reaction mixture was shown to be the unchanged bromo ether by comparison of both the vapor-phase chromatograms and the infrared spectra[41] of the samples. In each instance the infrared spectra of the pure bromo ether and the recovered sample were superimposable, indicating that significant epimerization of the bromo ether had not occurred.

In subsequent experiments, where no bromo ether was recovered, mixtures of 4.5 g. (0.02 mole) of the bromo ether, 5.2 g. (0.08 gram-atom) of zinc powder, 20 ml. of ethanol and 2 ml. of water were refluxed with stirring for 6 hr. The octene mixtures were isolated and analyzed as previously described.

B. Reaction with Sodium.—Mixtures of 4.5 g. (0.02 mole) of the bromo ether, 1 g. (0.04 gram-atom) of sodium (cut into small pieces) and 20 ml. of tetrahydrofuran (distilled from sodium) were refluxed with stirring for 6 hr., filtered and distilled. The 4-octene mixtures were collected and analyzed as previously described. A small forerun obtained in each distillation consisted of a mixture of the 4-octenes (not included in the yield reported) and tetrahydrofuran. Since the composition of the olefin mixtures in the foreruns was essentially the same (within ±1%) as the composition of the olefin mixtures isolated, no error in olefin composition was introduced by this procedure.

Reaction of the 1-Bromo-1,2-diphenyl-2-methoxyethanes with Zinc.—Mixtures of 291 mg. (0.001 mole) of the bromo ether, 654 mg. (0.01 gram-atom) of zinc powder, 24 ml. of ethanol and 1 ml. of water were refluxed with stirring for the specified times (Table I), poured into aqueous ammonium chloride and extracted with ether. After the ether extract had been dried over magnesium sulfate and concentrated, a solution of the residue in petroleum ether was chromatographed on Merck acid-washed alumina. The hydrocarbon fractions, eluted with petroleum ether, were combined and the infrared spectrum[39] of the crude product was determined. These spectra were compared with spectra[39] of *cis*- and *trans*-stilbene which have distinctive bands at 920 and 965 cm.$^{-1}$, respectively. In no case could *cis*-stilbene be detected in the product; the maximum amount of *cis*-stilbene which would escape detection by this method was estimated to be 4%. The olefin yields reported in Table I represent the amount of crude *trans*-stilbene, melting within the range 117–124°, which was isolated from each hydrocarbon fraction. The later fractions from the chromatogram proved to be oils. In one reaction of the *erythro*-bromo ether VII (Table I) a small amount of the crude *erythro*-bromo ether VII, m.p. 110–117°, was recovered. Also, in one reaction of the *threo*-bromo ether the infrared spectrum of the crude oil from the later fractions of the chromatogram was obtained. No *cis*-stilbene could be detected in the oil whose spectrum would be consistent with presence of the *erythro*-bromo ether VII. Thus, the possibility that partial epimerization of the bromo ethers VII occurs prior to elimination is not excluded.

As a control experiment to establish that *cis*-stilbene is not isomerized to *trans*-stilbene under the conditions of the reaction, a mixture of 180 mg. (0.001 mole) of *cis*-stilbene, 167 mg. (0.001 mole) of *threo*-2-bromo-3-methoxybutane, 654 mg. (0.01 gram-atom) of zinc powder, 24 ml. of ethanol and 1 ml. of water was refluxed for 70.5 hr. and worked up as described above. The infrared spectrum[39] of crude hydrocarbon fraction (242 mg.) from the chromatogram was very similar to the spectrum of *cis*-stilbene. The maximum amount of *trans*-stilbene which could have been present in the mixture was estimated to be 2%.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE FLORIDA STATE UNIVERSITY]

Chemical Effects of the Trifluoromethyl Group.[1,2] V. Reactions of Ethyl β-Trifluoromethylglycidate; the Synthesis of 2-Amino-3-hydroxy-4,4,4-trifluorobutyric Acid

BY H. M. WALBORSKY AND M. E. BAUM

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2-Amino-3-hydroxy-4,4,4-trifluorobutyric acid (III) was synthesized by reducing the phenylhydrazone of 2-keto-3-hydroxy-4,4,4-trifluorobutyric acid (II). Ammonolysis of ethyl β-trifluoromethylglycidate (VI) gave as the sole product the amide of III. This is in direct contrast to the products obtained by ammonolysis of other glycidic ester derivatives. This reversal of ring opening is due to the strong electron-withdrawing power of the CF_3 group. $LiAlH_4$ reduction of VI did not lead to a mixture of glycols but yielded exclusively 4,4,4-trifluorobutan-1,3-diol.

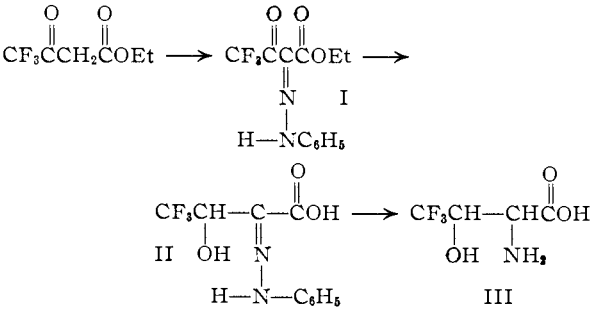
Introduction

Because of the potential antimetabolic activity[3] of amino acids containing the CF_3 group a number of these acids have been prepared.[2-4] In the course of their syntheses some unique chemical effects attributable to the CF_3 group have been observed and discussed.[2-4]

In continuation of these studies the synthesis of the CF_3 analog of threonine has been attempted. Owing to the strong electron-withdrawing power of the CF_3 group, the preparation of 2-amino-3-hydroxy-4,4,4-trifluorobutyric acid (III) by ammonolysis of ethyl β-trifluoromethylglycidate was made possible. In the present paper, the synthesis of III is described and the effect of the CF_3 group is discussed.

