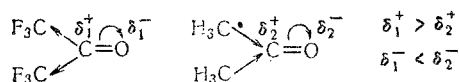


SOME REACTIONS OF HEXAFLUOROACETONE

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and E. M. Rokhlin

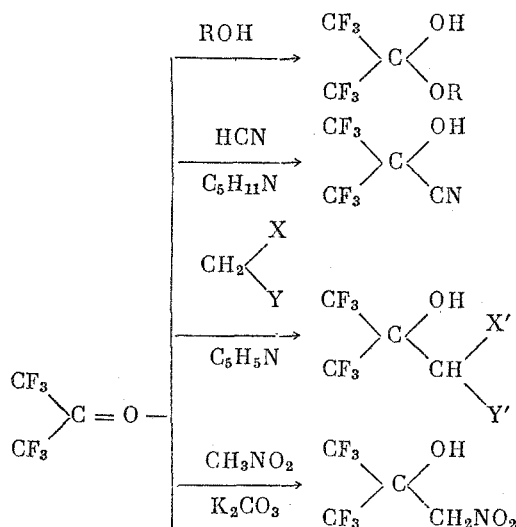
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Translated from *Izvestiya Akademii Nauk SSSR, Otdelenie Khimicheskikh Nauk*,
No. 4, pp. 684-692, April, 1962
Original article submitted November 24, 1961

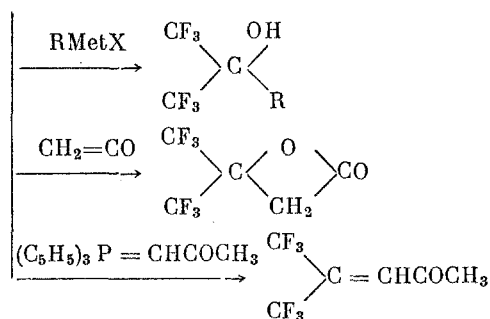
Some years ago we started a study in our laboratory of the properties of fluorine-containing ketones and, in particular, of hexafluoroacetone, the simplest and most accessible [1] perfluoro ketone. Before we began our researches on hexafluoroacetone only isolated cases had been described in the literature of the reaction of this ketone with nucleophilic reagents, namely the reactions with water [2], semicarbazide [2, 3], 2,4-dinitrophenylhydrazine [4], and trifluoromethylmagnesium bromide [5]. While our researches were in progress, some American authors [6] published the results of an investigation of the reaction of hexafluoroacetone with 2-chloroethanol in presence of potassium carbonate and with sodium acetylide. A study of the chemical properties of hexafluoroacetone was of interest because in view of the powerful electron-acceptor effect of two trifluoromethyl groups this compound could be expected to behave in an unusual way. The increase in the partial positive charge on the carbon atom and reduction in the partial negative charge on the oxygen atom must result in strongly marked electrophilic character in the hexafluoroacetone



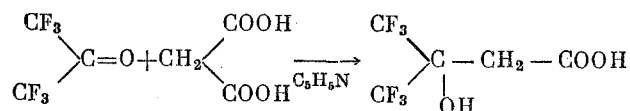
molecule. Actually, hexafluoroacetone reacts with nucleophilic reagents much more readily than the usual ketones (e.g., acetone) do and even more readily than many aldehydes. On the other hand, it reacts with more difficulty with electrophilic reagents.

