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REACTION OF HEXAFLUOROACETONE WITH 2-PHENYL-4-BENZYLOXAZOLONE-5

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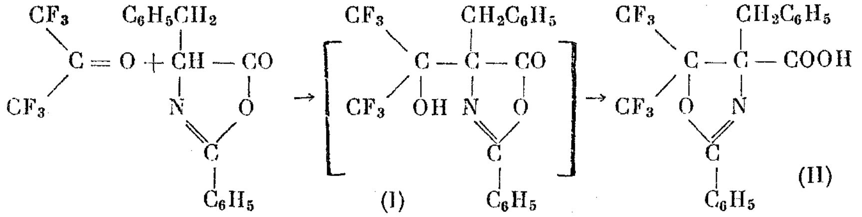
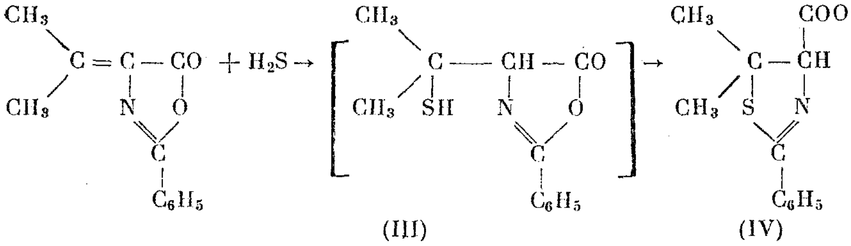
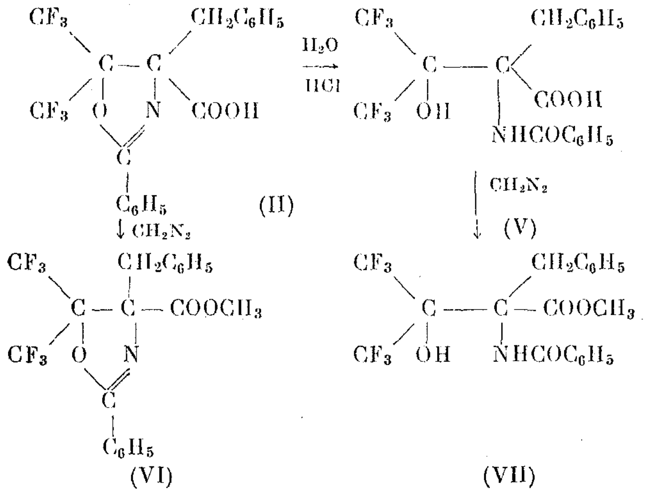
Hexafluoroacetone reacts with 2-phenyloxazolone-5 to form α-benzamidohexafluorodimethylacrylic acid [1]. Such an ease of formation of an unsaturated compounds is particularly unusual for a reaction of hexafluoroacetone with an active methylene group [2, 3]. While studying the mechanism of this reaction, we investigated the interaction of hexafluoroacetone with 2-phenyl-4-benzyloxazolone-5. Since there is no possibility of dehydration to an unsaturated compound here, one had to expect the formation of hydroxyoxazolone (I). However, the reaction product under ordinary conditions (pyridine solution, room temperature) turned out to be 2-phenyl-4-benzyl-5,5-bis-(trifluoromethyl)oxazoline-4-carboxylic acid (II), formed most likely by isomerization of hydroxyoxazolone (I). This isomerization suggests a conversion of the intermediately formed mercaptooxazolone (III) to substituted thiazolinecarboxylic acid (IV) [4]

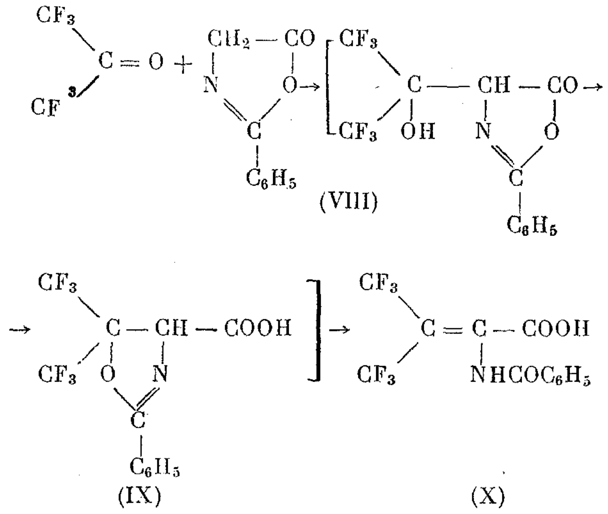




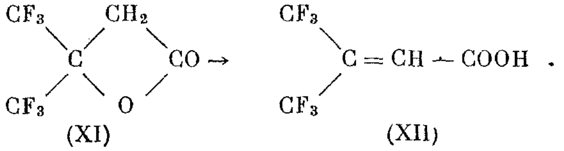
The acid (II) dissolves in a sodium bicarbonate solution, and is recovered unchanged as a precipitate on acidification. Treatment with concentrated hydrochloric acid in dioxane converts it to a serine derivative, i.e., α-benzamido-α-benzyl-β-hydroxy-β,β-bis(trifluoromethyl)propionic acid (V). Methylation of acids (II) and (V) with the help of diazomethane yields the corresponding methyl esters (VI) and (VII).



