SYNTHESIS OF FLUORODINITROBUTYRIC ACIDS AND SOME OF THEIR DERIVATIVES

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Investigations into the fluorination of various nitro compounds by elemental fluorine have shown that this reaction is easily controlled if it is carried out in polar solvents which ensure the formation of the nitro-compound anion. In this case fluorination only occurs at the position of the anionic reaction center to form the corresponding fluorinated nitro compounds:

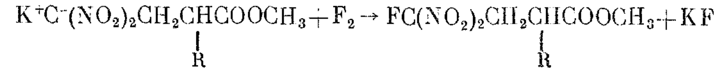
$$R(NO_2)_2C^-M^+ + F_2 \rightarrow R(NO_2)_2CF + MF$$

Various polynitroalkanes [1-3], and nitro alcohols [4, 5], which besides the anionic center have other possible centers of attack, have been successfully fluorinated in this way. In all the cases mentioned the respective fluoronitro compounds were obtained. Continuing the investigation of this interesting reaction, we fluorinated an aqueous solution of dipotassium γ, γ-dinitrobutyrate, which has two reaction centers. It was supposed that under specific kinetic conditions the two centers would be able to participate successively in the reaction to form γ-fluoro-γ, γ-dinitrobutyric acid as a result of the following reactions:

$$K^+C^-(NO_2)_2CH_2CH_2COO^-K^+ + F_2 \rightarrow FC(NO_2)_2CH_2CH_2COO^-K^+ + KF$$
$$F_2 + 2H_2O \rightarrow H_2O_2 + 2HF$$
$$FC(NO_2)_2CH_2CH_2COO^-K^+ + HF \rightarrow FC(NO_2)_2CH_2CH_2COOH + KF$$

However, instead of the expected acid, its peroxide was obtained [6], which indicated that both reaction centers interacted with the elemental fluorine.

In the present work we have made a new attempt to synthesize γ-fluoro-γ,γ-dinitrobutyric acid, starting from derivatives of γ,γ-dinitrobutyric acid which have one anionic center: the potassium salts of methyl γ,γ-dinitrobutyrate and the nitrile. In addition to this potassium salt, the potassium salt of methyl γ,γ-dinitro-α-methylbutyrate was fluorinated under the same conditions. Fluorination of aqueous solutions of the salts takes place very gently to form the respective fluorinated methyl esters, which separate from the solution during the course of the reaction as colorless oily liquids:



$$K^+C^-(NO_2)_2CH_2\underset{\displaystyle R}{\underset{|}{C}}HCOOCH_3 + F_2 \rightarrow FC(NO_2)_2CH_2\underset{\displaystyle R}{\underset{|}{C}}HCOOCH_3 + KF$$

$R = H,\ CH_3$

The esters are readily purified by vacuum distillation and after purification have a characteristic pleasant odor. An aqueous solution of the potassium salt of γ,γ-dinitrobutyronitrile was also successfully fluorinated:

$$K^+C^-(NO_2)_2CH_2CH_2CN + F_2 \rightarrow FC(NO_2)_2CH_2CH_2CN + KF$$

It should be noted that under the conditions selected for the process, unlike the method of solid-phase fluorination, the nitrile group is practically unaffected by elemental fluorine.

The γ-fluoro-γ,γ-dinitrobutyronitrile was isolated from the reaction mixture as a heavy oily liquid, which distilled at 77-79°C under a vacuum of 0.5 mm. However, numerous distillations failed to free it from impurities. On storage the distillate — a colorless liquid — gradually became yellow after a few days. For this reason the γ-fluoro-γ,γ-dinitrobutyronitrile, was purified by double low-temperature recrystallization from ether; a crystalline substance melting at 23°C was isolated. After this purification it does not change color on storage in the liquid state and is an extremely stable substance suitable for various preparations. To obtain more rigid proof for the structure of the compounds obtained an alternative synthesis was performed by the Michael reaction of fluorodinitromethane with acrylonitrile and methyl acrylate:

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$$CH_2=CHCN + HC(NO_2)_2F \rightarrow FC(NO_2)_2CH_2CH_2CN$$
$$CH_2=CHCOOCH_3 + HC(NO_2)_2F \rightarrow FC(NO_2)_2CH_2CH_2COOCH_3$$

