spectively. These results indicated that the rearranged product was 13-methyl-12-tetradecen-1-ol acetate (5).

**13-Methyl-12-tetradecen-1-ol Acetate (5).** (12-Hydroxydodecyl)triphenylphosphonium bromide, prepared according to Schaub et al.[14] (3.1 g, 5.9 mmol), was suspended in THF (50 mL). Methyllithium (9.1 mL, 1.5 M in ether, 14 mmol) was added dropwise while the mixture was kept below 10 °C. After 0.5 h, excess acetone was added. The reaction mixture was allowed to stand at room temperature for 2 h. A small amount of water was added, and the ether and THF were removed at reduced pressure. The residue was extracted with pentane, washed twice with water and brine, and dried ($Na_2SO_4$). After evaporation of the pentane, the residue was acetylated with acetic anhydride/pyridine in the usual manner. Workup and distillation yielded 5: bp 120 °C (0.025 mm) (bath temperature) (short-path still) in a 20% yield. The analytical sample was purified by HPLC: IR $\nu$ 2922 (s), 2855 (s), 1733 (s), 1360 (m), 1233 (s), 1035 (m) $cm^{-1}$; $^1H$ NMR $\delta$ 1.20 (br s, chain $CH_2$), 1.58 (s, 3 H, *cis*-$CH_3C{=}C$), 1.68 (s, 3 H, *trans*-$CH_3C{=}C$), 1.74 (s, 3 H, $CH_3CO_2$), 3.98 (t, 2 H, $CH_2OCOCH_3$, $J$ = 7 Hz), 5.21 (t, 1 H, olefinic, $J$ = 7 Hz); $^{13}C$ NMR $\delta$ 17.72, 20.53, 25.87, 26.31, 28.5-30.4, 64.35, 125.41, 130.93, 169.92; GC/MS *m/e* (relative intensity) 268 ($M^+$, 2), 208 (M - 60, 13), 124 (11), 123 (11), 110 (17), 109 (21), 97 (20), 96 (49), 95 (54), 83 (29), 82 (100), 81 (36), 70 (12), 69 (97), 68 (35), 67 (35), 61 ($CH_3COOH_2^+$, 10). Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.03; H, 11.79.

The compound had a congruent mass spectrum and identical GLC retention times on both polar and nonpolar columns with the rearrangement product of 4.

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## Anodic Trifluoromethylation of Acrylic Acid. Synthesis of Diethyl (2,2,2-Trifluoroethyl)malonate and Trifluorinated Analogues of Barbital and Amobarbital

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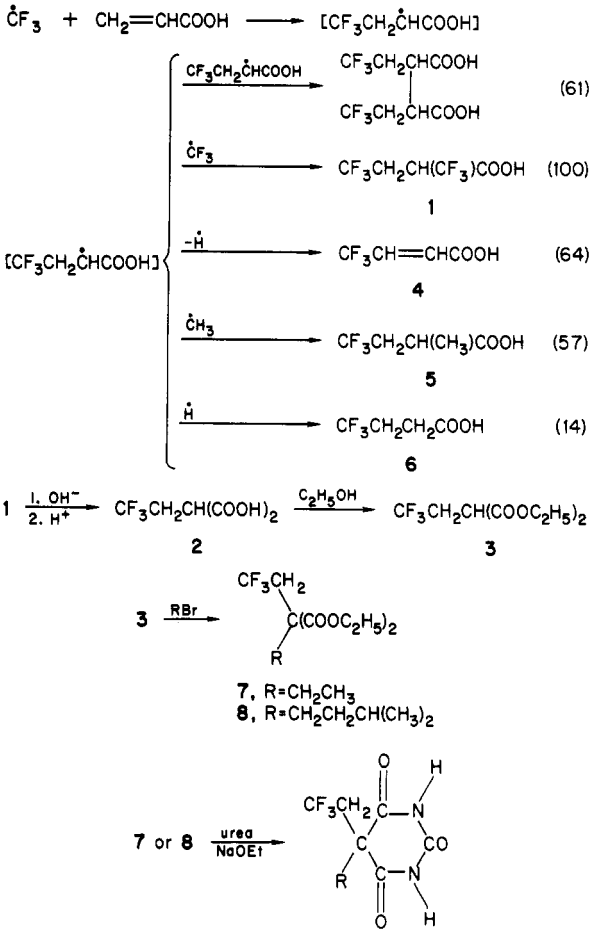
Oxidation of trifluoroacetate ions at an anode produces trifluoromethyl radicals which have been shown to react with olefinic cosolutes to yield more or less complex mixtures of mono- and bis-trifluoromethylated materials.[1-5] When it is fairly easy to isolate a pure product from such a mixture this may represent the most economical preparative procedure, especially for compounds containing functional groups that could not survive treatment with powerful fluorinating agents such as sulfur tetrafluoride. Several useful syntheses based on this approach have recently been described,[6-8] and a further one is presented here.

