[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Aminolysis of Esters of Negatively Substituted Acetic Acids

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The reactions of ethyl γ,γ,γ-trifluoroacetoacetate with primary, secondary, and tertiary amines were studied. Salts were obtained in all cases. The effect of heat on these salts was studied.

The reaction of a secondary amine with ethyl nitroacetate yielded a salt which formed the ammonium salt of the corresponding amide on heating.

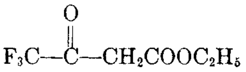
It was found that the carbon-carbon bond in ethyl nitrosoacetoacetate was cleaved with both primary and secondary amines.

With ethyl nitrosomalonate, however, the carbon-carbon bond was cleaved with secondary amines and the carbon-oxygen bond with primary amines.

Previous work has shown that ethyl trichloroacetate gives amides when treated with primary amines and urethans when treated with secondary amines.[2]

Ethyl trifluoroacetate, however, undergoes the same type of cleavage with both primary and secondary amines, forming amides in both cases.[3]

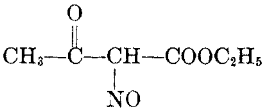
In view of these interesting and different behaviors, it seemed desirable to examine the aminolysis of esters of other negatively substituted acetic acids. The following esters were selected for this investigation:


$F_3C-\overset{\overset{O}{\|}}{C}-CH_2COOC_2H_5$

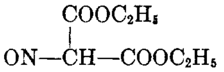
I

$O_2N-CH_2COOC_2H_5$

II


$CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{NO}{|}}{CH}-COOC_2H_5$

III

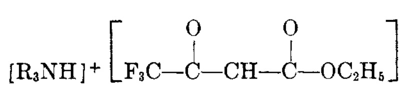

$ON-\overset{\overset{COOC_2H_5}{|}}{CH}-COOC_2H_5$

IV

Ethyl γ, γ, γ-trifluoroacetoacetate (I) and ethyl nitroacetate (II) represent monosubstituted types and ethyl nitrosoacetoacetate (III) and ethyl nitrosomalonate (IV) may be regarded as ethyl esters of disubstituted acetic acids. In all cases the substituents are strongly electron-attracting groups.

Swarts[4] reported the formation of a salt from ethyl γ, γ, γ-trifluoroacetoacetate and ammonia. He made no attempt to elucidate the structure of this salt but noted that when heated it formed the corresponding imino compound ($H_3C-\underset{\underset{NH}{\|}}{C}-CH_2COOC_2H_5$). This work has been repeated and confirmed in this laboratory.

In the course of the present investigation, ethyl γ, γ, γ-trifluoroacetoacetate was treated with primary, secondary, and tertiary amines. Addition compounds were obtained in all cases. They were purified by fractional distillation *in vacuo*. These salts had similar properties. When treated with cupric acetate, the copper derivative of ethyl γ, γ,-γ-trifluoroacetoacetate was formed. When treated with dry hydrogen chloride or picric acid, the corresponding amine hydrochlorides or picrates were formed. The salts of ethyl γ, γ, γ-trifluoroacetoacetate are quite soluble in most organic solvents. In view of the fact that the salt with triethylamine was very similar in behavior to those formed from primary and secondary amines and the fact that the infrared absorption curves for all three types were very similar also, the following structure is suggested for the salts.


$[R_3NH]^+\left[F_3C-\overset{\overset{O}{|}}{C}-CH-\overset{\overset{O}{|}}{C}-OC_2H_5\right]^-$

As pictured, the anion is stabilized by considerable resonance energy. The characteristic absorption bands for these salts are shown in Table I.

When the above compounds were heated at 100° under pressure, they behaved differently depending on the type of amine used in making the salt. The salt derived from a primary amine formed an imino compound similar to the compound obtained from the ammonium salt by Swarts.[4] The secondary amine salt formed the corresponding amide of the ester and the tertiary amine salt was recovered practically unchanged when heated. The characteristic absorption bands for the imino compounds are included in Table I.

The infrared data in Table I are not easy to interpret. The 5.74 μ band for ethyl acetoacetate has been ascribed to the ketone carbonyl group and the 6.06 μ band to the chelated enolate.[5]

The 5.74 μ and 5.82 μ bands are now shown to be characteristic of ethyl γ, γ, γ-trifluoroacetoacetate also but the 6.06 μ band is shifted to 5.95 μ. If one accepts the 5.74, 5.82, and 5.95 μ bands as being characteristic of the ketone, ester, and chelated enolate groups in the fluoro ester, certain conclusions may be drawn.

