THE CYCLIZATION OF ISOPRENOID COMPOUNDS

COMMUNICATION 5. THE LOW-TEMPERATURE CYCLIZATION OF GERANIOL ACETATE"

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As has been shown earlier, under conditions of acid-catalyzed cyclization, isoprenoid alcohols give only products of the p-menthane type [1], and compounds of the cyclogeraniol series can be obtained with yields not higher than 30% only by cyclization of the corresponding acetates [2, 3].

In the present work, the possibility of using the method of low-temperature cyclization which we have used previously for isoprenoid ketones [4-6] and acids [7] for the ionone-type cyclization of isoprenoid alcohols and their acetates has been studied. It has been found that when the cyclization of geraniol [1] is carried out under the influence of 100% sulfuric acid in solution in nitropropane at -70° , α -cyclogeraniol (II) can be obtained with a yield of about 30%. This shows the possibility in principle of changing the structural direction of cyclization (in the ionone or the menthane direction) according to the conditions of carrying out the reaction. Geraniol acetate (Ia) also cyclizes readily under the conditions of low-temperature cyclization, giving cyclogeraniol acetate with a yield averaging about 70%, and this can be used as a method for its preparative production. The structure of the cyclization products was shown by



saponification to the corresponding α -cyclogeraniol, the 3,5-dinitrobenzoate of which gave no depression of the melting point in admixture with an authentic sample. The acetate of 3-methylgeraniol likewise cyclizes smoothly, forming the acetate of 6-methyl- α -cyclogeraniol, as a mixture of geometrical isomers, with a yield of 65-70%.



To analyze quantitatively the mixtures of products of the cyclization of general acetate, we used the method of gas-liquid chromatography [8]. As has been shown earlier, this method enables mixtures of the acetates of geraniol and of α - and β -cyclogeraniols to be separated sharply, as may be illustrated by the chromatogram given in Fig. 1.

By using this method of analysis we showed that the product of the cyclization of geraniol acetate at -70° contains about 82-85% of α -cyclogeraniol acetate mixed with 3% of α -cyclogeraniol and 12-15% of the hydration product of the initial geraniol acetate. β -Cyclogeraniol acetate has not been found in this mixture. We studied the acetate in detail. It was found that, in this case, as also in the cyclization of the methyl ester of geranic acid, to complete the reaction a considerable excess of sulfuric acid (about 5 mole per 1 mole of acetate) is necessary; under these conditions, the reaction is complete in about 10 min at -70° (table, experiment 1).

Exp. No.	Ratio of H_2SO_4 and starting material, moles	Solvent	Temp	Time, min.	Total yield of reaction products	Content in the mixture, %			
						(Ia)	(111)	(IIa)	(IV)
		Cycliz	ation of	gerani	ol acetate	e .			
1 2 3 4 5 6	5:1 5:1 2,5:1 2,5:1 2,5:1 2,5:1	$C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$	$\begin{vmatrix} -70 \\ -70 \\ -40 \\ -70 \\ -70 \\ -70 \\ -70 \\ -70 \\ -40 \end{vmatrix}$	$ \left \begin{array}{c} 10\\ 180\\ 10\\ 10\\ 60\\ 180\\ 60 \end{array}\right $	70 65 55 80		$ \begin{array}{c c} 15 \\ - \\ 30 \\ 50 \\ 40 \end{array} $	85 85 35 35 60	
		Conversions	of α -cy	clogera	niol aceta	ite			
7 8 9 10 11 12 13	5:1 5:1 10:1 5:1 5:1 5:1 5:1	$C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{3}$ $C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$ $C_{3}H_{7}NO_{2}$	$ \begin{array}{c}70 \\70 \\70 \\40 \\40 \\40 \\40 \end{array} $	10 180 10 60 10 60 10 10	90 80 65 70 70 65 80			100 100 90 65 75 —	-10 -10 35 25 100 100



Fig. 1. Chromatogram: peak 1) β -cyclogeraniol; peak 2) α -cyclogeraniol; peak 3) α -cyclogeraniol acetate; peak 4) geraniol acetate; peak 5) 2-acetoxymethyl-1,1,3-trimethylcyclohexan-3-ol; peak 6) 2,6-dimethyloct-6-ene-2,8-diol 8-acetate; length of column 2.5 m, diameter 5 mm; 20% silicone elastomer on 0.1-0.5 mm firebrick; column temperature 152°; carrier gas-nitrogen, 43 ml/min; volume of the sample 4 μ l. When the amount of acid is reduced to 2.5 mole per 1 mole of acetate, the reaction is markedly retarded. If, under these conditions, the reaction is broken off after an hour by decomposing the reaction mixture with water (table, experiment 5), a product which corresponds, according to the results of elementary analysis, to a hydration product of the initial geraniol acetate and which is converted into the latter on dehydration can be isolated. By analogy with the hydration of the ester of geranic acid studied earlier [7], we assign to the hydration product of geraniol acetate the structure of the 8-acetate of 2,6-dimethyloct-6-ene-2,8-diol (VIII)



