Synthesis and Properties of Fluorine-Containing Heterocyclic Compounds. VI. Reactions of Fluorinated 3-Keto Esters with Amines

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The reactions of fluorinated 3-keto esters with aliphatic primary amines and 1,2-diaminoethane have been studied. The factors which determined the preferential formation of five- or seven-membered rings, from 1,2-diaminoethane and ethyl 4,4,4-trifluoro-3-ketobutanoate (**1**), were established. Possible reaction paths for these cyclizations are proposed. The reactions of **1** with amines were extended to substituted 1,2-diamines, 1,3-diamines, 1,2- and 1,3-amino alcohols, and cysteine. The stereochemistry of some of the substituted imidazolidineacetic esters was investigated.

The reactions of aromatic 1,2-diamines and ethyl 3-ketobutanoate have been the subject of several publications.[1] The formation of various products under different reaction conditions has generated continued interest in this field. The condensation of ethyl 4,4,4-trifluoro-3-ketobutanoate (**1**) with various aromatic amines has been investigated in this laboratory.[2] More recently we became interested in the reactions of **1** with 1,2-diaminoethane.[3] The reactions of aliphatic 1,2-diamines with 3-ketobutanoates have received much less attention than those of their aromatic analogs.[4] Ethyl 3-phenyl-3-ketopropanoate and 1,2-diaminoethane were reported to give 7-phenyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one in low yields.[5] When ethyl 3-ketobutanoate was treated with 1,2-diaminoethane, the expected 1,4-diazepin-5-one was not formed.[6] A product identified as diethyl 3,3′-(*N*,*N*′-diaminoethyl)bis-2-butenoate was isolated instead.

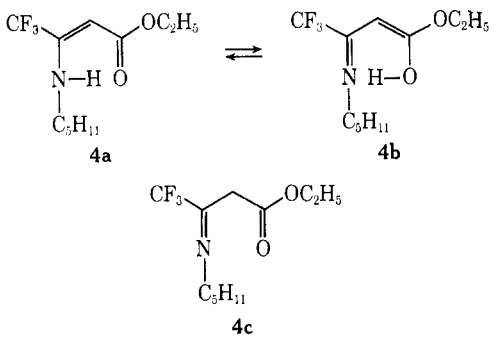
The reactions of fluorinated 3-ketobutanoates with aliphatic diamines proved to be more complex. Recently, we have reported the isolation of 1,2,3,4-tetrahydro-7-trifluoromethyl-1,4-diazepin-5-one (**2**) and ethyl 2-(trifluoromethyl)-2-imidazolidineacetate (**3**) from the reaction of 1,2-diaminoethane and **1**.[3] The yields of **2** and **3** were low (16 and 25%, respectively) and a large amount of undistillable tarry product was also obtained. The purpose of the present investigation was to establish favorable conditions for these condensations and to elucidate the mechanism of addition of 1,2-diamines to 3-keto esters.

Results and Discussion

The condensation of the keto ester, **1**, and 1,2-diaminoethane was conducted in different solvents and the order of addition of the reactants was varied. When **1** was added to the diamine, in refluxing benzene, the yield of imidazolidine, **3**, was increased to 36%, while the yield of diazepinone, **2**, decreased to 10%. In ethanol only the imidazolidine (18.5%) was obtained although the isolation of other diazepines has been reported under similar conditions.[7]

When 1,2-diaminoethane was added to **1**, in refluxing benzene, the yield of **3** increased to 81% but again no diazepinone could be isolated. The results obtained from various experiments pointed to the following trends: higher temperatures and a basic medium promoted diazepinone formation. An acidic medium increased the percentage of imidazolidine. Nonpolar solvents improved the yields of both **2** and **3**. This data suggested that the pH of the medium determined the initial site of attack. To differentiate between the two possible sites of attack in **1**, the keto carbonyl or the ester carbonyl, by the amine, the reaction of **1** with 1-aminopentane was investigated. It was expected that under acidic conditions an enamine, 3-(1-pentylamino)-4,4,4-trifluoro-2-butenoate (**4**) would be formed. In basic medium, an amide, *N*-(1-pentyl)-3-keto-4,4,4-trifluorobutanamide should be obtained.

When 1-aminopentane was added to a refluxing benzene solution of **1**, **4** was obtained in good yield. The ir spectrum of **4**, in carbon tetrachloride, showed two bands of about equal intensity in the carbonyl stretching region at 1670 and 1630 cm^{-1} and a weak (about 5%) band at 1740 cm^{-1}. Also two concentration-independent bands at 3280 and 3225 cm^{-1} were present. The higher carbonyl frequency band at 1670 cm^{-1} could be assigned to the hydrogen-bonded α,β-unsaturated ester carbonyl (**4a**), and the 1630-cm^{-1} band to the α,β-unsaturated imine (**4b**). The two bands in the 3200-



cm^{-1} region were assigned to the NH and -OH stretch of **4a** and **4b**, respectively. Further evidence for the existence of the tautomeric equilibrium **4a** $\rightleftharpoons$ **4b** and the virtual absence of **4c** was supplied by the nmr spectrum of **4** which showed a broad peak at δ 8.27 (1 H) for the NH–OH proton and a sharp singlet at δ 5.04 (1 H) for the vinyl hydrogen but no absorption for the 2-methyl-

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(1) (a) J. Davoll, *J. Chem. Soc.*, 308 (1960); (b) A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim. Acta*, **43**, 1298 (1960); (c) R. Barchet and K. W. Merz, *Tetrahedron Lett.*, **33**, 2239 (1964); (d) F. D. Popp and A. C. Noble in *Advan. Heterocycl. Chim.*, **8**, p 66 (1967).

(2) (a) F. B. Wigton and M. M. Joullié, *J. Amer. Chem. Soc.*, **81**, 5212 (1959); (b) A. S. Dey and M. M. Joullié, *J. Heterocycl. Chem.*, **3**, 113, 120 (1965).

(3) M. M. Joullié, G. M. J. Slusarczuk, A. S. Dey, P. V. Venuto, and R. H. Yocum, *J. Org. Chem.*, **32**, 4103 (1967).

(4) (a) W. Ried and W. Hohne, *Chem. Ber.*, **87**, 1811 (1954); (b) A. E. Martell, R. L. Belford, and M. Calvin, *J. Inorg. Nucl. Chem.*, **5**, 170 (1958); (c) G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, **83**, 2099 (1961).

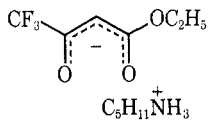
(5) W. Ried and P. Stahlhofen, *Chem. Ber.*, **90**, 828 (1957).

(6) C. M. Hofmann and S. R. Safir, *J. Org. Chem.*, **27**, 3565 (1962).

(7) D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc. C*, 780 (1966).

ene protons of **4c**. Similar results have been observed for the products of amines with 1,3-dicarbonyl compounds.[4b,5,8,9] The same type of tautomeric equilibrium has also been postulated for these products.

