

Disproportionation of Unsymmetrical Disulfides (2).—Except for slight variations in procedures of isolation, the following method was used for all unsymmetrical disulfides. Approximately 1 mmole of the unsymmetrical disulfide was accurately weighed and added to 10 ml of redistilled 95% ethanol in a carefully cleaned 10-ml vial. The vial was sealed, protected from light with aluminum foil, and kept at 100° for the appropriate time.¹⁵ After being cooled, the reaction mixture was evaporated and the residue was thoroughly washed with *n*-hexane (except for the *p*-NO₂ (7) and *m*-CN (10) derivatives discussed below). Evaporation of the hexane usually gave a pure sample of the symmetrical benzyl disulfide (11), which was characterized in typical instances by mixture melting point, infrared spectrum, and thin layer chromatography (single spots in all instances) with benzene as eluent. In the case of the *p*-cyano derivative, it was necessary to purify the product by washing with a little petroleum ether (bp 30–50°). "Disproportionation, %" in Table II was calculated as (millimoles of symmetrical disulfide formed $\times 2 \times 100$) / (millimoles of unsymmetrical disulfide used).¹⁶

For the *m*-CN (10) and *p*-NO₂ (7) derivatives, it was convenient to follow the disproportionations by estimating the amount of 2-(*n*-decylamino)ethyl disulfide dihydrochloride (12) formed. Thus in these instances the residue from evaporation of the reaction mixture was first washed thoroughly with ether (200 ml) and then with benzene (20 ml) leaving the pure *n*-decylaminoethyl disulfide dihydrochloride, identified by its superimposable infrared spectrum with those of authentic samples and thin layer chromatography (10:90 ethanol-chloroform). With each of the components 3–10, the validity of each separation procedure was checked by mixing known amounts of reactant and products; results were usually within 5% of the known composition.

Rate constants (*k*) were obtained by plotting $\log C_0/C$ vs. time (Figure 1), where C_0 is the initial concentration of ca. 1 mmole and *C* is the concentration at time *t* (deduced by subtraction of "disproportionation, %" from Table II) and then multiplying the slope by 2.303. Half-lives (Table II) were calculated from the equation $t_{1/2} = 0.693/k$.

Experiments on the Nature of the Disproportionation Reaction.

A. Extent of Completion.—*p*-Cyanobenzyl 2-(*n*-decylamino)ethyl disulfide hydrochloride (8, 0.4036 g, 1.004 mmole) was dissolved in 95% ethanol (10 ml) in a vial protected from light and was heated for 120 hr at 100° in the usual manner. The

(15) It was noticed that, after completion of an experiment, removing the aluminum foil and briefly rewarming the vial on the water bath redissolved any reactant and product which had precipitated; it is on this type of observation that the statement of homogeneity during the reaction is based (see Discussion).

(16) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

reaction mixture was evaporated at room temperature and the residue was thoroughly rubbed and washed with warm dry ether (200 ml). The solid was separated by filtration and was washed with a little benzene (5 ml), dried, and weighed: yield of 12, 0.2428 g (95%), mp 265° dec. It was shown to be pure 12 by its superimposable infrared spectrum and by using thin layer chromatography with ethanol-chloroform (10:90) as eluting solvent. The ether filtrate was evaporated to give 0.1537 g (103%) of *p*-cyanobenzyl disulfide. Thin layer chromatography using benzene as eluent showed this material to be nearly pure. Purification was effected by chromatography on Merck acid-washed alumina using benzene-chloroform (90:10) for elution. The product, 0.1352 g (91%), had mp 146–147° and mmp 146–147° (lit.¹² mp 148°). It was further identified by its superimposable infrared spectrum. It showed only one spot using thin layer chromatography, which had an R_f value identical with that of an authentic sample.

B. Extent of Reversibility.—A solution of *p*-chlorobenzyl disulfide (0.1576 g, 0.500 mmole) and 2-(*n*-decylamino)ethyl disulfide dihydrochloride (12, 0.2529 g, 0.500 mmole) in 10 ml of 95% ethanol was heated for 95 hr at 100°. The reaction mixture was cooled and the contents were evaporated at room temperature. The residue was rubbed well with *n*-hexane (250 ml) and solid was separated by filtration. Evaporation of the filtrate gave pure *p*-chlorobenzyl disulfide (0.1575 g, 100% recovery), which was identified by mixture melting point, infrared spectrum, and thin layer chromatography using benzene for elution. The residue, 0.2526 g (100%), had an infrared spectrum identical with that of pure 12. Thin layer chromatography (10:90 of 95% ethanol-chloroform) showed the product to be almost pure and revealed only a barely discernible trace of the unsymmetrical disulfide (6); the only strong spot had an R_f value identical with that of the symmetrical disulfide 12.

C. Disproportionation of a Disulfide Free Base.—*p*-Chlorobenzyl 2-(*n*-decylamino)ethyl disulfide hydrochloride (6, 0.4111 g, 1.00 mmole) was dissolved in 95% ethanol (9 ml) plus ethanolic sodium ethoxide (1 ml, containing 1.00 mmole of sodium ethoxide). The solution was heated in a sealed vial protected from light for 1 hr at 100°. The reaction mixture was cooled and acidified with HCl gas and then was evaporated to dryness. Extraction of the residue with hexane and evaporation of the hexane extract gave 0.0908 g (58% disproportionation) of *p*-chlorobenzyl disulfide, identified by mixture melting point, infrared spectrum, and thin layer chromatography (only one spot) using benzene for elution.

Registry No.—3, 13116-74-0; 4, 13116-75-1; 5, 13116-76-2; 6, 13116-77-3; 7, 13116-78-4; 8, 13116-79-5; 9, 13135-40-5; 10, 13116-80-8; 12, 13116-81-9.