The physical constants and IR-spectra of the compounds obtained by the different methods were identical. It should be noted that fluorodinitromethane enters into nucleophilic addition reaction somewhat less readily than nitroform, which is explained completely satisfactorily by the large difference in their ionization constants [7, 8]. γ-Fluoro-γ,γ-dinitrobutyric and γ-fluoro-γ,γ-dinitro-α-methylbutyric acids were prepared by hydrolysis of the methyl esters in hydrochloric acid, and both acids were converted into the acid chlorides by reaction with thionyl chloride. The fluoronitrobutyryl chlorides, as would be expected, are reactive acylating reagents. The disubstituted hydrazide of γ-fluoro-γ,γ-dinitrobutyric acid, and also various amides and esters, were prepared from them:

$$FC(NO_2)_2CH_2CHRCOCl + HX \rightarrow FC(NO_2)_2CH_2CHRCOX + HCl$$

(I) $R=H$ $X=OCH_3$	(XI) $R=H$ $X=OCH_2CH_3$
(II) $R=CH_3$ $X=OCH_3$	(XII) $R=CH_3$ $X=OCH_2CH_3$
(VIII) $R=H$ $X=NH_2$	(XIII) $R=H$ $X=OCH_2C(NO_2)_3$
(IX) $R=H$ $X=HNCH_3$	

It should be noted that in the case of the ester XIII the acylation reaction only proceeded sufficiently well in the presence of anhydrous aluminum chloride as catalyst [9]. The 2, 2, 2-trinitroethyl ester of γ-fluoro-γ,γ-dinitrobutyric acid (XIII) can also be prepared by the method for preparation of its nonfluorinated analog [10], by reesterification of the methyl ester with 2, 2, 2-trinitroethanol in anhydrous sulfuric acid:

$$FC(NO_2)_2CH_2CH_2COOCH_3 + HOCH_2C(NO_2)_3 \xrightarrow{H_2SO_4}$$
$$\rightarrow FC(NO_2)_2CH_2CH_2COOCH_2C(NO_2)_3 + CH_3OSO_2OH + H_2O$$

The isomer of the ester XIII with fluorine in the alkyl radical — 2-fluoro-2, 2-dinitroethyl γ,γ,γ-trinitrobutyrate — can be obtained, like compound XIII, from the respective acyl chloride and 2-fluoro-2, 2-dinitroethanol, and also by reesterification according to the method described in [10]. The 2-fluoro-2, 2-dinitroethanol required for these purposes was prepared from fluorodinitromethane and formalin. As our experience has shown, fluorination of the potassium salt of 2, 2-dinitroethanol [4] is less suitable for the preparation of this compound. We will therefore give a detailed description of the preparation of 2-fluoro-2, 2-dinitroethanol (XIV) by the Henri reaction, which ensures a good yield of the desired product with extremely high quality.

EXPERIMENTAL METHOD

Methyl γ-Fluoro-γ, γ-Dinitrobutyrate (I)

Fluorination. Fluorine (6.5 g), diluted 1:30 with nitrogen by volume, was bubbled through a solution of 0.13 mole potassium salt of methyl γ,γ-dinitrobutyrate in 1.2 liter water with stirring at 5-8°C. The solution became colorless towards the end of the reaction, when the organic layer was separated from the aqueous and dissolved in 100 ml ether. The ethereal solution was washed with water (3 × 75 ml) and dried over anhydrous magnesium sulfate. After removal of the solvent the product was twice redistilled under vacuum; the yield was 16.5 g (60%), with boiling point 91-92°C (1-2 mm), $n_D^{20} = 1.4346$ and $d_4^{20} = 1.4250$. It had the following composition: 28.54% C, 3.37% H, 13.40% N, 8.55% F, MR 38.08; mol.wt. 209; $C_5H_7N_2O_6F$. The theoretical composition is: 28.58% C, 3.36% H, 13.33% N, 9.04% F; MR 38.08; mol.wt. 210.

Michael Reaction. To a solution of 20.0 g fluorodinitromethane in 120 ml ethanol 13.8 g methyl acrylate was added dropwise at 48-50°C with stirring. The reaction mixture was kept at 78-80°C for 1.5 h and, after cooling to room temperature, was diluted with 250 ml water. Methyl γ-fluoro-γ,γ-dinitrobutyrate separated, was washed with water, dried over phosphorus pentoxide, and distilled; the yield was 16.8 g (50%), boiling at 92-93°C (1-2 mm) with $n_D^{20} = 1.4347$.