The addition of **1** to a refluxing benzene solution of 1-aminopentane afforded a waxy solid whose molecular formula was $C_{11}H_{20}F_3NO_3$. The same product could be formed by mixing the amine and **1** at room temperature, either neat or in carbon tetrachloride solution. The ir spectrum of this product showed broad bands in the 3300–2400-cm^{-1} region and a band at 1580 cm^{-1} typical of amine salts. Two relatively weak carbonyl bands at 1680 and 1640-cm^{-1} were also present. This data suggested **5**, a structure similar to that of metal chelates.



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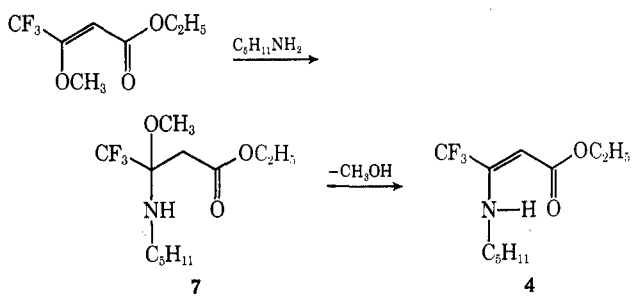
However, dicarbonyl chelates show only one carbonyl band with shoulders at higher and lower frequencies,[10] indicating a closer equivalence of the two carbonyls than that present in **5**. The nmr spectrum also supported this structure by showing the expected alkyl resonances and a singlet at δ 5.05 (1 H) assigned to the vinyl proton. A relatively sharp peak at δ 7.88 (3 H) was assigned to the alkyl ammonium ion. Its narrow half-width (3 Hz) indicated rapid exchange and equivalence of the three protons on the nmr time scale.

Compound **5** could be converted to **4** by heating **5** at 150° for a short period of time. Although these conditions were more drastic than those used in the original condensation of **1** with 1,2-diaminoethane, the isolation of **5** suggested the possibility of a similar salt as a precursor in the reaction of **1** with diamines.

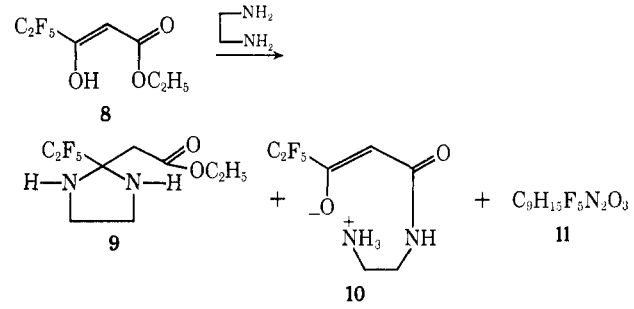
When ethyl 3-methoxy-4,4,4-trifluoro-2-butenoate (**6**) was treated with 1-aminopentane at 0°, ethyl 3-methoxy-3-(1-pentylamino)-4,4,4-trifluorobutanoate (**7**) was isolated. At room temperature **7** eliminated methanol and in about 3 days a quantitative conversion to **4** occurred. These results supported the possibility



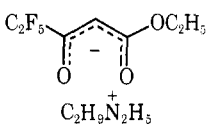
7 **4**

of an intermediate carbinolamine in the reaction of 1,2-diaminoethane and **1**.

The addition of 1,2-diaminoethane to a refluxing benzene solution of ethyl 3-keto-4,4,5,5,5-pentafluoropentanoate (**8**) yielded three products, ethyl 2-(perfluoroethyl)-2-imidazolidineacetate (**9**), *N*-(2-aminoethyl)-3-hydroxy-4,4,5,5,5-pentafluoro-2-pentenamide (**10**), and an addition compound of molecular formula $C_9H_{15}F_5N_2O_3$ (**11**). The ir of **11**, in chloroform, showed a broad absorption band at 3400–2300 cm^{-1} and a band at 1570 cm^{-1} characteristic of amine salts. A single carbonyl absorption was seen at 1675 cm^{-1}. The nmr spectrum of **11** in deuteriochloroform showed a quartet at δ 4.04 (2 H, J = 7 Hz) and a triplet at 1.22 (3 H, J = 7 Hz) due to the ester methylene and methyl groups. A singlet at δ 2.90 (4 H) was assigned to the methylenes of the diamine. The area under the two remaining peaks at δ 5.07 and 5.37 integrated to six protons; by time-averaging, the ratio was shown to be exactly 1:5. The smaller peak was assigned to the vinyl proton (δ 5.07) and the larger one at 5.37 to the ammonium ion protons. The five protons formed a rather sharp peak 4 Hz wide at half-height, suggesting rapid exchange. Their position indicated that they were more shielded than those of **5**. A structure consistent with the above information is the 1,2-diaminoethane salt of **8**, which may be formulated as **11**. The structural assignment for this



8 **9** **10** **11**



11

compound is supported by its facile transformation into the amide salt **10**. This is in contrast with the behavior of **5**. When **5** is heated, the ammonium ion catalyzes the attack as the ketone carbonyl and **4** is formed exclusively. In compound **11**, one of the amino groups appears to be favorably located for nucleophilic attack at the ester carbonyl.

When 1,2-diaminoethane was added to an ice-cold solution of **1** in carbon tetrachloride, a salt (**12**) was obtained in almost quantitative yield. Although stable at room temperature when dry, this salt decomposed in solution making spectroscopic studies difficult. Its ir spectrum was similar to that of **11**. Its nmr spectrum, less than 1 min after solution, in deuteriochloroform, showed the same peaks as **11** and peaks due to the ammonium ion and vinyl proton at δ 5.12 and 5.04, respectively. Within 5 min the latter peaks coalesced into a broad peak and a new peak appeared at δ 2.75. Integration of this spectrum was not possible. When a chloroform solution of **12** was allowed to stand overnight at room temperature, it yielded the corresponding amide salt **13**. When this salt was heated at 170° for a short time, the diazepinone **2** was obtained.

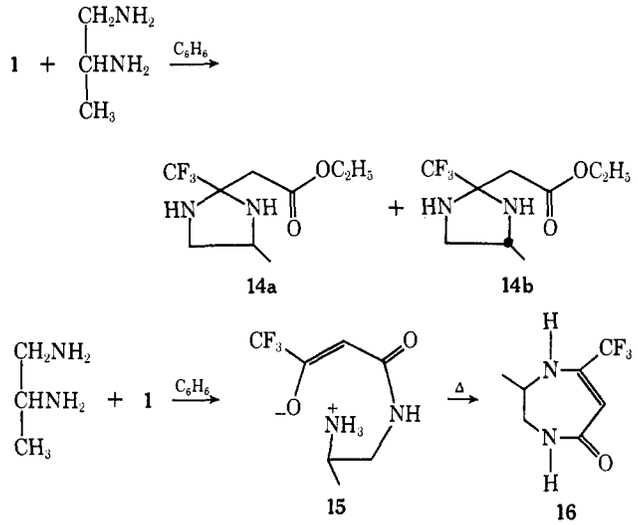
To extend the scope of this reaction, the condensation of **1** with substituted 1,2-diamines was studied. The addition of 1,2-diaminopropane to **1** afforded a good yield of the expected ethyl 4-methyl-2-(trifluoromethyl)-2-imidazolidineacetate (**14**). An isomeric mixture of two *dl* pairs in which the methyl and trifluoro-

(8) M. M. Joullié, S. Nasfay, and L. Rypstat, *J. Org. Chem.*, **21**, 1358 (1956).