Reduction of Difluoronitroacetate Esters. The Preparation and Properties of 2,2,2-Difluoronitroethanol and the Novel Formation of Hemiacetals by Reduction

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Received October 3, 1966

Alkyl and benzyl difluoronitroacetates are reduced primarily to hemiacetals by sodium borohydride in anhydrous solvents. In aqueous solvents, 2,2,2-difluoronitroethanol is the only product. Esterification and condensation reactions of difluoronitroethanol are described.

The reduction of aldehydes, ketones, and esters with complex metal hydrides is a well-known method for providing a wide variety of alcohols.¹ However, to obtain a nitro alcohol by reduction of a nitro carbonyl compound, selective reduction is necessary in order to retain the nitro group. Under certain conditions, sodium borohydride and even lithium aluminum hydride can be used to reduce the carbonyl groups preferentially in compounds which also contain nitro

groups three and four carbons removed from the reduction site, but no examples have been reported for reduction of a carbonyl group α to the carbon-nitro group. For example, Feuer² reduced methyl 4-nitropentanoate and 4,4-dinitropentanoate esters to the corresponding nitro alcohols with lithium aluminum hydride in ether at -60° and Shechter³ obtained nitro alcohols from nitro ketones at 20° by the action of sodium borohydride in methanol solution. In each of

(1) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956.

(2) H. Feuer and T. J. Kucera, *J. Am. Chem. Soc.*, **77**, 5740 (1955).

(3) H. Shechter, D. E. Ley, and L. Zeldin, *ibid.*, **74**, 3664 (1952).

TABLE I
 DIFLUORONITROACETATE REDUCTIONS BY SODIUM BOROHYDRIDE

| Acetate ester | Solvent | NaBH ₄ /ester mole ratio | Reaction time, ^a min (temp, °C) | Relative abundance of product acetates, ^b % | | |
|---------------|---------------------------------------|--|---|--|----------|--------------------|
| | | | | Alcohol | Aldehyde | Hemiacetal |
| Methyl | 50% H ₂ O-DME ^c | 0.64/0.60 | 22 (-10-0) (pH 4 to autogenous) | 5 | 45 | 45 ^d |
| Methyl | DME | 0.64/0.60 | 20 (25) | 32 | 8 | 60 |
| Methyl | 50% H ₂ O-DME | 0.64/0.60 | 25 (0-10) (pH 7.8) | 11 | 46 | 43 |
| Methyl | 50% H ₂ O-DME | 0.64/0.60 | 25 (0-10) | 14 | 45 | 41 |
| Ethyl | DME | 0.60/0.059 | 45 (25-30) | 10 | 8 | 82 |
| Isopropyl | DME | 0.11/0.12 | 40 (20-24) | | | (45 ^e) |
| Isopropyl | 50% H ₂ O-DME | 0.054/0.054 | 15 (20-24) | 15 | 22 | 63 |
| Benzyl | 50% H ₂ O-DME | 0.086/0.086 | 15 (18-22) | (32 ^f) | | |
| Benzyl | 50% H ₂ O-DME | 0.043/0.043 | 10 (0-2) | 22 | 7 | 7 |
| Benzyl | 50% H ₂ O-DME | 0.1/0.055 | 15 (18-20) | 23 | 32 | 11 |
| Benzyl | 50% H ₂ O-DME | 0.51/0.51 | 30 (10-12) | (70 ^g) | | |

^a Autogenous basicity except where indicated. ^b Products were isolated as a mixture of acetates for analytical purposes. Gross yields of the acetates ranged from 20 to 45%; the percentages given in the column reflect the relative abundance of the three reduction products by glpc analysis. ^c DME = dimethoxyethane. ^d Alcohol = 2,2,2-difluoronitroethanol (acetate); aldehyde = difluoronitroacetaldehyde (diacetate); hemiacetal = alkyl difluoronitroacetaldehyde hemiacetal (acetate); general structure, NO₂CF₂CH(OR)-(OOCCH₃). ^e Isolated yield of hemiacetal based on starting material. ^f Isolated yield of alcohol. ^g Isolated yield of alcohol; this method was used for subsequent alcohol preparations; in tetrahydrofuran, 52% yield.

these studies, as in other reported reductions by metal hydrides, the normal course of the reaction was the reduction of the carbonyl group to an alcohol group.

We were interested in studying the reactions of 2,2,2-difluoronitroethanol, a weakly basic alcohol whose derivatives have not been reported. When this research was started in 1962, difluoronitroethanol was not known; a low-yield process since published was an autoclave method difficult to use.⁴ Although none of the prior reports concerned reduction of esters having the nitro group α to the carbonyl group, the reduction of difluoronitroacetate esters by the method of Shechter³ was considered to be the best approach. However, instead of producing 2,2,2-difluoronitroethanol under the reduction conditions used by Shechter, the alkyl difluoronitroacetates gave a mixture principally of the corresponding alkyl difluoronitroacetaldehyde hemiacetal, O₂NCF₂CH(OH)OR, and difluoronitroacetaldehyde, O₂NCF₂CHO. Difluoronitroethanol was formed only in very small amounts. This result led us to study the novel partial reduction of difluoronitroacetates by sodium borohydride and to characterize the reaction forming the hemiacetal. In subsequent research, we were able to devise a facile synthesis of 2,2,2-difluoronitroethanol, much improved over previous methods, and to prepare previously unreported derivatives of this alcohol.

