The reaction of *p*-chlorobenzenediazonium chloride with itaconic acid gives an unsaturated monobasic acid, identified as α-*p*-chlorobenzylacrylic acid by the following synthesis: *p*-Chlorobenzalmalonic acid was reduced to *p*-chlorobenzylmalonic acid,[6a] which was converted by the Mannich reaction (with piperidine and formaldehyde) into piperidinomethyl - *p* - chlorobenzylmalonic acid, which was in turn pyrolyzed[6b] to give α-*p*-chlorobenzylacrylic acid.

$$C_5H_{10}NCH_2—C(COOH)_2CH_2C_6H_4Cl = CH_2=C(COOH)CH_2C_6H_4Cl + C_5H_{10}NH + CO_2$$

Itaconic acid reacts with other diazotized bases in the same way.

$$ArN_2Cl + CH_2=C(COOH)CH_2COOH = ArCH_2—C(COOH)=CH_2 + CO_2 + N_2 + HCl$$

In the above reactions, presumably initiated by a chain mechanism,[2b,3a] the transient formation of the ion ($R'CHAr-\overset{+}{C}(COOH)CH_2COOH$) is postulated, followed by the loss of carbon dioxide and hydrogen ion. When R′ is COOH, the final product is an itaconic acid; when R′ is hydrogen, the final product is an acrylic acid. Thus, the diazo reaction with both aconitic and itaconic acids involves decarboxylation.

(6) For the parent acids: *cf.* (a) L. Claisen and L. Crismer, *Ann.*, **218**, 139 (1883); (b) C. Mannich and E. Ganz, *Ber.*, **55**, 3495 (1922).

Experimental

Coupling Reactions.—The amine (0.025 mole) dissolved in 6 ml. of warm concd. hydrochloric acid, diluted with 10 ml. of water, then cooled with 5 g. of crushed ice, was diazotized by addition of sodium nitrite (0.025 mole) in 7 ml. of water. The diazo solution was added with stirring to the acid, aconitic or itaconic (0.025 mole), 1 g. of cupric chloride and 5.75 g. of sodium acetate in 20 ml. of water. The temperature was kept at 30–35°. Brisk effervescence usually followed. After standing overnight, the products were isolated from the solid or semi-solid matter that had separated by extraction with 10% aqueous sodium bicarbonate and acidification with dilute hydrochloric acid. The precipitated acids from aconitic acid were oils. However, in several cases concentration of their solutions in ether–benzene (1:1) yielded crystals. Upon irradiation (about two hours) with traces of bromine in ether–chloroform, removal of the solvent, and recrystallization from hot water, the melting point rose to that of the aryl itaconic acid (Table I). The products from itaconic acid were α-benzylacrylic acids (Table II), crystallized from water.

α-*p*-Chlorobenzylacrylic acid and its dibromide were synthesized by another route as described. The relevant details, including those for the intermediates, are shown in Table III.

The authors desire to thank Prof. T. R. Seshadri for his interest in this work.

DELHI, INDIA

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

Addition Reactions to Ethyl γ,γ,γ-Trifluorocrotonate

BY HARRY M. WALBORSKY AND MEYER SCHWARZ

RECEIVED FEBRUARY 23, 1953

The preparation of ethyl γ,γ,γ-trifluorocrotonate is reported. The addition of unsymmetrical reagents to the double bond is investigated and it is demonstrated that the CF_3 group does not reverse the normal mode of addition. The dissociation constant of γ,γ,γ-trifluorocrotonic acid is $7.1 \pm 0.1 \times 10^{-4}$.

The direction of addition of unsymmetrical reagents to ethyl γ,γ,γ-trifluorocrotonate was of interest in order to determine whether the trifluoromethyl group or the carbethoxy group would be the controlling factor. In the former case, the trifluoromethyl group might be expected to direct the entering anion to the α-carbon atom through an inductive or hyperconjugative effect[1] as illustrated in I. If the carbethoxy group were more important, the nucleophilic reagent would react at the β-position. The determining factor would thus be the resonance stabilization produced by interaction of the carbethoxy group with the double bond (II).