(9) F. C. Pennington and W. D. Kehret, *ibid.*, **32**, 2034 (1967).

(10) R. L. Belford, A. E. Martell, and M. Calvin, *J. Inorg. Nucl. Chem.*, **2**, 11 (1956).

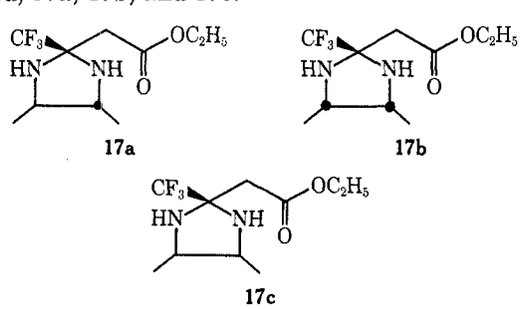
methyl groups may be cis or trans was expected (**14a**, **14b**).



Separation of the possible isomers could not be accomplished either by distillation on a spinning-band column or by vapor phase chromatography on a variety of columns. Evidence for an isomeric mixture was provided by the nmr spectrum. The peaks due to the ester methylene, ring methylene, α-methylene, and NH protons were found at δ 4.16 (2 H, J = Hz), ~3.2, 2.63, and 2.51, respectively. The ring methine proton was hidden under the α-methylene and NH protons (5 H). The peak due to the ester methyl at δ 1.28 (J = 7 Hz) was partly superimposed upon two doublets due to the methyl groups of the cis and trans forms at δ 1.14 (J = 6 Hz) and 1.11 (J = 6 Hz). The trans isomer would be expected to be somewhat less shielded although this assignment is not certain.[11]

When **1** was added to 1,2-diaminopropane, a solid was formed in addition to the imidazolidine mixture **14**. This solid was the amide salt, *N*-(2-aminopropyl)-3-hydroxy-4,4,4-trifluoro-2-butenamide (**15**) which was converted to 1,2,3,4-tetrahydro-2-methyl-7-trifluoromethyl-1,4-diazepin-5-one (**16**) by heating. The position of the methyl group in the compounds was not ascertained. It was assumed that the primary amino group would attack the ester carbonyl preferentially since it should be less sterically hindered.

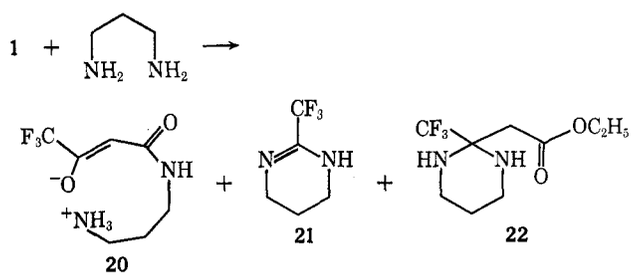
The next substituted diamine used was 2,3-diaminobutane prepared by the reduction of dimethylglyoxime with Raney aluminum–nickel alloy in aqueous sodium hydroxide. A mixture of the *dl* and meso isomers was used; thus a mixture of three geometric isomers was expected, **17a**, **17b**, and **17c**.



Vapor phase chromatography of the product showed only two peaks of about equal area. These peaks appeared to be due to the reaction products of the two isomeric diamines, imidazoline **17a** from the *dl* isomer and a mixture of **17b** and **17c** from the meso isomer. The lower boiling material (A) was a solid at room temperature while the higher boiling material (B) was a liquid and probably a mixture of two isomers. The ir spectra of A and B were almost identical and very similar to the spectrum of **14**. The nmr spectra of A and B were, however, quite different.

The nmr spectra of both A and B showed the ester methylene peak at δ 4.16 (2 H, J = 7 Hz), the α-methylene peak at 2.61 (2 H), the NH protons at 2.74 (2 H), and the ester methyl group at 1.28 (3 H, J = 7 Hz). Isomer A exhibited a broad peak at δ 2.75 (2 H) which could be assigned to the ring methine protons and two doublets centered at 1.12 and 1.08 (6 H, J = 5.5 Hz) which could be assigned to the methyl side chains. The spectrum of B showed a multiplet centered at δ 3.45 (2 H) ascribed to the ring methine groups and a doublet at 0.97 (6 H, J = 6.3 Hz) assigned to the methyl side chains. These results are consistent with those obtained for 2,2,4,5-tetramethyl-1,3-dioxolane where the chemical shift of the ring methines in the trans isomer were 0.77 ppm upfield from the cis isomer and the methyl side chain in the trans isomer absorbed 0.10 ppm downfield from that of the cis isomer (J = 5.9 and 6.3 Hz, respectively).[12] These data appear to support the assignment of the cis–trans form **17a** to isomer A and that of cis–cis or trans–trans **17b** or **17c** to isomer B. Since no doubling of the methyl peaks is evident, only one isomer appears to be present. The assignment of the doubling of the methyl peaks in A to cis–trans isomerism was supported by the nmr spectrum of ethyl 4,4-dimethyl-2-(trifluoromethyl)-2-imidazolidineacetate (**18**). The peaks due to the ester methylene, α-methylene, and ester methyl are at δ 4.16 (2 H, J = 7 Hz), 2.61 (2 H), and 1.28 (3 H, J = 7 Hz), respectively. These chemical shifts are identical with those of the dimethylimidazolidine isomers. A peak at δ 2.87 (2 H) was assigned to the ring methylene protons and the NH proton absorption was a smeared out peak between δ 2.1 and 3.1 (2 H) which disappeared upon deuterium exchange with D_2O. The methyl side chains absorbed at δ 1.17 (3 H) and 1.22 (3 H). The difference in chemical shift between these two peaks, 3 Hz, is in good agreement with the values of 2 Hz for **14** and 2.5 Hz for **17a**.

Similarly, the addition of **1** to a refluxing benzene solution of 1,3-diaminopropane produced a mixture of at least three products, **20**, **21**, and **22**.



The most insoluble product precipitated from the reaction mixture and was formulated as the amide salt,

(11) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

(12) F. A. L. Anet, *ibid.*, **84**, 747 (1962).

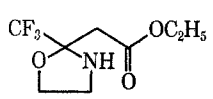
N-(3-aminopropyl)-3-hydroxy-4,4,4-trifluoro-2-butenamide (**20**), in agreement with the analytical and spectroscopic data. Attempts were made to convert **20** into the corresponding diazocinone. Although water was lost, only a polymer was obtained. Evaporation of the benzene afforded a semisolid mixture from which the known[13] 3,4,5,6-tetrahydro-2-(trifluoromethyl)pyrimidine (**21**) was isolated.

The third component of the mixture was ethyl 2-(trifluoromethyl)-2-perhydropyrimidineacetate (**22**) which was best obtained by inverting the addition sequence, that is, adding the diamine to the ester. The ir spectrum of **22** showed the carbonyl stretching at 1732 cm^{-1} with shoulders at 1738 and 1745 cm^{-1}. The NH stretching vibrations appeared at 3370 and 3350 cm^{-1} suggesting hydrogen bonding to the ester carbonyl. The nmr spectrum of **22** also supported its structure.