**Scheme I**




Other investigators had reported that electrolysis of trifluoroacetic acid with methyl or ethyl acrylate in aqueous acetonitrile or methanol gave mainly dimeric products and small amounts of esters of 2-(trifluoromethyl)-4,4,4-trifluorobutyric acid (1).[1,4] The latter is of interest in light of the fact that the trifluoromethyl groups of 2-trifluoromethyl carboxylic acids are apparently rapidly hydrolyzed in aqueous base to give the corresponding malonic acids.[9,10] It was therefore decided to seek conditions under which 1 would be a major electrolysis product and then attempt to convert it to the previously unknown and potentially very useful (2,2,2-trifluoroethyl)malonic acid (2). This was indeed accomplished, but the usefulness of 2 is severely limited because it loses carbon dioxide much more readily than malonic acid. It was, however, possible to obtain its diethyl ester (3) from which a number of new trifluoromethylated compounds can be prepared, including analogues of barbital and amobarbital. The key reactions are summarized in Scheme I.

### Results and Discussion

Trial electrolyses were carried out with trifluoroacetic acid and acrylic acid, methyl acrylate, or higher esters of acrylic acid, in mixtures of water with several organic solvents, including methanol, acetonitrile, acetic acid, 2-

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propanol, and acetone. In each case, pouring the reaction mixture into water gave a dense oil whose $^{19}F$ NMR spectrum showed a number of overlapping multiplets. This was consistent with the assumption[1,4] that trifluoromethyl radicals first added to the double bond to give $CF_3CH_2\dot{C}HCOOH$ radicals which then reacted to form stable products by several competing pathways. In spite of their complexity, the spectra allowed the product composition to be determined semiquantitatively, giving the approximate relative amounts (mole ratios) shown in the scheme. In a typical run, the amount of **1** formed represented about 44% of the incorporated trifluoromethyl groups. The spectra also showed that the products were essentially independent of the current density, that the reaction was not affected by adding small amounts of base to neutralize part of the trifluoroacetic acid, and that the best yield of **1** was obtained by using unesterified acrylic acid with aqueous 60% acetone as the solvent. Compound **5** was formed only when acetone was the cosolvent, presumably by combination of $CF_3CH_2\dot{C}HCOOH$ with methyl radicals resulting from the oxidation of acetone.[11] Some of this material was eventually isolated and found to be identical with a sample produced by saponifying the ester obtained by electrochemical trifluoromethylation of methyl methacrylate.[12]

A preliminary distillation gave a mixture free of dimeric or oligomeric products. This was hydrogenated to convert **4** to **6**, because of the likelihood that basic hydrolysis of **4** would produce maleic or fumaric acid,[13] which might interfere with the eventual isolation of **2**. After hydrolysis with aqueous sodium hydroxide and acidification, the remaining fluorinated byproducts, now mainly **5** and **6**, could be removed from the aqueous mixture by extraction with chloroform, leaving a solution from which nearly pure, white solid **2** could be isolated. Attempts to prepare an analytically pure sample were unsuccessful owing to the fact that **2** loses carbon dioxide very readily. This offers a novel method for the preparation of **6**, but **6** is now more conveniently obtainable by oxidizing 4,4,4-trifluorobutanal, produced by anodic trifluoromethylation of allyl alcohol.[8]

The ease of decarboxylation of **2** also made it impossible to condense the acid with benzaldehyde in pyridine containing a catalytic amount of piperidine. The NMR spectrum showed that the only fluorinated product was **6**. In a separate experiment, a solution of **2** in pyridine was more than half converted to **6** on standing at room temperature for a day. Fortunately, esterification of the freshly prepared crude acid gave a good yield of **3**, which was stable enough to be vacuum-distilled and then stored at room temperature without special precautions.

