tates the following: a Prins type reaction, a dehydrohalogenation, a fluorination with antimony trifluoride and finally the oxidation with potassium permanganate. It has been found that esters of difluoroacetic acid, from which other derivatives may be readily prepared, can be obtained in good yields by a simple two-step process using a commercially available fluorine compound as the starting material.

This method consists of the preparation of 1-ethoxy-1,1,2,2-tetrafluoroethane by the reaction of sodium ethoxide on 1-chloro-1,1,2,2-tetrafluoroethane (Freon 124A) followed by the hydrolysis of the ether to ethyl difluoroacetate with concentrated sulfuric acid. The tetrafluoroether has also been prepared in a yield of 90% by the addition of ethanol to tetrafluoroethylene.[5]

The ether hydrolysis gives slightly lower yields than with other α-difluoro ethers,[6] but the over-all yield of ester is in the neighborhood of 40%. Since the total time involved is only about six hours, the method offers a very convenient preparation of difluoroacetate esters.

Experimental

1-Ethoxy-1,1,2,2-tetrafluoroethane.—Fifty-six g. (1 mole) of technical potassium hydroxide was dissolved in 150 ml. of 95% ethanol, the solution added to a pressure vessel and cooled thoroughly in a Dry Ice–acetone-bath. A conventional type, high pressure rocking autoclave was used in these experiments since it was available. The pressure in the bomb was so low that it failed to register on a 5000 lb. gage and, therefore, it is probable that simpler and lighter equipment could be used for this reaction. Sixty-eight g. (0.5 mole) of CHF_2CF_2Cl was added, the vessel sealed and heated with shaking for three hours at 120°. The loss of liquefied Freon (b. p −12°) at Dry Ice temperatures was negligible. After washing, the crude product may be used directly for the hydrolysis. Distillation gave 66–70% of $CHF_2CF_2OC_2H_5$, boiling at 57–58°, with no appreciable forerun or residue.

Ethyl Difluoroacetate.—Hydrolysis of the tetrafluoroether at 10° as previously described[6] for α-difluoroethers gives 40–50% yields of ester but is difficult to control. The following method is preferable. To a suitable flask equipped with thermometer, stirrer, and reflux condenser were added 29 g. (0.2 mole) $CHF_2CF_2OC_2H_5$, 10 g. of 96% sulfuric acid, and 5–10 g. powdered glass or quartz. If enough siliceous material is present, damage to glassware is almost entirely prevented. Unpleasant fumes can be avoided by absorbing the evolved gases in water if the bubbles emerge through a layer of mercury to prevent clogging in the delivery tube with silica. The reaction began immediately and the mixture was refluxed with stirring until the liquid temperature climbed at least 20° above the original 55–57°; about three hours were required for this operation. The mixture was then poured onto ice and the layers separated. After washing and drying, the product was distilled to give 4–5 g. of unreacted ether and 15 g. of ethyl difluoroacetate, b. p. 99–100°, corresponding to a yield of 60%. The yields can probably be increased when the reaction is carried out on a larger scale.

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[5] Rigby and Schroeder (to du Pont) U. S. Patent 2,409,315 1946).

[6] Young and Tarrant, THIS JOURNAL, 71, 2432 (1949).

NEW COMPOUNDS

Degradation Products of the Lactone of 6-Hydroxymethyl-1,3-benzodioxan-7-carboxylic Acid

6-Hydroxymethyl-1,3-benzodioxan-4-one-7-carboxylic Acid Lactone.—One and one-tenth grams of 6-hydroxymethyl-1,3-benzodioxan-7-carboxylic acid lactone[1] was dissolved in 50 cc. of glacial acetic acid by heating. When the solution was just starting to boil, it was removed from the hot-plate and 3.5 g. of chromium trioxide was added at such a rate as to keep the mixture boiling vigorously. When boiling had ceased, 175 cc. of water was added and the dark green solution was cooled overnight in the refrigerator. Filtration and thorough washing gave 0.45 g. of white needles, which after several crystallizations from benzene melted at 215–216°. The compound gave positive dioxanoyl and phthalide ring tests.[1]

Anal. Calcd. for $C_{10}H_6O_5$: C, 58.26, H, 2.93. Found: C, 58.27, 58.05; H, 3.29, 3.40.

5-Carboxy-6-hydroxyphthalide.—Two-tenths gram of the dioxanonyl phthalide was saponified in 10% sodium hydroxide solution and after acidification and cooling 0.18 g. of a white solid was recovered. Several crystallizations from a minimum amount of methanol gave 0.15 g., m. p. 275–276° with darkening. The compound gives a deep red color with ferric chloride and in aqueous sodium hydroxide exhibits a blue fluorescence.

