CONDENSATION OF HEXAFLUOROACETONE WITH CYANOHYDRINS OF ALIPHATIC ALDEHYDES

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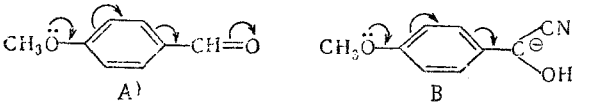
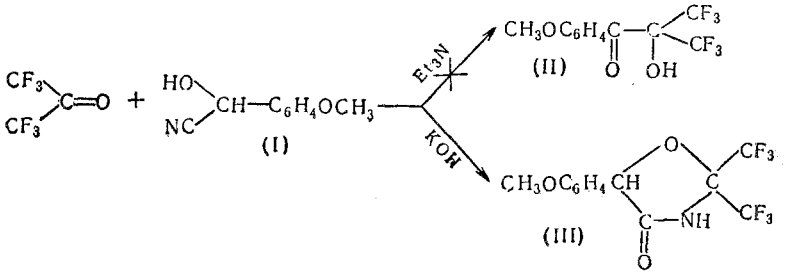
It is known that para-substituted aromatic aldehydes form symmetrical benzoins with difficulty or not at all, whereas they readily condense with other aldehydes with formation of unsymmetrical benzoins [1]. Pivalaldehyde behaves analogously [2]. In the case of electron-donating substituents the formation of a symmetrical benzoin is inhibited by the weakening of the electrophilic character of the carbonyl group of the aldehyde (A), though the same substituent strengthens the electrophilic character of the anion of the cyanohydrin (B), which promotes the formation of the mixed benzoin [3]. It is known that hexafluoroacetone reacts extremely readily with nucleophilic reagents,



A) B

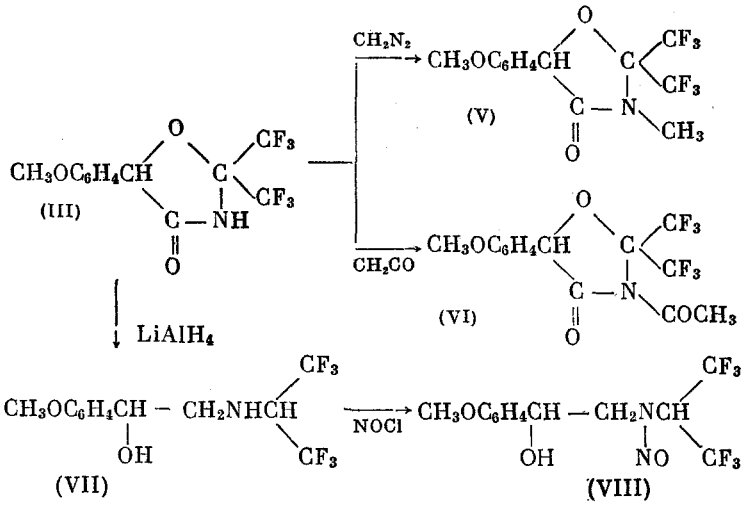
in some cases surpassing not only ketones, but also aldehydes, in activity [4]. It might therefore be expected that the reaction of hexafluoroacetone with p-anisaldehyde cyanohydrin (I) in presence of triethylamine would lead to the mixed benzoin – 3,3,3-trifluoro-2-hydroxy-4'-methoxy-2-(trifluoromethyl)propiophenone (II). By this method Lapworth obtained benzoin from benzaldehyde and mandelonitrile [5].



(I) (II) (III)

However, instead of the expected benzoin (II), by the treatment of an ethereal solution of a mixture of the cyanohydrin (I) and hexafluoroacetone with aqueous alkali we obtained a 90% yield of 5-p-methoxyphenyl-2,2-bis-trifluoromethyl-4-oxazolidinone (III). In a similar way we obtained 4-oxazolidinones from the cyanohydrins of benzaldehyde, p-nitrobenzaldehyde, and p-(dimethylamino)benzaldehyde. The structure and properties of the oxazolidinones obtained were investigated in detail for the case of (III). It was found that the introduction of two trifluoromethyl groups in the 2-position of 4-oxazolidinone results in substantial changes in the reactions of the heterocycle and in its stability. Thus, whereas the nonfluorinated analog of (III) – 5-p-methoxyphenyl-2,2-dimethyl-4-oxazolidinone (IV) – is broken down by alkali at 190° and by acid at room temperature, (III) undergoes no change when heated to 250° with 10% alcoholic alkali and to 100° with concentrated hydrochloric acid. Because of their inductive effect the trifluoromethyl groups also increase the mobility of the hydrogen of the imino group, as a result of which (III) readily dissolves not only in caustic alkalies (which is a general characteristic of 4-oxazolidinones [6]), but also in sodium bicarbonate solution.