If the reaction mixture giving the hydration product (III) on decomposition with water is kept for some time (1 hour) at -40° , the predominant formation of the normal cyclization product takes place. Geraniol acetate cyclizes far

more readily and rapidly than the methyl ester of geranic acid [4], which is probably connected with the highly nucleophilic character of the 6,7-double bond in it as compared with the same bond when conjugated with the carboxyl group in geranic acid. We have made a detailed study of the behavior of α -cyclogeraniol acetate (IIa) under the conditions which we used earlier for the isomerization of α -ionone into the β -isomer [4]. It was found that, as in the case of α -ionone, the α -isomer is very stable at -70° and is recovered completely unchanged after being kept for 3 hours with 5 moles of sulfuric acid (table, experiment 8). However, simply increasing the amount of acid to 10 moles per 1 mole of α -cyclogeraniol acetate leads to its further conversion even at -70° , and after only an hour a considerable amount (about 30%) of its hydration product (IV) could be isolated (table, experiment 10).

The structure of the product (IV) follows from its elementary analysis and ease of dehydration leading to the formation of a mixture of cyclogeraniol acetates containing, according to the results of gas-liquid chromatography, mainly the α -isomer (80%), mixed with about 15-20% of the



 β -isomer. The formation of the hydration product (IV) takes place far more readily than the isomerization of α -ionone into the β -isomer under comparable conditions. Thus, at -40° under the action of 5 moles of sulfuric acid in nitromethane solution α -ionone is isomerized into β -ionone almost completely after only 10 hours [4] while under analogous conditions α -cyclogeraniol acetate is completely converted into the hydration product (IV) after only 10 minutes (table, experiment 13). It is interesting that a striking difference in the ease with which the hydration reaction takes place in nitromethane and in nitropropane is found. Thus, in the presence of 5 moles of sulfuric acid in nitromethane, the hydration reaction (strictly speaking the formation of the intermediate complex giving the hydration product on decomposition with water) is complete after 10 min, while in solution in nitropropane it requires ~1 hour for completion (compare experiments 13 and 12 in the table). The experimental results described above permit the mechanism of the conversions observed to be illustrated in the following way



The isolation of the product (III) when the cyclization is not carried to completion indicates with sufficient certainty the formation in the first phase of the reaction of intermediate complexes of the type of A and B, which are generally accepted in considering the mechanism of the hydration of olefins [9]. On the other hand, a carbonium ion of type D [10, 11] cannot be an intermediate stage in the cyclization reaction, since, if this were not the case, cyclization should lead directly to the hydration product (IV), which does not in fact take place. On this basis, it may be considered that the most probable intermediate product in the cyclization reaction has the type C structure (non-classical cation or π -complex).

The idea of the formation of such intermediate products is one of Ruzicka's main assumptions in considering questions of the biogenesis of the terpenes [12]. The results which we have obtained may be considered as one of the arguments in favor of the correctness of this assumption. It was of definite interest to study the behavior of β -cy-clogeraniol acetate under acid conditions; however, this could not be carried out, since it resinified completely even under fairly mild conditions (-40°). Consequently, it is impossible to exclude the possibility that in the cyclization of geraniol acetate, as in the subsequent conversions of α -cyclogeraniol acetate, the formation of a certain amount of the β -isomer, which cannot be isolated on account of its polymerization, takes place. The amount of this isomer cannot be large (the yields of distilled products generally amounted to 70-80%) and the possibility of its formation in no way essentially affects the scheme given above.

EXPERIMENTAL*

The initial geraniol was obtained by a known method [13] and purified through its calcium chloride complex; its acetate was prepared by acetylation with ketone. The α -cyclogeraniol acetate used in the hydration experiments was obtained from α -cyclogeranic acid (by reducing its methyl ester with lithium aluminum hydride), and subsequent acetylation with ketone. The individuality of the starting materials and the composition of the reaction products were determined in all cases by the method of gas-liquid chromatography using a silicone elastomer deposited on refractory brick as the liquid phase. The temperature of the analysis was 140-160°, and the carrier gas was nitrogen, 35-40 ml/min. As a rule, the mixture of acetates of geraniol and of α - and β -cyclogeraniols was separated from the products of their hydration by vacuum distillation. When mixtures containing hydration products were analyzed by gas-liquid chromatography, it was necessary to use glass columns with a glass evaporator to avoid dehydration.