Results

Hemiacetals.—The reduction of methyl difluoronitroacetate in methanol with sodium borohydride produced a principal product whose structure assignment as a hemiacetal was based on infrared spectrum, elemental analysis, and nmr spectrum. The infrared spectrum contained the bands expected of an alcoholic product, namely a strong broad hydroxyl band, a strong nitro absorption peak, a retention of the CF and CH peaks, and no carbonyl absorption peak. Elemental analysis of the methyl difluoronitroacetate reduction product suggested a compound C₃H₅F₂NO₄, only two hydrogen atoms different from the original ester.

(4) D. M. Gardner, R. E. Oesterling, and M. Hauptschein, U. S. Patent 3,203,999 (Aug 31, 1965).

Among various possible elemental combinations the most logical seemed to be a hemiacetal structure, NO₂CF₂CH(OH)OCH₃. Nuclear magnetic resonance supported this structural assignment. The proton spectrum gave two singlet peaks for the hydroxyl and methyl groups and one triplet peak for the asymmetric CH in the ratio of 3:1:1, respectively. The fluorine spectrum had four doublet peaks corresponding to the spectrum expected of a CF₂ adjacent to an asymmetric carbon atom.

Although the difluoronitro hemiacetals could be isolated in their pure form, the loss in yield during work-up was severe. Consequently, for the study of the reaction the products were converted to stable acetate derivatives using acetic anhydride. The sodium borohydride reduction of difluoronitroacetate esters was influenced primarily by the structure of the starting ester and the solvent system; these factors were more directive in their influence than were conditions of temperature, stoichiometry, and reaction period. In anhydrous solvents such as methanol, dimethoxyethane, or tetrahydrofuran, the principal products were the corresponding alkyl hemiacetal and small amounts of difluoronitroacetaldehyde and 2,2,2-difluoronitroethanol. Table I summarizes the experimental conditions used. Optimum preparation of the hemiacetal was obtained by addition of the ester to a slurry of sodium borohydride in dimethoxyethane at room temperature; control of basicity of the system was unnecessary. Other hydride catalysts were unusable. Lithium aluminum hydride produced an explosion in two instances and lithium borohydride produced no isolable products.

A second product, isolated occasionally during the hemiacetal experiments, was later identified as difluoronitroacetaldehyde. This compound was somewhat unstable as the hydrate and was most easily obtained as its diacetate. An independent synthesis of the aldehyde and its diacetate by aluminum chloride catalyzed sodium borohydride reduction of methyl difluoronitroacetate confirmed the assigned structure.

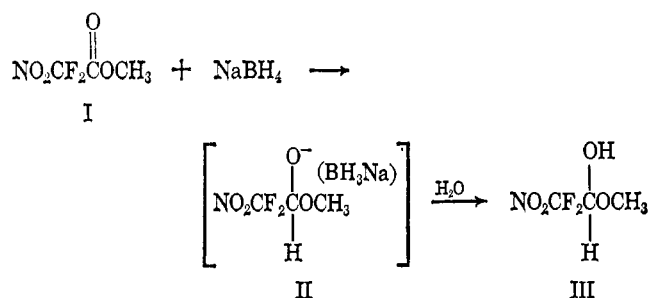
2,2,2-Difluoronitroethanol.—A noticeable feature of the anhydrous systems was the heterogeneity of the reaction mixture, which in itself may have contributed

TABLE II
 ESTERS OF DIFLUORONITROETHANOL

| Ester | Registry no. | Method | Yield, % | Bp (mm) or mp, °C | Calcd, % | | | Found, % | | |
|------------|--------------|----------------------------|----------|-------------------|----------|------|------|----------|------|------|
| | | | | | C | H | N | C | H | N |
| Acetate | 13168-68-8 | (Ac) ₂ O, 25° | 70 | 54 (20) | 28.40 | 2.91 | 8.30 | 28.57 | 3.06 | 8.21 |
| Malonate | | Azeotrope in benzene | 54 | 110 (54) | 26.10 | 1.86 | 8.76 | 26.30 | 1.62 | 8.70 |
| Acrylate | 13168-69-9 | Azeotrope in benzene | 70 | 58 (15) | 33.05 | 2.76 | 7.75 | 33.04 | 2.98 | 7.38 |
| Maleate | 13168-70-2 | Azeotrope in benzene | 56 | 102 (0.05) | 28.75 | 1.79 | 8.35 | 28.35 | 1.83 | 8.19 |
| Fumarate | 13168-71-3 | Catalysis of acid chloride | 22 | 45-46 | 28.75 | 1.79 | 8.35 | 28.85 | 1.96 | 8.03 |
| Ithaconate | 13168-72-4 | Azeotrope in benzene | 47 | 110 (0.05) | 31.10 | 2.30 | 8.05 | 31.21 | 2.49 | 8.50 |

to incomplete reduction by precipitation of the intermediate borate salts. Since the acetates and sodium borohydride both could be dissolved in 50% aqueous dimethoxyethane, a water solution of borohydride was added to an aqueous solution of ethyl difluoronitroacetate at room temperature. Difluoronitroethanol was the only product of the reaction. The methyl and isopropyl esters produced mixtures of all possible reduction products. In a study of leaving-group effect, reduction of benzyl difluoronitroacetate achieved a striking improvement over our previous experience in producing the alcohol. Difluoronitroethanol was the exclusive fluoronitro product and was obtained in 55-70% yields. An optimum procedure was developed which consisted of adding an aqueous sodium borohydride solution to an equimolar amount of benzyl ester dissolved in an aqueous tetrahydrofuran. Other conditions are summarized in Table I.

Normally sodium borohydride has no effect on an ester group. There have been few reports of ester reduction by this reagent and no reports in which the hemiacetal was isolated as a major product. The reduction of a difluoronitroacetate (I) to a hemiacetal (III) apparently involves transfer of a hydride ion to the carbonyl group to produce an alkoxide ion which coordinates with the borohydride (II) and forms the hemiacetal (III) upon hydrolysis during work-up.



