CONDENSATION OF HEXAFLUOROACETONE WITH CYANOHYDRINS

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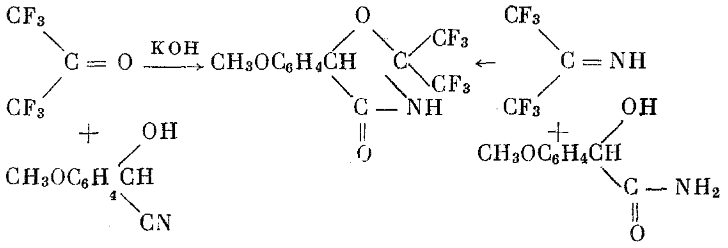
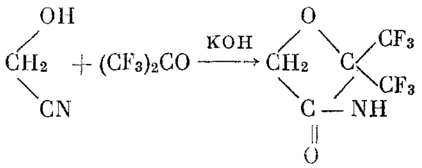
Previously we had reported [1] that the condensation of hexafluoroacetone with the cyanohydrins of aromatic aldehydes in the presence of alkali leads to 2,2-bis(trifluoromethyl)-5-aryl-4-oxazolidones. The structure of the most detailed studied compound, 2,2-bis(trifluoromethyl)-5-p-methoxyphenyl-4-oxazolidone, was proved conclusively by counter synthesis from hexafluoroacetone imine and the amide of p-methoxymandelic acid.

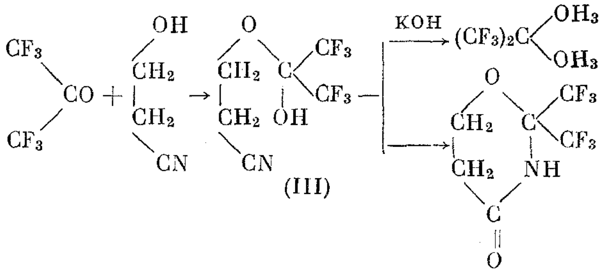


The nitrile of glycolic acid enters into the reaction in the same manner as the cyanohydrins of aromatic aldehydes.



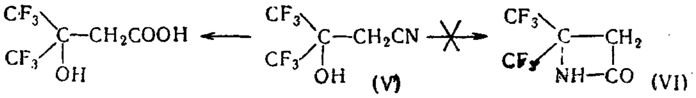
(II)

The reaction of hexafluoroacetone with ethylene cyanohydrin goes in an entirely different manner. In this case the polyketal (III) is formed, which in the presence of the alkali is decomposed into the starting components. The same thing happens when (III) is heated in an open system or even when treated with water. Only when the heating was done in a sealed ampul were we able to obtain 2,2-bis(trifluoromethyl)-4-ketotetrahydro-1,3-oxazine (IV) in low yield.



(IV)

It could be expected that the nitrile of β-hydroxy-β,β-bis(trifluoromethyl)propionic acid (V), under the reaction conditions found by us, would give the β-lactam (VI). However, only the corresponding acid was obtained when (V) was treated with alkali. We were also unable to obtain (VI) when (V) was heated at 200° in the presence of triethylamine hydrochloride.



EXPERIMENTAL

2,2-Bis(trifluoromethyl)-5-p-methoxyphenyl-4-oxazolidone (I). A mixture of 0.1 g of p-methoxymandelic acid and 0.2 g of hexafluoroacetone imine [2] was heated in a sealed ampul at 160° for 18 h. The mixture was treated with ether and filtered. The ether was washed with 5% NaOH solution and then with water. The alkaline extracts were acidified and the obtained oil was extracted with ether. We obtained 0.1 g (51% of theory) of the oxazolidone (I), m. p. 122-124° (from heptane). The mixed melting point with the authentic compound [1] was not depressed.

2,2-Bis(trifluoromethyl)-4-oxazolidone (II). 4.5 g of hexafluoroacetone was passed into a solution of 1.25 g of glycolonitrile in 10 ml of absolute ether. The next day, the mixture was poured into 30 ml of 10% alcoholic NaOH solution,* diluted with water, acidified, and extracted with ether. After distilling off the ether and hexafluoroacetone hydrate we obtained 1.85 g (37.6% of theory) of (II), m. p. 74-76° (from heptane). Found: C 26.82; H 1.34; F 51.8; N 6.42%. $C_5H_3F_6O_2N$. Calculated: C 26.9; H 1.39; F 51.3; N 6.27%. Infrared spectrum: 1755 cm^{-1} (C=O group), 3092, 3190 cm^{-1} (N=H bond).