Since the method of carrying out the experiments was a standard one, descriptions of only the most typical experiments are given below, the remaining material being incorporated in the table.

Cyclization of geraniol (I). A solution of 10.0 g of geraniol in 10 ml of nitropropane was added to a solution of 15 ml of sulfuric acid (100%) in 50 ml of nitropropane with stirring at such a rate that the temperature did not rise above -60° (~5 min). The mixture was kept for a further 5 minutes at this temperature and was then poured into ice water and extracted with petroleum ether. The extract was washed with water, sodium bicarbonate solution, and water again, and dried with sodium sulfate. After distilling off the solvent and vacuum distillation, 2.9 g of α -cyclogeraniol (II) with b.p. 65-68° (1 mm), n_D^{20} 1.4848, was obtained. According to data in the literature [3]: b.p. 73° (at 4 mm); n_D^{20} 1.4843. By the usual method, 0.5 g of (II) yielded 0.9 g of the 3,5-dinitrobenzoate which, after recrystallization from methanol, had m.p. 60.5-61.5° and gave no depression of the melting point in admixture with an authentic sample of α -cyclogeraniol 3,5-dinitrobenzoate. Found: C 58.89, 58.70; H 5.98, 6.02%. C₁₇H₂₀O₆N₂. Calculated: C 58.61; H 5.78%.

<u>Cyclization of geraniol acetate (Ia)</u>. In a similar manner to the preceding experiment, 10.0 g of (Ia) yielded 6.5 g of α -cyclogeraniol acetate (IIa) with b.p. 85-87° (1 mm); n_D^{20} 1.4676. According to data in the literature [3]: b.p. 98° (10 mm), n_D^{20} 1.4632. Found: C 73.73, 73.57; H 10.03, 10.00%. C₁₂H₂₀O₂. Calculated: C 73.42; H 10.26%. From the results of gas-liquid chromatography, the (Ia) contained 85% of the α -isomer, with 12% of (III) and 3% of (II).

On saponification, 5.0 g of the α -cyclogeraniol acetate yielded 3.1 g of α -cyclogeraniol (II) with b.p. 60-64° (5 mm), n_D²⁰ 1.4848, which gave a 3,5-dinitrobenzoate with m.p. 60.5-61°, identical with that described above.

<u>Cyclization of 3-methylgeraniol acetate</u>. The initial 3-methylgeraniol was obtained from 3-methyllinalool by the method described earlier for the synthesis of geraniol from linalool [3]. The yield of 3-methylgeraniol was 50%; the product obtained had b.p. 76-80° (1 mm), n_D^{20} 1.4813, and gave a diphenylurethane with m.p. 96-97° (from petroleum ether). According to data in the literature [14]: b.p. 93-94° (2 mm), n_D^{20} 1.4814. The 3-methylgeraniol acetate was obtained by acetylation with ketone.

A solution of 10 g of the 3-methylgeraniol acetate obtained above in 15 ml of nitropropane was added with stirring to a solution of 15 ml of sulfuric acid (100%) in 50 ml of nitropropane at -70° . The solution was stirred for a further 5 min and was then poured into a mixture of 250 ml of ice water and 150 ml of ether. After the usual working up and distillation, this yielded 7.0 g of 6-methyl- α -cyclogeraniol acetate (IVa) with b.p. 92-95° (1 mm), n_{D}^{22} 1.4710. Found: C 74.20, 74.00; H 10.56, 10.75%. C₁₃H₂₂O₂. Calculated: C 74.24; H 10.54%.

From the results of gas-liquid chromatography, the acetate obtained consisted of a mixture (1:1) of two structural isomers (apparently cis-trans isomers with respect to the position of the methyl group at C₆). Saponification of 4.0 g of the 6-methyl- α -cyclogeraniol with alcoholic alkali yielded 2.7 g of 6-methyl- α -cyclogeraniol with b.p. 69-71° (1 mm), n²⁰_D 1.4890, 3.5-dinitrobenzoate liquid. According to data in the literature [15]: b.p. 110-115° (10 mm) n²⁰_D 1.4862.