A similar course is followed in lithium aluminum hydride reductions of esters in anhydrous systems as a first step, but in subsequent steps the alcohol oxygen bond is cleaved.⁵ The formation of a hemiacetal from an ester in dry dimethoxyethane using sodium borohydride indicates that the alcohol oxygen bond cleavage in this solvent is incomplete. Apparently the sodium borohydride salt of each intermediate (II) is too stable for the bond between the alcohol oxygen and the carbonyl to cleave quantitatively in dry solvent systems. Precipitation of the salt by the solvent undoubtedly contributes to this situation.

Aqueous solvent systems probably promote the alcohol oxygen carbonyl bond cleavage, particularly for the benzyl ester. In aqueous alcohols no products

were obtained, in contrast to the reported reduction of nitroaldehydes and ketones in aqueous methanol. The evidence does indicate that the difluoronitroacetates reduce in stepwise fashion and that completion of reduction does not depend entirely upon conditions or stoichiometry. At present it appears that hemiacetal formation is confined to reductions in dry nonhydroxylic solvents.

Difluoronitroethanol Derivatives.—Several methods for the synthesis of esters of negatively substituted alcohols were tried with difluoronitroethanol and unsaturated acids or their chlorides. Positive results were obtained with fumaryl chloride, using titanium tetrachloride catalysis. Poor results were obtained from direct esterification in polyphosphoric acid and with *p*-toluenesulfonic acid catalyst in benzene. The best over-all results were obtained by the normal sulfuric acid catalyzed direct esterification with water removed azeotropically from benzene. Esterification conditions and results are summarized in Table II. The esterification of acrylic acid was successful only if the starting alcohol and acid were better than 98% pure. Only a minimum amount of sulfuric acid catalyst could be used to avoid decomposition and polymerization. The difluoronitroethyl acrylate was a stable, water-white liquid which had no tendency to polymerize on storage at room temperature.

Methods chosen for an attempted preparation of methylene bis(difluoronitroethyl)malonate (VI) were (a) the zinc chloride catalyzed condensation of the malonate (IV) with paraformaldehyde in refluxing glacial acetic acid⁶ and (b) the reaction of an organic or sodium salt of the malonate (IV) with chloromethyl ether in diethyl ether.⁷ At the outset, it was found that neither reaction gave the desired unsaturated methylene malonate (VI); instead, the reactions gave two new products which have been identified as propane carboxylate derivatives.

Chloromethyl ether reacted either with the difluoronitroethyl malonate in the presence of triethylamine or with the sodium salt. The product from both reactions was a white solid. Its infrared spectrum was very similar to that of the parent ester but was not the spectrum expected from the desired methylene malonate (VI). On the basis of elemental analysis, the new compound appeared to be the malonate ester condensed with a second molecule through a CH₂ grouping, *i.e.*, tetrakis(β,β -difluoronitroethyl)-1,1,3,3-propane tetracarboxylate (VII). The assignment of this structure was supported by the proton (H¹) nmr spectrum, which had three triplets in an area ratio of 4:1:1. The

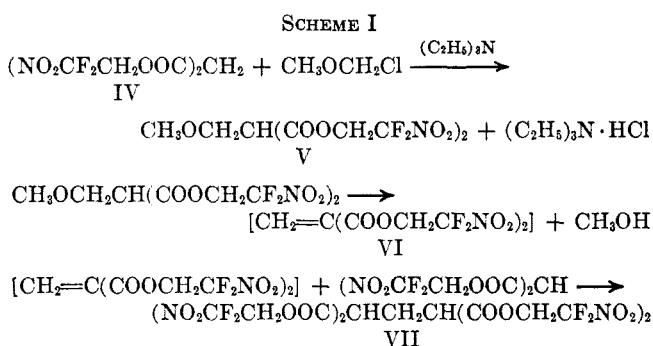
(6) M. Masuna and T. Asakara, Japanese Patent 2219 (May 20, 1953); *Chem. Abstr.*, **49**, 1780g (1955).

(7) G. Vasilieu and N. Barbeleau, *Analele Univ. C. I. Parhon Ser. Stiint. Nat.*, **16**, 99 (1957); *Chem. Abstr.*, **52**, 1238h (1959).

(5) Reference 1, p 391.

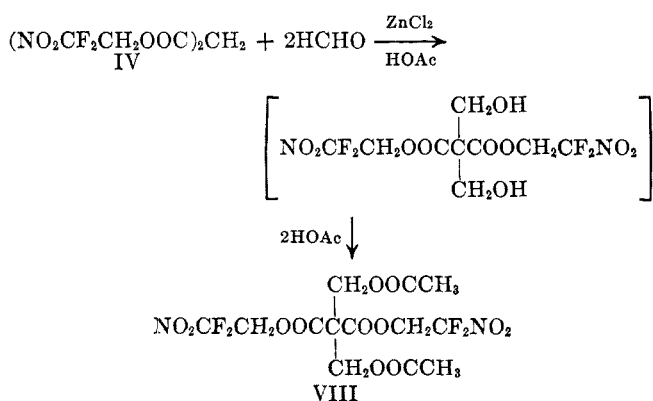
triplet of largest area was from the $-\text{CH}_2\text{CF}_2-$ group, while the two smaller ones derived from the CH being split by the CH_2 and the CH_2 doublet giving rise to a triplet owing to coupling with the CH neighboring protons. The structure was confirmed by a series of experiments degrading the product to easily identifiable fragments. The tetracarboxylate was hydrolyzed to propanetetracarboxylic acid, a known compound which was then decarboxylated to glutaric acid and identified by mixture melting point and nmr. Similarly, the analogous ethyl 1,1,3,3-propanetetracarboxylate, a known compound, was hydrolyzed to the same acid.