Methyl γ-Fluoro-γ, γ-Dinitro-α-Methylbutyrate (II)

The yield of the product obtained under fluorination conditions from potassium γ,γ-dinitro-α-methylbutyrate was 20.5 g (70%), boiling at 62-63°C (1-2 mm) with $n_D^{20} = 1.4330$ and $d_4^{20} = 1.3408$. It had the following composition: 32.02% C, 4.22% H, 12.57% N, 8.72% F; MR 42.94; mol.wt. 217; $C_6H_9N_2O_6F$. The theoretical composition is 32.15% C, 4.05% H, 12.50% N, 8.47% F; MR 42.81; mol.wt. 224.

γ-Fluoro-γ,γ-Dinitrobutyronitrile (III)

Fluorination. Fluorine (17.0 g), diluted 1:25 with nitrogen (by volume), was passed through a solution of 66.0 g potassium salt of γ,γ-dinitrobutyronitrile in 1.2 liter water with stirring at 1-3°C until the solution became colorless. Ethereal extracts (3 × 150 ml) from the reaction mixture were combined, washed with 3% sodium carbonate solution (2 × 200 ml) and water (2 × 100 ml), dried over magnesium sulfate, and cooled for 1 h to between —55 and —60°C after evaporating to 150 ml. The crystalline product was filtered off and recrystallized from ether (50 ml). The yield of the nitrile was 35.5 g (60%); it boiled at 77.5-78.5°C (0.5 mm) and melted at 22.7-23.0°C with n_D^{25} = 1.4466. It had the following composition: 27.32% C, 1.97% H, 23.80% N, 10.51% F; mol.wt. 173; $C_4H_4N_3O_4F$. The theoretical composition is: 27.13% C, 2.28% H, 23.73% N, 10.73% F; mol.wt. 177.

Michael Reaction. To a solution of 20.5 g fluorodinitromethane in 90 ml ethanol at 50-60°C with stirring was slowly added dropwise 8.7 g acrylonitrile, and the reaction mixture was kept at boiling point for 6 h. It was then cooled to 20°C and after 12 h was diluted with water. The nitrile, which separated as an oil, was treated as in the preceding experiment. After recrystallization from ether the product melted at 23°C.

γ-Fluoro-γ,γ-Dinitrobutyric Acid (IV)

To 450 ml boiling 20% hydrochloric acid was slowly added dropwise 0.15 mole methyl γ-fluoro-γ,γ-dinitrobutyrate, and after standing for 4-6 h the homogeneous solution was evaporated to dryness. The acid which remained was recrystallized from chloroform. The yield was 27.6 g (94%), melting at 37°C. The product had the following composition: 25.00% C, 2.31% H, 14.60% N, 10.22% F; $C_4H_5N_2O_6F$. The theoretical composition is: 24.50% C, 2.57% H, 14.28% N, 9.69% F.

γ-Fluoro-γ,γ-Dinitro-α-Methylburyric Acid (V)

This acid was obtained by hydrolysis of methyl γ-fluoro-γ,γ-dinitro-α-methylbutyrate under the conditions used in the preceding experiment; the yield was 30 g (95%), melting at 85-86°C. The product had the following composition: 28.46% C, 3.32% H, 13.26% N, 9.41% F; $C_5H_7N_2O_6F$. The theoretical composition is: 28.59% C, 3.36% H, 13.33% N, 9.04% F.

γ-Fluoro-γ,γ-Dinitrobutyryl Chloride (VI)

A 0.14-mole quantity of γ-fluoro-γ,γ-dinitrobutyric acid was added in portions with stirring to 17 ml thionyl chloride at 18-20°C. The homogeneous solution formed was slowly heated to boiling and kept for 1.5-2 h. The excess thionyl chloride was distilled off, and the acyl chloride was distilled under vacuum. The yield was quantitative, and the product boiled at 103-104°C (1-2 mm); n_D^{20} = 1.4580; d_4^{20} = 1.5442. The product had the following composition: 22.20% C, 1.91% H, 13.00% N, 16.98% Cl; MR 37.42; mol.wt. 206; $C_4H_4N_2O_5ClF$. The theoretical composition is: 22.39% C, 1.88% H, 13.06% N, 16.52% Cl; MR 37.86; mol.wt.214.