The same effect in the trifluoromethyl groups is manifested also in the unusual ease with which (III) is methylated with diazomethane to give (V) and is acylated with ketene to give (VI). The structures of (V) and (VI) were confirmed by their infrared spectra (see below). Under the same conditions the nonfluorinated oxazolidinone (IV) reacts neither with diazomethane nor with ketene.

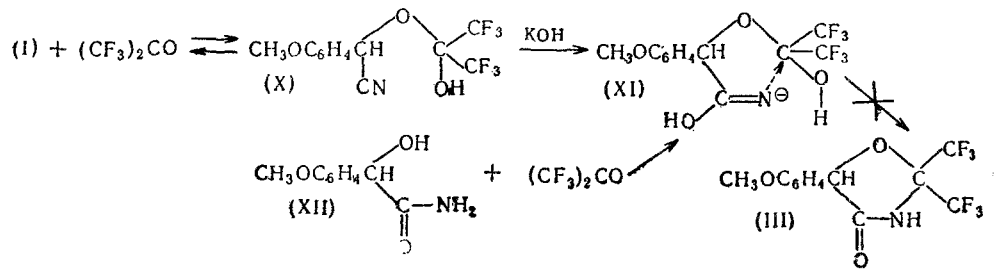


The oxazolidinone (III) is stable to the action of zinc and hydrochloric acid and to sodium borohydride, but it is reduced smoothly by lithium aluminum hydride at room temperature with opening of the ring* and formation of p-methoxy-α-[[[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]amino]methyl]benzyl alcohol (VII), which is converted by nitrosation into the N-nitroso derivative (VIII). When the amino alcohol (VII) is treated with alkali about one-half of its fluorine is mineralized, and we isolated a compound with basic properties, which was probably 2,5-bis-p-methoxyphenylmorpholine (IX).

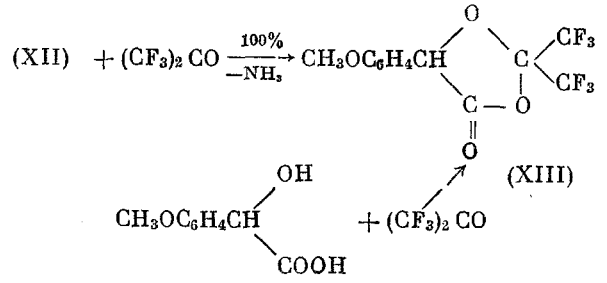
The structures of the 4-oxazolidinone (III) and its derivatives (V) and (VI) are confirmed by their infrared spectra. All three compounds give an intense band at 1750 cm^{-1} (C = O group). (III) gives characteristic absorption in the 3000-3200 cm^{-1} region (stretching vibrations of the N—H bond). The structures of (V) and (VI) as N-derivatives of the oxazolidinone (II) having an amide, and not an imidol, structure are confirmed also by absence of absorption at 1650-1680 cm^{-1} characteristic for 3-oxasoline derivatives [8]. The displacment of the C = O absorption bands of (III), (IV), and (V) toward the shorter waves as compared with the nonfluorinated oxazolidinones probably arises from the effect of the trifluoromethyl groups. A similar though less marked displacement was observed on the introduction of a chloromethyl or acetyl group into the 2-position of 4-oxazolidinone [8].

The usual method of preparing 4-oxazolidinones is based on the condensation of carbonyl compounds with cyanohydrins or α-hydroxy acid amides in presence of acid catalysts [6, 8]. The essential difference in the method that we have found is the use of a catalyst of alkaline character. It is interesting that the yield of (III) depends greatly on the way in which the reaction mixture is treated with alkali. A high yield of (III) is achieved only when an ethereal solution of the cyanohydrin (I) and hexafluoroacetone is added to the alkali, i.e., with maintenance of a strongly alkaline medium throughout the whole reaction. This is related to the fact that the hemiketal (X) formed by reaction between hexafluoroacetone and (I) is unstable (cf. [9]). Thus, on standing in air it decomposes rapidly into its original components. It is evident that such decomposition occurs in presence of small amounts of alkali. Only under certain conditions (excess of alkali) does the conversion of (X) into (III) occur. The formation of (III) might have been regarded as the result of the intramolecular nucleophilic replacement of the hydroxyl of the 2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl group in the anion (XI), formed by the action of alkali on the hemiketal (X). However, p-methoxymandelamide (XII) does not form (III) at all under the same conditions, but only breaks down into the original components. Heating of hexafluoroacetone with (XII) to 100° led to 5-p-methoxy-