There is a rational mechanism for the formation of the tetracarboxylate. It appears that the unsaturated methylene malonic ester (VI) formed and probably reacted with another mole of the ester by Michael addition. The double bond undoubtedly was activated and the conditions for anion formation preceding Michael addition were favorable (Scheme I). Support



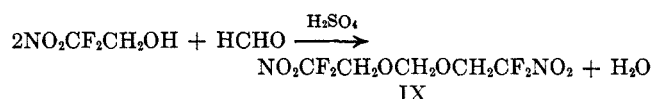
for the intermediate methylene malonate (VI) formation was provided by an experiment in which bromine in carbon tetrachloride was decolorized quickly when added to a fresh reaction solution after the reaction period. If the reaction mixture was allowed to stand overnight before addition of the bromine, decolorization was not achieved. This result indicated that the Michael addition was the slow step.

The condensation of formaldehyde with difluoronitroethyl malonate (IV) in acetic acid produced a colorless viscous liquid which was difficult to purify because of polymerization. The best preparation showed only one component by thin layer chromatography. Calculations from the elemental analysis indicated an empirical formula which corresponded to 2,2-bis(difluoronitroethylcarboxylate)-1,3-propanediol diacetate (VIII), the bisacetate ester of a diol formed by formaldehyde condensation at the site of



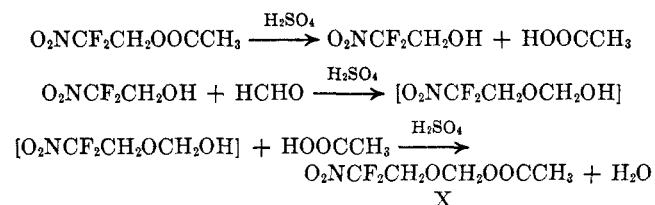
the acidic protons in the malonate starting ester. A proton nmr spectrum showed three peaks—one triplet and two singlets in a ratio of 1:1:1.5. The triplet was characteristic of $-\text{CH}_2$ splitting by fluorine in the alcohol moiety; the singlet of 1.5 ratio was at the position for the CH_3 group of an acetate ester, and the singlet of 1 ratio could be the primary CH_2 of the alcohol in the acetate ester.

Difluoronitroethanol would not form an acetal by normal means but was easily converted to its formal (IX) by using 90% sulfuric acid as solvent for the con-



densation of the alcohol with paraformaldehyde.⁸ An alternative approach which used the alcohol acetate and paraformaldehyde gave no advantage. An impurity which was usually formed during the reaction of the alcohol with formaldehyde was identified as the trioxymethylene bis(difluoronitroethyl) ether, formed apparently from incompletely depolymerized paraformaldehyde.

A hemiformal acetate (X), identified by nmr and infrared spectra, was produced as an impurity in the reaction of formaldehyde with difluoronitroethyl acetate by recondensation of acetic acid with the hemiacetal intermediate. Neither of these products was



observed in previous studies of formal preparations in sulfuric acid,⁸ but the isolation of the hemiacetal acetate provides evidence for the mechanism of formal formation involving a hemiacetal as an intermediate.

Experimental Section

The following procedures exemplify those used for the preparation of the compounds discussed in this paper. Results of reduction experiments which reflect variation in reaction conditions are summarized in Table II. Nuclear magnetic resonance data were obtained by W. R. Anderson, Jr., of the SRI Analytical Services Group; except where noted otherwise, all fluorine spectra are compared to CFCl_3 and proton to tetramethylsilane. The difluoronitroacetate esters were prepared by the method of Bissell.⁹ Elemental analyses were made by the Stanford University Microanalytical Laboratory.

Isopropyl Hemiacetal of Difluoronitroacetaldehyde.—To a stirring suspension of 4.0 g (0.107 mole) of sodium borohydride in 80 ml of 1,2-dimethoxyethane at 20–25° was added 21.96 g (0.12 mole) of isopropyl difluoronitroacetate over a 10-min period. The mixture was stirred for an additional 30 min and was then poured into 100 ml of ice water and extracted twice with 75 ml of diethyl ether. The ether solution was dried over MgSO_4 and filtered and the ether was evaporated at 35° (30 mm). The residue was then distilled yielding 9.95 g [45%, bp 60–62° (32 mm)] of isopropyl difluoronitrohemiacetal.

The hemiacetal was converted to its acetate by the following general procedure. A solution of 6.7 g of crude difluoronitroethylisopropyl hemiacetal was stirred in 20 ml of acetic anhydride at 35–40° for 18 hr. The solution was poured into 50 ml of cold water and stirred until the excess acetic anhydride was hy-

(8) M. E. Hill and K. G. Shipp, *J. Org. Chem.*, **31**, 853 (1966).

(9) E. R. Bissell, *J. Org. Chem.*, **26**, 5100 (1961).

droyzed. The mixture was extracted with 75 ml of methylene chloride and was washed twice with 100 ml of water. The pure acetate was obtained by distillation, bp 82–83° (28 mm).

Anal. Calcd for $C_7H_{11}F_2NO_3$: C, 36.60; F, 16.70; N, 6.17. Found: C, 36.90; F, 16.75; N, 6.16.