Anal. Calcd. for $C_9H_6O_5$: C, 55.67; H, 3.12. Found: C, 55.16, 55.34; H, 3.15, 3.24.

5-Carbomethoxy-6-hydroxyphthalide.—The hydroxy acid, 0.42 g. in 100 cc. of methanol, was treated with an ethereal solution of diazomethane,[2] both at 5° in the usual manner. The residue was taken up in methanol and thrown out with water to give 0.26 g., m. p. 166–167°. An additional crystallization by the same procedure elevated the melting point to 170.0–170.4°. Saponification gave the original hydroxy acid.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.66; H, 3.84. Found: C, 57.61, 57.73; H, 3.95, 4.08.

[1] Buehler, Harris, Shacklett and Block, THIS JOURNAL, 68, 574 (1946).

[2] "Organic Syntheses," Vol. XV, John Wiley and Sons, Inc., New York, N. Y., 1935, p. 4, note 7.

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2-Sulfanilylimino-3-butylbenzothiazoline

2-(N-Acetylsulfanilyl)-imino-3-butylbenzothiazoline.—To a solution of 41.2 g. (0.2 mole) of 3-butylbenzothiazolone imide[1] in 150 ml. of pyridine, 46.6 g. (0.2 mole) of acetylsulfanilyl chloride was gradually added. After standing overnight, the mixture was warmed on a steam-bath for twenty minutes. The white crystalline material which had formed was collected on a Buchner funnel, washed with water and recrystallized from alcohol. The yield of dry product was 68 g. (84%); m. p. 179–181°. Recrystallization from Cellosolve did not change the melting point.

Anal. Calcd. for $C_{19}H_{21}N_3O_3S_2$: N, 10.42. Found: N, 10.65.

2-Sulfanilylimino-3-butylbenzothiazoline (I).—A mixture of 50 g. (0.124 mole) of 2-(N-acetylsulfanilyl)-imino-3-butylbenzothiazoline, 135 ml. of concentrated hydrochloric acid, 300 ml. of alcohol and 300 ml. of water was

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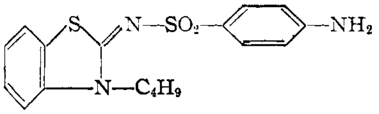
[1] Obtained through the courtesy of Sharples Chemicals, Inc.



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heated at refluxing temperature for an hour or until complete solution had been effected. An excess of ammonia was added to the clear solution whereupon a white solid precipitated at once; m. p. 187–189°. The product was collected, dried and recrystallized from 250 ml. of Cellosolve; yield 37.8 g. (84% yield) of desired product; m. p. 191–192°. Further recrystallization did not change the melting point.

Anal. Calcd. for $C_{17}H_{19}N_3O_2S_2$: N, 11.63. Found: N, 11.71.

The presence of a free primary aromatic amino group was confirmed by diazotization and coupling with 2-naphthol to produce a red dye.

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Crystalline Carbobenzoxy Derivatives of DL-Valine and DL-Leucine[1]

The carbobenzoxy derivatives of DL-leucine[2] and of L-leucine[3] have been reported as oils. The corresponding L-valine derivative has been reported as an oil which crystallized after weeks of storage.[4] In studies of peptide synthesis[5] and in enzyme-substrate investigations[6] crystalline, preferably pure, carbobenzoxy derivatives of DL-valine and DL-leucine were sought. The procedure given below has served to yield these derivatives readily in a few days in an analytically pure, crystalline condition. Seeds of the carbobenzoxy-DL-valine thus obtained have been used to induce crystallization in an oily mass in another laboratory.[7]

Carbobenzoxy-DL-valine.—Eleven and seven-tenths gram (0.10 mole) of DL-valine (Dow) was dissolved in 25 ml. of 4 *N* sodium hydroxide. With cooling in an ice-bath, there were added simultaneously with stirring, over a period of forty-five minutes, 25 ml. of 4 *N* sodium hydroxide and 23 ml. of carbobenzoxy chloride solution[8] (from 200 g. of 20% phosgene in toluene and 38 ml. of benzyl alcohol, allowed to react and then concentrated under reduced pressure to 80 g.). The solution was acidified with hydrochloric acid, which deposited an oil. The mass was crystallized by dissolving in dilute sodium hydroxide, reprecipitating with hydrochloric acid and permitting it to stand overnight in the refrigerator; yield, 21 g. (84%) with a m. p. of 75–77° (uncor.). In later preparations, ether or ethyl acetate was used to extract the initial oil obtained upon acidification, and the extracts were dried and the solvent removed by evaporation. The residue was crystallized by dissolving in benzene, precipitating with hexane, and seeding with material from the first preparation; yields, 16 g. (65%) and 20.5 g. (82%), m. p. 76–78° (uncor.). *Anal.* Calcd. for $C_{12}H_{17}O_4N$: N, 5.58. Found: N, 5.59. The m. p. reported for the L isomer was 64–65°.[4]