2-(β-Cyanoethoxy)-2-hydroxyhexafluoropropane (III). With ice water cooling, 13.5 g of hexafluoroacetone was passed into a solution of 5.25 g of ethylene cyanohydrin in 30 ml of absolute ether. The next day the ether was distilled off in vacuo. The solid residue was recrystallized from a mixture of hexane and benzene. We obtained 13.2 g (84% of theory) of the polyketal (III), m. p. 73-76°. Found: C 30.03; H 2.31; N 5.86%. $C_6H_5F_6O_2N$. Calculated: C 30.18; H 2.23; N 5.92%. Infrared spectrum: 2270 cm^{-1} (C≡N group).

A solution of 1.4 g of polyketal (III) in 8 ml of water was extracted with ether, and the ether extract was dried over magnesium sulfate. Fractional distillation gave 0.78 g (72% of theory) of hexafluoroacetone hydrate, b. p. 53-55° (80 mm).

11.6 g of polyketal (III) was heated using a reflux condenser, which was connected to a trap cooled to −78°. The pot temperature was raised from 140 to 180° in 1 h. Here we collected 7.5 g (92% of theory) of hexafluoroacetone in the trap.

2,2-Bis(trifluoromethyl)-4-ketotetrahydro-1,3-oxazine (IV). 17 g of polyketal (III) was heated in a sealed ampul at 150° for 16 h. The mass was extracted with ether, and the ether extract was washed first with 10% caustic solution, and then with water. The alkaline extracts were acidified, and the obtained oil was extracted with ether. The residue from distilling off the ether and hexafluoroacetone hydrate was sublimed at 1 mm and 120-150°. We obtained 2.45 g (14% of theory) of the oxazine, m. p. 120-121° (from benzene). Found: C 30.35; H 2.26; F 48.62; N 6.05%. $C_6H_5F_6O_2N$. Calculated: C 30.18; H 2.23; F 48.11; N 5.92%. Infrared spectrum: 1719 cm^{-1} (C=O group), 3092, 3200 cm^{-1} (N–H bond).

β-Hydroxy-β,β-bis(trifluoromethyl)propionitrile (V). With ice cooling, 26 g of hexafluoroacetone was passed into a solution of 13 g of cyanoacetic acid in 25 ml of absolute pyridine. After 24 h the mass was poured into 200 ml of hydrochloric acid (1 : 5), cooled to 0°, after which it was extracted with ether and the ether extract was dried over magnesium sulfate. Fractional distillation gave 24.6 g (77.8% of theory) of the hydroxy nitrile, b. p. 182-184°, 120-122° (80 mm); n_D^{20} 1.3431. Found: C 29.04; H 1.44; N 6.85%. $C_5H_3F_6ON$. Calculated: C 29.01; H 1.45; N 6.76%.

0.88 g of the hydroxy nitrile was mixed with 0.4 g of aniline. Recrystallization from heptane gave 1.16 g (90% of theory) of the aniline salt of the hydroxy nitrile (V), m. p. 50-52°. Found: C 44.15; H 3.33; F 37.64%. $C_{11}H_{10}F_6ON_2$. Calculated: C 43.98; H 3.34; F 38.1%.

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*When treated with aqueous caustic, like in [1], the yield of (II) was 4-6%.

A mixture of 0.51 g of the hydroxy nitrile and 8 ml of 10% NaOH solution was heated under reflux for 7 h, acidified, and extracted with ether. We obtained 0.5 g (90% of theory) of β-hydroxy-β,β-bis(trifluoromethyl)-propionic acid, m. p. 79-82°. The mixed melting point with the authentic compound [3] was not depressed.

SUMMARY

1. The reaction of hexafluoroacetone imine with the amide of p-methoxymandelic acid gave 2,2-bis(trifluoromethyl)-5-p-methoxyphenyl-4-oxazolidone.

2. A study was made of the condensation of hexafluoroacetone with glycolonitrile and with ethylene cyanohydrin.

LITERATURE CITED

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