Because of the inductive effect of fluorine, 2,2,2-trifluoroethanol is more acidic than ethanol by about 5 orders of magnitude.[14] In the same way, the methine protons of **3** become sufficiently acidic to allow it to be alkylated with excess ethyl iodide and potassium carbonate in refluxing acetone;[15] the conversion was nearly quantitative in 42 h. With 1-bromo-3-methylbutane or 1-bromooctane, the reflux time had to be increased to 8 to 12 days, but the yield was nearly as good. In a trial reaction with 2-bromopentane in refluxing 3-pentanone, the $^{19}F$ NMR spectrum showed that after 1 week about 50% of the starting material had been alkylated, about 22% remained unchanged, and the remainder had been converted to an unidentified trifluoromethylated byproduct.

Diethyl ethyl(2,2,2-trifluoroethyl)malonate (**7**) and diethyl isoamyl(2,2,2-trifluoroethyl)malonate (**8**) reacted with urea and sodium ethoxide to form disubstituted barbituric acids.[16] Unfortunately, like known dialkylbarbituric acids, these apparently exist in more than one polymorphic form, making sharp, reproducible melting difficult to obtain.[17,18] Their pharmacological properties have not yet been investigated.

## Experimental Section

Reagents and solvents were commercial materials. $^{19}F$ NMR spectra were obtained at 84.669 MHz with a Perkin-Elmer R-32 spectrometer. Fluorine chemical shifts in $CDCl_3$ solutions were measured with an external 1,1,2-trichlorotrifluoro-1-propene standard and converted to the $\phi^*$ scale by adding −62.80 ppm. When $CF_3COOH$ was the solvent, its resonance was used as an internal standard and the shifts converted to $\phi^*$ values by adding −79.32 ppm. All melting or boiling temperatures are uncorrected.

**(2,2,2-Trifluoroethyl)malonic Acid (2).** Each electrolysis mixture consisted of 17.1 mL (250 mmol) of acrylic acid and 45 mL (584 mmol) of trifluoroacetic acid in 120 mL of acetone and 80 mL of water. The solution was electrolyzed in the cell described previously[6] with water cooling at a roughly constant current of 1 to 1.3 A until 0.9 Faradays had been used. It was then poured into 500 mL of water, the oily layer isolated, and the aqueous solution extracted with two 50-mL portions of dichloromethane. The combined nonaqueous material from six identical runs was distilled at 1 atm to recover the solvent and remove acetone and then distilled at 4.5 torr. About 80 g of distillate was obtained as a single fraction while the temperature gradually rose to 90 °C. This was diluted with 80 mL of glacial acetic acid and hydrogenated at 3 atm over 0.15 g of 5% Pd/C for 1 h, when hydrogen uptake had ceased. The filtered solution was poured into 700 mL of water, the oil isolated, and the water layer extracted 3 times with 50 mL of dichloromethane. The solvent was removed from the nonaqueous layers in vacuo and the residual oil poured into a solution of 48 g of sodium hydroxide in 450 mL of water; an exothermic reaction immediately ensued. After about 1 h this was filtered to remove some precipitated sodium fluoride and washed with 50 mL of dichloromethane. The aqueous solution was acidified with 100 mL of concentrated hydrochloric acid, washed 3 times with 45 mL of chloroform, and then extracted with four 75-mL portions of ether. Evaporation of the ether solution left 25.5 g of crude solid **2**.

**Diethyl (2,2,2-Trifluoroethyl)malonate (3).** A 25.5-g sample of crude **2**, 82 mL of ethanol, 145 mL of benzene, and 12 mL of concentrated sulfuric acid were refluxed for 18 h. Slight etching of the apparatus was observed, suggesting that a little hydrogen fluoride was present, but this had no important effect on the reaction. The mixture was distilled to reduce its volume to about 110 mL and poured into water, the oil isolated, and the aqueous layer extracted with benzene. The combined organic layers were washed with saturated aqueous sodium bicarbonate and with water, distilled to remove benzene, and further distilled at 4.5 torr. A fraction collected between 66 and 69 °C (mostly 68–69 °C) consisted of 24.1 g of essentially pure **3**: $^1H$ NMR (12%, $CDCl_3/Me_4Si$) $\delta$ 4.24 (q, $J$ = 7.5 Hz, 4 H, 3.63 (t, $J$ = 7 Hz, 1 H), $\delta$ 2.81 (doublet of quartets, $J^d$ = 7 Hz, $J^q$ = 10.5 Hz, 2 H), 1.27 (t, $J$ = 7.5 Hz, 6 H); $^{19}F$ $\phi^*$ −66.83 (t, $J$ = 10.5 Hz). Anal. Calcd for $C_9H_{13}F_3O_4$: C, 44.63; H, 5.41. Found: C, 44.46; H, 5.12. A little additional **3** was obtained from the adjacent fractions, bringing the total to 25.4 g (7% overall yield based on the acrylic acid used to prepare **2**).