Proton nmr¹⁰ (reference H^1 to external water and F^{19} to hexafluoroacetone, 40-Mc Varian spectrometer) gave a doublet at +157 cps for the isopropyl CH_3 , a singlet at +119 cps (acetate CH_3), a triplet at -97 cps (aldehyde CH), a septet at +40 cps (isopropyl CH); fluorine nmr gave two doublets at +799 and +949 cps for the CF_2 . In a similar manner, methyl difluoronitroacetate was reduced to methyl difluoronitroacetaldehyde hemiacetal, bp 58° (35 mm), acetate ester bp 86° (28 mm); each was identified by elemental and nmr analysis. Proton nmr¹⁰ for the hemiacetal (reference H^1 to external water and F^{19} to hexafluoroacetone, 40-Mc Varian spectrometer) gave a singlet at +59 cps for CH_3 , singlet at +3 cps (OH), triplet at -8 cps (aldehyde CH); fluorine nmr gave two doublets at +920 and +1074 cps for the CF_2 . Benzyl difluoronitroacetate was reduced to the hemiacetal and identified as its acetate.

Anal. Calcd for $C_{11}H_{11}F_2NO_5$: C, 48.00; H, 4.00; N, 5.10. Found: C, 47.88; H, 4.09; N, 5.09.

The proton nmr ($CDCl_3$ solvent) gave a singlet at τ 2.7 for the phenyl group, a multiplet at τ 3.6 (asymmetric CH), a singlet at τ 5.2 (benzyl CH_2), and a singlet at τ 8.0 (acetate CH_3).

Difluoronitroacetaldehyde Diacetate.—To a stirring suspension of 3.7 g (0.028 mole) of aluminum chloride and 15.0 g (0.081 mole) of isopropyl difluoronitroacetate in 50 ml of 1,2-dimethoxy ethane at 25–30° was added 3.20 g (0.081 mole) of sodium borohydride at such a rate that the temperature did not rise above 35°. After the exothermic reaction had subsided, the mixture was stirred 1 hr. The reaction mixture was poured into 50 ml of cold water containing 10 ml of concentrated HCl, extracted with 75 ml of ether, dried over $MgSO_4$, and filtered. Evaporation of the solvent left a small amount of liquid which was then refluxed in 5 ml of acetic anhydride for 5 hr. The reaction solution was poured into 50 ml of ice water and enough sodium bicarbonate was added to bring the solution to pH 8. After 1 hr the aqueous solution was extracted with 50 ml of ether, dried over $MgSO_4$, filtered, and evaporated to a residual liquid. The crude product was distilled at 92° (28 mm) giving 1.59 g (8%, based on 0.081 mole of starting ester) of difluoronitroacetaldehyde diacetate.

Anal. Calcd for $C_8H_7F_2NO_6$: C, 32.00; H, 3.10; N, 6.29. Found: C, 31.70; H, 3.40; N, 6.16.

Proton nmr¹⁰ (reference H^1 to external water and F^{19} to hexafluoroacetone, 40-Mc Varian spectrometer) gave a singlet at +118 cps for acetate CH_3 , a quartet at -97 cps (CH); the fluorine nmr gave a doublet at +899 cps for the CF_2 ($J = 6.1$ cps). The difluoronitroacetaldehyde diacetates isolated from the $NaBH_4$ reduction experiments were identical with this compound as shown by the same retention times and infrared analysis.

2,2,2-Difluoronitroethanol.—A solution of 9.80 g (0.259 mole) of sodium borohydride in 60 ml of water was added over 20 min to a stirred solution of 60 g (0.252 mole) of benzyl difluoronitroacetate, bp 65° (0.7 mm), in 150 ml of tetrahydrofuran and 90 ml of water at 10–12°. The reaction mixture was stirred vigorously an additional 10 min until the exotherm had subsided. The solution was extracted vigorously twice with 300 ml of ether, dried over $MgSO_4$, and the ether removed *in vacuo*. Fractional distillation produced 22.7 g (70%) of 2,2,2-difluoronitroethanol, bp 59–61° (22 mm), 94% pure. Redistillation gave a 90% recovery of alcohol greater than 97% purity, n_D^{20} 1.3747.

Anal. Calcd for $C_7H_7F_2NO_3$: C, 18.90; H, 2.37; N, 11.00. Found: C, 18.83; H, 2.49; N, 10.93.

Proton nmr ($CDCl_3$ solvent) gave a singlet at τ 6.0 (OH), triplet at τ 5.8 (CH_2 , $J = 8.04$ cps); fluorine nmr gave a triplet at 91.0 ppm ($J = 8.89$ cps).

2,2,2-Difluoronitroethyl Acrylate.—A solution of 57.6 g (0.8 mole) of freshly distilled acrylic acid, 50.8 g (0.4 mole) of difluoronitroethanol, 3 ml of 96% sulfuric acid, and 15 mg of hydroquinone in 100 ml of benzene was allowed to reflux until the theoretical amount of water was collected in a Dean-Stark trap (30 hr). The solution was washed twice with 150 ml of water followed by 150 ml of saturated sodium bicarbonate solution. The solu-

tion was dried over $MgSO_4$, filtered, and the benzene was removed at 25–30° (25 mm). Distillation of the residue gave 50 g (69.5%) of 2,2,2-difluoronitroethyl acrylate, bp 58° (15 mm). Other esters were prepared by similar or standard methods outlined in Table II.

Bis(2,2,2-difluoronitroethyl)formal.—To a solution of 1.59 g (0.016 mole) of paraformaldehyde in 3.5 ml of 90% sulfuric acid was added 8.98 g (0.07 mole) of 2,2,2-difluoronitroethanol with vigorous stirring over a period of 2 min. The solution was stirred for 1 hr and then poured into 50 ml of ice water. The water-insoluble material was extracted into 35 ml of methylene chloride and dried over $MgSO_4$ and the solvent was removed at 30° (18 mm). Distillation of the residue gave 5.5 g (60%) of bis(difluoronitroethyl)formal, bp 67–68° (0.6 mm), and 2.5 g (22%) of $O_2NCF_2CH_2O(CH_2O)_2CF_2NO_2$, bp 84° (4 mm).