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(1) To whom all inquiries should be addressed.

(2) Joullié and Day, *J. Am. Chem. Soc.*, **76**, 2990 (1954).

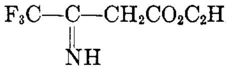
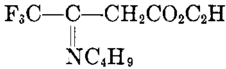
(3) Joullié, *J. Am. Chem. Soc.*, **77**, 6662 (1955).

(4) Swarts, *Bull. sci. acad. roy. Belg.*, [5] **12**, 679 (1926).

(5) Rassmussen and Brattain, *J. Am. Chem. Soc.*, **71**, 1073 (1949).

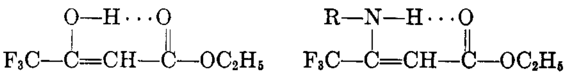
TABLE I

INFRARED BANDS[a] OF CCl_4 SOLUTIONS

Compound	2 µ region	3 µ region	5 µ region	6 µ region	7 µ region	8 µ region
$F_3CCOCH_2CO_2C_2H_5$		3.35 (m)	5.74 (m) 5.82 (m) 5.95 (v.s.)	6.90 (m)	7.30 (s) 7.85 (v.s.)	8.20 (v.s.) 8.35 (v.s.) 8.60 (v.s.)
 $F_3C—C(=NH)—CH_2CO_2C_2H_5$	2.84 (m) 2.98 (m)	3.34 (m)	5.91 (s)	6.05 (s) 6.36 (s) 6.94 (m)	7.30 (s) 7.58 (v.s.)	8.15 (v.s.) 8.72 (v.s.)
 $F_3C—C(=NC_4H_9)—CH_2CO_2C_2H_5$		3.34 (m)	5.96 (s)	6.10 (v.s.) 6.95 (m)	7.30 (s) 7.74 (v.s.)	8.28 (v.s.) 8.75 (v.s.)
$F_3CCOCH_2CO_2C_2H_5{\cdot}C_4H_9NH_2$		3.35 (s)	5.95 (s)	6.10 (s) 6.35 (s) 6.90 (m)	7.30 (m) 7.82 (v.s.)	8.40 (v.s.) 8.85 (v.s.)
$F_3CCOCH_2CO_2C_2H_5{\cdot}(C_2H_5)_2NH$		3.35 (s) 3.62 (s) 3.95 (s)	5.95 (s)	6.18 (v.s.) 6.38 (s) 6.80 (s)	7.35 (m) 7.85 (v.s.)	8.50 (v.s.) 8.90 (v.s.)
$F_3CCOCH_2CO_2C_2H_5{\cdot}C_4H_8ONH$[b]		3.35 (m)	5.95 (s)	6.18 (s) 6.35 (s) 6.85 (m)	7.82 (v.s.)	8.40 (v.s.) 8.85 (s)
$F_3CCOCH_2CO_2C_2H_5{\cdot}C_4H_8NH$[c]		3.34 (s)	5.90 (s)	6.05 (s) 6.15 (s) 6.34 (s) 6.90 (m)	7.34 (m) 7.84 (v.s.)	8.44 (v.s.) 8.80 (s)
$F_3CCOCH_2CO_2C_2H_5{\cdot}(C_2H_5)_3N$		3.35 (s)	5.95 (v.s.)	6.35 (s) 6.85 (m)	7.30 (m) 7.85 (v.s.)	8.45 (v.s.) 8.85 (v.s.)

[a] m = medium; s = strong; v.s. = very strong. [b] Morpholine salt. [c] Pyrrolidine salt.

The carbonyl stretching band for the keto group noted for ethyl γ, γ, γ-trifluoroacetoacetate is missing in the spectra of the imino compounds of the ester and the amine salts of the ester. This is to be expected of the imines since the C=N group absorbs in the range 5.89–5.86 µ and strong bands were found for the imino compounds in this region. Actually the imino compounds could form the same type of chelated enolates as mentioned for the ester.