Since the reaction of 2-amino alcohols with carbonyl compounds is a well-known method for the synthesis of oxazolidines, it was of interest to explore the reaction of **1** with 2-aminoethanol. While the expected oxazolidine was obtained in good yield, the formation of an oxazepinone could not be detected. The ir spectrum of ethyl 2-(trifluoromethyl)-2-oxazolidineacetate (**23**) showed a great similarity to that of the imidazolidines: the ester carbonyl band at 1728 cm^{-1} with shoulders at 1735 and 1750 cm^{-1}, a region free of absorption between 1700 and 1500 cm^{-1}, and an intense peak of the $-CF_3$ group at 1172 cm^{-1}. The single NH stretching band at 3340 cm^{-1}, insensitive to dilution, indicated a stronger hydrogen bond to the ester carbonyl than is present in imidazolidines.

The nmr spectrum of **23** was quite complicated. Except for the ester methyl and methylene, all other protons were magnetically nonequivalent and contributed to the splitting. The α-methylene protons gave rise to an AB quartet centered at δ 2.77 (2 H, J = 15 Hz) and the ring methylenes absorbed between δ 3 and 4 giving rise to many poorly resolved peaks.

Several other commercially available amino alcohols were condensed successfully with **1** and esters related to **1** to yield the corresponding five-membered rings (**24**–**27**). Cysteine gave ethyl 4-carboxy-2-(trifluoromethyl)-2-thiazolidineacetate (**28**). The physical con-



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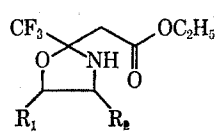
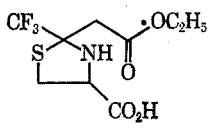


24, $R_1 = CH_3$; $R_2 = H$
25, $R_1 = H$; $R_2 = CH_3$



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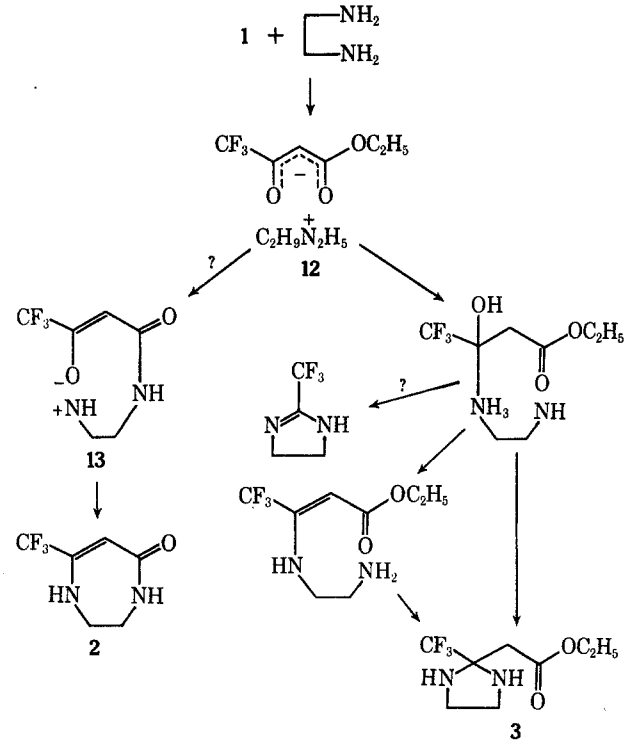
stants for these compounds are shown in Table I. 3-Aminopropanol reacted with **1** to yield ethyl 2-(trifluoromethyl)-2-(1,3-oxazine)acetate (**29**).

(13) R. N. Johnson and H. M. Woodburn, *J. Org. Chem.*, **27**, 3958 (1962).

A possible reaction sequence for the reaction of **1** with 1,2-diaminoethane is shown below.

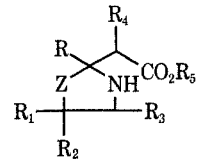


This reaction sequence is consistent with the available data. Since salt formation is the first step in the reaction, the ability of the ester to enolize is important. This reaction is rapid since only a proton transfer is involved. The salt may then react intramolecularly to form either the amide salt (thermodynamic control) or the carbinolamine (kinetic control). That the formation of the carbinolamine should be rapid is supported by the reaction of the enol ether with amines. The carbinolamine could undergo an intramolecular nucleophilic displacement to give directly the imidazolidine or the enamine. Although the enamine can cyclize to **3**, such a reaction might be predicted to be slower since cyclization of ethyl 3-(2-hydroxyethylamino)-4,4,4-trifluoro-2-butenoate to the corresponding oxazolidine (**22**) was shown to be much slower than the formation of **22** from **1** and 2-aminoethanol. Another possible product, 2-trifluoromethylimidazoline, was not found in the reaction mixture although it is a known compound.[13] However, an analogous compound was obtained in the reaction of **1** with 1,3-diaminopropane.

The proposed scheme for the reaction of **1** with 1,2-diaminoethane clarifies somewhat the results reported by previous workers for the condensation of ethyl 3-ketobutanoate and ethyl 3-phenyl-3-ketopropanoate with the same diamine.[4,6] The only product isolated from the first reaction was reported to be diethyl 3,3′-(*N*,*N*′-1,2-diaminoethyl)bis-2-butenoate. We repeated this condensation to investigate the presence of other products, but we were only able to obtain better yields (60%) of the bisenamine. The same result was obtained with *tert*-butyl 3-ketobutanoate. In both cases evolution of water was more rapid than in the case of **1** and 1,2-diaminoethane, suggesting fast dehydration to the enamine. With the more enolic 3-phenyl-3-ketopropanoate, the corresponding diazepinone and diamide were isolated. These could arise from a salt similar to

TABLE I

PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR THE FIVE-MEMBERED RINGS[a]



Compd no.	R	R_1	R_2	R_3	R_4	R_5	Z	Bp (mm) or mp, °C	$n^{25}D$
3	CF_3	H	H	H	H	C_2H_5	NH	40.5–41.0	
9	C_2F_5	H	H	H	H	C_2H_5	NH	85–86 (3.5)	1.4035
14[b]	CF_3	CH_3	H	H	H	C_2H_5	NH	114.5– (20)	1.4173
17[b]	CF_3	CH_3	H	CH_3	H	C_2H_5	NH	93–97 (5)	
18	CF_3	CH_3	CH_3	H	H	C_2H_5	NH	120–120.5 (14.5)	1.4181
19	CF_3	H	H	H	H	$C(CH_3)_3$	NH	96–98 (4.8)	1.4247
23	CF_3	H	H	H	H	C_2H_5	O	108–109 (25)	1.4016
24	CF_3	CH_3	H	H	H	C_2H_5	O	100.5–101 (15)	1.4007
25	CF_3	H	H	CH_3	H	C_2H_5	O	99–99.5 (13)	1.4007
26	CF_3	H	H	H	H	$C(CH_3)_3$	O	92–92.5 (7.5)	1.4055
27	CF_3	H	H	H	CH_3	C_2H_5	O	84–85 (6.5)	1.4060
28	CF_3	H	H	CO_2H	H	C_2H_5	S	124.5–125.5	

[a] Satisfactory analytical values (±0.30% for C, H, N, F, and S) were reported for all compounds. [b] Mixture of isomers.