Results and Discussion

Syntheses of 2-Amino-3-hydroxy-4,4,4-trifluorobutyric Acid (III). Method A.—Ethyl trifluoroacetoacetate was diazotized with benzenediazonium chloride in 62% yield. The crude material contained a small amount of red impurity

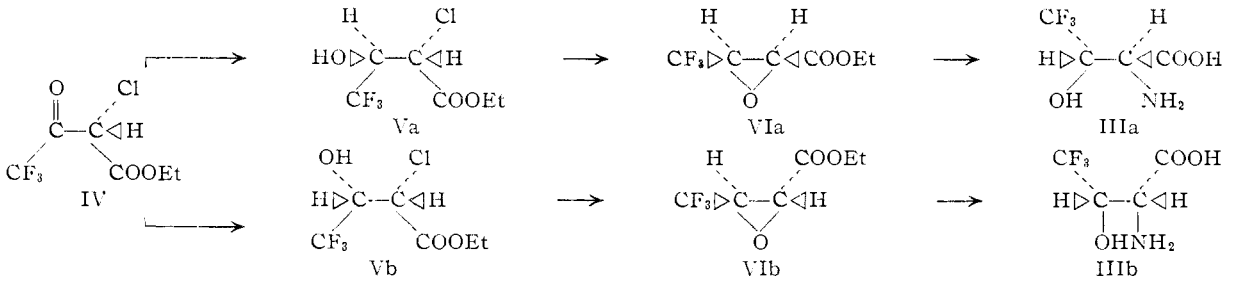


(1) This investigation was supported by a research grant, number C-1461, from The National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) (a) Presented in part before the Division of Organic Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956; (b) Paper IV of this series: H. M. Walborsky and J. Lang, THIS JOURNAL, **78**, 4314 (1956).

(3) H. M. Walborsky, M. Baum and D. F. Loncrini, *ibid.*, **77**, 3637 (1955).

(4) H. M. Walborsky and M. Schwarz, *ibid.*, **75**, 3241 (1953); H. M. Walborsky and M. E. Baum, *J. Org. Chem.*, **21**, 538 (1956).



which could be removed by treatment with an ethereal solution of stannous chloride. A minor product isolated from the diazotization reaction was shown to be the phenylhydrazone of ethyl glyoxalate.

Reduction of I by sodium borohydride in methanol yielded a mixture of the ethyl (6.2%) and methyl (35.4%) esters of II, the latter being formed by *trans* esterification by the solvent during the course of the reduction. Saponification of the individual esters to their corresponding acids resulted in the formation from the methyl ester of an acid m.p. 146–147° and from the ethyl ester of an acid m.p. 162–163°. That these acids (II) are geometric isomers is based on the following: (1) The ultraviolet spectra of the two acids and their corresponding esters are very similar to the spectrum of the phenylhydrazone of 2-keto-3-hydroxybutyric acid[5] (see Experimental). (2) Geometric isomerism is often observed in phenylhydrazone formation.[6] (3) Reduction (*vide infra*) of both acids gave the same amino acid III.

Catalytic reduction of the isomeric acids proceeded to give about 30% yield of the amino acid III and 30% yield of another product. Important to note, however, is that both isomeric acids produced the same amino acid as shown by melting point and mixed melting point of the amino acids themselves and of their N-benzoyl derivatives. The infrared spectra were also identical.

From the catalytic reduction a 30% yield of another product was isolated which proved to be the cyclohexylamine salt of II. The cyclohexylamine probably arose from reduction of aniline that is formed by hydrogenolysis of II or by hydrogenolysis of the cyclohexylhydrazine derivative of II that may have been formed during the reduction. Authentic samples of the stereoisomeric salts were prepared and shown to be identical with those isolated from the reduction mixture.

It was thought that the yield of amino acid in catalytic reduction stage might be materially increased if an acid were added to tie up the cyclohexylamine that is formed during the reduction. There resulted however, only a slight increase in yield of the amino acid from 30 to 39%.

Method B. Attempted Asymmetric Synthesis.—The synthesis of the trifluoro analogs of threonine and allothreonine offers somewhat more than the usual difficulty because of the presence of two asymmetric centers in the molecule. Since they are adjacent to each other, a synthesis that would introduce the second asymmetric group in the presence of the first should lead to an asymmetric synthesis in a manner predictable according to Cram's Rule of Asymmetric Induction.[7] This in turn should be of assistance in assigning the structural relationship of the amino acids that are eventually formed, provided that the mechanisms of the subsequent reactions are understood. The following reaction scheme shown illustrates the proposed syntheses.

This reaction scheme can only be possible if certain conditions are met: (1) The reduction by sodium borohydride should follow Cram's Rule of Asymmetric Induction to yield predominantly Vb. (2) The ring closure of Va and Vb must occur in a stereospecific manner to produce VIa and VIb. (3) The ammonolysis of the glycidic ester must occur by a stereospecific *trans* opening of the oxide ring at the α-carbon atom to yield the α-amino-β-hydroxy acid and not the β-amino-α-hydroxy acid.

Reduction by Sodium Borohydride.—Ethyl 2-chloro-3-keto-4,4,4-trifluorobutyrate[8] (IV) was prepared in 87% yield. This was followed by reduction to the chlorohydrin esters by sodium borohydride in 26% yield of pure isomers. Distillation in a Podielniak column separated the mixture into two isomers, boiling at 87.5 and 93.0° (11 mm.). The ratio of low to high boiling isomers was seven to four. On the basis of Cram's rule, where H is small, Cl the medium sized group and the carbethoxy the large group, the more abundantly formed isomer, in this case the low boiling one (Vb), has the *erythro* structure.