$F^-CF_2=CH—\overset{+}{C}HC(=O)OEt$ I

$CF_3—\overset{+}{C}H=CH=C(O^-)OEt$ II

Henne and co-workers[2] have shown that ionic addition (both acid- and base-catalyzed) as well as radical addition of unsymmetrical reagents to 3,3,3-trifluoropropene yields exclusively "anti-Markovnikow" products. Thus the addition of hydrogen bromide produced 1,1,1-trifluoro-3-bromopropane. In this case the CF_3 group polarized the double bond so that the terminal carbon atom possessed the lowest electron density. The strong polarizing effect of the CF_3 group was clearly demonstrated.

On the other hand, it is well known that when one adds hydrogen iodide,[3] hydrogen bromide,[3] alcohol[4] and ammonia[5] to ethyl crotonate, the nucleophilic attack of these unsymmetrical reagents is directed at the β-carbon atom to yield β-substituted derivatives of ethyl butyrate.

The system under investigation, ethyl γ,γ,γ-trifluorocrotonate, was prepared by the dehydration of ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate. The dehydration of alcohols which have a trifluoromethyl group adjacent to the carbon atom containing the hydroxyl group, has been described as difficult.[6] Conventional methods of dehydration (potassium acid sulfate or concd. sulfuric acid) gave no unsaturated products. The yield using phosphorus pentoxide was too low for preparative use. The carbinol was finally converted to the

(1) N. Haszeldine, *J. Chem. Soc.*, 3483 (1952).

(2) A. Henne, *et al.*, THIS JOURNAL, **72**, 3369, 4756 (1950); **73**, 5527 (1951).

(3) W. Hemilian, *Ann.*, **174**, 324 (1874).

(4) Purdie and Marshall, *J. Chem. Soc.*, **59**, 478 (1891).

(5) K. Morsch, *Monatsh.*, **60**, 50 (1932).

(6) K. Campbell, J. Knobloch and B. Campbell, THIS JOURNAL, **72**, 4380 (1950).

olefinic compound in 80% yield by the boric anhydride procedure of Brandenberger and Galat.[7] The dehydration product was a 4:1 mixture of ethyl γ,γ,γ-trifluorocrotonate and γ,γ,γ-trifluorocrotonic acid.[8]

The addition of hydrogen bromide, with or without promoters (benzoyl peroxide or aluminum bromide), to ethyl γ,γ,γ-trifluorocrotonate yielded ethyl β-bromo-γ,γ,γ-trifluorobutyrate. When the olefinic ester was treated with aqueous or gaseous ammonia, β-amino-γ,γ,γ-trifluorobutyramide[9] was obtained and found to be identical with the product obtained from the hydrogenation, in the presence of ammonia, of ethyl β-amino-γ,γ,γ-trifluorocrotonate.[10] The addition of formic acid and subsequent hydrolysis gave β-hydroxy-γ,γ,γ-trifluorobutyric acid.[11]

It has been demonstrated, therefore, that of the two possible influences, the resonance of the carbethoxy group with the double bond plays the important role in directing the addition to the double bond. The trifluoromethyl group was unable to exert enough influence to reverse the normal mode of addition as it did in the cases of 3,3,3-trifluoropropene[2] and 3,3,3-trifluoropropyne.[1]

When ethyl β-bromo-γ,γ,γ-trifluorobutyrate or ethyl β-*p*-bromobenzenesulfoxy-γ,γ,γ-trifluorobutyrate was treated with ammonia, β-amino-γ,γ,γ-trifluorobutyramide was obtained. We suggest that this is a two-step reaction, involving elimination followed by addition. The possibility of direct substitution is unlikely, since this would involve displacement of a bromine or *p*-bromobenzenesulfoxy group on a secondary carbon atom adjacent to a CF_3 group. Even substitution of 2,2,2-trifluoroethyl *p*-bromobenzenesulfonate has thus far been impossible in our hands.[12] The proposal finds additional support in the fact that elimination of hydrogen bromide or *p*-bromobenzenesulfonic acid can be accomplished very readily, by sodium acetate in ethanol–water mixture, to yield the unsaturated ester. Analogous results have been observed in substitution reactions of diethyl α-bromosuccinate.[13]

The dissociation constant of γ,γ,γ-trifluorocrotonic acid was calculated using the method described by Harned and Owens[14] and was found to be $7.1 \pm 0.1 \times 10^{-4}$.

Acknowledgment.—This investigation was supported by a research grant from the National Cancer Institute, of The National Institutes of Health, Public Health Service.