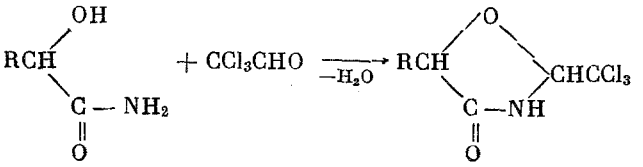
*Lithium aluminum hydride effects the decyclization of 3-alkyl-2-phenyl-4-thiazolidinones in a similar way with simultaneous reduction of the amide function into an amine [7].



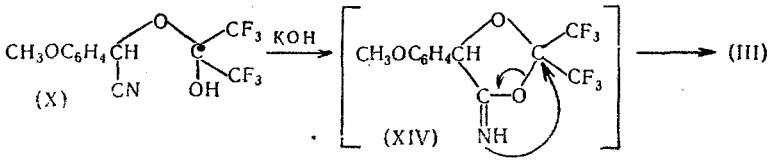
phenyl-2,2-bistrifluoromethyl-1,3-dioxolan-4-one (XIII), whose structure was proved by its synthesis from p-mandelic acid and hexafluoroacetone [10].



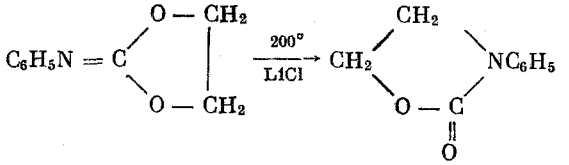
The dioxolanone (XIII) is formed also when the reaction is conducted in presence of p-toluenesulfonic acid. Unlike hexafluoroacetone, chloral forms 2-(trichloromethyl)-4-oxazolidinone derivatives under these conditions [11].



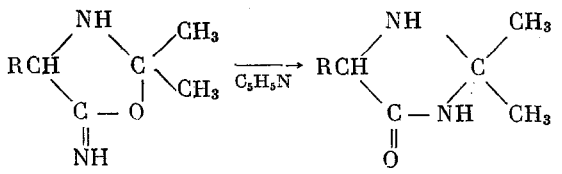
The fact of the formation of (XIII) is in accord with the known strength of a C—O bond adjacent to two trifluoromethyl groups. This bond is broken with relative ease only in the course of isomerization associated with the opening of the ring [12]. We therefore suppose that the conversion of (X) into (III) is effected via the intermediate dioxolanimine (XIV). The rearrangement of (XIV) under the action of alkali, which is associated with the migration of the hemiacetal residue to the doubly bound nitrogen, leads to the final product (III).* Transformations of this type,



known as the rearrangement of straight-chain imidic esters into substituted amides, have been fairly well studied. However, it is usually brought about either by acid catalysts (H_2SO_4 [13], BF_3 [14]) or purely thermally [15]. The only cases of the rearrangement of cyclic imidic esters known are the conversion of ethylene carbonate anil into 3-phenyl-2-oxazolidinone [16] by heating it with LiCl to 200° and the formation of 4-imidazolidinones by the treatment of supposed 5-iminooxazolidines with pyridine [17].

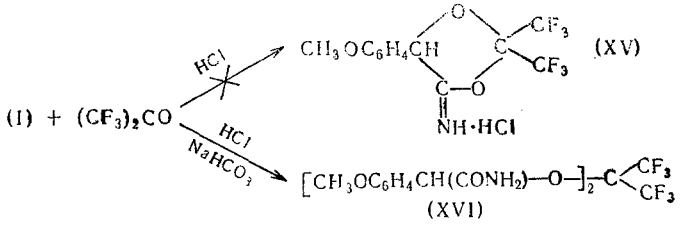


*We obtained the oxazolidone (III) also by heating a mixture of the cyanohydrin (I) and hexafluoroacetone with catalytic amounts of triethylamine hydrochloride to 170°.

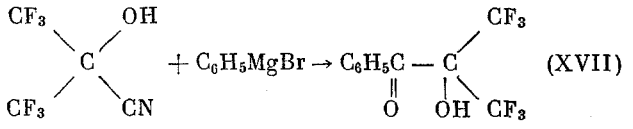


To prove the proposed mechanism we attempted to isolate the imidic ester (XIV) in the form of its hydrochloride (XV).