Ring Closure to Glycidic Ester.—The ring closure of the chlorohydrin ester to the glycidic ester with base should be a stereospecific inversion,[9] so that the glycidic ester formed from the *erythro* isomer Vb would have the *trans* configuration (VIb) and that from the *threo*-chlorohydrin ester Va the *cis* configuration.

However, ring closure by sodium hydride of the chlorohydrin esters Va and Vb produced the same glycidic ester as shown by the boiling point, index of refraction, infrared absorption spectra and the formation of identical glycidic amides. Apparently sodium hydride caused isomerization to the more stable isomer to occur, presumably the *trans*, by the abstraction of the α-hydrogen of VI. The isomerization of glycidic ketones with base has recently been studied by Cromwell and Setterquist,[10] and the mechanism of this isomerization discussed.

(5) R. E. Bowman and C. S. Franklin, *J. Chem. Soc.*, 1583 (1957).
(6) L. J. Simon, *Compt. rend.*, **131**, 682 (1900).
(7) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 3022 (1952).
(8) H. H. Hill, E. B. Towne and J. B. Dickey, *ibid.*, **72**, 3289 (1950).
(9) S. Winstein and H. J. Lucas, *ibid.*, **61**, 1576 (1939); H. J. Lucas and C. W. Gould, *ibid.*, **63**, 2541 (1941).
(10) N. H. Cromwell and R. A. Setterquist, *ibid.*, **76**, 5752 (1954).

It is of interest to note that when aqueous ammonia, a weaker base than sodium hydride, was used to form the epoxide ring from the isomeric chlorohydrins the identical glycidic amides were obtained. The effect of the weaker base may have been cancelled out by the change of solvent from ether to water, the latter being a better solvator of ions.

Since both the Darzens reaction[11] and the sodium hydride closing of the chlorohydrin ester[12] to the glycidic ester involve a common intermediate, namely, the chloro alcoholate anion, any indication of the nature of the product from the Darzens reaction would serve as a guide in formulating a tentative structure of the fluorinated glycidic ester. English and Heywood[12] have found that the Darzens condensation product of *n*-butyraldehyde and ethyl chloroacetate had the *trans* configuration, by relating it to *erythro*-ethyl α,β-dihydroxycaproate which was prepared by unambiguous means. This seems to indicate that under the equilibrating conditions of this reaction the thermodynamically more stable *trans* isomer is formed. Cromwell and Setterquist also obtained *trans*-*o*-nitrobenzalacetophenone oxide[13] in high yield from a Darzens condensation. Accordingly, the *trans* configuration has tentatively been assigned to the fluorinated glycidic ester VIb. Since the opening of epoxides with ammonia is stereospecific in a *trans* sense,[14] the amino acid derived from this reaction should have the *erythro* structure.

Ammonolysis.—There still exists the question of whether the α-amino-β-hydroxy, the β-amino-α-hydroxy or a mixture of these two isomers was formed. The early literature gives scant information on the direction of opening of glycidic esters by ammonia and amines.[15] Some of the results reported are in dispute[16] and in the main the results have not been critically examined. Recent work,[17] however, indicates that ammonia and amines attack the β-carbon of the glycidic esters to yield α-hydroxy-β-amino amides.

When ethyl β-trifluoromethylglycidate (VI) was treated with ammonium hydroxide and ammonium carbonate[18] the amino acid was isolated directly, rather than the amide, and shown to be identical with the amino acid obtained from the reduction of ethyl 2-phenylazo-3-hydroxy-4,4,4-trifluorobutyrate. In contrast to the work of Martynov[17] the attack by ammonia is at *the α-carbon of the glycidic ester.* Treatment of the chlorohydrin ester V or the glycidic ester VI with ammonia produced the α-amino-β-hydroxy-4,4,4-trifluorobutyramide (VII) which upon acid hydrolysis yielded the identical amino acid produced previously as shown by infrared spectra, melting points and mixed melting points of the N-benzoyl derivatives.

Although the α-amino-β-hydroxy acid or amide was the sole product isolated from the ammonolysis of the glycidic ester, it was thought desirable to search for the isomeric α-hydroxy-β-amino compound. Since the trifluoromethyl group has been shown to have a profound effect on adjacent basic or acidic groups, it would therefore be possible to separate the isomers by means of preferential elution from an ion exchange column. The pK_1 and pK_2's of various ω-trifluoromethylamino acids have been reported.[2] 2-Amino-4,4,4-trifluorobutyric acid and 3-amino-4,4,4-trifluorobutyric acid were shown to differ in base strengths by a factor greater than 10^2 in the expected order. The effect of the CF_3 group on the adjacent hydroxyl is best illustrated by the ability of trifluoroethanol to decompose sodium carbonate. The secondary hydroxyl group in 2-amino-3-hydroxy-4,4,4-trifluorothreonine was shown to have pK_3 12.7.

The reaction of ethyl β-trifluoromethylglycidate with concentrated ammonium hydroxide at room temperature yielded the theoretical amount of the aminohydroxybutyramide. The 2-hydroxy-3-amino amide should have an essentially neutral hydroxyl group and a relatively weak basic amino group. The isomer with the reverse orientation should possess a weakly acidic alcohol group and a normally basic amino group. On a sulfonated ion exchange column, IR-120, the former compound may be weakly absorbed and toward a quaternary ion-exchange column (Dowex 1-x10), be inert. The latter compound, on the contrary, would be strongly absorbed on the sulfonated resin and probably weakly so by the quaternary resin. Passage of 0.280 g. of the crude amide through Dowex 1-x10 with a large volume of water eluted only 0.002 g. The material on the column was then removed as the hydrochloride with dilute hydrochloric acid in 83% yield. The hydrochloride was then passed through IR-120 and only 0.003 g. was found in the water wash. The material was then eluted from the column at a *p*H of 10 with dilute ammonium hydroxide. The retention on Dowex 1-x10 illustrates that the material contains an acidic group, which can only be ascribed to a hydroxyl group adjacent to the CF_3. Not more than 0.002 g., less than 1%, could have the reverse orientation.