(7) W. Brandenberger and A. Galat, THIS JOURNAL, **72**, 3275 (1950).

(8) N. Haszeldine (ref. 2) has recently reported a different synthesis of this acid.

(9) It is interesting to note that the amide and not the ester was the product of this reaction. Morsch (ref. 6) had shown that ethyl crotonate under identical or more strenuous conditions yielded the β-amino ester. Gordon, Miller and Day (THIS JOURNAL, **71**, 1246 (1949)), demonstrated that a hydroxylic solvent was necessary for ammonolysis. Yet in the present case, ammonolysis was obtained in liquid ammonia.

(10) F. Swarts, *Bull. Sci. Acad. Roy. Belg.*, [5] **12**, 679 (1926).

(11) R. Jones, THIS JOURNAL, **69**, 1819 (1947).

(12) Unpublished results.

(13) J. Volhard, *Ann.*, **242**, 157 (1887).

(14) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Am. Chem. Soc., Monograph Series, No. 95, Reinhold Publ. Corp., New York, N. Y., 1943, pp. 316–325.

Experimental[15]

Ethyl β-Hydroxy-γ,γ,γ-trifluorobutyrate.—In a glass lined bomb were placed 110 g. (0.6 mole) of ethyl trifluoroacetoacetate,[16] 100 ml. of anhydrous ether and 4 g. of palladium on charcoal (5%) catalyst. The hydrogenation was carried out at 1500 lb. pressure and 125°. The reaction was complete after 8 hr. The bomb contents were filtered, solvent stripped and residue distilled to yield 100 g. (0.54 mole, 90%) of product b.p. 90–91° at 50 mm.

The *p*-bromobenzenesulfonate derivative was prepared by the pyridine method, m.p. 69.5–70.5° from ligroin.

Anal. Calcd. for $C_{11}H_{12}O_5SF_3Br$: C, 35.57; H, 2.99. Found: C, 35.76; H, 3.10.

Ethyl γ,γ,γ-Trifluorocrotonate and γ,γ,γ-Trifluorocrotonic Acid.—In a 500-ml. three-necked flask equipped with a Dean and Stark trap were placed 322 g. (1.75 moles) of ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate and 70 g. (1 mole) of boric anhydride (prepared by fusing boric acid in a nickel crucible). The mixture was slowly heated in a Woods metal-bath and the temperature maintained at 180° until all the boric anhydride dissolved. The temperature was rapidly raised to 350°. The distillate consisted of two phases, the lower water phase was discarded and the upper phase was returned to the flask. This operation was repeated four times. The distillate was then dissolved in petroleum ether (30–40°), dried over phosphorus anhydride, solvent evaporated and residue distilled to yield 160 g. (1 mole, 55%) of ester, b.p. 114–115°, $n^{22}D$ 1.3610.

Anal. Calcd. for $C_6H_7O_2F_3$: C, 42.86; H, 4.17. Found: C, 42.76; H, 4.17.

The residue in the flask was distilled to yield 66 g. (0.47 mole, 27%) of acid, b.p. 145–150°. Recrystallization from pentane gave pure acid, m.p. 54–55°; neut. equiv. found, 142; calcd., 140.

Anal. Calcd. for $C_4H_3O_2F_3$: C, 34.29; H, 2.14. Found: C, 34.22; H, 2.19.

The amide was prepared by saturating an ether solution of the ester with gaseous ammonia, m.p. 146.5–147.5° from ether–petroleum ether.

Anal. Calcd. for $C_4H_4ONF_3$: C, 34.53; H, 2.89. Found: C, 34.71; H, 2.82.

Addition of Hydrogen Bromide.—The addition of hydrogen bromide to ethyl γ,γ,γ-trifluorocrotonate yielded the same product under all conditions used (no catalyst, aluminum bromide or benzoyl peroxide). In a typical experiment, 6 g. (0.036 mole) of ethyl γ,γ,γ-trifluorocrotonate was dissolved in 15 ml. of ethyl bromide and placed in a glass tube. The solution was saturated at 0° with hydrogen bromide and the tube was sealed. The tube was heated at 100° for ten hours, cooled, opened, poured onto ice, and extracted with pentane. The solvent was stripped and the residue distilled to yield 7 g. (0.029 mole, 80%) of ethyl β-bromo-γ,γ,γ-trifluorobutyrate, b.p. 98–99° at 100 mm., $n^{24.5}D$ 1.3940.