11 and 12. In the case of ethyl 3-ketobutanoate such a salt is not possible; thus no diazepinone is formed. Ethyl 4,4,4-trichloro-3-ketobutanoate, which is sufficiently enolic to form a salt, was reported to yield only a diazepinone.[14] In this case, the carbinolamine which would result from attack at the keto carbonyl could be expected to undergo a haloform-type of cleavage rather than forming the imidazolidine.

Experimental Section[15]

General.—Compound 1 was prepared by the procedure of McBee, *et al.*[16] However, if this procedure was followed exactly, an explosion occurred on three consecutive runs. Thus the conditions were modified as described for the preparation of ethyl 3-keto-4,4,5,5,5-pentafluoropentanoate (8). No accidents occurred in about 20 runs. Compound 1 was purified through its copper chelate.[17] 1,2-Diaminoethane (Fisher, 99%) was stored over calcium hydride and used without purification. Unless otherwise indicated the keto ester–amine condensations were conducted in a wide-mouth reaction flask with a four-necked head equipped with a Dean–Stark trap, an efficient condenser and a drying tube. The reactions were stirred magnetically and heated with a heating mantle. Reagents were added from a weighing buret that served as an addition funnel. After the reaction was completed, the solvent was removed under reduced pressure, and the residue distilled *in vacuo*, first on a short-path apparatus and then on a spinning-band column.

1,2,3,4-Tetrahydro-7-trifluoromethyl-1,4-diazepin-5-one (2).—A flask containing 1.98 g (0.01 mol of *N*-(2-aminoethyl)-3-hydroxy-4,4,4-trifluoro-2-butenamide (12) was heated in an oil bath at 160–170° for 0.5 hr. The reaction melted and foamed, and water vapor was evolved. After being heated for 15 min the melt solidified. The yield was almost quantitative. Recrystallization from methanol afforded 0.85 g (47%) of pure diazepinone 2: mp 191–192° (lit.[3] mp 191.5–192.5°); ir (KBr) 1650 and 1560 cm^{-1} (amide C=O); in dilute $HCCl_3$ solution 3424 cm^{-1} (*cis*-amide and *sec*-amide NH); nmr (in acetone-d_6) δ 7.33 (broad s, 1 H, amide NH), 6.92 (broad s, 1 H, amine NH), 4.93 (s, 1 H, vinyl), 3.48 (m, 4 H, ring methylene.)

Ethyl 2-(Trifluoromethyl)-2-imidazolidineacetate (3).—A solution of 6.0 g (0.1 mol) of 1,2-diaminoethane in 10 ml of benzene was added, over a period of 0.5 hr, to 18.4 g (0.1 mol) of 1 dissolved in 100 ml of refluxing benzene. The reaction mixture was refluxed for 5 hr. Water was collected in a Dean–Stark tube, the solvent was removed by distillation, and the residue distilled in a short-path apparatus at 15 mm to afford 18.3 g (81%) of 3, bp 110–113° (15 mm). The distillate solidified in the receiver and was recrystallized from CCl_4: mp 40.5–41° (lit.[3] mp 40.5–41°); ir 1729, 1735 (sh), 1745 cm^{-1} (sh) (NH); nmr δ 1.26 (t, 3 H, CH_2 ester), 4.15 (q, 2 H, J = 7 Hz, CH_2 ester), 2.61 (s, 2 H, α-methylene), 3.05 (s, 4 H, ring methylenes).

Reaction of 1-Aminopentane with 1. A. Addition of Amine to Keto Ester, in Benzene. Ethyl 3-(1-Pentylamino)-4,4,4-trifluoro-2-butenoate (4).—1-Aminopentane (4.35 g, 0.05 mol) in 10 ml of benzene was added over a period of 2 hr to a solution of 9.2 g (0.05 mol) of 1 in 100 ml of refluxing benzene and the mixture heated for an additional hour. The enamine 4 was obtained: 10.8 g (86%); bp 104° (10.0 mm); $n^{25}D$ 1.4375.

Anal. Calcd for $C_{11}H_{18}F_3NO_2$: C, 52.17; H, 7.16; F, 22.51; N, 5.53. Found: C, 52.33; H, 7.34; F, 22.38; N, 5.42.

B. Addition of Keto Ester to Amine, in Benzene.—To 4.35 g (0.05 mol) of 1-aminopentane dissolved in 100 ml of refluxing benzene was added 9.2 g (0.05 mol) of 1 over a period of 1 hr and the reaction refluxed for an additional hour. After the solvent and volatile substances were removed under reduced pressure, the residue, 12.5 g (83.5%), solidified upon standing overnight. It was a waxy solid, mp 76–80°. Distillation on a short-path apparatus, bp 88–89° (6.0 mm), gave a product that did not solidify completely, $n^{25}D$ 1.4355. This was a mixture of amine salt 5 and enamine 4. When the mixture was heated at 150°, the salt was converted to the enamine, $n^{25}D$ 1.4372. The ir of this product was identical with the ir of the material prepared by method A.

C. Addition of Amine to Keto Ester, Neat. Salt of Ethyl 3-Hydroxy-4,4,4-trifluorobutenoate with 1-Aminopentane (5).—

(14) D. K. Wald and M. M. Joullié, *J. Org. Chem.*, **31**, 3369 (1966).

(15) Melting points were determined on a calibrated Thomas–Hoover apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The infrared spectra were determined on a Perkin-Elmer 521 double-beam spectrophotometer either as potassium bromide pellets or as solutions in 0.2-mm sodium chloride cells. High dilution spectra were determined in 10-mm quartz cells. Nuclear magnetic resonance spectra were determined either on a Varian Associates HA-60-EL or A-60A spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as internal standard (δ). All spectra are taken in CCl_4 unless otherwise noted. The ultraviolet spectra were obtained on a Cary 14 spectrophotometer in 1-cm quartz cells. Mass spectra were obtained on a Consolidated Electrodynamics Corp. 21-130 cycloidal mass spectrometer. Some mass spectra were recorded by the Morgan Schaffer Corp., Montreal, Canada. Vapor phase chromatographic analyses were carried out on a F & M Model 700 chromatograph with a thermal conductivity detector, helium carrier gas at a flow rate of 60 cc per min, using 6 ft long, 0.25 in. o.d. packed columns. The oven temperature was programmed at 10° per minute from 70° to the upper limit of the packing used. For preparative work, an Aerograph Autoprep A-700 instrument was employed. Solid samples were recrystallized to constant melting point and dried in an Abderhalden drying pistol *in vacuo*. Liquid samples were redistilled on a Nester–Faust NF-190 spinning-band column (6 × 450 mm, 23 theoretical plates).

(16) E. T. McBee, O. R. Pierce, H. W. Kilbourne, and E. R. Wilson, *J. Amer. Chem. Soc.*, **75**, 3152 (1953).

(17) A. L. Henne, M. S. Newman, L. L. Quill, and R. A. Staniforth, *ibid.*, **69**, 1819 (1947).