A portion of the crude amide was put on IR-120 column and upon elution with water and ammonium hydroxide there was obtained a total of 0.008 g. (4.5%) from 0.178 g. of the amide. When the ammonium hydroxide eventually raised the *p*H of the elutes to 11, there was eluted 0.142 g., which was crystallized to give the same material obtained by crystallization of the crude amide.

From these experiments an upper limit of 4.5% could be set to the amount of material reacting to give the 2-hydroxy-3-amino compound by attack

(11) M. Ballester and P. D. Bartlett, THIS JOURNAL, **75**, 2042 (1953).

(12) W. C. Woodland, R. B. Carlin and J. C. Warner, *ibid.*, **75**, 5840 (1953).

(13) However, upon prolonged treatment with sodium methoxide, the *trans* isomer was converted to the *cis*. This does not invalidate the conclusion that the *trans* isomer is the expected product, because under the conditions of this experiment the *cis* isomer was insoluble in the medium and precipitated out of solution.

(14) W. S. Emerson, THIS JOURNAL, **67**, 516 (1945); A. J. Castro and C. R. Noller, *ibid.*, **68**, 203 (1946); R. Ghirardelli and H. J. Lucas, *ibid.*, **79**, 734 (1957).

(15) M. S. Newman and B. V. Magerlein in "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 424; S. Winstein in "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 35.

(16) O. von Schickh, *Ber.*, **69**, 941 (1936); *C. A.*, **28**, 260 (1934).

(17) V. F. Martynov, Zh. D. Vasyutina and L. P. Nikulina, *Zhur. Obshchei Khim.*, **26**, 1405 (1956), and earlier papers in this series.

(18) N. D. Cheronis and K. H. Spitzmueller, *J. Org. Chem.*, **6**, 349 (1941).

of ammonia at the β-carbon of the glycidic ester.

The glycidic ester was also treated with ethylamine to yield the N-ethyl derivative. The product was obtained in 93% yield and required only one recrystallization from ether to raise it to a constant melting point, thus indicating high homogeneity of the product.

The apparent reversal in the orientation of opening of the oxide ring is another example of an interesting chemical effect due to the trifluoromethyl group. A number of factors associated with the strong electronegativity of the CF_3 group may be responsible for the preferential attack at the α-carbon of the fluorinated glycidic ester.

Reactions of negatively substituted epoxides with various nucleophilic reagents[19-21] have indicated that bond formation is more important in the transition state than is bond breaking.[22] Since the CF_3 group is more electronegative than a carbethoxy group, one might expect that ammonia and amines would attack the β-carbon of ethyl β-trifluoromethylglycidate. However, the results obtained show that the reverse is true. The disparity between the reactions studied by other workers and this one may be due to the much greater effect that the CF_3 group has on strengthening the carbon-to-oxygen bond adjacent to it, as compared to other electronegative groups studied, such as *p*-chlorophenyl, *p*-nitrophenyl and chloromethyl groups. The increase in strength of the carbon-to-oxygen bond adjacent to a CF_3 group is accompanied by a decrease in the bond length, and therefore introduces a greater strain in the oxirane ring relative to other negatively substituted epoxides. The decrease in the length of one of the bonds in the three-membered ring increases the ring strain already present, and facilitates the ionization of the epoxide oxygen; that is, bond breaking has become more important.

The bond strengthening effect on a carbon-to-oxygen bond adjacent to a CF_3 group has frequently been noted. For example trifluoroethanol is inert toward hydrobromic acid.[23] The displacement of the tosyl group by halide in trifluoroethyl *p*-toluenesulfonate could only be effected at 240°.[24] Trifluoroisopropyl alcohol and other secondary alcohols were not dehydrated by sulfuric acid.[25] Electron diffraction studies on trifluoroethanol indicate that the carbon-to-oxygen bond is shortened.[26]

$LiAlH_4$ Reduction of VI.—Since the ammonolysis of VI yielded III, showing that opening of the epoxide occurred at the α-position, it was of interest to determine what direction ring opening would take when VI was reduced by lithium aluminum hydride. The products from this reduction would be either a 1,2-glycol or a 1,3-glycol or a mixture of these two, which may be readily analyzed by periodic acid oxidation.

The reduction of VI by lithium aluminum hydride yielded a glycol which gave a negative periodate test indicating that the epoxide was opened exclusively at the α-carbon. The phenylurethan derivative of the glycol was prepared and no depression in melting point was found between it and the phenylurethan prepared from an authentic sample of 1,3-dihydroxy-4,4,4-trifluorobutane.

Reduction of ethyl 3-methylglycidate by lithium aluminum hydride resulted in a mixture of 1,2- and 1,3-glycols as evident from periodic acid titration.

Acknowledgment.—We wish to thank Dr. Robert Harrell for his assistance in obtaining and interpreting the ultraviolet spectra.

