344. *Studies of Trifluoroacetic Acid. Part XVIII.*[1] *Reaction of* N-*Aroylglycines with Perfluoro-carboxylic Anhydrides.*

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Trifluoroacetic anhydride with hippuric acid gave 2-phenyl-4-(2,2,2-trifluoro-1-hydroxyethylidene)oxazol-5-one (II) in 90% yield. With water this gave 1-benzamido-3,3,3-trifluoropropane-2,2-diol (VI). Pentafluoropropionic and heptafluorobutyric anhydrides afforded analogous products. *N*-Anisoyl- and *N*-*p*-nitrobenzoyl-glycine also gave oxazolones with trifluoroacetic anhydride. The ketone hydrate (VI) has been reduced to the alcohol: it also formed a cyanohydrin (XI) which was hydrolysed to β-amino-α-hydroxy-α-trifluoromethylpropionic acid (XII).

ATTENBURROW, ELLIOTT, and PENNY[2] treated sodium hippurate with acetic anhydride in the presence of a heterocyclic base and obtained 4-1′-hydroxyethylidene-2-phenyloxazol-5-one (I), and this reaction was extended by Bullerwell and Lawson[3] to other anhydrides, compounds corresponding to (I) being produced. We have found that hippuric acid and trifluoroacetic anhydride react in a similar way, to give the pale yellow oxazolone (II). Other carboxylic acid–trifluoroacetic anhydride mixtures form[4] powerful acylating reagents; this cyclisation could proceed through such an intermediate. Compound (II) was best obtained (90% yield) by using a three-fold excess of trifluoroacetic anhydride in acetone.

The oxazolone structure (II), based on analogy[2,3] and analyses, is confirmed by other results. The compound gave a green colour with ferric chloride (enol) and was sufficiently acidic to be titrated with phenolphthalein as indicator. The ultraviolet spectrum was similar to those[5] for 4-alkylidene-2-aryloxazol-5-ones with a hetero-atom at position 1′:

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[1] Part XVII, Bourne, Burdon, and Tatlow, *J.*, 1959, 1864.

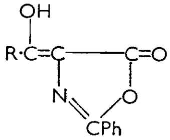
[2] Attenburrow, Elliott, and Penny, *J.*, 1948, 310.

[3] Bullerwell and Lawson, *J.*, 1952, 1350.

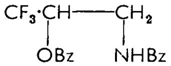
[4] Tedder, *Chem. Rev.*, 1955, **55**, 787; Bourne, Stacey, Tatlow, and Worrall, *J.*, 1958, 3268.

[5] Sheinker and Golovner, *Doklady Akad. Nauk S.S.S.R.*, 1951, **79**, 269 (*Chem. Abs.*, 1952, **46**, 35i); Trenner in "The Chemistry of Penicillin," ed. Clarke, Johnson, and Robinson, Princeton Univ. Press, Princeton, N.J., 1949, p. 429.

such compounds usually show a band between 230 and 300 mμ (ε *ca.* 10,000) and a stronger one between 320 and 400 mμ (ε *ca.* 25,000). Compound (II) had an inflexion at 300 mμ (ε 9700) and a maximum at 345 mμ (ε 23,800). Further, reaction with boiling water gave carbon dioxide and 1-benzamido-3,3,3-trifluoropropane-2,2-diol (VI) (84% yield), and the latter was reduced with Raney nickel and hydrogen or sodium borohydride to the benzamido-alcohol [isolated as the known[6] *O*-benzoyl derivative (IX)]. The reaction with water presumably occurred by hydrolysis, ketonisation, and decarboxylation of the resultant β-keto-acid. The process is similar to the conversions of the oxazol-5-one[2] (I) and its homologues[3] into carbon dioxide and alkyl benzamidomethyl ketones (*e.g.*, V) by boiling water, and to the Dakin–West reaction[7] in which *N*-acylamino-acids are converted by acetic anhydride in pyridine into *N*-acylaminoalkyl methyl ketones [the Dakin–West reaction is supposed[2] to involve hydrolysis and subsequent decarboxylation of oxazolones analogous to (I)].