**Diethyl Ethyl(2,2,2-trifluoroethyl)malonate (7).** A 14-g (58 mmol) sample of **3** was mixed with 12 g (87 mmol) of powdered anhydrous potassium carbonate, 19.2 mL (240 mmol) of ethyl

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iodide, and 30 mL of acetone and refluxed for 42 h. NMR spectra of aliquots withdrawan at intervals indicated that this amount of time is required for essentially complete reaction. 100 mL of benzene were added, the mixture filtered, and the filtrate distilled, first at 1 atm and then at 4.5 torr. The fraction boiling between 75 and 81 °C (mostly 77–79 °C) consisted of 14.2 g (90%) of **7** sufficiently pure to be used to prepare the substituted barbituric acid: $^1$H NMR (12%, $CDCl_3/Me_4S$:) $\delta$ 4.22 (q, $J$ = 7 Hz, 4 H); 2.86 (q, $J$ = 11.2 Hz, 2 H); 2.13 (q, $J$ = 7.5 Hz, 2 H); 1.25 (t, $J$ = 7 Hz, 6 H); 0.87 (t, $J$ = 7.5 Hz, 3 H); $^{19}$F NMR $\phi$* −62.24 (t, $J$ = 11.2 Hz).

**Diethyl Isoamyl(2,2,2-trifluoroethyl)malonate (8).** This was prepared from 23.3 g (96 mmol) of **3** and 60.4 g (400 nmol) of 1-bromo-3-methylbutane essentially as above, except that the mixture was refluxed for 12 days. A fraction boiling between 90 and 103 °C (mostly 100–103 °C) at 4.5 torr consisted of 25 g (84%) of nearly pure **8**: $^1$H NMR (12%, $CDCl_3/Me_4Si$) $\delta$ 4.21 (q, $J$ = 7 Hz, 4 H), 2.84 (q, $J$ = 11 Hz, 2 H), 2.07 (complex multiplet, 2 H), 0.9–1.9 (complex multiplet, 3 H), 1.24 (t, $J$ = 7 Hz, 6 H), 0.89 (d, $J$ = 6 Hz, 6 H); $^{19}$ F NMR $\phi$* −62.18 (t, $J$ = 11 Hz).

**5-Ethyl-5-(2,2,2-trifluoroethyl)barbituric Acid (Trifluorobarbital).** A 5.0-g (83 mmol) sample of urea, 3.6 g (157 mmol) of sodium, and 47 mL of dry ethanol were mixed and heated until homogeneous. Then, 14.2 g (52 mmol) of **7** and 5 mL of ethanol were added, and the mixture was heated under reflux with an oil bath at 105 °C for 10 to 12 h. Ethanol was removed from the cooled mixture at reduced pressure and 75 mL of water added to the yellow residue. The solution was washed 3 times with 30 mL of ether, the combined ether solutions were extracted twice with 25 mL of water, and the combined aqueous layers were neutralized by dropwise addition of concentrated hydrochloric acid. A total of 9.8 g (78%) of crude solid product was obtained from the chilled solution and recrystallized from hot water. The NMR spectra of trifluorobarbital and trifluoroamobarbital were observed by using 0.08 g of material dissolved in 0.6 mL of trifluoroacetic acid containing 2 vol % tetramethylsilane: $^1$H NMR $\delta$ 3.11 (q, $J$ = 9.7 Hz, 2 H), 2.26 (q, $J$ = 7.5 Hz, 2H), 1.07 (t, $J$ = 7.5 Hz, 3 H); $^{19}$F NMR $\phi$* −65.52 (t, $J$ = 9.7 Hz); Anal. Calcd for $C_8H_9F_3N_2O_3$: C, 40.34; H, 3.81. Found: C, 40.02; H, 3.88.