However, when an ethereal solution of (I) and hexafluoroacetone was treated with hydrogen chloride the full ketal of hexafluoroacetone with p-methoxymandelamide (XVI) was obtained.



As we did not succeed in obtaining the mixed benzoin (II) under the conditions of the benzoin condensation, 3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propiophenone (XVII) was prepared by Gautier's reaction [1] from hexafluoroacetone cyanohydrin:



The carbonyl group in (XVII) was found to have little activity in addition reactions. Thus, it does not react with Grignard reagents under conditions under which its nonfluorinated analog – 2-hydroxy-2-methylpropiophenone – smoothly forms pinacolones [18].

EXPERIMENTAL

5-p-Methoxyphenyl-2,2-bistrifluoromethyl-4-oxazolidinone (III). A. Hexafluoroacetone (1.5 ml) was passed into a solution of 1 g of p-anisaldehyde cyanohydrin in 5 ml of dry ether. On the next day the mixture was poured into 15 ml of 10% aqueous sodium hydroxide. The mixture was shaken vigorously; the alkaline layer was separated, and the ether layer was washed with water; the combined alkaline extracts were acidified with hydrochloric acid. The oil that came down crystallized on standing. We obtained 1.82 g (89.6%) of the oxazolidinone, m. p. 124-125° (from heptane). Found: C 43.87; H 2.76; F 35.22; N 4.25%; mol. wt. 321 (determined by titration with 0.1 N NaOH). $C_{12}H_9F_6O_3N$. Calculated: C 43.81; H 2.74; F 34.69; N 4.25%; mol. wt. 329.

B. Hexafluoroacetone (3.5 ml) was passed into a solution of 2.5 g of p-anisaldehyde cyanohydrin in 30 ml of dry ether. Ether was vacuum-distilled off. The residue was heated in a sealed glass tube with 0.5 g of triethylamine hydrochloride for seven hours at 170-180°. The reaction mixture was dissolved in ether, and the precipitate was filtered off. The residue remaining after the removal of ether was vacuum-distilled at 1 mm. The fraction of b. p. 125-160° had m. p. 119-122° after crystallization from heptane; a mixture with a sample of (III) prepared by method A melted at 122-125°. We obtained 2.1 g (40.8%) of (III). Infrared spectrum: 1750 cm^{-1} (C=O), 3080, 3190 cm^{-1} (N–H).

0.62 g of the oxazolidinone (III), 1.2 g of potassium hydroxide, and 12 ml of alcohol were heated together at 250° for 5.5 h. After acidification and removal of alcohol we obtained 0.44 g of (III), identical to the starting substance. 0.95 g of (III) was heated with 15 ml of concentrated hydrochloric acid for six hours in a boiling water bath. 0.7 g of (III) was filtered off; it was identical to the starting substance. By method A we also prepared:

5-Phenyl-2,2-bistrifluoromethyl-4-oxazolidinone (21.8% yield), m. p. 86-87° (from heptane). Found: C 44.02; H 2.27; F 35.96; N 4.82%. $C_{11}H_7F_6O_2N$. Calculated: C 44.22; H 2.34; F 38.12; N 4.67%.

5-p-Nitrophenyl-2,2-bistrifluoromethyl-4-oxazolidinone (80% yield), m. p. 137-139° (from benzene). Found: C 38.29; H 1.81; F 32.79; N 8.25%. $C_{11}H_6F_6O_4N_2$. Calculated: C 38.41; H 1.74; F 33.15; N 8.13%.

5-p-(Dimethylamino)phenyl-2,2-bistrifluoromethyl-4-oxazolidinone (68.5% yield), m. p. 124.124.5° (from heptane). Found: C45.21; H 3.63; F 32.17; N 8.09%. $C_{13}H_{12}F_6O_2N_2$. Calculated: C 45.60; H 3.51; F 33.4; N 8.20%.