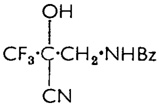
(I) $R = CH_3$
(II) $R = CF_3$
(III) $R = C_2F_5$
(IV) $R = C_3F_7$



$CF_3{\cdot}\underset{OBz}{CH}{-}\underset{NHBz}{CH_2}$

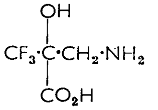
(IX)

$CH_3{\cdot}CO{\cdot}CH_2{\cdot}NHBz$
(V)



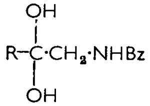
$CF_3{\cdot}\overset{OH}{\underset{CN}{C}}{\cdot}CH_2{\cdot}NHBz$

(XI)



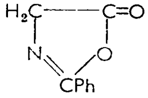
$CF_3{\cdot}\overset{OH}{\underset{CO_2H}{C}}{\cdot}CH_2{\cdot}NH_2$

(XII)



$R{-}\overset{OH}{\underset{OH}{C}}{\cdot}CH_2{\cdot}NHBz$

(VI) $R = CF_3$
(VII) $R = C_2F_5$
(VIII) $R = C_3F_7$



(X)

The ketone hydrate (VI) formed a cyanohydrin (XI) in 58% yield on being treated with potassium cyanide and then sulphuric acid. This cyanohydrin was hydrolysed by acid to give, in low yield, the known[8] β-amino-α-hydroxy-α-trifluoromethylpropionic acid (XII). In an attempted hydrolysis of the ketone hydrate (VI) to the unknown 1-amino-3,3,3-trifluoropropan-2-one, only benzoic acid was isolated.

Reactions of hippuric acid with pentafluoropropionic and heptafluorobutyric anhydride similarly gave high yields of the coloured oxazolones (III and IV) which had ultraviolet spectra very similar to that of the oxazolone (II). These compounds, in boiling water, gave the corresponding α-benzamido-ketone hydrates (VII and VIII in good yields. Also, *N*-*p*-anisoyl- and *N*-*p*-nitrobenzoyl-glycine with trifluoroacetic anhydride gave the analogous 2-*p*-methoxyphenyl- and 2-*p*-nitrophenyl-4-(2,2,2-trifluoro-1-hydroxyethylidene)oxazol-5-ones, the last in 60% yield even without acetone as diluent. The *p*-nitrophenyloxazolone was hydrolysed to the corresponding 1-*p*-nitrobenzamido-ketone.

N-Cinnamoyl-, *N*-furoyl-, *N*-*o*-nitrobenzoyl-, and *N*-(3,5-dinitrobenzoyl)-glycine all reacted with trifluoroacetic anhydride to give coloured products, which were probably analogous oxazolones but could not be purified sufficiently to give correct analyses.

The formation of the oxazolones (II, III, and IV) probably proceeded *via* 2-phenyloxazol-5-one (X) itself formed by dehydration of hippuric acid by the anhydride, since this oxazolone (X) reacted with one molecular proportion of trifluoroacetic anhydride to give the product (II) in 81% yield. Attenburrow *et al.*[2] also considered 2-phenyloxazol-5-one (X) to be an intermediate; acetic anhydride[3] with hippuric acid gave the oxazolone (X), but, in the absence of a basic catalyst, further reaction to give the 4-substituted oxazolone

[6] Jones, *J. Amer. Chem. Soc.*, 1948, **70**, 143.
[7] Dakin and West, *J. Biol. Chem.*, 1928, **78**, 91, 745.
[8] Burdon, McLoughlin, and Tatlow, *J.*, 1960, 3184.

(I) did not occur.[2] That perfluoro-carboxylic anhydrides react with the oxazolone (X) in the absence of a base is probably due to the greater electrophilic character of the carbon atoms of their carbonyl groups. The reaction between aromatic aldehydes and the oxazolone (X) also takes place [9] in the absence of a base: the carbonyl group of an aromatic aldehyde would be expected to be more electrophilic than that of an alkanecarboxylic anhydride. It is also possible that the perfluorocarboxylic acids formed during the reactions might, as they are strong acids, increase the electrophilic nature of the anhydride carbonyl groups by protonation.[10] Thus, perfluoro-carboxylic anhydrides should react with other activated methylene groups in the absence of basic catalysts; preliminary work shows this to be so.