Experimental[27]

Ethyl 2-Phenylhydrazono-3-keto-4,4,4-trifluorobutyrate (I).—A benzenediazonium chloride solution was prepared from 23.3 g. (0.250 mole) of aniline and 17.5 g. (0.252 mole) of sodium nitrite in 260 ml. of water and 81.5 ml. (0.975 mole) of concentrated hydrochloric acid. This solution (maintained at 0–5°) was added over a period of 50 min. with vigorous stirring and cooling (below 10°) to a mixture of 111.0 g. (1.35 moles) of sodium acetate dissolved in 192 ml. of water and 46.0 g. (0.250 mole) of ethyl 4,4,4-trifluoroacetoacetate taken up in 520 ml. of ethanol. The mixture was allowed to stir for an additional 5.0 hr. at room temperature. The solids were removed by filtration, and washed well with water. The water wash was added to the filtrate to give an additional crop. The combined solids were dissolved in ether and the aqueous phase was tapped off. The solvent was removed, and the residue was extracted with petroleum ether (30–60°) in a Soxhlet apparatus. Several crops of product were obtained, having a weight of 45.0 g. (62%), m.p. 75–79°. A sample was recrystallized from petroleum ether; m.p. 82–83°, λ_{max} 360 and 249 mμ (ε 25,800 and 11,100).

Anal. Calcd. for $C_{12}H_{11}N_2O_3F_3$: C, 50.00; H, 3.85. Found: C, 50.10; H, 3.96.

The crude material also was purified by dissolving in ether, giving a red solution, which was then decolorized by addition of a saturated solution of stannous chloride in ether. The ether was washed several times with water, then dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. The residue was crystallized from ether–petroleum ether (30–60°) to give the light yellow product, m.p. 81–82°.

The insolubles from the petroleum ether extraction, weighing 3.5 g., were recrystallized several times from ether–petroleum ether (30–60°), to give almost colorless crystals of phenylhydrazone of ethyl glyoxalate, m.p. 126–127° (lit.[28] 128°).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29. Found: C, 62.87; H, 6.29.

Phenylhydrazone of Ethyl 2-Keto-3-hydroxy-4,4,4-trifluorobutyrate.—A solution of 6.15 g. (0.167 mole) of sodium borohydride in 300 ml. of methanol was added to a slurry of 48.0 g. (0.167 mole) of I in 500 ml. of methanol with cooling to maintain the temperature below 15°. The solids went into solution and, after the addition of the sodium borohydride, the solution was allowed to remain at room temperature for an additional hour. Most of the solvent was removed *in vacuo*, and about a liter of water was added until no further precipitation was caused. The solids were removed and taken up in ether to be dried over anhydrous sodium sulfate. The residue after removal of the solvent was then triturated with low boiling petroleum ether (30–60°). The solubles were crystallized from ether–petroleum ether (30–60°) to give 17.0 g. (35.4%) of light yellow product, m.p.

(19) J. N. Brönsted, *et al.*, THIS JOURNAL, **51**, 428 (1929).

(20) R. Fuchs and C. A. VanderWerf, *ibid.*, **76**, 1631 (1954).

(21) A. Feldstein and C. A. VanderWerf, *ibid.*, **76**, 1626 (1954).

(22) For an excellent discussion on the effect of electronic factors on the direction of SN2 ring opening in unsymmetrical epoxides see ref. 21.

(23) F. Swarts, *Compt. rend.*, **197**, 1261 (1939).

(24) E. T. McBee, D. H. Campbell and C. W. Roberts, THIS JOURNAL, **77**, 3149 (1955).

(25) R. N. Haszeldine and A. G. Sharpe, "Fluorine and its Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 91.

(26) R. L. Livingston and G. Vaughan, THIS JOURNAL, **78**, 2711 (1956).

(27) Melting points and boiling points are uncorrected. Analyses were performed by E. Thommen, Basel, Switzerland. Ultraviolet measurements were made on a Beckman DK-1 spectrophotometer.

(28) J. Scheiber and P. Herold, *Ber.*, **46**, 1105 (1913).

103–104°, of the methyl ester of II, λ_{max} 344 and 235 mμ (ε 18,800 and 9,500), λ_{infl} 294 mμ (ε 3700).

Anal. Calcd. for $C_{11}H_{11}F_3N_2O_3$: C, 47.83; H, 4.01; N, 10.14. Found: C, 48.06; H, 3.95; N, 10.15.

The petroleum ether insolubles were crystallized from ethanol–water to give 3.0 g. (6.2%) of almost colorless product, m.p. 153–154°, of the ethyl ester of II, λ_{max} 330 and 231 mμ (ε 22,100 and 11,900), λ_{infl} 293 mμ (ε 8,100).

Anal. Calcd. for $C_{12}H_{13}F_3N_2O_3$: C, 49.66; H, 4.51; N, 9.65. Found: C, 49.93; H, 4.62; N, 9.88.

Phenylhydrazone of 2-Keto-3-hydroxy-4,4,4-trifluorobutyric Acid (II).—One gram (0.00346 mole) of the ester and 4.0 ml. of 3 *N* sodium hydroxide were heated on the steam-bath for about 1.0 minute to dissolve the solids. The solution was cooled and acidified with hydrochloric acid. The gummy precipitate crystallized shortly on cooling; it was removed by filtration and washed well with water.

Saponification of the low melting ester (m.p. 103–104°) yielded 0.66 g. (73% yield) of yellow crystalline acid, m.p. 146–147° from ether–petroleum ether (30–60°), λ_{max} 331 and 235 mμ (ε 17,300 and 8,600), λ_{infl} 295 mμ (ε 7500).

Anal. Calcd. for $C_{10}H_8F_3N_2O_3$: C, 45.80; H, 3.46; N, 10.69. Found: C, 45.89; H, 3.50; N, 10.62.