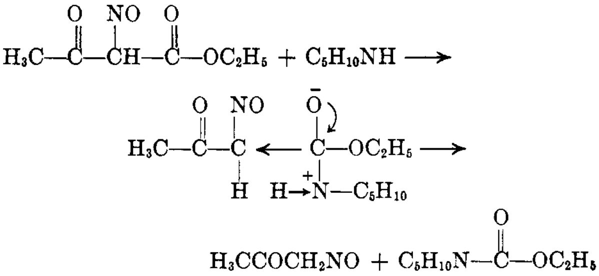
It has been demonstrated in another series of compounds, that the N—H group can participate in conjugate chelation in the same manner as the O—H group and to approximately the same degree.[5]

The fact that the normal carbonyl band is missing from the ammonium salts is not so readily explained. It has been reported, however, that metal chelates of acetylacetone show no normal carbonyl band absorption.[6]

It seems quite probable, therefore, that the chelate character of the ammonium salts accounts for the absence of the normal carbonyl absorption band. At the moment it does not appear possible to assign the bands in the 6.05 µ to 6.35 µ region.

Ethyl nitroacetate also forms salts with amines. The formation of a salt with ammonia has been reported previously.[7] This salt when heated formed the ammonium salt of the corresponding amide. Assuming that primary amines would react in the same way as ammonia, ethyl nitroacetate was treated with a secondary amine only, in the course of the present work. With piperidine, for example, a salt was obtained which formed the piperidinium salt of the corresponding amide when heated.

Ethyl nitrosoacetoacetate behaved like ethyl trichloroacetate when treated with a secondary amine. With piperidine, for example, it formed the corresponding urethan.



In contrast to the other esters studied previously which contained electron-attracting substituents, ethyl nitrosoacetoacetate also formed a urethan when treated with a primary amine, namely *n*-butylamine. Although *n*-butyl urethan was not isolated in an analytically pure form, its identity was established by comparing its infrared spectrum with that of an authentic sample of *n*-butyl urethan. The two spectra were identical. Apparently the reaction with *n*-butylamine follows the same mechanism as the reaction with piperidine.

Ethyl nitrosomalonate behaved like ethyl trichloroacetate[2] when treated with primary and secondary amines. With piperidine, cleavage to the corresponding urethan occurred and with *n*-butylamine the corresponding diamide was formed.

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(6) Duval, Freymann, and Lecomte, *Bull. soc. chim. France*, **5**, 106 (1952).

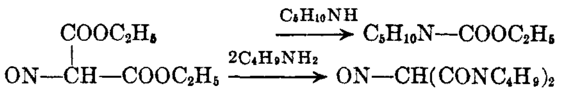
(7) Steinkopf, *Ber.*, **37**, 4626 (1905).

TABLE II

ANALYTICAL DATA AND PHYSICAL CONSTANTS

Compound	M.p., °C.	B.p., °C.	Mm.	Yield, %	n_D^{25}	Analysis Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
SALTS											
$F_3CCOCH_2CO_2C_2H_5 \cdot CH_3NH_2$	148–149			96	...	39.09	38.78	5.58	5.77	6.51	6.39
$F_3CCOCH_2CO_2C_2H_5 \cdot C_3H_7NH_2$		85	1	70	...	44.40	44.46	6.63	6.47	5.76	5.89
$F_3CCOCH_2CO_2C_2H_5 \cdot C_4H_9NH_2$	62–63			94	...	46.69	46.43	7.04	7.02	5.44	5.24
$F_3CCOCH_2CO_2C_2H_5 \cdot (C_2H_5)_2NH$	98–99			95	...	46.69	46.45	7.04	6.99	5.44	5.70
$F_3CCOCH_2CO_2C_2H_5 \cdot C_5H_{10}NH$[a]	67–68			94	...	49.05	49.01	6.72	6.72	5.20	5.16
$F_3CCOCH_2CO_2C_2H_5 \cdot C_4H_8ONH$[b]	75–76			94	...	44.28	43.94	5.94	5.76	5.16	5.09
$F_3CCOCH_2CO_2C_2H_5 \cdot C_4H_8NH$[c]	61–62			96	...	47.04	46.95	6.31	6.39	5.48	5.58
$F_3CCOCH_2CO_2C_2H_5 \cdot (C_2H_5)_3N$		34	1	93	1.4418	50.52	50.51	7.77	7.70	4.90	4.90
IMINES											
$F_3C{-}\overset{\overset{NH}{\Vert}}{C}{-}CH_2CO_2C_2H_5$		27	2	84	1.4018	39.37	39.19	4.37	4.49	7.64	7.48
$F_3C{-}\underset{\underset{NC_4H_9}{\Vert}}{C}{-}CH_2CO_2C_2H_5$		54	1	60	1.4355	50.20	49.98	6.73	6.75	5.86	5.83
AMIDES											
$F_3C{-}\overset{\overset{NC_4H_9}{\Vert}}{C}{-}CH_2CONHC_4H_9$	38–40			15	...	54.12	54.36	7.95	8.00	10.52	10.52
$F_3C{-}COCH_2CON(C_2H_5)_2$		47	1	42	1.4335	45.49	45.71	5.73	5.95	6.63	6.50