Anal. Calcd for $C_5H_5F_4N_2O_8$: C, 22.51; H, 2.25; N, 10.50. Found: C, 22.94; H, 2.53; N, 10.32. *Anal.* Calcd for $C_7H_{10}F_4N_2O_8$: C, 25.70; H, 3.07; N, 8.58. Found: C, 25.83; H, 3.16; N, 8.39.

Nmr for bis(difluoronitroethyl)formal gave a singlet at τ 5.26 for aldehyde CH_2 (area ratio 1), a triplet at τ 5.70 (alcohol CH_2 , area ratio 1); fluorine nmr gave triplet at 93.0 ppm (alcohol CF_2). A similar experiment using difluoronitroethyl acetate as the source of the alcohol produced the formal and 2,2,2-difluoronitroethyl hemiacetal acetate.

Anal. Calcd for $C_8H_7F_2NO_5$: C, 30.00; H, 3.55; N, 7.07. Found: C, 29.82; H, 3.50; N, 7.10.

Proton nmr gave a singlet at τ 4.7 for the aldehydic CH_2 , a singlet at τ 8.5 (acetate CH_3), a triplet at τ 5.5 (alcohol CH_2 , $J = 8.0$).

Anal. Calcd for $C_{16}H_{12}F_8N_4O_{16}$: C, 27.40; H, 1.80; N, 8.55. Found: C, 27.55; H, 1.87; N, 8.26.

Tetrakis(β,β,β -Difluoronitroethyl)-1,1,3,3-propane Tetracarboxylate.—To a solution of 25.0 g (0.077 mole) of bis(2,2,2-difluoronitroethyl) malonate and 7.70 g (0.077 mole) of triethylamine in 500 ml of benzene was added 7.5 g (0.093 mole) of chloromethyl ether over a period of 10 min. The reaction mixture was stirred for 4 hr; during this time the solution color progressed from yellow to colorless. The solution was washed with 125 ml of 1 N HCl followed by 200 ml of water, dried over $MgSO_4$, and concentrated *in vacuo* at 40° (18 mm). The product was 20 g of liquid material, which crystallized on standing overnight at -10°. Recrystallization from 100 ml of chloroform gave 12.0 g (51%) of tetrakis(β,β,β -difluoronitroethyl)-1,1,3,3-propane tetracarboxylate. A similar reaction, run with the sodium salt of the malonate, produced a 40% yield of the tetracarboxylate.

1,1,3,3-Tetracarboxypropane.—A suspension of 2.0 g (0.065 mole) of tetrakis(β,β,β -difluoronitroethyl)-1,1,3,3-propane tetracarboxylate was stirred at room temperature in 20 ml of 10% potassium hydroxide for 72 hr. The solution was filtered, neutralized to pH 2 with 12 N hydrochloric acid, saturated with sodium chloride, and extracted vigorously with three 200-ml portions of ether. The ether was dried over magnesium sulfate, filtered, and concentrated at 30–40° (18 mm). A small amount of solid material remained which was recrystallized from ether and chloroform to give 0.2 g (14%) of product melting at 174–176°.

Anal. Calcd for $C_7H_7O_8$: C, 38.20; H, 3.63. Found: C, 38.26; H, 3.68.

The tetracarboxypropane was decarboxylated at 185° to glutaric acid, which showed no depression of mixture melting point with an authentic sample of glutaric acid and was identical by infrared analysis.

2,2-[Bis(β,β,β -difluoronitroethyl) carboxylate]propanediol 1,3-Diacetate.—A stirring mixture of 10 g (0.030 mole) of bis(difluoronitroethyl) malonate, 1.26 g (0.014 mole) of paraformaldehyde, and 0.5 g (0.0004 mole) of zinc chloride was allowed to react at 110° in glacial acetic acid for 48 hr. During this time complete solution was obtained. This solution, after cooling, was poured into 150 ml of cold water, extracted with methylene chloride, washed with a saturated sodium bicarbonate solution, dried, and filtered. Evaporation of the ether left 10 g of material, which was dissolved in 100 ml of methylene chloride and chromatographed on acid-washed aluminum oxide. Of the three fractions collected, the first and third fractions each contained three to four components. The second fraction was homogeneous by thin layer chromatography on silica gel and weighed 2.0 g (14%).

Anal. Calcd for $C_{13}H_{14}N_2F_4O_{12}$: C, 33.51; H, 2.90; N, 6.0. Found: C, 33.41; H, 2.70; N, 6.0.

(10) Determined by Lawrence Radiation Laboratory, Livermore, Calif.

Proton nmr (solvent CDCl_3) gave a triplet at τ 5.1 for the alcohol CH_2 ($J = 7.7$ cps), a singlet at τ 5.5 (diol CH_2), a singlet at τ 7.90 (acetate CH_3).

Registry No.—IV, 13168-64-4; VII, 13168-65-5; IX, 13168-66-6; X, 13168-67-7; 2,2,2-difluoronitroethanol, 3766-88-9; isopropyl hemiacetal of difluoronitroacetaldehyde, 13168-73-5; methyl difluoronitroacetaldehyde, hemiacetal, 13168-74-6; difluoronitroacetaldehyde diacetate, 13168-75-7; trioxymethylene bis(difluoronitro-

ethyl) ether, 13168-76-8; 1,1,3,3-tetracarboxypropane, 4721-45-3; 2,2-[bis(β,β,β -difluoronitroethyl) carboxylate]propanediol, 13168-77-9.

Acknowledgments.—This work was performed under contract with the U. S. Atomic Energy Commission; technical direction was provided by the Lawrence Radiation Laboratory (LRL). The authors especially appreciate the helpful discussions and suggestions of Dr. E. R. Bissell, LRL, Livermore, Calif.