The examples of the reaction of hexafluoroacetone with nucleophilic reagents studied in our laboratory are fairly numerous: the addition of alcohols with formation of hemiacetals [7], the addition of hydrocyanic acid in presence of pyridine [8], the Knoevenagel-Doebner reaction [7-10], the reaction with nitromethane [9], the reaction with organometallic compounds [7], the reaction with ketene [11], and the Wittig reaction [12]:

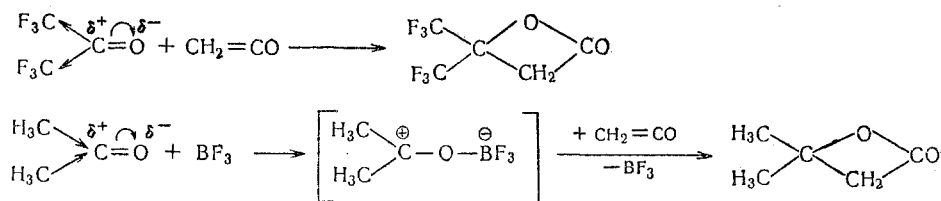




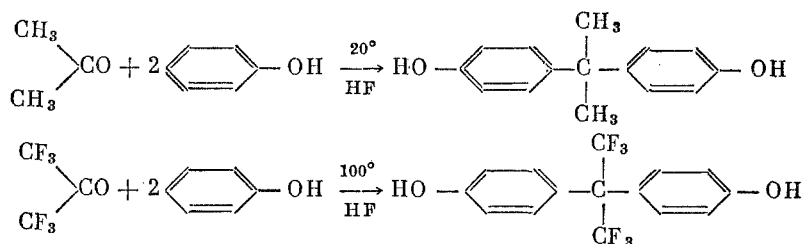
In some cases there is direct proof that hexafluoroacetone is more active than acetone in these reactions. Thus, in pyridine solution acetone does not react with malonic acid under the conditions under which hexafluoroacetone reacts almost quantitatively [9]



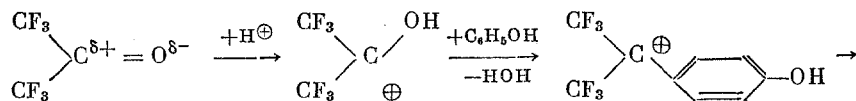
Also, hexafluoroacetone reacts with ketene in absence of catalysts at -78° [11], whereas for reaction of acetone with ketene it is necessary first to activate the ketene with an acid catalyst, e.g., boron trifluoride [13].

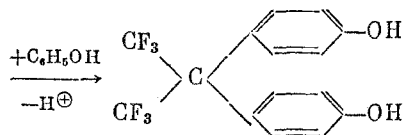


As regards the reaction of hexafluoroacetone with electrophilic reagents, the number of examples of such reactions is limited because of the low activity of hexafluoroacetone. Thus, from acetone and phenol in anhydrous hydrogen fluoride at room temperature 4,4'-isopropylidenediphenol is formed [14], whereas hexafluoroacetone does not react at all under these conditions, and only at 100° does it give the expected product, 4,4'-(hexafluoroisopropylidene)diphenol [7, 14]:

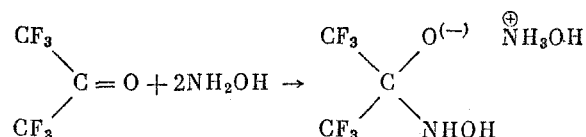


The lower activity of hexafluoroacetone is clearly to be explained by the fact that the given reaction starts with electrophilic attack of a proton on the oxygen atom of the carbonyl compound [14]:

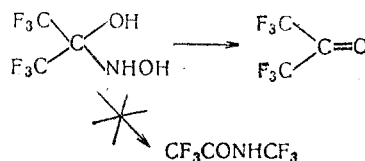




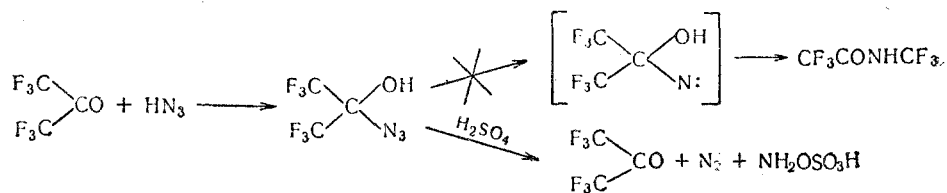
The present paper is concerned with some further reactions of hexafluoroacetone that have been studied in our laboratory. Hexafluoroacetone readily reacts with hydroxylamine with formation of the hydroxylamine salt of N-(hexafluorohydroxyisopropyl)hydroxylamine:



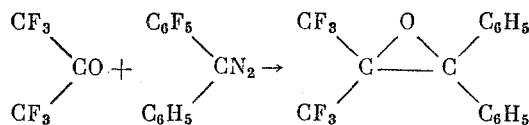
On treatment with concentrated sulfuric acid this compound does not undergo the Beckmann rearrangement, but is decomposed with formation of hexafluoroacetone:



The strongly marked electrophilic character of hexafluoroacetone ensures its ready reaction with such a weakly nucleophilic compound as hydrazoic acid. The reaction of ketones with hydrazoic acid usually occurs only in presence of acid catalysts. Reaction begins with electrophilic attack on the carbonyl oxygen atom; the intermediately formed hydroxy azide, which it is generally impossible to isolate, immediately undergoes decomposition and rearrangement (the Schmidt rearrangement [15]). Hexafluoroacetone reacts with hydrazoic acid without catalysts with formation of 2-azido-hexafluoro-2-propanol; a similar hydroxy azide was obtained by England [16] from perfluorocyclobutanone and hydrazoic acid. Attempts to convert 2-azido-hexafluoro-2-propanol into 2,2,2-trifluoro-N-(trifluoromethyl) acetamide by heating it with sulfuric acid were not successful: instead of the Schmidt rearrangement, there occurred the reverse reaction of cleavage of the hydroxy azide with liberation of hexafluoroacetone.

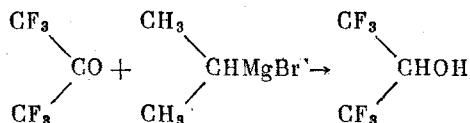


Reaction of hexafluoroacetone, with diazodiphenylmethane in the usual way led to 1,2-epoxy-1,1,-diphenyl-2,2-bistrifluoromethylethane:



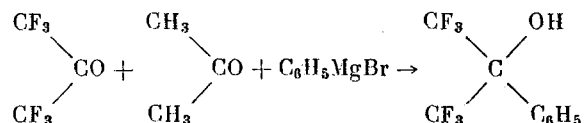
The analogous reaction of other fluorinated ketones with unsubstituted diazomethane was studied by Simons and Wiley [6].

On reaction of hexafluoroacetone with ethylmagnesium bromide the corresponding tertiary alcohol was formed [7]. However, with isopropylmagnesium bromide hexafluoroacetone does not give isopropylbistrifluoromethylmethanol: only the reduction product, hexafluoroisopropyl alcohol, is obtained (on the reduction of carbonyl compounds with Grignard reagents, see e.g., [17]).

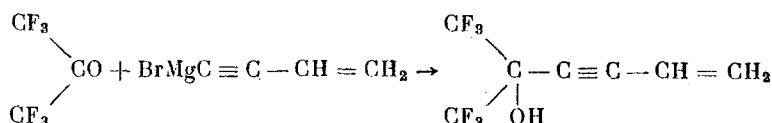


The same secondary alcohol was obtained in our laboratory by the reduction of hexafluoroacetone with sodium borohydride [18].

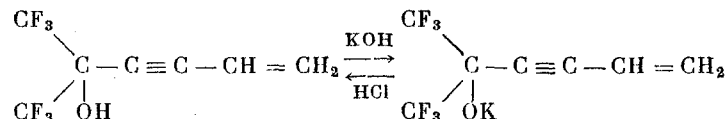
Still another confirmation of the special readiness with which hexafluoroacetone reacts with nucleophilic reagents was obtained in the study of the reaction of hexafluoroacetone with phenylmagnesium bromide in presence of an equivalent amount of acetone. This gave α,α -bistrifluoromethylbenzyl alcohol, and the presence of acetone had no effect on the yield of the fluorinated alcohol.