5-p-Methoxyphenyl-2,2-dimethyl-4-oxazolidinone (IV). A solution of 0.81 g of p-methoxymandelamide (XII) and 0.13 g of p-toluenesulfonic acid in 40 ml of acetone was boiled for five hours. The residue remaining after the removal of acetone was treated with sodium bicarbonate solution and recrystallized from alcohol. We obtained 0.51 g (47%) of (IV), m. p. 181-183°. Found: C 64.75; H 6.78; N 6.40%. $C_{12}H_{15}O_3N$. Calculated: C 65.21; H 6.79; N 6.34%. Infrared spectrum: 1700 cm^{-1} (C = O). (IV) was decomposed completely when heated at 200° with 1% alcoholic potassium hydroxide for four hours or treated with concentrated hydrochloric acid at 20° for one day. When (IV) was treated with diazomethane or ketene [see preparation of (V) and (VI)], no reaction was observed.

5-p-Methoxyphenyl-3-methyl-2,2-bistrifluoromethyl-4-oxazolidinone (V). Ethereal diazomethane was added to 1 g of a solution of 1 g of the oxazolidinone (III) in 10 ml of ether until no more nitrogen came off. The ethereal solution was washed with 5% aqueous sodium hydroxide and water, and it was dried with magnesium sulfate. Ether was driven off, and we obtained 0.88 g (83%) of (V), b. p. 103-105° (2 mm), m. p. 45-70° (from petroleum ether). Found: C 45.55; H 3.24; F 33.47; N 4.19%. $C_{13}H_{11}F_6O_3N$. Calculated: C 45.58; H 3.21; F 33.20; N 4.08%. Infrared spectrum: 1750 cm^{-1} (C = O).

3-Acetyl-5-p-methoxyphenyl-2,2-bistrifluoromethyl-4-oxazolidinone (VI). A slow stream of ketene was passed for one hour into a solution of 2 g of the oxazolidinone (III) in dry ether. The residue remaining after the removal of ether was distilled. We obtained 1.81 g (80%) of (VI), b. p. 128-130° (2 mm). Found: C 44.66; H 3.09; F 31.24; N 4.48%. $C_{14}H_{11}F_6O_4N$. Calculated: C 45.27; H 2.96; F 30.75; N 3.77%. Infrared spectrum: 1750, 1770 cm^{-1} (two C = O groups).

p-Methoxy-α-[[[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]amino]methyl]benzyl alcohol (VII). 12.2 g of the oxazolidinone (III) was dissolved in 100 ml of dry ether, and 5 g of lithium aluminum hydride was added with stirring. Stirring was continued for three hours. On the next day the reaction mixture was decomposed with water and then with dilute acid. The ether layer was separated and dried with magnesium sulfate. Ether was driven off, and the residue was drive off, and the residue was distilled. We obtained 8.3 g (70.3%) of (VII); b. p. 107-109° (1 mm); d_4^{20} 1.387, n_D^{20} 1.4510. Found: C 45.57; H 4.28; F 35.13; N 4.90%; MR 61.53. $C_{12}H_{13}F_6O_2N$. Calculated: C 45.45; H 4.11; F 35.90; N 4.42%; MR 61.625.

1 g of the amino aclohol (VII) was boiled for 90 min with 20 ml of 10% alcoholic potassium hydroxide. 39.3% of the fluorine contained in (VII) was eliminated as F^-. Alcohol was driven off, and water was added to the residue; the precipitate was filtered off, treated with 25% sulfuric acid, and extracted with ether. After the evaporation of ether we obtained 0.1 g (20.7%) of 2,5-bis-p-methoxyphenylmorpholine (IX), m. p. 145-147° (from benzene with the addition of heptane). Found: C 71.57; H 6.85; N 5.09%. $C_{18}H_{20}O_3N$. Calculated: C 72.24; H 7.03; N 4.72%.

p-Methoxy-α-[[nitroso[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]amino]methyl]benzyl alcohol (VIII). Nitrosyl chloride (1 ml) was passed into a solution of 1.76 g of the amino alcohol (VII) in 4 ml of dry pyridine, and after 20 min the reaction mixture was poured into ice water and acidified with hydrochloric acid. The oil that came down was extracted with ether. After the removal of ether we obtained 1.38 g (72%) of (VIII), m. p. 62-63° (from petroleum ether). Found: C 41.76; H 3.76; F 33.50; N 8.24%. $C_{12}H_{12}F_6O_3N_2$. Calculated: C 41.62; H 3.47; F 32.93; N 8.09%.

5-p-Methoxyphenyl-2,2-bistrifluoromethyl-1,3-dioxolan-4-one (XIII). A mixture of 3 ml of hexafluoroacetone and 0.5 g of p-methoxymandelamide (XII) was heated in a sealed glass tube at 100° for 12 h. Excess of hexafluoroacetone was drive off, and the residue was treated with 10% sodium hydroxide, filtered off, and washed with water. We obtained 0.83 g (90.7%) of (XIII), m. p. 60-62° (from heptane). Found: C 43.62; H 2.44; F 34.27%. $C_{12}H_8F_6O_4$. Calculated: C 43.64; H 2.40; F 34.54%.

