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ESTERS OF (TRIFLUOROMETHYL)MALONIC ACID – CH ACIDS

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Controlled alcoholysis of esters of α-hydrohexafluoroisobutyric acid (I) has been reported to form esters of (trifluoromethyl)malonic acid (II) [1]. Here during an assessment of the preparative potential of the reaction we observed the simultaneous formation of products of exhaustive alcoholysis, esters of methanetricarboxylic acid (III) (see below). In this context we thought it useful to compare the reactivities of esters (I) and (II), whose properties have not been studied.

$$\underset{(I)}{(CF_3)_2CHCOOCH_3} \xrightarrow[R_3N]{CH_3OH} \underset{(II)}{CF_3CH(COOCH_3)_2} \xrightarrow[R_3N]{CH_3OH} \underset{(III)}{CH(COOCH_3)_3}$$

Results of NMR spectroscopy show that diester (II) dissociates in the presence of tertiary amines to form salts of the corresponding carbanion. Dissociation is 100% even when an equimolar quantity of a weak base such as pyridine is used. A qualitatively different picture emerges with ester (I), in that even in excess pyridine only partial dissociation takes place. Only when a strong base such as triethylamine is used does ester (I) dissociate completely.

The susceptibility of esters (I) and (II) to acid–base dissociation and the possibility of further reactions of the resulting salts of the carbanions are the principal factors that determine the properties of these compounds. Thus, esters (I) and (II) are characterized by a different response to caustic alkali. Analytical experiments have revealed that exhaustive hydrolysis of diester (II) in 0.1 N KOH is almost instantaneous, whereas under these conditions ester (I) is completely hydrolyzed only after 2-3 h. Determination of the consumption of alkali against phenolphthalein and against methyl orange and of the fluoride ion content in the hydrolyzate shows that the following reactions are involved:

$$(II) + 5KOH \rightarrow 3KF + KHCO_3 + KOOCCH_2COOCH_3 + CH_3OH + H_2O$$

$$(I) + 8KOH \rightarrow 6KF + KHCO_3 + KOOCCH_2COOCH_3 + 3H_2O$$

This is supported by the results of controlled alkaline hydrolysis; when esters (I) and (II) are treated with calculated quantities of AcOK, diester (II) is converted to dimethyl malonate, while ester (I) gives methyl β,β,β-trifluoropropionate (IV)

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$$(II) + 3CH_3COOK + 2H_2O \rightarrow 3KF + CO_2 + CH_2(COOCH_3)_2 + 3CH_3COOH$$

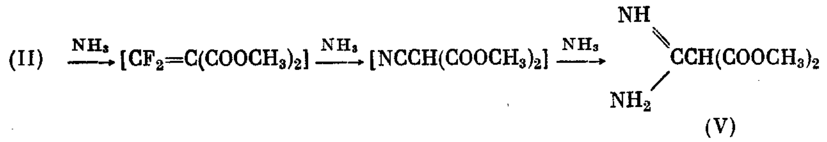
$$(I) + 3CH_3COOK + 2H_2O \rightarrow 3KF + CO_2 + \underset{(IV)}{CF_3CH_2COOCH_3} + 3CH_3COOH$$

Treatment of esters (I) and (II) with AcOK in aqueous methanol gives triester (III); the yield is quantitative

$$(II) + 3CH_3COOK + CH_3OH + H_2O \rightarrow (III) + 3KF + 3CH_3COOH$$

$$(I) + 6CH_3COOK + 2CH_3OH + 2H_2O \rightarrow (III) + 6KF + 6CH_3COOH$$

As expected, we were unable to prepare the amide and diamide of the corresponding fluorocarboxylic acids by ammonolysis of esters (I) and (II): degradation of the trifluoromethyl groups predominates. Thus, ammonolysis of diester (II) does not affect the carbalkoxy groups and the amidinodiester of methanetricarboxylic acid (V) is quantitatively formed; the following sequence of reactions seems to be involved:



$$(II) \xrightarrow{NH_3} [CF_2{=}C(COOCH_3)_2] \xrightarrow{NH_3} [NCCH(COOCH_3)_2] \xrightarrow{NH_3} (NH)(NH_2)CCH(COOCH_3)_2$$