Much interest was presented by the study of the reaction of hexafluoroacetone with 3-buten-1-ynylmagnesium bromide with the object of preparing 1,1-bistrifluoromethyl-4-penten-2-yn-1-ol, the nonfluorinated analog of which is capable of a number of interesting transformations [19]. Hexafluoroacetone reacts smoothly with 3-buten-1-ynylmagnesium bromide in diethyl or dibutyl ether with formation of the expected alcohol, which was isolated as an azeotropic mixture with the solvent.

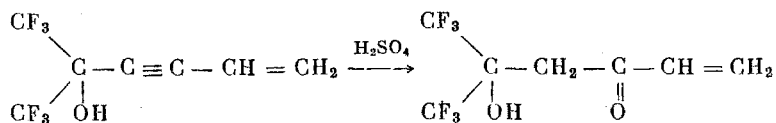


On treatment of the azeotrope with concentrated alkali the corresponding salt of the alcohol is liberated, as occurs in the case of other bistrifluoromethylmethanols [7]. The pure alcohol can be isolated by treatment with acid.



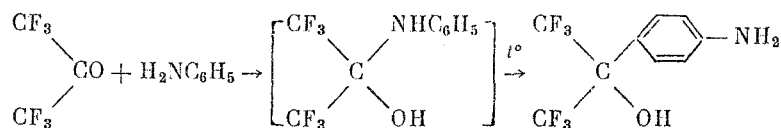
Another method of resolving the azeotropic mixture, namely treatment with concentrated sulfuric acid [7], cannot be used in the given case, as the alcohol is then hydrated. As a result of hydration 1,1-bistrifluoromethyl-4-penten-2-yn-1-ol is probably converted into a β -hydroxy ketone, like (phenylethynyl)bistrifluoromethylmethanol [7].

The fact that 1-hydroxy-1,1-bistrifluoromethyl-4-penten-3-one is not dehydrated into the corresponding divinyl ketone under the conditions of reaction is explained by the effect of the trifluoromethyl groups, the presence of which strengthens the C-O link.

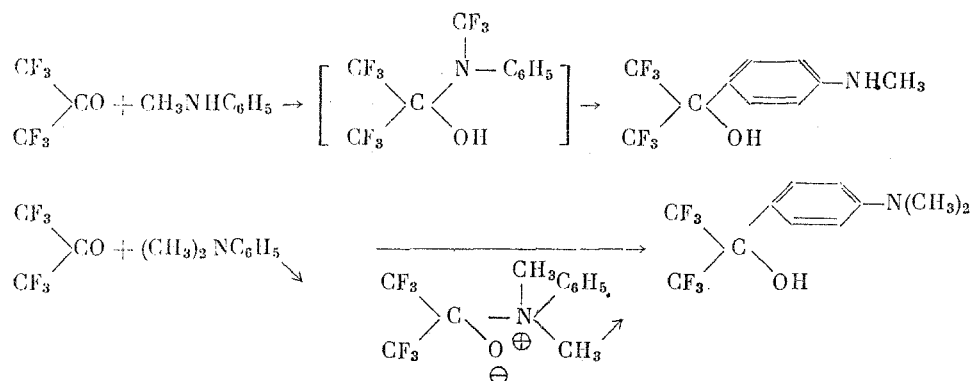


By the polymerization of 1,1-bistrifluoromethyl-4-penten-2-yn-1-ol in presence of benzoyl peroxide a colorless glassy mass is formed, softening point about 150°.