γ-Fluoro-γ,γ-Dinitro-α-Methylbutyryl Chloride (VII)

This product was obtained from γ-fluoro-γ,γ-dinitro-α-ethylbutyric acid with quantitative yield under the conditions of the preceding experiment; it boiled at 75-76°C (1-2 mm); n_D^{20} = 1.4542; d_4^{20} = 1.4544. It had the following composition: 26.33% C, 2.32% H, 12.13% N, 15.72% Cl; MR 42.66; mol.wt. 221; $C_5H_6N_2O_5ClF$. The theoretical composition is: 26.27% C, 2.65% H, 12.26% N, 15.51% Cl; MR 42.91; mol.wt. 229.

γ-Fluoro-γ,γ-Dinitrobutyrylamide (VIII)

To 50 ml 15% aqueous ammonia solution between —10 and —5°C and with stirring was added dropwise 22.4 g γ-fluoro-γ,γ-dinitrobutyryl chloride. After standing for 20 min at 0°C the crystalline precipitate was filtered off, washed with water (15 ml, 0°C), dried, and recrystallized from 1,2-dichloroethane. The yield was 16.3 g (80%), melting at 44.5-45°C. It had the following composition: 24.44% C, 3.00% H, 21.60% N, 9.41% F, mol.wt. 193; $C_4H_6N_3O_5F$. The theoretical composition is: 24.62% C, 3.10% H, 21.54% N, 9.74% F; mol.wt. 195.1.

γ-Fluoro-γ,γ-Dinitrobutyrylmethylamide (IX)

To 60 ml 15% aqueous methylamine solution between 0 and —2°C, 21.0 g γ-fluoro,γ,γ-dinitrobutyryl chloride was added dropwise with stirring. After standing for 30 min at 2°C the precipitate was filtered off, washed with 20 ml iced water, dried, and recrystallized from 1,2-dichloroethane. The yield was 14.5 g (71%), melting at 40.5-41°C. It had the following composition: 28.90% C, 3.57% H, 20.20% N, 9.00% F; mol. wt. 204; $C_5H_8N_3O_5F$. The theoretical composition is: 28.71% C, 3.86% H, 20.09% N, 9.08% F; mol.wt. 209.1.

Disubstituted γ-Fluoro-γ,γ-Dinitrobutyryl Hydrazide (X)

To a mixture of 16.0 g hydrazine hydrate and 50 ml ether between —10 and —5°C was added dropwise with stirring 22.7 g γ-fluoro-γ,γ-dinitrobutyryl chloride in 50 ml ether. After standing for 2 h at 0°C the crystals were filtered off, thoroughly washed with water (0°C), dried, and recrystallized from 1,2-dichloroethane. The yield was 13.2 g (64%), melting at 208-209°C. The product had the following composition: 24.80% C, 2.40% H, 21.44% N, 10.00% F; $C_8H_{10}N_6O_{10}F_2$. The theoretical composition is: 24.75% C, 2.60% H, 21.65% N, 9.79% F.

Ethyl γ-Fluoro-γ,γ-Dinitrobutyrate (XI)

To 100 ml ethanol at 15-17°C was added dropwise with stirring 0.15 mole γ-fluoro-γ,γ-dinitrobutyryl chloride, and the mixture was kept at boiling point for 4 h. The excess ethanol was removed, and the ethyl ester was distilled. The yield was quantitative, and the product boiled at 76-77°C (1-2 mm); $n_D^{20} = 1.4309$; $d_4^{20} = 1.3326$. The product had the following composition: 32.12% C, 4.21% H, 12.50% N, 8.69% F; MR 43.50; mol.wt. 226; $C_6H_9N_2O_6F$. The theoretical composition is: 32.15% C, 4.05% H, 12.50% N, 8.48% F; MR 42.81; mol.wt. 224.