A 2.1 g sample of the 6-methyl- α -cyclogeraniol acetate was hydrogenated in CH₃COOH solution over platina (from PtO₂). After the absorption of 1 mole of hydrogen, hydrogenation ceased (even on heating to 60°); 1.70 g of 6-methyldihydrocyclogeraniol acetate with b.p. 82-84° (1 mm); n¹⁸_D 1.4638, was obtained, which, on saponification gave 6-methyldihydrocyclogeraniol with b.p. 85-87° (1 mm), n²⁰_D 1.4790.

Hydration of α -cyclogeraniol acetate (IIa). A solution of 2.0 g of α -cyclogeraniol acetate (IIa) in 5 ml of nitromethane was added over 6 min with stirring at -35° to a solution of 2.7 g (5 mole per mole of acetate) of sulfuric acid (100%) in 10 ml of nitromethane. After the mixture had been kept at this temperature for 5 minutes, it was worked up as described above. This yielded 1.75 g of 2-acetoxymethyl-1,1,3-trimethylcyclohexan-3-ol (IV)

^{*}Carried out with the participation of T. N. Chernova.

in the form of a viscous liquid with b.p. 120-125° (3 mm), n_D^{20} 1.4720. Found: C 67.71, 67.55; H 10.15, 9.98%. C₁₂H₂₂O₃. Calculated: C 67.25; H 10.35%.

Dehydration of 1.5 g of this product (heating with KHSO₄ at 100° for 20 min in the vacuum of a water-jet pump) yielded 1.2 g of cyclogeraniol acetate (IV) with b.p. 83-84° (2 mm), n_D^{20} 1.4680. According to the results of gas-liquid chromatography, the dehydration product contained about 80-85% of α -cyclogeraniol acetate, mixed with the β isomer and an unidentified component. The saponification product from (IV) gave a crystalline 3,5-dinitrobenzoate with m.p. 45-51°, from which, after repeated crystallization from methanol, crystals with m.p. 56-58°, giving no depression of the melting point with the 3,5-dinitrobenzoate of authentic α -cyclogeraniol were obtained. The 3,5-dinitrobenzoate of β -cyclogeraniol had m.p. 82-83°; the 2-acetoxymethyl-1,1,3-trimethylcyclohexan-3-ol (IV) is not oxidized by chromic anhydride in acetic acid in the cold, and on heating oxidation takes place with destruction of the molecule. On saponification by the usual method, it yielded 2-hydroxymethyl-1,1,3-trimethylcyclohexan-3-ol in the form of a very viscous liquid with b.p. 115-120° (1 mm), n_D^{20} 1,4840, giving a 3,5-dinitrobenzoate (with a yield of ~50%) melting at 111,5-112° (from methanol). Found: C 55,47, 55,35; H 6,22, 6,13%. C₁₇H₂₂O₇N₂. Calculated: C 55,73; H 6,05%.

Hydration of geraniol acetate (Ia). A solution of 2.0 g of geraniol acetate in 3 ml of nitropropane was added over 10 min, with stirring and cooling to -70° , to a solution of 0.8 ml of sulfuric acid in 7.5 ml of nitropropane. The mixture was kept at this temperature for a further 3 hours and was then worked up as described above. Distillation of the reaction product yielded two fractions: fraction I) 0.55 g with b.p. 65-70° (1 mm); n_D^{20} 1.4652; and fraction II) 0.6 g with b.p. 70-73° (0.09 mm), n_D^{20} 1.4670. From the results of analysis by gas-liquid chromatography, fraction I consisted of almost pure α -cyclogeraniol acetate. Fraction II, when chromatographed in a glass column with a glass evaporator, gave a peak corresponding to the hydration product of (III) and differing sharply from the peak of the hydration product of cyclogeraniol acetate (IV). From the results of elementary analysis, fraction II represents the product of the addition of 1 molecule of water to geraniol acetate. Found: C 66.84, 67.02; H 10.10, 10.31%. C₁₂H₂₂O₃. Calculated: C 67.25; H 10.35%.

On heating the substance (III) with potassium bisulfate at 100°, dehydration took place with the formation of geraniol acetate as the main product.

SUMMARY

1. The applicability of the method of low-temperature cyclization to the cyclization of the acetates of isoprenoid alcohols by ionone-type cyclization has been shown. A preparative method for the production of α -cyclogeraniol acetate has been given.

2. With a small amount of acid, the cyclization of geraniol acetate takes place slowly, and, by carrying it out incompletely, the product of the hydration of the initial acetate (III) has been isolated.

3. Under the conditions of a large excess of acid, α -cyclogeraniol acetate does not isomerize into the β -isomer, but gives the hydration product (IV).

4. The mechanism of the conversion described has been considered.

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