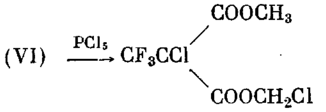
(V)

The relative stability of salts of the carbanion of diester (II) makes possible halogenation under the conditions of basic solvolysis: chlorination and bromination of diester (II) give the corresponding dimethyl (trifluoromethyl)halomalonates (VI) and (VII) in good yield

$$4(II) + 3C_6H_5SO_2NNaCl + 2H_2O \rightarrow \underset{(VI)}{3CF_3CCl(COOCH_3)_2} + 3NaF + CO_2 + CH_2(COOCH_3)_2 + 3C_6H_5SO_2NH_2$$

$$(II) + Br_2 + CH_3COOK \rightarrow \underset{(VII)}{CF_3CBr(COOCH_3)_2} + KBr + CH_3COOH$$

Haloesters (VI) and (VII) are characterized by the stability of the carbalkoxy groups and by the lability of the α-halogen. Thus, we unsuccessfully attempted to convert these haloesters into the acid chlorides. Even when haloesters (VI) and (VII) were heated for many hours with $SOCl_2$ in the presence of pyridine (at 80°C) or with $SbCl_5$ (at 180°C) we found no signs of any reaction. When chloroester (VI) was heated with PCl_5 in an autoclave (250°C, 6 h) chlorination took place; we isolated methyl chloromethyl (trifluoromethyl)chloromalonate (VIII) as the sole identifiable product



$$(VI) \xrightarrow{PCl_5} CF_3CCl(COOCH_3)(COOCH_2Cl)$$

(VIII)

Analytical experiments have shown that haloesters (VI) and (VII) are quantitatively reduced by KI in aqueous AcOH

$$CF_3CHal(COOCH_3)_2 + 2KI + CH_3COOH \rightarrow (II) + KHal + CH_3COOK + I_2$$

We have found such lability of α-halogens in α-chloro- and α-bromohexafluoroisobutyronitriles [2]. This similarity, together with that between the properties of diester (II) and those of α-hydrohexafluoroisobutyronitrile [2-4], demonstrate that the total electronic effects of the two carbalkoxy and the trifluoromethyl groups, on the one hand, and of the nitrile and two trifluoromethyl groups on the other are identical.

These observations also imply that the total electron-withdrawing effect of the carbalkoxy and two CF_3 groups in ester (I) is undoubtedly less. A still lower total electron-withdrawing effect typifies the Cl atom and two CF_3 groups, as exemplified by our study of chlorohexafluoropropane [5]. All these comparisons demonstrate conclusively that the CH acidities of these compounds fall into the order: $CF_3CH(COOR)_2 \approx (CF_3)_2CHCN > (CF_3)_2CHCOOR \gg (CF_3)_2CHCl$.

A graphic illustration of the relative CH acidities of ester (I) and diester (II) is provided by the changes in the NMR spectrum of the ester (I) — triethylamine system when diester (II) is introduced, which indicate that the reaction

$$(CF_3)_2\bar{C}COOCH_3 + (II) \rightarrow (I) + CF_3\bar{C}(COOCH_3)_2$$

takes place.

Diester (II) reacts with all bases more rapidly than ester (I), and hence the conversion of (I) to (II) in all types of basic solvolysis cannot be used preparatively. These and similar general considerations should be taken into account in interconversions and other reactions of CH acids under the conditions of basic solvolysis.