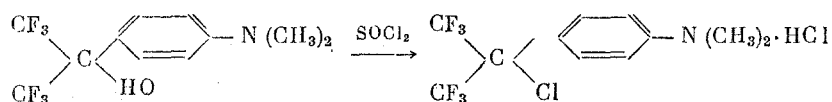
The reaction of hexfluoroacetone with aniline was described earlier [14]. Here, as a result of the rearrangement of the intermediately formed geminal hydroxy amine we obtained p-amino- α,α -bistrifluoromethylbenzyl alcohol:



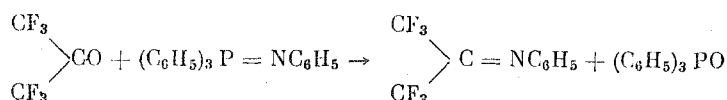
In the present work we studied the reaction of hexafluoroacetone in the form of its hydrate with N-methyl- and N,N-dimethyl-anilines. In spite of the fact that in the latter case a geminal hydroxy amine cannot be formed, the corresponding alcohols were obtained from both of the aniline derivatives. Therefore, either hexafluoroacetone attacks the para position of the dimethylaniline molecule directly; or a bipolar ion with an ammonium nitrogen is formed intermediately.



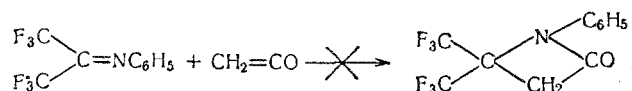
By the reaction of p-dimethylamino- α,α -bistrifluorobenzyl alcohol with thionyl chloride in the cold we obtained p-(chlorohexafluoroisopropyl)-N,N-dimethylaniline hydrochloride:



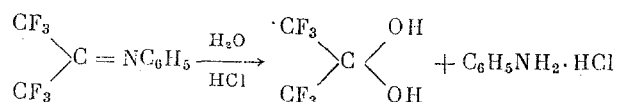
As we did not succeed in eliminating water from the primary product of the addition of aniline to hexafluoroacetone, the anil of hexafluoroacetone was prepared by a roundabout way: with the aid of N,P,P,P-tetraphenylphosphine imine (cf. [20]):



This anil was found to be a compound of low activity; thus, it is not affected by prolonged boiling with water. Treatment with ketene, even in presence of pyridine or boron trifluoride etherate, did not lead to the formation of the corresponding β -lactam: only the unchanged anil was isolated.

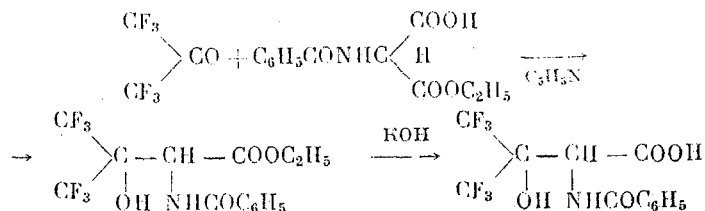


On treatment of the anil with concentrated hydrochloric acid in the cold it is hydrolyzed:



As mentioned above, in the Knoevenagel-Doebner reaction hexafluoroacetone gives a hydroxy compound [7, 9]. By using ethyl hydrogen benzamidomalonate in this reaction we obtained a derivative of substituted serine,

namely ethyl 2-benzamido-3-hydroxy-3,3-bistrifluoromethylpropionate. Hydrolysis of this ester gave the corresponding free acid.



EXPERIMENTAL

Hydroxylamine Salt of N-(Hexafluoroisopropyl)hydroxylamine. Excess of hexafluoroacetone was passed into a suspension of 5.4 g of hydroxylamine in 50 ml of dry ether. The mixture was left overnight, and the ethereal solution was then decanted from the small amount of undissolved precipitate. Ether was distilled off, and we obtained 4.5 g (32.6%) of the salt, m.p. 60-63° (from heptane). Found: C 15.56; H 2.71; F 48.71; N 12.11%, $\text{C}_3\text{H}_6\text{F}_6\text{O}_3\text{N}_2$. Calculated: C 15.52; H 2.61; F 49.12; N 12.07%.

When the hydroxylamine salt was heated with 96% sulfuric acid to 100°, an 86% yield of hexafluoroacetone was collected in a trap cooled with solid carbon dioxide; the dianiline salt of the hydrate had m.p. 64-66°, undepressed by admixture of a known sample.