**5-Isoamyl-5-(2,2,2-trifluoroethyl)barbituric Acid (Trifluoroamobarbital).** By essentially the same procedure, 16.5 g (76%) of this product were prepared from 24.3 g (78 mmol) of **8** and recrystallized from water/ethanol: $^1$H NMR $\delta$ 3.11 (q, $J$ = 9.7 Hz, 2 H), 2.2 (complex multiplet, 2 H), 1.0 to 1.8 (complex multiplet, 3 H), 0.91 (d, $J$ = 6 Hz, 6 H); $^{19}$F NMR $\phi$* −65.63 (t, $J$ = 9.7 Hz). Anal. Calcd for $C_{11}H_{15}F_3N_2O_3$: C, 47.14; H, 5.40. Found: C, 47.53; H, 5.13.

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## Alkylating Properties of Phosphate Esters. 1. Oxygen → Nitrogen Methyl Transfer in Dimethyl 2-Pyridylmethyl Phosphate

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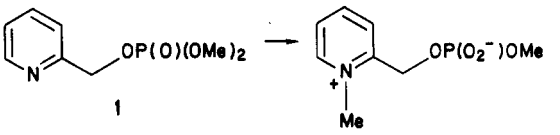
The growing interest in nucleophilic displacement at the carbon atom of phosphate esters stems from at least two sources. First, alkylation of nucleotides by trialkyl phosphates[1] is related to studies on alkylated nucleosides which have been found in nucleic acids. Second, the "triester method" for the synthesis of oligonucleotides involves cleavage of the methyl phosphotriester intermediate by nitrogen[2] or sulfur[3] nucleophiles. In phosphates containing both a nucleophilic center and an electrophilic carbon in the phosphate ester group, alkyl transfer results in isomerization and formation of the zwitterionic product. This reaction has been employed[4] in the synthetic approach to phospholipid analogues where the *O*-methyl is transferred to the $\beta$-dimethylamino group in a phosphate triester. Although this isomerization is believed[4] to be inter-not intramolecular, no evidence for the mechanism was given. For the decomposition of 2-(dimethylamino)ethyl phosphates, Manninen[5] claimed, on the basis of "the effect of the different concentrations" and "the appearance of the intermediate products" in the $^1$H NMR spectra of the reaction mixture, that the methyl transfer is a bimolecular process.

In continuation of our interest in the electrophilic reactivity of phosphate esters,[6] we report the results of our study on the isomerization of dimethyl 2-pyridylmethyl phosphate (**1**) to the corresponding zwitterionic derivative **2**.




1 2 (1)

The triester **1** was chosen as a model substrate because not only should its reactions be free of any intermediate formation of the aziridinium ion, observed for aliphatic $\beta$-aminoalkyl esters,[5] but also because, in view of a recent report on selectivity in dealkylation of phosphate esters,[7] competing alkylation by the 2-pyridylmethyl group, is not expected. We found that **1** is not a reactive methylating agent with respect to the 2-pyridyl nitrogen; it is unchanged after 4 months at room temperature (in pure form or in $Me_2SO$-$d_6$) or after refluxing for several hours in $CDCl_3$, $(CD_3)_2CO$, or $CD_3CN$. The low reactivity of **1** contrasts with that of the $\beta$-(dimethylamino)ethyl analogue, in which the isomerization was complete after 28 days at 20 °C.[4] Since the Swain–Scott parameters $n$ for triethylamine and 2-picoline differ by only 0.34 unit,[8] the difference in reactivity of **1** and the $\beta$-(dimethylamino)-ethyl substrate results not from the difference in the nucleophilicity of nitrogen atoms but probably from steric hindrance offered by the bulky 2-[(dimethoxylphosphoryl)oxy]methyl substituent in **1**. Isomerization of **1** can however be easily achieved in aqueous media.[9] When a solution of **1** (1.7 M) in $D_2O$ is refluxed for 2 h, all substrate disappears, and **2** is formed as the major (spectral yield, 88%) product.

The conversion of **1** into **2** is easily seen in the $^1$H NMR spectra of the solution taken before and after the reaction. The only other product observed was methanol (ca. 12%), formed by the hydrolysis of **1** and/or **2**.[10] If the isomer-

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(9) We have observed that alkylating properties of trialkyl phosphates are greatly enhanced in hydroxylic solvents (particularly in water) relative to other solvents of comparable polarity. This medium effect is currently being investigated in our laboratory.

(10) Under the same conditions, trimethyl phosphate (TMP) yields a similar quantity of methanol.

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