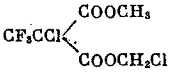
EXPERIMENTAL

The ^{19}F NMR spectra were recorded with a Hitachi—Perkin—Elmer R-20 spectrometer at a field strength of 14,092 Oe and a frequency of 56.456 MHz. Chemical shifts were measured in parts per million of the field relative to CF_3COOH (external standard). The PMR spectra were recorded with the same instrument; chemical shifts were referred to hexamethyldisiloxane (internal standard) (Table 1).

Methyl α-Hydrohexafluoroisobutyrate (I). A mixture of dimethyl sulfate (126 g, 1.0 mole) and potassium α-hydrohexafluoroisobutyrate (117 g, 0.5 mole) was heated at 70-80°C for 1 h. The mixture was cooled to 10-20°C and the resulting precipitate of potassium methyl sulfate was filtered off. The mother liquor was fractionated. We obtained (I) (95 g, 90%) as a colorless liquid with bp 90-91°C; n_D^{20} 1.3060. Found: C 28.37; H 1.83; F 54.00%. $C_5H_4O_2F_6$. Calculated: C 28.57; H 1.90; F 54.29%.

Methanolysis of (I). To a stirred mixture of (I) (21.0 g, 0.1 mole) and triethylamine (10.1 g, 0.1 mole) cooled with ice was gradually added dropwise anhydrous methanol (8.0 g, 0.25 mole). The mixture was poured into dilute HCl (1:1) (50 ml). The heavy oil was removed, washed with water (2 × 10 ml), and dried with H_2SO_4 (sp. gr. 1.84 (30 ml) the mixture was periodically agitated. After 2 h it was poured onto an equal volume of ice. The heavy oil was removed and washed successively with water (20 ml), 10% aqueous $NaHCO_3$ (2 × 10 ml), and again with water (20 ml) it was dried over $MgSO_4$. Fractionation yielded dimethyl (trifluoromethyl)malonate (II) (12.0 g, 60%) as a colorless liquid with bp 75-76°C (14 mm); n_D^{20} 1.3198; d_4^{20} 1.3758. Found: C 36.16; H 3.52; F 28.83%. $C_6H_7O_4F_3$. Calculated: C 36.00; H 3.50; F 28.50%. The still residue was recrystallized from methanol. We obtained trimethyl methanetricarboxylate (4.0 g, 22%) (III) as white prismoidal crystals with mp 44°C. Found: C 43.92; H 5.06%. $C_7H_{10}O_6$. Calculated: C 44.21; H 5.26%.

TABLE 1

Compound	Formula	PMR spectrum		^{19}F NMR spectrum		Alkalimetry				Iodometry
		δ, ppm	J, Hz	δ, ppm	J, Hz	time	equiv. $\overline{OH}$	equiv. $\overline{HCO_3}$	equiv. $\overline{F}$	equiv. iodine
(I)	$(CF_3)_2CHCOOCH_3$	4,07 sept 3,78 s	7,0 —	−12,1 d	7,0	3 h	7,90	0,96	5,88	—
(II)	$CF_3CH(COOCH_3)_2$	3,75 s 4,34 q	8,0	−11,7 d	8,0	10 min	5,08	0,96	3,10	—
(III)	$CH(COOCH_3)_3$	3,72 s 4,32 s	— —			10 min	1,96	1,02	–	–
(IV)	$CF_3CH_2COOCH_3$	1,50 q 4,10 s	9,5 —	−11,5 t	9,5	6 h	3,93	0,0	3,06	–
(VI)	$CF_3CCl(COOCH_3)_2$	3,84 s	—	−18,6 s	—	–	—	–	–	1,91
(VII)	$CF_3CBr(COOCH_3)_2$	3,70 s	—	−18,2 s	—	–	—	–	–	2,08
(VIII)	 $CF_3CCl\left\langle {COOCH_3 \atop COOCH_2Cl} \right.$	3,80 s 5,07 s	— —	−18,6 s	—	–	—	--	–	1,88

Alkaline Hydrolysis. A weighed quantity of the compound (0.01-0.03 g) was dissolved in 0.1 N KOH (20 ml) and after a certain time the excess alkali was titrated with 0.1 N HCl first against phenolphthalein and then against methyl orange. Independent experiments determined the fluoride ion content of the hydrolyzate (thoriometry). Table 1 shows: length of hydrolysis; consumption of alkali against phenolphthalein (equivalents of $\bar{O}H$); hydrolyzate content, equivalents of $HC\bar{O}_3$ (the difference between equivalents of $\bar{O}H$ against methyl orange and against phenolphthalein), and equivalents of fluoride ion.