2-Azido-2-hydroxy-2-(trifluoromethyl)propanol. Hexafluoroacetone (60 g) was passed into a water-cooled solution of 12.0 g of hydrazoic acid in 250 ml of dibutyl ether. On fractionation through a column we obtained 14.5 g of excess hexafluoroacetone and 43.23 g (74.2%) of the hydroxy azide; b.p. 69-70°; n_D^{20} 1.3310; d_4^{20} 1.6036. Found: C 18.02; H 0.82; F 53.11%; neutralization equivalent 103; MR 26.66. $\text{C}_3\text{HF}_6\text{ON}_3$. Calculated: C 17.23; H 0.48; F 54.55%; neutralization equivalent 104.5; MR 26.41.

On reaction of hexafluoroacetone with hydrazoic acid in diethyl ether we obtained an azeotropic mixture containing 77.1% of the hydroxy azide and 22.9% of diethyl ether; b.p. 85.5-86.7°; n_D^{20} 1.3420; d_4^{20} 1.2437. Found: C 28.89; H 3.68; F 42.06%; neutralization equivalent 138. 77.1% $\text{C}_3\text{HF}_6\text{ON}_3$ + 22.9% $\text{C}_4\text{H}_{10}\text{O}$. Calculated: C 28.14; H 3.47; F 42.06%; neutralization equivalent 136.

When the hydroxy azide was heated with 1% oleum in a boiling water bath, we collected 85% of the theoretical amount of hexafluoroacetone in a trap cooled with solid carbon dioxide. Semicarbazide, m.p. 160-163° (decomp.), undepressed by admixture of a known sample. We collected 99% of the theoretical amount of nitrogen in a gas holder.

1,2-Epoxy-1,1-diphenyl-2,2-bistrifluoromethylethane. Hexafluoroacetone (4.5 g) was passed into a solution of 5 g of diazodiphenylmethane in dry ether. After two days distillation gave 3.3 g (38.5%) of the epoxide; b.p. 105-107° (5 mm); m.p. 60-60.5° (from alcohol). Found: C 57.83; H 3.07; F 33.43%. $\text{C}_{16}\text{H}_{10}\text{F}_6\text{O}$. Calculated: C 57.83; H 3.01; F 34.33%.

Hexafluoroisopropyl Alcohol. Hexafluoroacetone (10.2 g) was passed into a solution of Grignard reagent (from 1.7 g of magnesium and 9.7 g of isopropyl bromide in 35 ml of dibutyl ether) at -25°. The mixture was acidified with dilute hydrochloric acid and extracted with dibutyl ether. Fractionation through a column gave 5.2 g of hexafluoroacetone hydrate and 5.2 g (93.5% on the hexafluoroacetone that reacted) of hexafluoroisopropyl alcohol; b.p. 57-58°; n_D^{22} 1.2750; $d_4^{20.5}$ 1.4563. Found: C 22.01; H 1.37; F 67.88%; MR 20.18. $\text{C}_3\text{H}_2\text{F}_6\text{O}$. Calculated: C 21.43; H 1.19; F 67.85%; MR 18.40.

Comparison of the Activities of Acetone and Hexafluoroacetone in Reaction with Phenylmagnesium Bromide. Hexafluoroacetone (12.3 g) was passed into a mixture of 100 ml of ether and 4.29 g of acetone at -60°. A Grignard reagent prepared from 1.79 g of magnesium and 11.6 g of bromobenzene in 80 ml of ether was added with stirring. After the usual treatment, by vacuum distillation we obtained 5 g of hexafluoroacetone hydrate and 11.2 g (97% calculated on the hexafluoroacetone that reacted and 65% calculated on the Grignard reagent) of α,α -bistrifluoromethylbenzyl alcohol, b.p. 72-74° (35 mm), identical with the product obtained in absence of acetone [7].