An attempt has been made to extend the reaction to *N*-aroyl derivatives of amino-acids other than glycine. However, under the conditions described in this paper, we have found no analogous oxazolones among the products; this could, as a Referee suggested, be because stabilisation by enolisation (cf. I—IV) cannot take place.

EXPERIMENTAL

Treatment of Hippuric Acid with Perfluoro-carboxylic Anhydrides.—(a) *Trifluoroacetic anhydride.* The anhydride (5·8 ml.) was added to a suspension of hippuric acid (2·50 g.) in dry acetone (20 ml.). The mixture became warm and the hippuric acid dissolved in about 15 min. to give a red solution. After 17 hr. at 10—15° a deep red precipitate had been formed and the mixture was poured into water (400 ml.). The pink precipitate was filtered off and washed with water to give material (3·23 g.), m. p. 225—229° (decomp.), which was sufficiently pure for most purposes. A sample (0·25 g.), recrystallised from benzene (*ca.* 100 ml.), gave the very pale yellow 2-*phenyl*-4-(2,2,2-*trifluoro*-1-*hydroxyethylidene*)*oxazol*-5-*one* (II) (0·12 g.), m. p. 227—231° (decomp; depending on the rate of heating) (Found: C, 51·1; H, 2·3%; equiv., 254. $C_{11}H_6F_3NO_3$ requires C, 51·4; H, 2·4%; equiv., 257). The equivalent weight was determined potentiometrically against 0·05N-sodium hydroxide in 0·01M-solution, the end-point being at about pH 7·5. The compound had $\lambda_{max.}$ at 345 mμ (ε 23,800) and a broad inflexion at 300 mμ (ε 9700) in ethanol: it gave a deep green colour with ethanolic ferric chloride.

A reaction carried out in the absence of acetone gave only a 50% yield of the oxazolone and much tar.

(b) *Pentafluoropropionic anhydride.* Hippuric acid (1·70 g.) was treated with pentafluoropropionic anhydride (8·80 g.) in dry acetone (15 ml.), as in (a), to give an orange-yellow crude product (2·09 g.), m. p. *ca.* 200—205° (decomp.), which was recrystallised from benzene to give yellow 4-(2,2,3,3,3-*pentafluoro*-1-*hydroxypropylidene*)-2-*phenyloxazol*-5-*one* (III) (1·45 g.), m. p. *ca.* 210—215° (decomp.); this m. p. varied greatly with the rate of heating, the one quoted was obtained by placing the sample in a heated (*ca.* 150°) zone and then raising the temp. to the m. p. in 1—2 min. The compound will melt with decomposition at 160° if kept at this temperature for about 30 min. (Found: C, 47·1; H, 1·8. $C_{12}H_6F_5NO_3$ requires C, 46·9; H, 2·0%). In ethanol the compound had $\lambda_{max.}$ at 346 mμ (ε 19,400) and a broad inflexion at 301 mμ (ε 8000).

(c) *Heptafluorobutyric anhydride.* Hippuric acid (2·00 g.) was treated with heptafluorobutyric anhydride (13·7 g.) in dry acetone (15 ml.), as in (a). The crude product was taken up in 0·5N-sodium hydroxide (200 ml.), and the resulting solution was filtered and acidified with 4N-sulphuric acid (this removed most of the absorbed heptafluorobutyric acid). The precipitated yellow solid (3·30 g.), m. p. 220—223° (decomp.), was recrystallised from benzene, to give the pale yellow-green 4-(2,2,3,3,4,4,4-*heptafluoro*-1-*hydroxybutylidene*)-2-*phenyloxazol*-5-*one* (IV) (2·73 g.), m. p. 226—228° (decomp.) (Found: C, 43·6; H, 1·8. $C_{13}H_6F_7NO_3$ requires C, 43·7; H, 1·7%). In ethanol the compound had $\lambda_{max.}$ at 347 mμ (ε 23,100) and a broad inflexion at 300 mμ (ε 8800).

In the absence of acetone only a 21% yield was obtained.

Reaction of 2-*Phenyloxazol*-5-*one* (X) *with Trifluoroacetic Anhydride.*—Trifluoroacetic

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[9] Crawford and Little, *J.*, 1959, 729.

