The mixture was hydrogenated at 50° and 35 p.s.i. of hydrogen. The mixture was filtered, evaporated, and the residue taken up in 5% sodium hydroxide. This solution was treated with charcoal, filtered, and acidified. The white solid III was recrystallized from water, m.p. 110–112°.[8] The infrared spectra of an authentic specimen of *m*-toluic acid was identical with the preceding acid.

Method B. An intimate mixture of 4 g. of II and 8 g. of soda-lime was heated in a tube and the distillate collected. This distillate yielded *ca.* 0.1 ml. of a liquid amine. A 1-ml. sample of pyridine was added to the liquid followed by a few drops of benzoyl chloride. The mixture was allowed to stand overnight and then worked up to yield a white solid. Recrystallization gave 50 mg. of white crystals, m.p. 140–141°. *N*(4-chlorobenzyl)benzamide is reported to melt at 141°.[9]

Method C. A mixture of 5 g. of II, 6 g. of potassium dichromate, 14 ml. of water, and 8 ml. of concd. sulfuric acid was refluxed 1 hr. Potassium dichromate, 5 g., and 5 ml. of concd. sulfuric acid were added to the reaction and the mixture refluxed 2 hr. The mass was cooled, filtered, and the precipitate washed with water. The solid was recrystallized from dioxane and gave 1.3 g. of white crystals, m.p. 293–295°. 4-Chloroisophthalic acid is reported to melt at 294.5°.[10]

3-Carbomethoxy-4-chlorobenzylamine hydrochloride. A mixture of 22.2 g (0.1 mole) of 3-carboxy-4-chlorobenzylamine hydrochloride and 235 ml. of absolute methanol was refluxed for 3 hr. and simultaneously saturated with hydrogen chloride. The mixture was cooled overnight. The precipitate was collected, washed with ether, and recrystallized from methanol to yield 16.5 g. (70%) of the desired product, m.p. 217–220°.

Anal. Calcd. for $C_9H_{11}Cl_2NO_2$: Cl, 30.04; N, 5.93. Found: Cl, 30.37; N, 6.00.

Methyl 2-chloro-5-(chloroacetylaminomethyl)benzoate. A mixture of 7 g. of 2-chloro-5-(chloroacetylaminomethyl)benzoic acid and 50 ml. of absolute methanol was heated on a steam bath while 1 ml. of concd. sulfuric acid was added dropwise. The solution was refluxed 1 hr., then was allowed to stand overnight, cooled in an ice bath, and filtered. The white solid was recrystallized from ethanol–water mixture, m.p. 83–84°.

Anal. Calcd. for $C_{11}H_{11}Cl_2NO_3$: Cl, 25.68; N, 5.07. Found: Cl, 26.01; N, 5.19.

N-Propyl 3-carboxy-4-chlorobenzylcarbamate. A mixture of 2.22 g. (0.01 mole) of 3-carboxy-4-chlorobenzylamine hydrochloride and 5 ml. of 4*N* sodium hydroxide was cooled in an ice bath. The solution was stirred vigorously and 0.01 mole of *n*-propyl chloroformate and 12.5 ml. of 4*N* sodium hydroxide added simultaneously over a 3-hr. period. The precipitate was discarded and the clear solution acidified with hydrochloric acid. The white solid was collected and recrystallized from ethanol and from chloroform, m.p. 131–133°.

Anal. Calcd. for $C_{12}H_{15}ClNO_4$: Cl, 13.00; N, 5.13. Found: Cl, 13.18; N, 5.30.

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Configurations of the Diastereomeric 4-Benzoyl-2,3-diphenylbutyric Acids and Derivatives[1]

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Received August 14, 1961

Disodio phenylacetate, prepared from phenylacetic acid and two molecular equivalents of sodium amide in liquid ammonia, has recently[2] been shown to undergo conjugate addition to benzalacetophenone to give keto acid I (Equation 1). Only one isomer of I was isolated from the reaction mixture. It has now been found that both isomers of I are produced in the conjugate addition, and the configurations of these keto acids and their derivatives have been established.

Neutralization of the reaction mixture in liquid ammonia by the addition of solid ammonium

(1) Supported by the National Science Foundation.

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