1,1-Bistrifluoromethyl-4-penten-2-yn-1-ol. Into a solution of the Grignard reagent from 2.67 g of magnesium and 12 g of ethyl bromide in 90 ml of dry ether we passed 6.4 g of butenyne and then 16.7 g of hexafluoroacetone

with cooling with ice and salt. After the usual treatment we obtained 17.5 g of an azeotropic mixture of the alcohol and diethyl ether containing 85.7% of the alcohol, i.e., 15.0 g (68.6%) of the pure alcohol. The boiling point of the azeotrope was 59-60° (80 mm); $n_D^{22.5}$ 1.3668; d_4^{20} 1.2795. Found: C 41.25; H 3.21; F 44.72%. 85.7% $C_7H_4F_6O$ + 14.3% $C_4H_{10}O$. Calculated: C 42.27; H 3.00; F 44.72%. In an analogous way we obtained the azeotrope with dibutyl ether, b.p. 60-62° (65 mm).

For the isolation of pure 1,1-bistrifluoromethyl-4-penten-2-yn-1-ol the azeotrope with dibutyl ether was treated with 50% potassium hydroxide. The resulting salt was washed with petroleum ether and introduced into dilute hydrochloric acid; the oil that separated was dried and distilled. We obtained 1,1-bistrifluoromethyl-4-penten-2-yn-1-ol; b.p. 61-63° (77 mm); n_D^{21} 1.3672; d_4^{20} 1.3753. Found: C 38.14; H 1.93%; MR 36.66. $C_7H_4F_6O$. Calculated: C 38.53; H 1.83%; MR 34.43.

When the alcohol was heated in a boiling water bath in presence of benzoyl peroxide in an atmosphere of nitrogen, the liquid gradually thickened and was finally converted into a colorless glass of softening point about 150°.

1-Hydroxy-1,1-bistrifluoromethyl-4-penten-3-one. 17.5 g of the azeotropic mixture of 1,1-bistrifluoromethyl-4-penten-2-yn-1-ol and diethyl ether was treated with 30 ml of concentrated sulfuric acid. The mixture was poured into water and extracted with ether. By distillation of the ether extract we obtained 3.9 g of unchanged 1,1-bistrifluoromethyl-4-penten-2-yn-1-ol, 2.9 g (24%) of 1-hydroxy-1,1-bistrifluoromethyl-4-penten-3-one, and 3.7 g of resinous residue. The boiling point of 1-hydroxy-1,1-bistrifluoromethyl-4-penten-3-one was 40-42° (3 mm); $n_D^{20.5}$ 1.3625; d_4^{20} 1.4564. Found: C 34.48; H 2.62; F 48.83%. $C_7H_5F_6O_2$. Calculated: C 35.59; H 2.54; F 48.30%. 2,4-Dinitrophenylhydrazone, m.p. 131-131.5° (from alcohol). Found: C 37.13; H 2.42; F 27.43; N 13.73%. $C_{13}H_{10}F_6H_5N_4$. Calculated: C 37.43; H 2.40; F 27.40; N 13.46%.

p-Methylamino- α,α -bistrifluoromethylbenzyl Alcohol. A mixture of 7 ml of unpurified hexafluoroacetone hydrate (see [8] and [14]) and 7 ml of N-methylaniline was boiled for 14 hours under reflux. Distillation gave 7 g of the alcohol; b.p. 135-140° (20 mm); m.p. 87-89° (from carbon tetrachloride and then from benzene). Found: C 43.58; H 3.31; F 39.31; N 5.31%. $C_{10}H_5F_6ON$. Calculated: C 43.95; H 3.32; F 41.73; N 5.19%.

