425. *The Application of the Arndt–Eistert Reaction to Halogenated Aliphatic Acids.*

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The Arndt–Eistert reaction has been examined as a means of preparing acids of the series $CX_3\cdot[CH_2]_n\cdot CO_2H$ (where X = Cl or F). Propionic esters were obtained in reasonable yields, but yields of the amide, anilide, and acid were very poor. Since the halogen atoms in βββ-trichloropropionic ester are extremely labile, it appears to be impossible to proceed beyond this member of the chlorinated acid series.

Since trifluoroacetic acid is available commercially it seemed that the easiest way to obtain a series of acids containing the trifluoromethyl group would be by the Arndt–Eistert reaction. This method (for references up to 1942, see Backmann and Struve, " Organic Reactions," John Wiley & Sons, 1942, Vol. I, pp. 38—62) has been applied to halogenated aliphatic acids in only three previous cases (Buckle, Pattison, and Saunders, *J.*, 1949, 1471; Buckle and Saunders, *J.*, 1949, 2774). We now record our attempts to prepare acids of the type $CF_3\cdot[CH_2]_n\cdot CO_2H$ and, for comparison, the trichloro-analogues. Trifluoro- and trichloro-diazoacetone were prepared in yields which, although not as high as those generally obtained from aromatic chlorides, compare very favourably with those usual in the aliphatic series. Both diazo-ketones resemble diazoacetone in being quite stable at room temperature and were distilled under reduced pressure without appreciable decomposition (Wolff, *Annalen*, 1912, **394**, 251; Arndt and Amende, *Ber.*, 1928, **61**, 1122). The yield of trifluorodiazoacetone was particularly dependent on careful distillation and the residue gave two fractions, both containing fluorine and chlorine, which have not been identified because, while residue was being conserved, polymerisation occurred.

Conversion of the diazo-ketones into the esters of the homologous acids was much more successful than into the amides and the yield of chlorinated ester was much superior to that of the fluorinated ester. Direct preparations of the higher anilide and free acid were attempted only from trifluorodiazoacetone; because yields from this were poor and because the chlorine atoms in derivatives of trichloropropionic acid were so labile that treatment even with very weak alkali caused hydrolysis, the work was not extended to trichlorodiazoacetone.

Acid hydrolysis of trichloropropionic ester also failed to give the free acid (cf. Ladd and Sargent, U.S.P. 2,515,306, for hydrolysis of γγγ-trichlorobutyric esters) and it was concluded that further ascent of this series was not practicable. In the trifluoro-acids further ascent would be tedious but, despite this, the method is simpler and gives yields as good as other available processes (Henne, Pelley, and Alm, *J. Amer. Chem. Soc.*, 1950, **72**, 3370; McBee and Truchan, *ibid.*, 1948, **70**, 2910).

EXPERIMENTAL

Trifluorodiazoacetone.—Trifluoroacetyl chloride (11·7 g., 0·09 g. mol.) (Henne, Alm, and Smook, *J. Amer. Chem. Soc.*, 1948, **70**, 1968) was slowly distilled (at least 1 hr.) into stirred, ice-cold, ethereal diazomethane (0·22 mole in 600 ml.). There was vigorous evolution of nitrogen which ceased as soon as all of the acid chloride had been added. After at least 2 hr. the mixture was allowed to reach room temperature, and the ether was distilled at 35° (bath-temperature) through an 8″ column packed with Fenske helices in a very slow stream of air. Vacuum-distillation of the residue gave *trifluorodiazoacetone* (7·5 g., 62·5%), b. p. 25°/1 mm. (Found: F, 41·2. $C_3HON_2F_3$ requires F, 41·3%).

Ethyl ββ*β-Trifluoropropionate.*—Trifluorodiazoacetone (7 g.) in absolute alcohol (150 ml.) was stirred at 65° and a slurry of silver oxide [from 20% silver nitrate (20 ml.)] in absolute alcohol (40 ml.) added at intervals during 30 min., nitrogen being evolved and some of the silver oxide reduced. The mixture was then refluxed for 18 hr., treated with charcoal, cooled, and filtered, and the solvent distilled off through a column. Distillation of the residue gave *ethyl* βββ-*trifluoropropionate* (3·1 g., 40·4%), b. p. 50°/12 mm., n_D^{24} 1·3912 (Found: F, 36·4%; equiv., 159, 152. $C_5H_7O_2F_3$ requires F, 36·5%; equiv., 156).

Trichlorodiazoacetone.—This was prepared similarly from trichloroacetyl chloride (15 g., 0·08 mole) in ether (100 ml.) and diazomethane (0·21 mole) in ether (600 ml.). Evolution of nitrogen continued for about 1 hr. after the addition of the chloride and the mixture was kept overnight at room temperature before the ether was removed under reduced pressure at 20°. Vacuum-distillation of the residue gave *trichlorodiazoacetone* (13·6 g., 88%), b. p. 60°/1 mm. (Found: Cl, 56·7. $C_3HON_2Cl_3$ requires Cl, 56·5%).

Ethyl βββ-*Trichloropropionate.*—The ester was prepared in the same way as the trifluoro-derivative from trichlorodiazoacetone (13·6 g.) in absolute alcohol (200 ml.) and the same amount of silver oxide slurry. After 29 hr.' refluxing distillation of the residue left after removal of the alcohol gave *ethyl* βββ-*trichloropropionate* (11 g., 74%), b. p. 97°/14 mm., n_D^{20} 1·5140 (Found: Cl, 51·8. $C_5H_7O_2Cl_3$ requires Cl, 51·8%). Equivalent-weight determinations with 0·5N-sodium hydroxide at 100° gave values of 55, 56, and 53 owing to hydrolysis of all three chlorine atoms.