Considering the results obtained, the probable mechanism of the reaction between hexafluoroacetone and 2-phenyloxazolone-5 not substituted in the 4-position is as follows: The original reaction product, hydroxyoxazolone (VIII), isomerizes to substituted oxazolinecarboxylic acid (IX), which then rearranges with cleavage of the oxazoline ring to give α-benzamidohexafluorodimethylacrylic acid (X).



The fact that the C—O bond which is adjacent to the trifluoromethyl groups, is much easier cleaved during isomerization which involves ring rupture than during dehydration of the hydroxy derivatives substantiates the known isomerization readiness of hexafluorodimethylpropiolactone (XI) to hexafluorodimethylacrylic acid (XII) [5]



EXPERIMENTAL

2-Phenyl-4-benzyl-5,5-bis-(trifluoromethyl)oxazoline-4-carboxylic acid (II). 2.8 g of 2-phenyl-4-benzyloxazolone-5 (prepared by reaction of N-benzoylphenylalanine with ketene; m. p. 67-69°; according to literature data [6]: m. p. 69-70°) was dissolved in 16 mm pyridine, and the resulting solution was cooled with water while 6.5 g hexafluoroacetone was passed through it. After a day the mixture was poured into dilute hydrochloric acid, and extracted with ether. The ether was distilled off, which yielded 2.3 g (49% of the theoretical) of the hydrate of hexafluoroacetone (II), m. p. 133-134° (from carbon tetrachloride). Found: C 54.74; H 3.31; F 26.80; N 3.30%. $C_{19}H_{13}F_6O_3N$. Calculated: C 54.69; H 3.14; F 27.32; N 3.36%.

Methyl ester of 2-phenyl-4-benzyl-5,5-bis-(trifluoromethyl)oxazoline-4-carboxylic acid (VI). To 0.28 g of acid (II), dissolved in 6 ml ether, was added an excess of an ether solution of diazomethane until an intense yellow color appeared. The solvent was removed, and the residue washed with a sodium bicarbonate solution. This yielded 0.29 g of (VI) (quantitative yield), m. p. 92-97° (from heptane). Found: C 55.43; H 3.28; F 27.50; N 3.16%. $C_{20}H_{15}F_6O_3N$. Calculated: C 55.68; H 3.51; F 26.42; N 3.25%. The ester (VI) was insoluble in dilute alkali.

α-Benzamido-α-benzyl-β-hydroxy-β,β-bis-(trifluoromethyl)propionic acid (V). Acid (II) (0.85 g) was dissolved in a mixture of 2 ml concentrated hydrochloric acid and 12 ml dioxane. After a day the solvent was removed, the residue reprecipitated by acidification of its bicarbonate solution. Yield of (V): 0.77 g (87% of the theoretical), m. p. 162.5-163° (from carbon tetrachloride). Found: C 51.76; H 3.58; F 26.54; N 3.18%. $C_{19}H_{15}F_6O_4N$. Calculated: C 52.42; H 3.47; F 26.19; N 3.22%.

Methyl ester of α-benzamido-α-benzyl-β-hydroxy-β,β-bis-(trifluoromethyl)propionic acid (VII). Acid (V) (0.28 g) in ether solution was treated with an excess of diazomethane, the solvent removed, and the residue washed with a sodium bicarbonate solution. This yielded 0.26 g (90% of the theoretical) of (VII), m. p. 134-135° (from a mixture of hexane and petroleum ether). Found: C 53.53; H 3.67; F 25.38; N 3.08%. $C_{20}H_{17}F_6O_4N$. Calculated: C 53.46; H 3.81; F 25.37; N 3.12%. Ester (VII) was soluble in dilute alkali, and precipitated unchanged on acidification.

SUMMARY

1. Hexafluoroacetone reacts with 2-phenyl-4-benzyloxazolone-5 to give 2-phenyl-4-benzyl-5,5-bis-(trifluoromethyl)oxazoline-4-carboxylic acid.

2. Hydrolysis of 2-phenyl-4-benzyl-5,5-bis-(trifluoromethyl)oxazolinecarboxylic acid gives a derivative of serine, i.e., α-benzamido-α-benzyl-β-hydroxy-β,β-bis-(trifluoromethyl)propionic acid.

3. The data obtained favor the view that during reaction of hexafluoroacetone with 2-phenyloxazolone-5 there is intermediate formation of 2-phenyl-5,5-bis-(trifluoromethyl)oxazoline-4-carboxylic acid, which then isomerizes to α-benzamidohexafluorodimethylacrylic acid.

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