p-Dimethylamino- α,α -bistrifluoromethylbenzyl Alcohol. A mixture of 8.5 ml of unpurified hexafluoroacetone hydrate (8, 11] and 8 ml of N,N-dimethylaniline was refluxed for ten hours. The precipitate was filtered off. Vacuum distillation gave 5.8 g of the alcohol; b.p. 130-133° (18 mm); m.p. 75-76° (from heptane and then from benzene). Found: C 45.78; H 3.82; F 35.43; N 4.90%. $C_{11}H_{11}F_6ON$. Calculated: C 46.00; H 3.86; F 39.69; N 4.88%.

p-(Chlorohexafluoroisopropyl)-N,N-dimethylaniline Hydrochloride. With cooling 6.4 ml of thionyl chloride was added to a solution of 3 g of p-dimethylamino- α,α -bistrifluoromethylbenzyl alcohol in 10 ml of ether. As a precipitate we obtained 2.9 g (81.4%) of the hydrochloride, m.p. 159-160° (from dichloroethane). Found: C 38.08; H 3.08; F 30.13; N 4.58; Cl 19.4%. $C_{11}H_{11}F_6NCl_2$. Calculated: C 38.61; H 3.24; F 33.32; N 4.09; Cl 20.7%.

Hexafluoroacetone Anil. Hexafluoroacetone (20 g) was passed into a suspension of 38.7 g of N,P,P,P-tetra-phenylphosphine imine in 185 ml of dry ether. The precipitate of triphenylphosphine oxide was filtered off. By distillation of the filtrate we isolated 17.53 g (65.3%) of the anil; b.p. 135-137°; 82° (120 mm); 48-49° (21 mm); n_D^{20} 1.415; d_4^{20} 1.3782. Found: C 44.81; H 1.87; F 49.33, N 6.46%; MR 43.66. $C_9H_5F_6N$. Calculated: C 44.83; H 2.09; F 47.28; N 5.81%; MR 43.67.

The anil was unchanged after prolonged boiling with water. When the anil was caused to react with concentrated hydrochloric acid in the cold with subsequent evaporation at room temperature, aniline hydrochloride was formed.

Ethyl 2-Benzamido-3-hydroxy-3,3-bistrifluoromethylpropionate. Hexafluoroacetone (13 g) was passed into a suspension of 5.35 g of ethyl hydrogen benzamidomalonate (21) in 30 ml of pyridine. After 2.5 hours the resulting solution was acidified with dilute hydrochloric acid, and 7.64 g (96%) of ethyl 2-benzamido-3-hydroxy-3,3-bistrifluoromethylpropionate, m.p. 107-109° (from heptane) was filtered off. Found: C 45.16; H 3.40; F 30.86; N 3.83%. $C_{14}H_{13}F_6O_4N$. Calculated: C 45.05; H 3.51; F 30.54; N 3.75%.

2-Benzamido-3-hydroxy-3,3-bistrifluoromethylpropionic Acid. Ethyl 2-benzamido-3-hydroxy-3,3-bistrifluoromethylpropionate (5 g) was dissolved in 5% potassium hydroxide (60 ml). After one day the solution was acidified with dilute hydrochloric acid, and 3.06 g of the acid was filtered off; a further amount - 1.07 g of the acid - was isolated from the aqueous filtrate by extraction with ether. The total yield of 2-benzamido-3-hydroxy-3,3-bistrifluoromethylpropionic acid was 4.13 g (89%); m.p. 151-152° (from dichloroethane). Found: C 41.55; H 2.53; F 32.17%. $C_{12}H_9F_6O_4N$. Calculated: C 41.75; H 2.63; F 33.02%.

SUMMARY

1. The reactions are described of hexafluoroacetone with a number of compounds: hydroxylamine, hydrazoic acid, diazodiphenylmethane, some organomagnesium compounds, N-methylated anilines, N,P,P,P-tetraphenylphosphine imine, and ethyl hydrogen benzamidomalonate.
2. The strongly marked electrophilic reactivity of hexafluoroacetone was confirmed.
3. Some reactions of compounds prepared from hexafluoroacetone are described.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