The high melting ester was treated in the same manner to yield 0.68 g. (75%) of almost colorless product, m.p. 162–163° from ether–petroleum ether (30–60°), λ_{max} 323 and 232 mμ(ε 19,000 and 9,800), λ_{infl} 292 mμ (ε 10,000).

Anal. Calcd. for $C_{10}H_8F_3N_2O_3$: C, 45.80; H, 3.46; N, 10.69. Found: C, 45.90; H, 3.50; N, 10.76.

Reduction of II. A. Reduction of Low Melting Acid.—A suspension of 4.0 g. (0.0153 mole) of II (m.p. 146–147°) in 160 ml. of water was reduced in the presence of 1.0 g. of platinum oxide at 3 atm. hydrogen for 7 hr., during which time a colorless solution was formed. The catalyst was removed by filtration and the aqueous was extracted with ether. The water was concentrated to 30 ml. and again extracted with ether. The ether extracts were combined, and the solids were crystallized from ether–petroleum ether (30–60°) to yield 1.21 g. of colorless crystalline cyclohexylamine salt of II, m.p. 156–157°, which did not depress the melting point of an authentic sample (*vide infra*).

Anal. Calcd. for $C_{16}H_{22}F_3N_2O_3$: C, 53.18; H, 6.14; N, 11.63; F, 15.77. Found: C, 53.42; H, 6.16; N, 11.57; F, 15.73.

One hundred and four milligrams of the salt was dissolved in 10 ml. of ethanol and 5 ml. of water and then titrated with alkali and back-titrated with acid, following the *p*H with a Beckman *p*H meter. A titration curve was typical of a neutral or salt-like material. At the acidic *p*H a yellow crystalline material appears, which after one recrystallization from ether–petroleum ether showed no depression in melting point on admixture with an authentic sample of II (m.p. 146–147°).

The aqueous solution from the reduction was evaporated to dryness, and the solids were crystallized from ethanol–water to yield 0.780 g. (30%) of 2-amino-3-hydroxy-4,4,4-trifluorobutyric acid, m.p. 192–194° dec. from ethanol–water.

Anal. Calcd. for $C_4H_6F_3NO_3$: C, 27.75; H, 3.49; N, 8.09. Found: C, 28.04; H, 3.57; N, 8.02.

A mixture of 0.182 g. (0.001 mole) of 2-amino-3-hydroxy-4,4,4-trifluorobutyric acid, 2 ml. of 1 *N* sodium hydroxide (0.002 mole) and 0.140 g. (0.001 mole) of benzoyl chloride was shaken at 0° for 20 min., and then acidified to congo red with concentrated hydrochloric acid. The solution was filtered and the solids were crystallized from benzene to give colorless crystals of N-benzoyl-2-amino-3-hydroxy-4,4,4-trifluorobutyric acid, m.p. 152–153°.

Anal. Calcd. for $C_{11}H_{10}F_3NO_4$: C, 47.66; H, 3.64. Found: C, 48.00; H, 3.93.

B. Reduction of High Melting Acid.—A suspension of 1.2 g. (0.0045 mole) of II (m.p. 162–163°) in 20 ml. of water was reduced in the presence of 0.25 g. of platinum oxide at an initial hydrogen pressure of 3 atm. for 10 hr. The white solids that had formed and the catalyst were removed by filtration. The solids were then dissolved in acetone and alcohol and filtered to remove the catalyst. Crystallization from ethanol–acetone gave the diasteromeric cyclohexylamine salt of II, m.p. 188–189°, which did not depress the melting point of an authentic sample (*vide infra*).

Anal. Calcd. for $C_{16}H_{22}F_3N_2O_3$: C, 53.18; H, 6.14; N, 11.63. Found: C, 53.58; H, 6.10; N, 11.69.

The salt was titrated in the same manner described previously and the crystals obtained at a low *p*H did not depress the melting point of authentic II (m.p. 162–163°).

The aqueous solution from the catalytic reduction after removal of the solids was evaporated to dryness *in vacuo;* crystallization of the residue yielded 0.220 g. (28%) of 2-amino-3-hydroxy-4,4,4-trifluorobutyric acid, m.p. 190–192° dec. from ethanol–water. No depression of the melting point occurred when a mixed melting point was taken with the amino acid prepared from reduction of the low melting II. The infrared spectra of both amino acid preparations were identical.

The N-benzoyl derivative of the amino acid was prepared, and no depression in melting point was found with the N-benzoyl derivative of the amino acid described in A. The infrared spectra of both N-benzoyl derivatives were identical.

Cyclohexylamine Salt of II. A.—To a solution of 0.200 g. (0.00201 mole) of cyclohexylamine in 10 ml. of water was added 0.500 g. (0.00191 mole) of II (m.p. 146–147°). After shaking for several minutes, all the yellow solids became decolorized, and the solids were removed by filtration. The solids were crystallized from ether–petroleum ether (30–60°), m.p. 156–157°.

B.—To a solution of 0.040 g. (0.000404 mole) of cyclohexylamine in 5 ml. of water was added 0.100 g. (0.000382 mole) of II (m.p. 162–163°). After shaking vigorously for 5 min. most of the solids float to the top. The solution was filtered, and the solids washed with ether to remove any unreacted acid. The solids were recrystallized from acetone; m.p. 188–189°.

Ethyl 2-Chloro-3-keto-4,4,4-trifluorobutyrate (IV).—Chlorine was passed into 450 g. (2.44 moles) of trifluoroacetoacetic ester, while stirring rapidly and cooling to maintain the temperature below 20°, for a period of 1.25 hours. The gain in weight was 180 g. Air was blown through the solution for 1.5 hr. until the vapors were non-acidic. After removing a small amount of forerun, the product was collected; 466 g. (87%), b.p. 67–71° at (35 mm.), $n^{23}D$ 1.3880 (lit.[5] b.p. 67–69°, $n^{19.5}D$ 1.3890).