Anal. Calcd. for $C_6H_8O_2F_3Br$: C, 28.93; H, 3.24. Found: C, 29.08; H, 3.34.

Addition of Ammonia.—Ethyl γ,γ,γ-trifluorocrotonate (6.5 g., 0.039 mole) and 6 ml. of liquid ammonia were heated in a sealed tube for 36 hours at 100°. The tube was opened and the ammonia was allowed to evaporate. The solid residue was recrystallized from acetonitrile to yield 5.8 g. (0.037 mole, 95%) of β-amino-γ,γ,γ-trifluorobutyramide, m.p. 120–121°.

Anal. Calcd. for $C_4H_7ON_2$: C, 30.77; H, 4.49; N, 17.95. Found: C, 30.88; H, 4.55; N, 17.85.

Addition of Aqueous Ammonia.—Ethyl γ,γ,γ-trifluorocrotonate (2 g., 0.012 mole) was shaken for 40 hours with 10 ml. of concd. ammonium hydroxide. At first a solid (unsaturated amide) was formed, which on further shaking slowly dissolved. The final solution yielded upon evaporation to dryness and several recrystallizations from acetonitrile 0.5 g. (0.0032 mole, 27%) of amino amide, m.p. 120–121°.

Synthesis of β-Amino-γ,γ,γ-trifluorobutyramide.—Ethyl β-amino-γ,γ,γ-trifluorocrotonate[11] (10 g., 0.05 mole) and

(15) Analyses performed by Dr. A. Elek, 4763 W. Adams Blvd., Los Angeles, California.

(16) A. Henne, M. Newman, L. Quill and R. Staniforth, THIS JOURNAL, **69**, 1819 (1947).

50 ml. of ether were placed in a hydrogenation bomb and saturated with ammonia. One gram of 5% palladium on charcoal catalyst was added and the hydrogenation was carried out at 1400 lb. pressure and at 125° for ten hours. The solvent was stripped and the residue was worked up to yield 0.6 g. (0.004 mole, 8%) of product, m.p. and mixed m.p. 120–121°.

Addition of Formic Acid.—Ethyl γ,γ,γ-trifluorocrotonate (10 g., 0.06 mole), 20 g. of 100% formic acid and 0.5 g. of toluenesulfonic acid were refluxed for 12 hours. The formic acid was removed *in vacuo* and the residue refluxed for four hours with a solution of 9 g. of sodium hydroxide dissolved in a mixture of 30 ml. of water and 10 ml. of alcohol. The solution was acidified and extracted with ether to yield 1 g. (0.007 mole, 12%) of β-hydroxy-γ,γ,γ-trifluorobutyric acid,[12] m.p. and mixed m.p. 74–76°.

Addition of Hydrogen Bromide to γ,γ,γ-Trifluorocrotonic Acid.—The acid (6 g., 0.043 mole) dissolved in 20 ml. of ethyl bromide was saturated with hydrogen bromide and heated in a sealed tube for five hours at 100°. After removal of solvent *in vacuo* and recrystallizing the residue from ether–petroleum ether (30–40°) there was obtained 8.9 g. (0.040 mole, 93%) of β-bromo-γ,γ,γ-trifluorocrotonic acid, m.p. 39–41°.

Anal. Calcd. for $C_4H_4O_2BrF_3$: C, 21.40; H, 1.80. Found: C, 21.71; H, 2.00.

Reaction of Ethyl β-Bromo-γ,γ,γ-trifluorobutyrate with: A. Ammonia.—The bromo ester (5 g., 0.02 mole) was shaken for 48 hours with 25 ml. of concd. ammonium hydroxide. Evaporation to dryness gave 1 g. (0.006 mole, 30%) of β-amino-γ,γ,γ-trifluorobutyramide, m.p. 120–121°.

B. Sodium Acetate.—The bromo ester (2 g., 0.009 mole) was in a solution of one gram of sodium acetate, 10 ml. of water and 20 ml. of ethyl alcohol. This was refluxed for six hours, diluted with 100 ml. of water and extracted with pentane. The solvent was evaporated and the residue distilled to yield 0.6 g. (0.004 mole, 60%) of ethyl γ,γ,γ-trifluorocrotonate, b.p. 114–115°, $n^{24}D$ 1.3605.