To 1.841 g (0.01 mol) of 1 in a serum-stoppered flask was added from a syringe, with stirring and cooling in ice, 0.872 g (0.01 mol) of 1-aminopentane. The reaction solidified almost immediately. Very rapid recrystallization from CCl_4 gave the pure salt **5**, mp 82.5–83.5°.

Anal. Calcd for $C_{11}H_{20}F_3NO_3$: C, 48.70; H, 7.43; F, 21.01; N, 5.16. Found: C, 48.74; H, 7.42; F, 20.89; N, 5.33.

Ethyl 3-Methoxy-4,4,4-trifluoro-2-butenoate (6).—A solution of 18.4 g (0.1 mol) of 1 in 50 ml of ether was treated with an excess of diazomethane prepared from 22 g of Du Pont ERX-101. The yellow solution was left standing overnight. The ether was removed by evaporation under nitrogen and the residue distilled, to give 16.7 g (85%) of **6**: bp 85–86° (90 mm); $n^{25}D$ 1.3834; vpc on SF-1265 column indicated 99+% purity; ir 1730 (C=O), 1667 (C=C), 1250, 1030 (CO vinyl ether), 1295 and 1155 (CO unsaturated ester), 1200 cm^{-1} (CF_3); nmr (neat) δ 5.78 (s, 1 H, vinyl) 4.05 (s, 3 H, OCH_3), 4.20 (2 H, J = 7 Hz, CH_2 ester), 1.28 (t, 3 H, J = 7 Hz, CH_3 ester).

Anal. Calcd for $C_7H_9F_3O_3$: C, 42.43; H, 4.58; F, 28.77. Found: C, 42.61; H, 4.75; H, 28.52.

Ethyl 3-Methoxy-3-(1-pentylamino)-4,4,4-trifluorobutanoate (7).—To 1.982 g (0.01 mol) of ice-cold **6**, 1-aminopentane (0.872 g, 0.01 mol) was added with stirring and cooling. The product formed was analyzed without any further purification: $n^{25}D$ 1.4222; ir 3370 (NH), 1730 cm^{-1} (C=O); nmr δ 3.28 (s, 3 H, OCH_3), 2.65 (s, 2 H, α-methylene).

Anal. Calcd for $C_{12}H_{22}F_3NO_3$: C, 50.52; H, 7.77; F, 19.98; N, 4.91. Found: C, 50.48; H, 7.49; F, 20.14; N, 4.97.

Upon attempted distillation or vapor phase chromatography, the compound lost methanol and was converted to **4**. Loss of methanol also occurred upon standing at room temperature for 2 or 3 days.

Ethyl 3-Keto-4,4,5,5,5-pentafluoropentanoate (8).—To a suspension of 0.5 mol of sodium hydride dispersion (in mineral oil) in 200 ml of anhydrous ether was added slowly, and with cooling, 96 g (0.5 mol) of ethyl perfluoropropanoate, followed by 44 g (0.5 mol) of ethyl acetate. The reaction was refluxed overnight, cooled, and poured onto a mixture of 300 g of ice and 30 ml of concentrated sulfuric acid. The ether layer was separated and the aqueous solution extracted three times with 100-ml portions of ether. The combined ether extracts were distilled (200 mm) to remove the ether; the residue was poured into a solution of 100 g of cupric acetate in 500 ml of water. The precipitated bis(ethyl pentafluoropropionoacetate)copper(II) was dried *in vacuo*, washed with petroleum ether to remove the mineral oil, and dried: yield, 100 g (76%); mp 154–155°.

Anal. Calcd for $C_{14}H_{12}CuF_{10}O_6$: C, 31.86; H, 1.91; F, 36.00. Found: C, 32.04; H, 2.25; F, 35.69.

The copper chelate was suspended in 200 ml of anhydrous ether, treated with hydrogen sulfide until all copper precipitated, and filtered through "Super Cel." The ether was evaporated and the residue distilled on a spinning-band column to yield 76.7 g (87%) of **8**: bp 142°; $n^{25}D$ 1.3630; ir 1670 and 1650 (sh) (C=O), also strong bands at 1250, 1220, and 1110 cm^{-1}.

Anal. Calcd for $C_7H_7F_5O_3$: C, 35.91; H, 3.02; F, 40.57. Found: C, 36.10; H, 3.08; F, 40.82.

Reaction of 1,2-Diaminoethane with Ethyl 3-Keto-4,4,5,5,5-pentafluoropentanoate. A. Addition of Amine to Keto Ester.—To a solution of 12.0 g (0.051 mol) of **8** in 80 ml of refluxing benzene was added dropwise, during 2 hr, 3.0 g (0.05 mol) of 1,2-diaminoethane dissolved in 20 ml of benzene. The reaction mixture was refluxed overnight and cooled to produce 5.9 g of a white solid which was redissolved in benzene, 1.2 g (9.7%) being insoluble. The insoluble material, *N*-(2-aminoethyl)-3-hydroxy-4,4,5,5,5-pentafluoro-2-pentenamide (**10**), was recrystallized from methanol: mp 202–206° dec; ir (KBr) 3400–2400 ($^+NH_3$), 3250 (amide ^+NH), 1645, 1630 (C=O), 1530 ($^+NH_3$), and also bands at 1565, 1250, and 740 cm^{-1}.

Anal. Calcd for $C_7H_9F_5N_2O_2$: C, 33.88; H, 3.65; F, 38.28; N, 11.29. Found: C, 34.04; H, 3.73; F, 38.32; N, 11.11.

The soluble part, 4.6 g (32%) of ethyl 3-hydroxy-4,4,5,5,5-pentafluoro-2-pentenoate salt with 1,2-diaminoethane (**11**), was again recrystallized from benzene, mp 117–117.5°.

B. Addition of Keto Ester to Amine.—To 3.0 g (0.05 mol) of 1,2-diaminoethane dissolved in 100 ml of refluxing benzene was added a solution of 12.0 g (0.051 mol) of **8** in 10 ml of benzene. A precipitate formed immediately upon addition of the first few drops of keto ester. The mixture was refluxed for 48 hr and cooled to afford 5.5 g of solid, which was separated with hot benzene into 4.0 g (32%) of **10** and 1.5 g (10%) of **11**. The benzene filtrate was evaporated and the residue distilled on a short-path apparatus, to yield 3.6 g (26%) of imidazolidine **9**.

Ethyl 3-Hydroxy-4,4,4-trifluoro-2-butenoate Salt with 1,2-Diaminoethane (12).—To a solution of 1.841 g (0.01 mol) of **1** in 10 ml of CCl_4 was added, with stirring and cooling in ice, 0.629 g (0.0105 mol) of 1,2-diaminoethane. The solid that formed was left in the ice bath for 1 hr, collected, washed with CCl_4, and dried. A salt (**12**) 2.24 g (91%), mp 84.5–86°, was obtained. The analytical sample was recrystallized from chloroform: mp 86.5–87.5°; ir (KBr) 3360, 3290 (bonded NH_2), 1700, 1660, 1630 (C=O, free and bonded), and also strong bands at 1270, 1180, and 1120 cm^{-1}; nmr ($DCCl_3$) δ 5.12 (s, 5 H, $^+NH_3$), 5.04 (s, 1 H, vinyl), 2.90 (s, 4 H, methylene), 4.04 (q, 2 H, J = 7 Hz, CH_2 ester), and 1.22 (t, 3 H, J = 7 Hz, CH_3 ester).