[10] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, p. 676.

anhydride (0·43 ml.) was added to a solution of 2-phenyloxazol-5-one (0·50 g.) in dry acetone (5 ml.). Treatment as in (a) above gave 2-phenyl-4-(2,2,2-trifluoro-1-hydroxyethylidene)-oxazol-5-one (II) (0·65 g.), m. p. and mixed m. p. 224—228° (decomp.).

Reaction of N-p-*Anisoylglycine with Trifluoroacetic Anhydride.*—*N-p*-Anisoylglycine (0·50 g.), suspended in dry acetone (2·5 ml.), was treated with trifluoroacetic anhydride (1·1 ml.) as in (a) above. The brown solid (0·69 g.), m. p. 175—185° (decomp.), was twice precipitated from acetone solution with light petroleum (b. p. 80—100°), to give the pale brown 2-p-*methoxyphenyl*-4-(2,2,2-*trifluoro*-1-*hydroxyethylidene*)*oxazol*-5-*one* (0·23 g.), m. p. 225—228° (decomp.; depending on the rate of heating) (Found: C, 50·4; H, 3·2. $C_{12}H_8F_3NO_4$ requires C, 50·2; H, 2·8%).

Reaction of N-p-*Nitrobenzoylglycine with Trifluoroacetic Anhydride.*—Trifluoroacetic anhydride (2·3 ml.) and *N-p*-nitrobenzoylglycine (0·75 g.) were refluxed together for 30 min. (there was no reaction at room temperature) and the resulting orange solution was kept at 10—15° for 24 hr. The red crystals which had been formed were filtered off, washed with carbon tetrachloride, and recrystallised from ethanol–carbon tetrachloride to give 2-p-*nitrophenyl*-4-(2,2,2-*trifluoro*-1-*hydroxyethylidene*)*oxazol*-5-*one* (0·61 g.), m. p. 212—214° (decomp.) (Found: C, 43·4; H, 1·6. $C_{11}H_5F_3N_2O_5$ requires C, 43·7; H, 1·7%).

Hydrolysis of the Oxazolones.—(a) 2-*Phenyl*-4-(2,2,2-*trifluoro*-1-*hydroxyethylidene*)*oxazol*-5-*one* (II). This compound (14·3 g.) was refluxed with water (50 ml.) for 1 hr., slowly dissolving while carbon dioxide was evolved (lime-water test). The colourless solution was extracted continuously with ether for 14 hr., and the extracts were dried ($MgSO_4$) and evaporated, to leave 1-*benzamido*-3,3,3-*trifluoropropane*-2,2-*diol* (VI) (11·65 g.), m. p. 107—109° (from benzene) (Found: C, 48·3; H, 3·9. $C_{10}H_8F_3NO_2,H_2O$ requires C, 48·2; H, 4·0%). In ethanol-hydrochloric acid this gave its 2,4-*dinitrophenylhydrazone*, m. p. 194—195° (from aqueous ethanol), depressed on admixture with 2,4-dinitrophenylhydrazine (Found: C, 46·8; H, 2·8. $C_{16}H_{12}F_3N_5O_5$ requires C, 46·7; H, 2·9%).

Hydrolysis of the ketone hydrate (VI) for 4 hr. with 5N-hydrochloric acid under reflux gave a quantitative yield of benzoic acid, but no other product could be isolated.

(b) 2-p-*Nitrophenyl*-4-(2,2,2-*trifluoro*-1-*hydroxyethylidene*)*oxazol*-5-*one*. This compound (0·25 g.) was refluxed with water (5 ml.). Isolation as in (a) gave 1,1,1-*trifluoro*-3-p-*nitrobenzamidopropane*-2,2-*diol* (0·05 g.), m. p. 106—107° (from benzene) (Found: C, 40·4; H, 2·8. $C_{10}H_7F_3N_2O_4,H_2O$ requires C, 40·8; H, 3·1%).

(c) 4-(2,2,3,3,3-*Pentafluoro*-1-*hydroxypropylidene*)-2-*phenyloxazol*-5-*one* (III). This compound (0·70 g.) was refluxed with water (100 ml.) for 1 hr. The colourless solution was filtered while hot to remove tar and then cooled to 0°. The crystals formed were 1-*benzamido*-3,3,4,4,4-*pentafluorobutane*-2,2-*diol* (VII) (0·33 g.), m. p. 96—98° (unchanged on recrystallisation from water) (Found: C, 44·1; H, 3·7. $C_{11}H_8F_5NO_2,H_2O$ requires C, 44·2; H, 3·4%).