[a] Piperidine salt. [b] Morpholine salt. [c] Pyrrolidine salt.



$$\underset{ON{-}CH{-}COOC_2H_5}{\overset{COOC_2H_5}{|}} \quad \xrightarrow{C_5H_{10}NH} C_5H_{10}N{-}COOC_2H_5 \qquad \xrightarrow{2C_4H_9NH_2} ON{-}CH(CONC_4H_9)_2$$

The yields, analyses, melting points or boiling points (mm.) and refractive indices for the compounds prepared in the course of this work are included in Table II.

EXPERIMENTAL

Ethyl γ,γ,γ-trifluoroacetoacetate. This compound was purchased from Peninsular Chemresearch, Inc., Gainesville, Florida, b.p. 132°, n_D^{25}1.3740.

Reaction of ethyl γ,γ,γ-trifluoroacetoacetate with ammonia. The reaction was carried out with both anhydrous and concentrated aqueous ammonia as described by Swarts.[4] The latter stated that the ammonium salt of the ester was formed with aqueous ammonia while the ammonium salt of the corresponding amide was formed with anhydrous ammonia. In the present work the ammonium salt of the ester was the only product obtained from the two methods. The melting points of the two products were the same and they both formed the copper derivative of the ester when treated with cupric acetate with or without a solvent. Furthermore, their infrared spectra were identical.

Reactions of ethyl γ,γ,γ-trifluoroacetoacetate with primary amines. With n-butylamine. n-Butylamine (7.3 g., 0.1 mole) was added gradually to 18.4 g. (0.1 mole) of cooled ethyl γ,γ,γ-trifluoroacetoacetate. An exothermic reaction took place and crystals formed almost at once. The crude product was purified by fractional distillation *in vacuo* and recrystallization from ethyl alcohol.

With methylamine. This reaction was carried out as with *n*-butylamine. The product was recrystallized from ethyl alcohol.

With n-propylamine. The reaction mixture was allowed to stand overnight and the product was purified by fractional distillation in vacuo.

Reactions of ethyl γ,γ,γ-trifluoroacetoacetate with secondary amines. With piperidine. This reaction was carried out in the same manner as with *n*-propylamine.

With morpholine. After standing overnight, the product was purified by fractional distillation *in vacuo* and recrystallization from ethyl alcohol.

With pyrrolidine. After standing overnight, the product was purified by fractional distillation *in vacuo* and recrystallization from petroleum ether (30–60°).

With diethylamine. This reaction mixture was allowed to stand overnight and the product was purified by recrystallization from ethyl alcohol.

Reaction of ethyl γ,γ,γ-trifluoroacetoacetate with a tertiary amine, triethylamine. This reaction was carried out in the same manner as with *n*-propylamine. The pure product is a liquid at room temperature.

Action of heat on the ammonium salts of ethyl γ,γ,γ-trifluoroacetoacetate. The ammonium salt was heated by Swarts' method and the imino compound was fractionally distilled *in vacuo* rather than at atmospheric pressure. The salt with *n*-butylamine was heated in a pressure bottle at 100° for 48 hours. After the heating period, the contents of the bottle were transferred to a separatory-funnel, and the lower layer was withdrawn and distilled *in vacuo* to obtain the corresponding imino compound. The upper layer when poured into water gave the N-*n*-butyl amide of the corresponding imino compound.

When the salt with diethylamine was treated in a similar manner the corresponding amide, N-diethyl γ,γ,γ-trifluoroacetoacetamide was obtained.

Under similar conditions the salt with triethylamine was recovered unchanged.

Preparation of ethyl nitroacetate. This compound was prepared by the oxidation of ethyl nitrosoacetoacetate by the method of Rodionov.[8] Better results were obtained as the result of two modifications. More dilute sulfuric acid was used (1:1.5) and the ether extract was washed with sodium bicarbonate solution before drying and distilling, yield 37%, b.p. 55.7° at 3 mm., n_D^{25} 1.4218.