Anal. Calcd for $C_8H_{15}F_3N_2O_3$: C, 39.36; H, 6.19; F, 23.34; N, 11.46. Found: C, 39.56; H, 6.20; F, 23.18; N, 11.60.

***N*-(2-Aminoethyl)-3-hydroxy-4,4,4-trifluoro-2-butenamide (13).**—A solution of 4.6 g (0.025 mol) of **1** and 1.5 g (0.025 mol) of 1,2-diaminoethane in 25 ml of cold chloroform was allowed to stand at room temperature. A white crystalline precipitate began to form and continued to increase over a period of 2 weeks. The amide salt **13**, 3.55 g (72%), was collected in several crops. The analytical sample was recrystallized from methanol: mp 163–164° dec (with gas evolution); ir (KBr) 1630 (C=O) and strong bands at 1240, 1180, and 1105 cm^{-1}.

Anal. Calcd for $C_6H_9F_3N_2O_2$: C, 36.37; H, 4.58; F, 28.77; N, 14.44. Found: C, 36.61; H, 4.67; F, 28.69; N, 14.05.

Reaction of 1,2-Diaminopropane with 1. A. Addition of 1 to Amine.—To 7.4 g (0.1 mol) of 1,2-diaminopropane dissolved in 100 ml of refluxing benzene was added over a period of 1 hr a solution of 18.4 g (0.1 mol) of **1** in 15 ml of benzene. The reaction was refluxed overnight and during this time 3.0 ml of lower phase were collected. A white precipitate suspended in solution was recovered by filtration to afford 3.1 g (14.5%) of the amide salt **15**, mp 189.5–190.5°. The analytical sample was recrystallized from methanol, mp 190–190.5°.

Anal. Calcd for $C_7H_{11}F_3N_2O_2$: C, 39.63; H, 5.23; F, 26.86; N, 13.20. Found: C, 39.84; H, 5.43; F, 26.66; N, 13.42.

The benzene filtrate was distilled and the residual oil fractionated on a short-path distillation apparatus at 6-mm pressure; 9.7 g (40.5%) of **14** was collected, bp 91–97°. This compound was redistilled on a spinning-band column, bp 93–94° at 10-mm pressure, $n^{25}D$ 1.4172.

Anal. Calcd for $C_9H_{15}F_3N_2O_2$: C, 45.00; H, 6.29; F, 23.73; N, 11.66. Found: C, 45.09; H, 6.51; F, 23.48; N, 11.78.

B. Addition of Amine to 1. Preparation of Ethyl 4-Methyl-2-(trifluoromethyl)-2-imidazolidineacetate (14).—To a solution of 18.4 g (0.1 mol) of **1** in 90 ml of refluxing benzene was added over a period of 1 hr 7.4 g (0.1 mol) of 1,2-diaminopropane dissolved in 10 ml of benzene. The reaction was refluxed for 3 hr; 2.2 ml of lower phase were collected. The benzene was removed by distillation and the residue left standing overnight. A trace of amide salt **15** crystallized and was removed by filtration (200 mg). The filtrate was distilled on a short-path distillation apparatus at 6-mm pressure and 16.35 g (68%) of the imidazolidine **14**, bp 95–96°, was collected. This sample was redistilled on a spinning-band column.

Preparation of Ethyl 4,5-Dimethyl-2-(trifluoromethyl)-2-imidazolidineacetate (17).—The above compound was prepared from 8.8 g (0.1 mol) of 2,3-diaminobutane and 18.4 g of **1** according to procedure B.

Preparation of 1,2,3,4-Tetrahydro-2-methyl-7-trifluoromethyl-1,4-diazepin-5-one (16).—*N*-(2-Aminopropyl)-4,4,4-trifluoro-3-hydroxy-2-butenamide (**3**) 2.12 g (0.01 mol), was heated in an erlenmeyer flask at its melting point for 15 min. The mixture foamed and water vapor was evolved. It was cooled, dissolved in chloroform, and left to crystallize; 1.4 g (72.5%) of colorless crystals, mp 135–136°, were obtained. The analytical sample was recrystallized from chloroform, mp 135.5–136°.

Anal. Calcd for $C_7H_9F_3N_2O$: C, 43.30; H, 4.67; F, 29.36; N, 14.43. Found: C, 43.43; H, 4.75; F, 29.58; N, 14.33.

Reaction of 1,3-Diaminopropane with 1. A. Addition of Keto Ester to Amine.—To 7.4 g (0.1 mol) of 1,3-diaminopropane dissolved in 100 ml of refluxing benzene was added over a period of 2 hr 18.4 g (0.1 mol) of **1** dissolved in 15 ml of benzene. The reaction turned turbid and a white precipitate formed. The mixture was heated overnight. The solid formed was collected by filtration to give 5.4 g (25.4%) of **20**, mp 181–183°. The compound was recrystallized from methanol, mp 183–184°.

Anal. Calcd for $C_7H_{11}F_3N_2O_2$: C, 39.63; H, 5.23; F, 26.86; N, 13.20. Found: C, 39.88; H, 5.31; F, 26.91; N, 13.26.

The benzene filtrate was distilled and a semisolid was obtained, bp 74–80° (1.55 mm). This material was dissolved in CCl_4 and placed in a refrigerator to crystallize. A solid, **21**, was obtained, 5.5 g (36%), mp 110–111° (lit.[13] mp 110–111°).

Anal. Calcd for $C_5H_7F_3N_2$: C, 39.48; H, 4.64; F, 37.47; N, 18.41. Found: C, 39.50; H, 4.80; F, 37.25; N, 18.39.

The carbon tetrachloride filtrate was distilled. It contained ethyl 2-(trifluoromethyl)-2-perhydropyrimidineacetate (**22**) which could not be obtained analytically pure by this method.

Ethyl 2-(Trifluoromethyl)-2-perhydropyrimidineacetate (22).—To a solution of 18.4 g (0.1 mol) of **1** in 120 ml of refluxing benzene was added over a 1-hr period 7.4 g (0.1 mol) of 1,3-diaminopropane dissolved in 20 ml of benzene. The reaction was refluxed overnight. The benzene was removed by distillation and the residual oil was distilled on a short-path apparatus at 2-mm pressure to yield 13.45 g (56%) of **10**, bp 84–85° (2 mm), $n^{25}D$ 1.4285.

Anal. Calcd for $C_9H_{15}F_3N_2O_2$: C, 45.00; H, 6.29; F, 23.73; N, 11.66. Found: C, 44.75; H, 6.09; F, 23.66; N, 11.91.

Reaction of 2-Aminoethanol with 1. General Procedure. Ethyl 2-(trifluoromethyl)-2-oxazolidineacetate (23). A. Addition of Amine to Keto Ester.—To a solution of 18.4 g (0.1 mol) of **1** in 80 ml of refluxing benzene was added over a period of 1 hr 6.1 g (0.1 mol) of 2-aminoethanol. The reaction mixture was heated for 5 hr. The benzene was removed by distillation and the residue distilled on a short-path apparatus.