Malonamide from βββ-*Trichloropropionic Ester.*—Ethyl trichloropropionate (5 g.) was refluxed at 110° for 3 hr. with an excess of aqueous sodium hydroxide (7·8 g. in 300 ml.), and the resultant homogeneous solution neutralised with N-hydrochloric acid (the volume of acid required indicated 93% hydrolysis). After evaporation to dryness the sodium salts were refluxed for 4 hr. with absolute alcohol (200 ml.) containing concentrated sulphuric acid (3 ml.). After cooling, neutralisation with sodium ethoxide, and centrifuging, the alcohol was distilled off. The residue of malonic ester (0·8 g.), b. p. 93°/17 mm., gave, after distillation and treatment with liquid ammonia, malonamide (0·09 g.), m. p. and mixed m. p. 170° (from water).

βββ-*Trifluoropropionamide.*—Trifluorodiazoacetone (5·5 g.) in absolute alcohol (150 ml.) was treated with a slurry of silver oxide (from 20 ml. of 20% silver nitrate solution), cooled in ice-water, and stirred while dry ammonia was bubbled in for 1½ hr., then allowed to attain room temperature (2—4 hr.). Ammonia was passed for a further 1½ hr. before heating with charcoal under reflux until excess of ammonia was expelled. Filtration and distillation of the solvent left a solid which on distillation gave βββ-*trifluoropropionamide* (0·7 g.), b. p. 130°/12 mm. The liquid crystallised to a deliquescent white solid at room temperature. Warming (50°) with 1—2 c.c. of 0·1N-hydrochloric acid, followed by evaporation to dryness, gave the ammonium salt (0·7 g., 12·4%), purified by sublimation at 136°/21 mm. (Found : F, 39·1; N, 9·7. Calc. for $C_3H_6O_2F_3N$: F, 39·3; N, 9·6%).

Attempts to prepare the amide in dioxan with aqueous ammonia (Arndt and Eistert, *Ber.*, 1935, **68**, 200; Berger and Avakian, *J. Org. Chem.*, 1940, **5**, 606) and to isolate the product as ammonium salt were unsuccessful.

The ammonium salt was also prepared from the ester (1 g.) by treatment with ammonium chloride (2 crystals) and liquid ammonia (excess). Evaporation of the ammonia left colourless crystals of the ammonium salt (0·5 g., 61·5%) which could not be distilled but sublimed (136°/20 mm.) (Found : N, 9·7%).

βββ-*Trichloropropionamide.*—Trichlorodiazoacetone (9·3 g.) in absolute alcohol (200 ml.) was treated as was the trifluoro-compound. After distillation of the solvent the brown solid residue was purified by sublimation (150°/8 mm.), to give βββ-*trichloropropionamide* (0·46 g., 5·3%) (Found : Cl, 60·1; N, 7·9. $C_3H_4ONCl_3$ requires Cl, 60·3; N, 7·9%).

βββ-*Trifluoropropionanilide.*—The method is based on that of Arndt and Eistert (*loc. cit.*), trifluorodiazoacetone (7·7 g.) being added gradually to a well-stirred solution of aniline (15 ml.) and 10% aqueous silver nitrate (20 ml.) in dioxan (150 ml.) at room temperature. The temperature was then raised to 115° during 2 hr. and kept thereat for 15 hr. The hot mixture was filtered, treated with charcoal, and evaporated to one-third volume. Crude product (1·5 g.) separated. Recrystallisation from alcohol gave pure βββ-trifluoropropionanilide (1·0 g., 8·9%), m. p. 118° (Found : F, 27·9. Calc. for $C_9H_8ONF_3$: F, 28·1%). Henne, Pelley, and Alm (*loc. cit.*) give m. p. 117·5—118°.

βββ-*Trifluoropropionic Acid.*—This was prepared by Walker's method (*J.*, 1940, 1304) from trifluorodiazoacetone (6·1 g.) in warm dioxan (166 ml.), fresh silver oxide (11·7 g.), and aqueous sodium thiosulphate (18·4 g. in 420 ml.). After 1·5 hr.' heating at 75° the mixture was allowed to cool and kept overnight. A small amount (*ca.* 0·1 g.) of βββ-trifluoropropionic acid, b. p. 144° (Found : F, 44·6. Calc. for $C_3H_3O_2F_3$: F, 44·5%) was obtained. Henne and Fox (*J. Amer. Chem. Soc.*, 1951, **73**, 2323) give f. p. 9·7°, b. p. 144·8°.

The sodium salt was prepared from the ethyl ester and the ammonium salt by hydrolysis with 0·1N-sodium hydroxide. From this were prepared the S-*benzylthiuronium*, m. p. 176° (from alcohol) (Found : F, 19·6. $C_{11}H_{13}O_2N_2SF_3$ requires F, 19·4%) (for method see Wild, "Organic Compounds," Cambridge Univ. Press, 1947, p. 148), and the *aniline* salt, m. p. 116° (from alcohol) (Found : equiv., 223. $C_9H_{10}O_2F_3N$ requires equiv., 221) by mixing dry ethereal solutions of the acid and aniline.

S-*Benzylthiuronium trifluoroacetate*, m. p. 173° (Found : F, 20·6. $C_{10}H_{11}O_2N_2SF_3$ requires F, 20·4%), and *aniline trifluoroacetate*, m. p. 122° (Found : F, 27·4%; equiv., 211. $C_8H_8O_2NF_3$ requires F, 27·54%; equiv., 207), were also prepared by the same method.

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