Ethyl 2-Chloro-3-hydroxy-4,4,4-trifluorobutyrate (V).—To a rapidly stirred mixture of 90.0 g. (0.412 mole) of ethyl 2-chloro-3-keto-4,4,4-trifluorobutyrate and 30 ml. of water was added a solution of 4.27 g. (0.112 mole) of sodium borohydride in 25 ml. of water with efficient cooling (Dry Ice–acetone-bath) to maintain the temperature below 5° over a period of 0.5 hr. The mixture was stirred an additional 17 hr. at room temperature and then extracted with ether. The ether was removed and the residue was distilled. A total of 65.0 g., b.p. 67–115° (35 mm.), was collected. This was distilled in a Wheeler column to separate 21.0 g. of unreacted chloroketone and 29.0 g. of crude chlorohydrin ester. The chlorohydrin mixture was distilled in a Podbielniak column, which removed an additional 2.45 g. of unreacted chloroketone, b.p. 53–55° (10 mm.), $n^{22}D$ 1.3895. This was followed by a run of 11.05 g., b.p. 87.5° at (11 mm.), $n^{22}D$ 1.3931, of low boiling chlorohydrin ester.

Anal. Calcd. for $C_6H_8F_3ClO_3$: C, 32.67; H, 3.66; Cl, 16.07. Found: C, 32.76; H, 3.84; Cl, 15.83.

After a small intermediate cut, 6.35 g., b.p. 93.0° at (11 mm.), $n^{22.5}D$ 1.4022, of high boiling chlorohydrin ester was collected. The total yield of pure chlorohydrin esters was 26%.

Anal. Calcd. for $C_6H_8F_3ClO_3$: C, 32.67; H, 3.66; Cl, 16.07. Found: C, 32.49; H, 3.77; Cl, 16.21.

Ethyl β-Trifluoromethylglycidate (VI).—To a suspension of 6.57 g. (0.272 mole) of sodium hydride in 75 cc. of anhydrous ether was added a solution of 60.0 g. (0.272 mole) of ethyl 2-chloro-3-hydroxy-4,4,4-trifluorobutyrate in 150 cc. of anhydrous ether over a period of 0.35 hr. with stirring and cooling. The mixture was allowed to stand overnight; 110 ml. of water was added and the aqueous layer was extracted with ether. The ether was removed and the residue distilled to yield 24.6 g. (49%) of product, b.p. 143–146°, $n^{23}D$ 1.3660.

The reaction was repeated on each of the pure isomeric chlorohydrins. The distillations were carried out in a Podbielniak column. From the low boiling chlorohydrin was obtained product b.p. 145–146°, $n^{23.5}D$ 1.3681; the high boiling chlorohydrin yielded product b.p. 146°, $n^{23.5}D$ 1.3680.

The infrared spectra of the glycidic esters from the two pure chlorohydrins were essentially identical.

β-Trifluoromethylglycidic Acid.—The aqueous solution from the previous experiment was acidified and extracted with ether. The ether was dried over anhydrous sodium sulfate, and then freed of low boiling material. Distillation of the residue yielded 0.5 g., b.p. 105° at (35 mm.), which solidified in the condenser. Crystallization from ether-petroleum ether (30–60°) gave shiny colorless crystals, m.p. 85–86°.

Anal. Calcd. for $C_4H_3F_3O_5$: C, 30.80; H, 1.93. Found: C, 30.61; H, 2.15.

β-Trifluoromethylglycidamide. A. From Glycidic Ester.—A mixture of 4.0 cc. of concd. ammonium hydroxide and 4.3 g. (0.0234 mole) of ethyl β-trifluoromethylglycidate was shaken for 5 min., at which time complete solution had been effected. The solution was concentrated on the water-pump, and the crystals were removed by filtration. Crystallization from ethanol–water gave 0.5 g. (13.8%) of product, (m.p. 121–123°).

Anal. Calcd. for $C_4H_4F_3NO_2$: C, 30.98; H, 2.60; N, 9.03. Found: C, 31.27; H, 2.88; N, 8.67.

Each of the glycidic esters obtained from the low and high boiling pure chlorohydrin esters was treated with ammonia in a similar manner. No depression was found in the melting point on admixture of the two preparations.

B. From Chlorohydrin Ester.—Each of the isomeric chlorohydrins, 0.5 g., were treated with 0.5 ml. of concd. ammonium hydroxide at room temperature with occasional shaking for 10 min., until all the oil went into solution. The solution was concentrated and extracted with ether. The ether was distilled and the residual oil weighed 0.350 to 0.400 g. Petroleum ether (30–60°) was added and after refrigeration the crystals were removed. The melting points did not depress each other, and each of the melting points did not depress authentic β-trifluoromethylglycidamide.

2-Amino-3-hydroxy-4,4,4-trifluorobutyric Acid (III).—A mixture of 5.2 g. of ammonium carbonate and 1.45 ml. of water was heated to 55° and 3.6 ml. of 6 *N* ammonium hydroxide was added. The mixture was allowed to stand at 40° for 0.5 hr. Then 2.0 g. (0.01064 mole) of ethyl β-trifluoromethylglycidate was added and allowed to remain at 40–45° for 36 hr. and 45–55° for 12 hr. The solution was concentrated to a low volume at 55° with a stream of air until all the solids disappeared, and then evaporated to dryness *in vacuo*. The residue, 1.0 g., m.p. 177–181°, was crystallized from ethanol–water to yield 0.25 g. (13%) of amino acid, m.p. 190–194° dec.