Methyl β,β,β-Trifluoropropionate (IV). To a stirred emulsion of (I) (21.0 g, 0.1 mole) in water (50 ml) cooled with ice was added dropwise a solution of AcOK (29.4 g, 0.3 mole) in water (100 ml). The mixture was heated under reflux until the evolution of CO_2 ceased (about 1 h), whereupon it was cooled to 10-20°C and extracted with ether (3 × 50 ml). The ethereal extracts were dried over $MgSO_4$ and fractionated. We obtained (IV) (12.8 g, 90%) as a colorless liquid with bp 83-84°C, n_D^{20} 1.3182. Found: C 33.42; H 3.71; F 40.52%. $C_4H_5O_2F_3$. Calculated: C 33.80; H 3.52; F 40.15%.

Dimethyl Malonate. This was prepared similarly from (II) and AcOK in 88% yield and identified by comparison with an authentic sample.

Trimethyl Methanetricarboxylate (III). To a stirred solution of (I) (21.0 g, 0.1 mole) in methanol (100 ml) cooled with ice was added dropwise a solution of AcOK (58.8 g, 0.6 mole) in a mixture of methanol (100 ml) and water (100 ml). The mixture was concentrated on a water bath until all the methanol had been removed; the residue from the mixture (150-160 ml) was cooled to 10-20°C and extracted with ether (3 × 50 ml). The ethereal extracts were dried over $MgSO_4$, the ether was evaporated, and the residue was recrystallized from methanol. We obtained (III) (17.7 g, 88%).

A similar procedure using (II) (20.0 g, 0.1 mole) and AcOK (29.4 g, 0.3 mole) in aqueous methanol gave (III) (18.3 g, 91%).

Ammonolysis of (II). A stream of NH_3 (about 10 liters) was bubbled through a solution of (II) (10.0 g, 0.05 mole) in absolute ether (40 ml) maintained at −10 to −20°C until the precipitation of white crystals ceased. The precipitate was removed and recrystallized twice from isopropanol to give dimethyl amidinomethanedicarboxylate (V) (5.8 g, 67%) as white prismoidal crystals with mp 84°C. Found: C 41.23; H 5.77; N 15.87%. $C_6H_{10}N_2O_4$. Calculated: C 41.38; H 5.75; N 16.09%.

Dimethyl (Trifluoromethyl)chloromalonate (VI). To a stirred emulsion of (II) (20.0 g, 0.1 mole) in water (50 ml) was added dropwise over 1 h a solution of N-chloro-N-sodiobenzenesulfonamide (30.0 g, 0.14 mole) in water (240 ml). The mixture was heated at 100°C for 1 h. On cooling to 10-20°C a large quantity of benzenesulfonamide was precipitated, which was filtered off. The mother liquor and the precipitate were washed with CH_2Cl_2 (3 × 20 ml); the combined washings were dried over $MgSO_4$. Subsequent fractionation gave (VI) (16.4 g, 96%) as a colorless strongly smelling liquid with bp 75-77°C (10 mm); n_D^{20} 1.3898, d_4^{20} 1.4084; 70% conversion. Found: C 31.14; H 2.70; F 24.75; Cl 15.31%. $C_6H_6O_4F_3Cl$. Calculated: C 30.70; H 2.56; F 24.31; Cl 15.14%.