Carbobenzoxy-DL-leucine.—Twenty-six and two-tenths grams (0.20 mole) of DL-leucine (Dow) was treated with carbobenzoxy chloride as above. Acidification of the reaction mixture with concentrated hydrochloric acid yielded an oil which was taken up with three 75-ml. portions of ether. The combined ethereal extracts were washed with 25 ml. of water and re-extracted carefully with three portions (75, 50 and 50 ml.) of saturated sodium bicarbonate solution. The combined bicarbonate extracts were then acidified with concentrated hydrochloric acid to congo red. The oil which separated was taken up with ether. The washed ethereal extract was dried over sodium sulfate.

The dry ethereal solution was then concentrated to a sirupy consistency by distilling off the solvent under reduced pressure, and the material was set into the freezer (−12°). There was some initial evidence of crystallization overnight. Fifty ml. of benzene was added and the mixture was heated to 50°. The sirup did not dissolve. Two hundred ml. of hexane was added and the mixture placed in the freezer. It was stirred periodically with a stirring rod which had a few crystals adhering to it. Crystallization commenced after one day and a white amorphous mass was obtained.

Since it gave evidence of melting at room temperature, the solid was filtered off in a cold room, washed with cold hexane and dried in a vacuum desiccator. Forty grams of product melting at 44–52° was obtained. This material was dissolved in a minimum amount of warm benzene and filtered. Sufficient hexane was added to the cold filtrate to cause some oiling, and the mixture was seeded. The material crystallized slowly, going through a gummy stage, but eventually it yielded a smooth, creamy paste. This was filtered off in the cold, dried by suction and then in a vacuum desiccator. The yield was 35.5 g. (67%), and the material melted at 45–48° (uncor.).

Anal. Calcd. for $C_{14}H_{19}O_4N$: N, 5.28. Found: N, 5.17, 5.14.

In later runs, the two derivatives were crystallized more readily by washing the oils obtained in syntheses from one-half mole of amino acid, with three 500-ml. portions of water and rubbing under renewed portions of hexane until crystallization ensued. The possibility of atmospheric seeding in repetitions cannot be excluded. The yield of carbobenzoxy-DL-valine by this last procedure was 113 g. (90%) with m. p. 74–76° (cor.) and 125 g. (94%) of carbobenzoxy-DL-leucine, m. p. 46–49° (cor.). N contents of the derivatives were, respectively, 5.56 and 5.24%.

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[1] Journal Paper No. J-1724 of the Iowa Agricultural Experiment Station, Project 1111. This project is supported in large part by the National Cancer Institute of the United States Public Health Service.

[2] Bergmann and Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937).

[3] Bergmann, Zervas and Fruton, *ibid.*, **115**, 593 (1936).

[4] Synge, *Biochem. J.*, **42**, 101 (1948).

[5] Fling and Fox, unpublished experiments.

[6] Fox, Pettinga, Halverson, and Wax, *Arch. Biochem.*, **25**, 21 (1950).

[7] Private communication from Dr. J. W. Hinman.

[8] Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

1-Benzyl-5-*p*-chlorophenylbiguanide Monohydrochloride

A mixture of 5.8 g. of *p*-chlorophenyldicyandiamide[1] and 5.4 g. of benzylamine hydrochloride was ground well in a mortar, and then by means of an oil-bath heated in a flask for a few moments at 190°. Heating was discontinued as soon as the melt turned dark and smoke began to form. The product was leached with several portions of boiling water. Upon cooling 7 g. (64% yield) of white crystalline 1-benzyl-5-*p*-chlorophenylbiguanide monohydrochloride was obtained; m. p. 220°. Recrystallization from dilute hydrochloric acid did not raise the melting point.

Anal. Calcd. for $C_{11}H_{16}ClN_5{\cdot}HCl$: N, 20.71. Found: N, 20.74.

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[1] Walther and Grieshammer, *J. prakt. Chem.*, [2] **92**, 251 (1915); Curd and Rose, *J. Chem. Soc.*, 729 (1946).