B. Addition of Keto Ester to Amine.—To 6.1 g (0.1 mol) of 2-aminoethanol was added slowly 2 ml of glacial acetic acid followed by 18.4 g (0.1 mol) of **1**. The mixture was heated at 130° for 2 hr and then distilled on a short-path apparatus to yield 9.7 g (43%) of **23**.

Procedure A was used to prepare the other oxazolidines shown in Table I (**23–27**). The yields obtained varied from 55 to 75%. Cysteine was condensed by the same procedure to yield 45% of ethyl 4-carboxy-2-trifluoromethyl-2-thiazolidineacetate (**28**, Table I).

Reaction of 1 with 3-Aminopropanol. Preparation of Ethyl 2-Trifluoromethyl-2-(1,3-oxazine)acetate (29).—To a solution of 18.4 g (0.1 mol) of **1** in 80 ml of refluxing benzene was added over a period of 1 hr 7.5 g (0.1 mol) of 3-aminopropanol. The reaction was refluxed overnight, the benzene removed by distillation, and the residue distilled on a short-path apparatus to yield 18.4 g (76%) of the oxazine **29**, bp 85–90° (3.5 mm). The compound was redistilled on a spinning-band column, bp 104–104.5° (15 mm), $n^{25}D$ 1.4117.

Anal. Calcd for $C_9H_{10}F_3NO_3$: C, 44.81; H, 5.85; F, 23.63; N, 5.81. Found: C, 44.59; H, 5.80; F, 23.72; N, 5.79.

Reaction of 23 with Methylmagnesium Iodide.—To a Grignard solution prepared from 4.8 g (0.2 g-atom) of Mg turnings and 28.4 g (0.2 mol) of iodomethane in 150 ml of anhydrous ether, a solution of 5.7 g (0.024 mol) of **23** in 15 ml of ether was added dropwise. The reaction was refluxed for 2 hr and allowed to stand overnight. The magnesium salt was decomposed with saturated ammonium chloride solution, and the ether layer separated and evaporated. The residue was distilled on a short-path apparatus to yield 13.5 g (89%) of ethyl 3-(2-hydroxyethylamino)-4,4,4-trifluoro-2-butenoate: bp 95–96° (1.5 mm); mp 23–24°; $\lambda_{max}^{C_6H_{14}}$ 285 mμ (log ε 4.18).

Anal. Calcd for $C_8H_{12}F_3NO_3$: C, 42.29; H, 5.33; F, 25.09; N, 6.17. Found: C, 42.47; H, 5.54; F, 24.92; N, 6.25.

A solution of 1.63 g (0.0072 mol) of ethyl 3-(2-hydroxyethylamino)-4,4,4-trifluoro-2-butenoate in 10 ml of benzene was refluxed and the progress of cyclization to **23** was followed. After 3 hr, only 5% of **23** was present, after 24 hr, 35% was observed. After 48 hr, about 60% of **23** was formed. This rate of formation of **23** is much slower than the rate observed for the condensation of **1** with 1-aminoethanol.

***tert*-Butyl 3-Keto-4,4,4-trifluorobutanoate (30).**—This ester was obtained by the method used for **1**, but as a hydrate, mp 69.5–70°, yield 56%. All attempts to dehydrate it resulted in decomposition. It was sublimed under reduced pressure to obtain an analytically pure sample.

Anal. Calcd for $C_8H_{11}F_3O_3H_2O$: C, 41.74; H, 5.69; F, 24.76. Found: C, 41.75; H, 5.89; F, 24.98.

The copper chelate of **30** was obtained in the usual manner, mp 141.5–142°.

Anal. Calcd for $C_{16}H_{20}F_6O_6Cu$: C, 39.55; H, 4.15; F, 23.46. Found: C, 39.80; H, 4.30; F, 23.34.

Ethyl 3-Keto-2-methyl-4,4,4-trifluorobutanoate (31).—This ester was also prepared by the method used for **1**: yield 50.2%; bp 85° (100 mm); $n^{25}D$ 1.3693 [lit.[18] bp 57.8 (26 mm); $n^{20}D$ 1.3650]. The copper chelate of **31** was obtained in the usual manner, mp 137–137.5°.

Anal. Calcd for $C_{14}H_{16}F_6O_6Cu$: C, 36.73; H, 3.52; F, 24.90. Found: C, 36.54; H, 3.54; F, 24.72.

Ethyl 2,2-Dimethyl-3-keto-4,4,4-trifluorobutanoate (32).—To a sodium amalgam, prepared from 14 g of sodium and 1 kg of mercury, was added under a stream of nitrogen, a solution of 70 g (0.25 mol) of triphenylchloromethane in 1.5 l. of anhydrous ether.[19] This mixture was shaken mechanically for 3 hr. The red solution was allowed to settle and was siphoned (under exclusion of air) into a nitrogen-swept erlenmeyer flask. Ethyl isobutyrate (24.0 g, 0.21 mol) and ethyl trifluoroacetate (28.4 g, 0.20 mol) were added and the solution was stirred magnetically for 1 hr. Glacial acetic acid (30 ml) and 100 ml of water were added to the solution. The ether layer was separated, washed, dried, and reduced in volume. The triphenylmethane formed was removed by filtration and the filtrate distilled on a spinning-band column to yield a pure sample of 32 g, bp 144.5–145.5°, $n^{25}D$ 1.3674.

Anal. Calcd for $C_8H_{11}F_3O_3$: C, 45.29; H, 5.23; F, 26.86. Found: C, 45.26; H, 5.19; F, 26.58.

When a solution of 10.3 g (0.0486 mol) of **32** in 100 ml of refluxing benzene was added dropwise to a solution of 3.0 g (0.05 mol) of 1,2-diaminoethane in 7 ml of benzene and the reaction mixture heated in the usual manner, no water separated. Evaporation of the benzene yielded a white solid identified as *N,N'*-bistrifluoroacetyl-1,2-diaminoethane, mp 202–202.5° (lit.[20] mp 201.5–202.5°). The presence of ethyl isobutyrate in this reaction and in the condensation of **20** with 2-aminoethanol indicated a reverse Claisen reaction.

Registry No.—**2**, 14120-51-5; **3**, 14120-52-6; **4**, 26717-82-0; **5**, 26717-83-9; **6**, 26717-84-0; **7**, 2617-85-1; **8**, 26717-86-2; **8** (copper chelate), 26785-67-1; **9**, 26717-87-3; **10**, 26717-88-4; **11**, 26717-89-2; **12**, 26717-90-8; **13**, 26717-91-9; **14**, 26717-92-0; **15**, 26717-93-1; **16**, 26717-94-2; **17**, 26717-95-3; **18**, 26717-96-4; **19**, 26717-97-5; **20**, 26717-98-6; **22**, 26717-99-7; **23**, 26718-00-3; **24**, 26718-01-4; **25**, 26717-71-5; **26**, 26717-72-6; **27**, 26717-73-7; **28**, 26717-74-8; **29**, 26785-70-6; **30**, 26717-75-9; **30** (copper chelate), 26736-15-2; **31** (copper chelate), 26736-16-3; **32**, 26717-76-0; ethyl 3-(2-hydroxyethylamino)-4,4,4-trifluoro-2-butenoate, 26717-77-1.

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