The Relative Abilities of Methoxy and Methylthio Substituents to Stabilize Double Bonds^{1a}

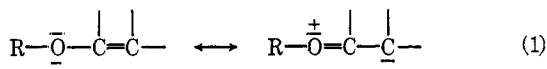
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Received March 3, 1967

Although the equilibrium between methyl 1-propynyl ether and methyl 2-propynyl ether could not be established, the latter was found to isomerize almost quantitatively to methyl propadienyl ether in the presence of catalytic amounts of strong base. The various 1-methoxy-3-methylthiopropenes and 3-methoxy-1-methylthiopropenes were synthesized; their equilibrium mixture was found to contain about 65% *trans*-1-methoxy-3-methylthiopropene, 32% *cis*-1-methoxy-3-methylthiopropene, 2% *trans*-3-methoxy-1-methylthiopropene, and 1% *cis*-3-methoxy-1-methylthiopropene. The synthesis of 1-methoxy-4-methylthio-2-butene was achieved, but on treatment with base the compound appeared to lose methanol to give 1-methylthio-1,3-butadiene. The equilibrium mixture of the methyl 4-methylthiobutenoates was found to contain about 42% of the *trans*-4-methylthiocrotonate, 34% *trans*-4-methylthio-3-butenate, and 24% *cis*-4-methylthio-3-butenate. Methyl *trans*-4-methoxycrotonate isomerized almost quantitatively to *cis*-4-methoxy-3-butenate, but the equilibrium between this product and its *trans* isomer was not established. It is concluded that methoxy substituents stabilize double bonds better than methylthio substituents do.

It has been pointed out previously, in the case of the formation of a fluoro olefin, that the presence of a highly electronegative atom on an unsaturated carbon atom should tend to destabilize the unsaturated compound, relative to similar saturated compounds.^{2,3} Thus, the high electronegativity of oxygen should tend to destabilize vinyl and ethynyl ethers. No equilibrium data seem to be available for ethynyl ethers, but several investigations in which allyl ethers have been isomerized almost quantitatively to vinyl ethers⁴⁻⁹ show that alkoxy substituents stabilize double bonds better than hydrogen or alkyl substituents do. This fact may be rationalized by the hypothesis that stabilization of the double bond by resonance (1) overwhelms the destabilizing electronegativity



effect. We have attempted to determine the effect of alkoxy substituents on triple bonds since the electronegativity effect should be larger (*sp* carbon is more electronegative than *sp*² carbon) and resonance stabil-

ization would be expected to be smaller.¹⁰⁻¹² We have also attempted to compare the ability of alkylthio substituents to stabilize double bonds with that of alkoxy substituents. This was done in the belief that the resonance effect of an alkylthio group attached to unsaturated carbon is significant, but less than that of alkoxy.^{13,14} We hoped to learn more about the relative importance of resonance and electronegativity effects, since the former should cause alkoxy groups to stabilize double bonds, relative to alkylthio groups, and the latter should cause alkoxy groups to destabilize double bonds, relative to alkylthio groups. Several reports of the isomerization of allyl sulfides to vinyl sulfides show that alkylthio substituents stabilize double bonds better than hydrogen or alkyl substituents do.¹⁵⁻²⁰ However, in most of the studies made with both the ethers and the sulfides, the equilibrium lies so far to the side of the vinyl compound that no reliable equilibrium constant could be obtained. For this and other reasons, there did not seem to be good evidence available as to whether an alkoxy or an alkylthio substituent stabilizes a double bond better.

(1) (a) This investigation was supported in part by Grant GP-2002 from the National Science Foundation; (b) to whom all correspondence should be addressed at the Evans Laboratory of Chemistry, The Ohio State University, Columbus, Ohio 43210.

(2) J. Hine and P. B. Langford, *J. Am. Chem. Soc.*, **78**, 5002 (1956).

(3) Cf. R. W. Taft, Jr., and M. M. Kreevoy, *ibid.*, **79**, 4011 (1957).

(4) A. J. Birch, *J. Chem. Soc.*, 1642 (1947).

(5) R. Paul, G. Roy, M. Fluchaire, and G. Collardeau, *Bull. Soc. Chim. France*, 121 (1950).

(6) R. Paul, M. Fluchaire, and G. Collardeau, *ibid.*, 668 (1950).

(7) W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).

(8) T. J. Prosser, *ibid.*, **83**, 1701 (1961).

(9) C. C. Price and W. H. Snyder, *ibid.*, **83**, 1773 (1961).

(10) There is evidence that carbon-carbon triple bonds interact less with conjugated carbonyl groups, for example, than do carbon-carbon double bonds.^{11,12}

(11) R. W. Taft, Jr., and D. J. Smith, *ibid.*, **76**, 305 (1954).

(12) J. Hine and W. C. Bailey, Jr., *ibid.*, **81**, 2075 (1959).

(13) Note, for example, the much larger difference between Hammett's *meta* and *para* substituent constants for methoxy compared with methylthio substituents.¹⁴

(14) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 87.

(15) D. S. Tarbell and M. A. McCall, *J. Am. Chem. Soc.*, **74**, 48 (1952).

(16) D. S. Tarbell and W. E. Lovett, *ibid.*, **78**, 2259 (1956).

(17) C. C. Price and W. H. Snyder, *J. Org. Chem.*, **27**, 4639 (1962).

(18) D. E. O'Connor and W. I. Lyness, *J. Am. Chem. Soc.*, **85**, 3044 (1963).

(19) D. E. O'Connor and C. D. Broaddus, *ibid.*, **86**, 2267 (1964).

(20) D. E. O'Connor and W. I. Lyness, *ibid.*, **86**, 3840 (1964).