2-Amino-3-hydroxy-4,4,4-trifluorobutyramide.—A mixture of 1.5 g. (0.00815 mole) of ethyl β-trifluoromethylglycidate and 10.0 ml. of concd. ammonium hydroxide was allowed to react in a sealed tube at 0° for 0.5 hr. with occasional shaking until most of the oil was converted to a crystalline mass. The tube was then left at room temperature for 17 hr. during which time a clear yellow solution formed. The solution was evaporated to dryness *in vacuo* on the steam-bath, then taken up in absolute ethanol and the solvent was again removed *in vacuo*. The oil which tends to crystallize on standing for several days weighed 1.43 g. Crystallization from ethanol gave product m.p. 118–121 which after one more crystallization was raised to a constant melting point of 122–123°.

Anal. Calcd. for $C_4H_7F_3O_2N_2$: C, 27.91; H, 4.10; N, 16.28. Found: C, 27.84; H, 4.13; N, 15.67.

The crude amide, 0.280 g., was dissolved in 2.0 ml. of water and put on 28 g. (60 meq.) of Dowex 1-x10. Only 0.002 g. was eluted with 100 ml. of water. A total of 0.284 g. (83% based on conversion of amino amide to the hydrochloride) was eluted with 60 ml. of 1 *N* hydrochloric acid. The fractions were combined, evaporated to dryness *in vacuo*, and 0.266 g. dissolved in 2.0 ml. of water was put on 20 g. (60 meq.) of IR-120. No material was eluted with 130 ml. of water and 120 ml. of 1 *N* ammonium hydroxide, during which time the *p*H of the eluates rose from 3 to 8. The next 60 ml. of 1 *N* ammonium hydroxide eluted 0.165 g. (75% recovery based on conversion to the free base). From this material was obtained 10 mg. of high melting material, decomposing at 187–192°, presumably the amino acid, and 0.110 g. of the amide, m.p. 118–120.

Another sample of crude amide weighing 0.176 g. was dissolved in 1.0 ml. of water and put on a column of 20 g. of IR-120. A total of 0.008 g. was eluted with 120 ml. of water and 60.0 ml. of 1 *N* ammonium hydroxide. The following 60 ml. of 1 *N* ammonium hydroxide raised the *p*H from 7 to 11 and 0.142 g. (80% recovery) was found in this fraction. The oil crystallized on standing, m.p. 113–115° which was raised to 116–119° after an ether wash; melting point undepressed with pure amide.

N-tEhyl 2-ethylamino-3-hydroxy-4,4,4-trifluorobutyramide.—In a sealed tube were placed 1.5 g. (0.00815 mole) of ethyl β-trifluoromethylglycidate and 15 cc. of ethylamine. After 0.5 hr. at 0°, a crystalline mass was formed (presumably the glycidamide) which was then allowed to stand at room temperature for 20 hr. The tube was cooled and opened, and the excess ethylamine was removed *in vacuo;* the crystalline residue m.p. 113–117°, 1.74 g. (93%), required one recrystallization from ether to raise the melting point to 133–134°, which remained constant on further recrystallization.

Anal. Calcd. for $C_8H_{15}F_3N_2O_2$: C, 42.10; H, 6.63; N, 12.28. Found: C, 42.35; H, 6.52; N, 12.21.

Ethyl β-methylglycidate was obtained by epoxidation of ethyl crotonate with peroxytrifluoroacetic acid according to the method of Emmons and Pagano[29] in 55% yield, b.p. 95–97° at 60 mm. (lit.[29] b.p. 88–92° at 50 mm.).

Lithium Aluminum Hydride Reduction of Glycidates. A.—An ether solution of 3.15 g. (0.0171 mole) of ethyl β-trifluoromethylglycidate was added rapidly to a slurry of 1.6 g. (0.0422 mole) of lithium aluminum hydride in ether, refluxed for 20 hr., and decomposed with ice and sulfuric acid. Benzene was added to the ether extracts, and the solvent was distilled; 0.8 g. (33%), b.p. 118° at 34 mm., lit.[30] b.p. 104–105° at 20 mm., was obtained, which gave a negative periodate test.

The monophenylurethan, m.p. 97–98° (from petroleum ether, 30–60°), did not depress the m.p. of a sample prepared from authentic 1,3-dihydroxy-4,4,4-trifluorobutane.[30]

Anal. Calcd. for $C_{11}H_{12}F_3NO_3$: C, 50.19; N, 4.80. Found: C, 50.31; H, 4.53.

B.—A solution of 2.0 g. (0.0154 mole) of ethyl β-methylglycidate in 10 cc. of ether was added to a slurry of 0.87 g. (0.0229 mole) of lithium aluminum hydride in 25 cc. of water, the ether was decanted and then distilled with benzene to remove water. The residue was distilled to yield 0.75 g. (54%) of an oil, b.p. 115–118° at 40 mm.

The oil was analyzed for 1,2-glycol by the procedure given by Siggia.[31] To 0.06–0.07 g. samples of the glycol was added 50 cc. of periodic acid solution, and allowed to stand at room temperature for 0.5 hr. in a glass-stoppered iodine flask. Then 10 cc. of a 20% potassium iodide solution was added, and the liberated iodine titrated with sodium thiosulfate, using several drops of 1% starch indicator near the end of the titration. Blank determinations were also run. The glycol mixture analyzed for 23.5% of 1,2-glycol.

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(29) W. D. Emmons and A. S. Pagano, THIS JOURNAL, **77**, 89 (1955).

(30) E. T. McBee, O. R. Pierce and D. D. Smith, *ibid.*, **76**, 3722 (1954).

(31) S. Siggia, "Quantitative Analysis via Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1954.