Ethyl γ-Fluoro-γ,γ-Dinitro-α-Methylbutyrate (XII)

This ester was obtained under the conditions used in the preceding experiment from γ-fluoro-γ,γ-dinitro-α-methylbutyryl chloride in quantitative yield. It boiled at 82-83°C (1-2 mm) with $n_D^{20} = 1.4300$ and $d_4^{20} = 1.2812$. It had the following composition: 35.15% C, 4.67% H, 11.89% N, 7.64% F; MR 47.98; mol. wt. 237; $C_7H_{11}N_2O_6F$. The theoretical composition is: 35.30% C, 4.68% H, 11.76% N, 7.98% F; MR 47.46; mol. wt. 238.

2,2,2-Trinitroethyl γ-Fluoro-γ,γ-Dinitrobutyrate (XIII)

From Acyl Chloride. To a solution of 21.0 g γ-fluoro-γ,γ-dinitrobutyryl chloride in 125 ml absolute 1,2-dichloroethane at 19-20°C with stirring was first added 25.2 g trinitroethanol followed by 26.0 g anhydrous aluminum chloride at 15-16°C. After keeping for 5 h at 85°C the cooled reaction mixture was poured into a mixture of 80 ml hydrochloric acid and 80 g ice. The dichloroethane solution was separated, washed with water, dried over anhydrous magnesium sulfate, and boiled with 6 g active charcoal for 3 h. After removing the 1,2-dichloroethane the product was recrystallized from carbon tetrachloride. The yield was 41.3 g (85%), melting at 41°C. The product had the following composition: 20.05% C, 1.74% H, 19.35% N, 5.08% F; mol.wt. 348; $C_6H_6N_5O_{22}F$. The theoretical composition is: 20.06% C, 1.68% H, 19.50% N, 5.29% F; mol. wt. 359.1.

From Methyl Ester. To 125.0 g anhydrous mixture of acids (8.5% nitric and 91.5% sulfuric) at 25°C was added dropwise 10.5 g methyl γ-fluoro-γ,γ-dinitrobutyrate, and 10.8 g 2,2,2-trinitroethanol was added in portions at 50°C. After 3 h at 60°C the reaction mixture was poured on to ice, and the organic layer was separated, washed with water, and dried over phosphorus pentoxide. After removal of the unreacted products the crystalline residue was recrystallized from carbon tetrachloride. The yield was 3.92 g (30%) with melting point 41°C.

2-Fluoro-2,2-Dinitroethanol (XIV)

To a solution of 30.0 g fluorodinitromethane in 120 ml water at 18-20°C was added dropwise 30 ml 35% formalin followed by 0.1-0.15 g anhydrous potassium carbonate. The reaction mixture took on a light yellow color and spontaneously heated to 35°C. After 1 h at 35-40°C (cooled with water first and then heated) the homogeneous colorless reaction solution was cooled to 12-15°C and was extracted with ether (90, 50, 50 ml). The extracts were combined, dried over magnesium sulfate, and the ether was removed under vacuum. The 2-fluoro-2,2-dinitroethanol which remained was distilled under vacuum; the yield was 30.6 g (80%), boiling at 62-63°C (1-2 mm) with $n_D^{20} = 1.4323$. Our previous results gave [4]: bp 62-66°C (1-2 mm); $n_D^{20} = 1.4338$.

2-Fluoro-2,2-Dinitroethyl γ,γ,γ-Trinitrobutyrate (XV)

To 100 ml 100% sulfuric acid at 17-18°C was added 17.6 g γ,γ,γ-trinitrobutyric acid, and 15.0 g 2-fluoro-2,2-dinitroethanol was added dropwise at 20-21°C. After stirring for 3 h the reaction mixture was left at room temperature for five days and then poured on to 300 g crushed ice. The precipitate was filtered off, washed with water, dried, and recrystallized from carbon tetrachloride. The yield was 11.8 g (42%), melting at 53.5°C. The product had the following composition: 20.31% C, 1.68% H, 19.55% N, 5.65% F; mol. wt. 373; $C_6H_6N_5O_{12}F$. The theoretical composition is: 20.06% C, 1.68% H, 19.50% N, 5.29% F; mol.wt. 359.

CONCLUSIONS

1. In the fluorination of aqueous solutions of salts of methyl γ,γ-dinitrobutyrates and γ,γ-dinitrobutyronitrile with elemental fluorine the reaction only occurs at the anionic center and forms C — F bonds.

2. γ-Fluoro-γ,γ-dinitrobutyric and γ-fluoro-γ,γ-dinitro-α-methylbutyric acids and some of their derivatives were prepared.

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