A mixture of 1 ml of hexafluoroacetone, 0.17 g of the hydroxy amide (XII), 0.05 g of p-toluenesulfonic acid, and 5 ml of toluene was heated in a sealed tube for eight hours at 150-170°. The product was washed with water, toluene was distilled off, and we obtained 0.21 g (64.3%) of (XIII), m. p. 59-61° (from heptane), undepressed by admixture of the substance obtained in the preceding experiment.

Hexafluoroacetone (1.6 ml) was passed into a solution of 0.41 g of p-methoxymandelic acid in 4 ml of dimethylformamide, and a little sodium acetate was then added. After four days the reaction mixture was poured into 15 ml of water. The precipitated oil was extracted with ether, and the extract was washed with alkali and dried. Ether was driven off, and the residue was crystallized from aqueous alcohol. We obtained 0.54 g (68.6%) of (XIII), m. p. 60-61°, undepressed in a mixture test.

Hexafluoroacetone (1.5 ml) was passed into a suspension of 0.47 g of (XII) in 5 ml of dry ether, and the precipitate went into solution. On the next day the ethereal solution was poured into 10 ml of 10% aqueous potassium hydroxide, the alkaline layer was separated and acidified, and the precipitated oil was extracted with ether. By vacuum fractionation we isolated hexafluoroacetone hydrate. The residue (0.3 g) was identified as the hydroxy amide (XII), m. p. 162-164°.

2,2'-(Hexafluoroisopropylidenedioxy)bis[2-p-methoxyphenylacetamide] (XVI). Hexafluoroacetone (2.6 ml) was passed into a solution of 1.4 g of p-anisaldehyde cyanohydrin in 15 ml of dry ether. On the next day the solution was saturated with dry hydrogen chloride and left at 0°. After one week a crystalline precipitate had formed and was treated with sodium bicarbonate. We obtained 0.84 g (40.6%) of (XVI), m. p. 168° (decomp.) (from benzene). Found: C 50.63; H 3.58; F 22.59; N 5.65%. $C_{21}H_{20}F_6O_6N_2$. Calculated: C 49.50; H 3.92; F 22.41; N 5.52%.

3,3,3-Trifluoro-2-hydroxy-2-(trifluoromethyl)propiophenone (XVII). 4.5 g of hexafluoroacetone cyanohydrin in 10 ml of ether was added to the Grignard reagent from 8.7 g of bromobenzene and 1.4 g of magnesium in 30 ml of ether with stirring and cooling and at such a rate that the temperature did not exceed −30°. The temperature was raised to 0° in the course of two hours, and it was kept at 0° for two hours. The mixture was decomposed with 1:5 hydrochloric acid, and the ether layer was separated and washed with 5% aqueous sodium hydroxide. The oil precipitated on acidification was extracted with ether, and the extract was dried with magnesium sulfate. The residue remaining after the removal of ether was vacuum-distilled. We obtained 2.88 g (45.4%) of (XVII); b. p. 110-112° (40 mm), b. p. 42.5-44° (from petroleum ether). Found: C 43.81; H 2.18; F 41.84%. $C_{10}H_6F_6O_2$. Calculated: C 44.13; H 2.20; F 41.90%.

SUMMARY

1. By the condensation of hexafluoroacetone with aromatic aldehyde cyanohydrins in presence of alkali 5-aryl-2,2-bistrifluoromethyl-4-oxazolidinones were obtained.

2. The introduction of two trifluoromethyl groups in the 2-position of 4-oxazolidinone raises the stability of the heterocycle toward alkalies and acids and increases the mobility of the hydrogen atom of the imino groups (reaction with diazomethane and ketene).

3. By the reaction of hexafluoroacetone with p-methoxymandelamide 5-p-methoxyphenyl-2,2-bistrifluoromethyl-1,3-dioxolan-4-one was obtained.

4. The formation of 5-aryl-2,2-bistrifluoromethyl-4-oxazolidinones is regarded as the result of the rearrangement of the intermediately formed 5-aryl-2,2-bistrifluoromethyl-1,3-dioxolan-4-imines due to the migration of the hemiacetal residue to the doubly bound nitrogen.

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