Dimethyl (Trifluoromethyl)bromomalonate (VII). To a stirred emulsion of (II) (20.0 g, 0.1 mole) and bromine (16.2 g, 0.1 mole) in water (50 ml) cooled with ice was added dropwise a solution of AcOK (9.8 g, 0.1 mole) in water (50 ml). The mixture was heated until the color of bromine disappeared and then cooled to 10-20°C. The heavy oily layer was removed, washed with water, and dried over $MgSO_4$. Subsequent fractionation yielded (VII) (10.5 g, 75%) as a colorless, strongly smelling liquid with bp 84-85°C (11 mm); n_D^{20} 1.4072. Found: C 26.11; H 2.36; F 20.05%. $C_6H_6O_4F_3Br$. Calculated: C 25.80; H 2.15; F 20.43%.

Methyl Chloromethyl (Trifluoromethyl)chloromalonate (VIII). A mixture of (VI) (7.0 g, 0.03 mole) and PCl_5 (13.0 g, 0.062 mole) was heated in a steel autoclave at 240-250°C for 6 h. Subsequent fractionation yielded (VIII) (3.2 g, 40%) as a colorless liquid with bp 82-84°C (10 mm). Found: C 26.49; H 2.02; F 21.40; Cl 26.16%. $C_6H_5O_4F_3Cl_2$. Calculated: C 26.78; H 1.81; F 21.20; Cl 26.40%.

Iodometry. A weighed quantity of the compound (0.04-0.06 g) was dissolved in methanol (10 ml), to which were added AcOH (3 ml) and 10% KI (10 ml). After 30 min the liberated iodine was titrated with 0.1 N $Na_2S_2O_3$ against starch. Table 1 summarizes the equivalents of iodine liberated.

CONCLUSIONS

1. Dialkyl (trifluoromethyl)malonates are rather stronger CH acids than alkyl α-hydrohexafluoroisobutyrates.

2. Halogenation of dialkyl (trifluoromethyl)malonates under the conditions of basic solvolysis gives dialkyl (trifluoromethyl)halomalonates.

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AMIDES OF α-HYDROHEXAFLUOROISOBUTYRIC ACID

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The reaction of α-hydrohexafluoroisobutyramide (I) with N-chloro-N-sodiobenzenesulfonamide in water gives α-chlorohexafluoroisobutyramide (II) [1]

$$\underset{\text{(I)}}{(CF_3)_2CHNH_2} \xrightarrow{C_6H_5SO_2NNaCl} \underset{\text{(II)}}{(CF_3)_2CClCONH_2}$$

We have now prepared α-bromohexafluoroisobutyramide (III) in quantitative yield by bromination of amide (I) in aqueous potassium acetate or mercuric acetate at 20°C; its structure was verified from the PMR and ^{19}F NMR spectra

$$\text{(I)} + Br_2 + CH_3COO^- \rightarrow \underset{\text{(III)}}{(CF_3)_2CBrCONH_2} + Br^- + CH_3COOH$$

We naturally supposed that such reactions could be used to prepare various N-substituted α-halohexafluoroisobutyramides. We selected N,N-diethyl-α-hydrohexafluoroisobutyramide (IV) as original substrate for halogenation; this can be prepared in good yield from hexafluorodimethylketene and diethylamine

$$(CF_3)_2C{=}CO + (C_2H_5)_2NH \rightarrow \underset{\text{(IV)}}{(CF_3)_2CHCON(C_2H_5)_2}$$

We found that under the experimental conditions amide (IV) was neither chlorinated nor brominated, being recovered unchanged. Nor were we able to halogenate amide (IV) by prolonged heating with N-bromosuccinimide or with N-bromophthalimide. The CH bond in amide (IV) obviously differs in lability from that in unsubstituted amide (I). The same conclusion follows from the response of these amides to caustic alkali. Thus amide (IV) is stable to 1 N KOH even in alcoholic solution at 80°C, whereas amide (I) undergoes exhaustive hydrolysis

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