Preparation of ethyl nitrosoacetoacetate. The method of Rodionov[8] was used to make this compound. The only modification involved washing the ether extract with sodium bicarbonate solution before drying and distilling, yield 75%, b.p. 107° at 3 mm., n_D^{25} 1.4557.

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[8] Rodionov, *et al.*, *J. Gen. Chem. U.S.S.R.*, **18**, 917 (1948).

Preparation of ethyl nitrosomalonate. This compound was prepared according to the directions of Schipper and Day.[9] Yield 80%, b.p. 130° at 1 mm., n_D^{25} 1.4530.

Reaction of ethyl nitroacetate with piperidine. Piperidine (38 ml., 0.38 mole) was added to a solution of 37.5 g. (0.28 mole) of ethyl nitroacetate. A precipitate formed almost immediately. The crystals were removed by suction filtration and purified by recrystallization from ethyl alcohol, yield 90%, m.p. 77–81°.

Anal. Calc'd for $C_9H_{18}N_2O_4$: C, 49.60; H, 8.32; N, 12.80. Found: C, 49.51; H, 8.47; N, 12.59.

Action of heat on piperidinium ethyl nitroacetate. Piperidinium ethyl nitroacetate (16.5 g., 0.076 mole) was heated at 100° in a pressure bottle for 12 hours. Fractional distillation *in vacuo* gave an oil, b.p. 65° at 3 mm., n_D^{25} 1.4695. It could not be obtained in analytically pure form. The analytical data suggested that the product was the piperidinium salt of N-nitroacetyl piperidine.

Reaction of ethyl nitrosoacetoacetate with piperidine. Ethyl nitrosoacetoacetate (27 g., 0.17 mole) and piperidine (20 ml., 0.202 mole) were mixed gradually at room temperature. After standing overnight, the solution was fractionally distilled *in vacuo* and "piperidine urethan" (carbethoxy piperidine) was obtained in yields of 60–70%, b.p. 52–53° at 3 mm., n_D^{25} 1.4566. These constants agree with those reported previously.[2] When distillation was carried out at atmospheric pressure, nitrosoacetone (m.p. 69°) was isolated also.

Reaction of ethyl nitrosoacetoacetate with n-butylamine. Ethyl nitrosoacetoacetate (16.6 g., 0.10 mole) was mixed gradually with 13 ml. (0.13 mole) of *n*-butylamine. After standing overnight, the solution was fractionally distilled *in vacuo*, yield 40%, b.p. 61–63° at 2 mm., n_D^{25} 1.4307. The analytical data for the product suggest that it is N-*n*-butylurethan. It has not been possible to obtain this product analytically pure.

Anal. Calc'd for $C_7H_{15}NO_2$: C, 57.90; H, 10.42; N, 9.65. Found: C, 56.80; H, 10.29; N, 10.19.

To confirm the identity of this compound, it was compared with an authentic sample of N-*n*-butylurethan prepared by the method of Werner.[10] The physical constants for the two products were in good agreement and the infrared spectra were identical.

Reaction of ethyl nitrosomalonate with piperidine. Ethyl nitrosomalonate (37.8 g., 0.2 mole) was mixed with 17 ml. (0.2 mole) of piperidine in 100 ml. of ether. The solution was refluxed for 5 hours. After removing the ether, fractional distillation *in vacuo* gave a 50% yield of "piperidine urethan," b.p. 54° at 3 mm., n_D^{25} 1.4570. As a further check the compound was analyzed.

Anal. Calc'd for $C_8H_{15}NO_2$: C, 61.12; H, 9.61; N, 8.91. Found: C, 61.16; H, 9.85; N, 8.76.

Reaction of ethyl nitrosomalonate with n-butylamine. This reaction was carried out in the same manner as with piperidine. After removing the ether, a semi-solid residue remained. This residue was washed with water and recrystallized from 85% ethyl alcohol. Yield of N,N'-di(*n*-butyl)-nitrosomalonamide, 42%, m.p. 120°.

Anal. Calc'd for $C_{11}H_{21}N_3O_3$: C, 54.30; H, 8.71; N, 17.28. Found: C, 54.68; H, 8.81; N, 17.39.

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[9] Schipper and Day, *J. Am. Chem. Soc.*, **74**, 350 (1952).

[10] Werner, *J. Chem. Soc.*, **115**, 1013 (1919).