(d) 4-(2,2,3,3,4,4,4-*Heptafluoro*-1-*hydroxybutylidene*)-2-*phenyloxazol*-5-*one* (IV). This compound (0·95 g.) was refluxed with water (400 ml.) as in (c), to give 1-*benzamido*-3,3,4,4,5,5,5-*heptafluoropentane*-2,2-*diol* (VIII) (0·61 g.), m. p. 86—88° (Found: C, 41·1; H, 2·8. $C_{12}H_8F_7NO_2,H_2O$ requires C, 41·3; H, 2·9%).

N-(2-*Benzoyloxy*-3,3,3-*trifluoropropyl*)*benzamide* (IX).—(*a*) A solution of the ketone hydrate (VI) (0·50 g.) in ethanol (50 ml.) containing Raney nickel (*ca.* 1 g.) was hydrogenated at room temperature and atmospheric pressure for 23 hr. About 42 ml. of hydrogen were taken up. The solution was filtered, the ethanol evaporated, and the solid residue treated with benzoyl chloride (1 ml.) in pyridine (20 ml.) at 10—15° for 13 hr. The mixture was poured into water and recrystallisation of the precipitate from aqueous ethanol afforded the *ON*-dibenzoyl derivative (IX) (0·43 g.), m. p. 127—128° (lit.,[6] 126·5—127·5°) (Found: C, 60·2; H, 4·1. Calc. for $C_{17}H_{14}F_3NO_3$: C, 60·5; H, 4·2%).

(*b*) A solution of sodium borohydride (0·30 g.) in water (5 ml.) was added to a solution of the ketone hydrate (0·10 g.) in water (10 ml.). Vigorous evolution of gas took place. After 3 hr. at 10—15°, 11N-hydrochloric acid (0·25 ml.) was added to destroy the excess of borohydride, followed by 10N-sodium hydroxide (5 ml.). Treatment with benzoyl chloride gave a precipitate of the dibenzoyl derivative (0·13 g.), m. p. and mixed m. p. 127—128°, unchanged by recrystallisation from aqueous ethanol.

β-*Benzamido*-α-*hydroxy*-α-*trifluoromethylpropionitrile* (XI).—1-Benzamido-3,3,3-trifluoropropane-2,2-diol (VI) (1·0 g.) was added to a solution of potassium cyanide (0·35 g.) in water (25 ml.) cooled to 0°. The ketone dissolved during 1 hr. as the mixture was stirred. Addition of 3N-sulphuric acid then precipitated the crude cyanohydrin, which was filtered off, and the aqueous phase was extracted with ether. Recrystallisation from benzene gave β-*benzamido-α-hydroxy-α-trifluoromethylpropionitrile* (XI) (0·6 g.), m. p. 111—113°, depressed on admixture with the starting material (Found: C, 51·0; H, 3·6; F, 22·3. $C_{11}H_9F_3N_2O_2$ requires C, 51·2; H, 3·5; F, 22·1%).

β-*Amino-α-hydroxy-α-trifluoromethylpropionic Acid* (XII).—The cyanohydrin (XI) (2·70 g.) was added, with stirring, to 98% sulphuric acid (3·5 ml.) and the solution was heated at 110° for 1 hr. Water (3 ml.) was added to the cooled mixture, and the resulting solution was refluxed for 2 hr. On being cooled, the solution deposited benzoic acid (1·28 g.), m. p. and mixed m. p. 119—120°, which was filtered off. The filtrate was neutralised with barium carbonate, the insoluble barium salts were filtered off and washed with warm water, and the combined filtrate and washings were evaporated to dryness *in vacuo*. The solid residue (0·23 g.) recrystallised from aqueous ethanol, to give β-amino-α-hydroxy-α-trifluoromethylpropionic acid (XII) (0·22 g.), m. p. 310° (decomp.). This compound had an infrared spectrum identical with that of material reported [8] previously.

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