Reaction of Ethyl β-*p*-Bromobenzenesulfoxy-γ,γ,γ-trifluorobutyrate with: A. Ammonia.—The ester (2 g., 0.005 mole) and 3 ml. of liquid ammonia were heated in a sealed tube at 40° for 10 hours. The tube was opened and the ammonia was allowed to evaporate. The residue was recrystallized from acetonitrile to yield 0.5 g. (0.003 mole, 60%) of β-amino-γ,γ,γ-trifluorobutyramide, m.p. 120–121°.

The yield using aqueous ammonium hydroxide was 50%.

B. Sodium Acetate.—The *p*-bromobenzenesulfoxy ester (2 g., 0.005 mole) was refluxed for six hours in a solution of 1 g. of sodium acetate dissolved in 25 ml. of water and 14 ml. of alcohol. The mixture was diluted with 200 ml. of water and extracted with pentane. The pentane extract yielded 0.03 g. (0.002 mole, 40%) of ethyl γ,γ,γ-trifluorocrotonate, b.p. 114–115°, $n^{25.5}D$ 1.3582.

TALLAHASSEE, FLORIDA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Quinolizidine Derivatives. A Study of the Reductive Cyclization of Some γ-(2-Pyridyl)-butyronitriles

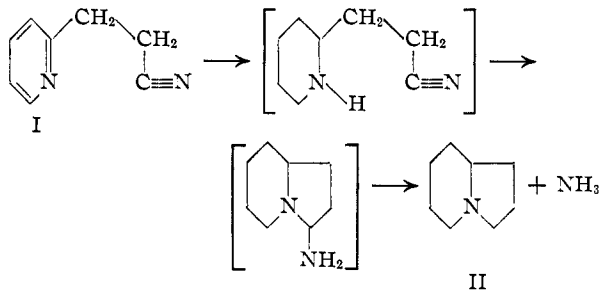
BY V. BOEKELHEIDE, W. J. LINN,[1] P. O'GRADY AND M. LAMBORG

RECEIVED FEBRUARY 5, 1953

It is shown that γ-(2-pyridyl)-butyronitriles, on mild hydrogenation over platinum in the presence of acid, undergo cyclization to yield quinolizidine derivatives. Since the requisite γ-(2-pyridyl)-butyronitriles can be conveniently prepared in good yield from either 2-vinylpyridine or ethyl 2-pyridylacetate, this two-step procedure is particularly useful for preparing 1- and 3-substituted quinolizidines, compounds which are of interest because of their relationship to the lupin alkaloids.

In a previous communication,[2] we described a method for preparing quinolizidine derivatives. The essential steps of this method were (1) the addition of an active methylene compound to 2-vinylpyridine in a Michael condensation,[2,3] and (2) the reductive cyclization of the resulting pyridyl ketone or ester over platinum. One of the possible applications of this method lies in the synthesis of members of the lupin alkaloids, and for this purpose a modification of the method was desired which would permit the synthesis of quinolizidine derivatives that were unsubstituted at the 4-position. In the present paper it is shown that the reductive cyclization of pyridyl nitriles is a general reaction and a convenient method for preparing quinolizidine and indolizidine derivatives of the desired type.

The expectation that pyridyl nitriles would undergo reductive cyclization was based on the following reasoning. If conditions could be found under which the rate of reduction of the pyridine ring would be considerably faster than the rate of reduction of the nitrile group, the resulting piperidyl nitrile, if properly chosen, would undergo intramolecularly the type of reductive alkylation commonly encountered in reductions of nitriles. The proposed reaction scheme is illustrated below for the case of β-(2-pyridyl)-propionitrile.



When β-(2-pyridyl)-propionitrile (I), prepared by the method of Frank and Mirza,[4] was subjected to hydrogenation over platinum in an acidic medium, it was converted to indolizidine (octahydropyrrocoline, II) in 43% yield. Having thus obtained experimental evidence supporting the proposed reaction scheme, we investigated the generality of the reaction.

By a modification of previous procedures,[2,3] it was found possible to effect addition of ethyl cyanoacetate and phenylacetonitrile to 2-vinyl-

(1) du Pont Company Postgraduate Fellow, 1952–1953.

(2) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

(3) W. von E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).

(4) We are indebted to Dr. R. L. Frank for this procedure, which is described in detail in the Ph.D. Thesis of John Mirza, University of Illinois, 1949.