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## SUPERACID CYCLIZATION OF HOMO- AND BISHOMOISOPRENOID ACIDS

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The superacid cyclization of a number of homo- and bishomoterpenoid acids, the products of which are  $\gamma$ - and  $\delta$ lactones —important natural compounds or intermediates for the synthesis and manufacture of valuable substances — was investigated. It is shown that the superacid cyclization of homo- and bishomoterpenoid acids to  $\gamma$ - and  $\delta$ lactones proceeds stereospecifically, chemoselectively, and structurally selectively, is general in character, and ensures high yields of the desired products.

We have previously shown [1-3] that the superacid cyclization of stereoisomeric isoprene alcohols and their acetates is a highly effective, structurally selective, chemospecific, and stereospecific process. The superacid cyclization of homoand bishomo-E,E-farnesols also proceeds similarly and gives the corresponding tetrahydrofuran and tetrahydropyran derivatives [4]. Considering the properties of superacids, one might have expected that they would also be effective in the cyclization of homo- and bishomoterpenoid acids to, respectively,  $\gamma$ - and  $\delta$ -lactones.

In the present communication we present the results of a study of the superacid cyclization of a number of homoand bishomoisoprenoid acids, the products of which should be  $\gamma$ - and  $\delta$ -lactones, which are important natural compounds and are of interest as intermediates for the synthesis or manufacture of substances of practical value.

Homogeranic acid (I) was the simplest subject of our study. The expected product of its cyclization — transtetrahydroactinidiolide (II) [5] and its cis isomer (III) are contained in tobacco [6]. It should be noted that dihydroactinidiolide (IV), into which tetrahydroactinidiolides II and III can be readily converted [7, 8], are components of the essential oils from *Actinidia polygama* [9] and *Acacia farnesiana* [10], the pheromone of red ants [8], and the fragrant substances that are responsible for the odor of tea [11, 12], tobacco [13], and tomatoes [14].

Numerous publications have been devoted to the study of the cyclization of homogeranic acid (I). Stannic chloride, tin triflat, and other reagents have been used as cyclizing agents [15, 16]. The reaction proceeds in good overall yields, but either a mixture of lactones II and III or cis-lactone III but not II is formed in all cases. The reason for this is the ready isomerization in an acidic medium of trans-lactone III to the thermodynamically more stable cis-lactone III. Moreover, isomerization can be suppressed only when dimethylaniline is added to tin triflat, and trans-lactone II is obtained in good yield [17].

The only reaction product, which is formed in 81% yield, that is obtained as a result of the cyclization of homogenatic acid (I) by means of fluorosulfonic acid in 2-nitropropane at -75°C to -80°C at a cyclizing reagent:substrate ratio of 5:1 is II; cis isomer III is not detected.

Under the same conditions trans- $\delta$ -lactone VI is obtained in 95% yield from geranylacetic acid [18]. Side products are also absent in this case. The cyclization of geranylacetic acid (V) was previously accomplished by the action of a mixture of sulfuric and formic acids [18] and 100% sulfuric [19] and tetrafluoroboric [20] acids. The highest yield of  $\delta$ -lactone VI (69%) was obtained in the reaction of V with tetrafluoroboric acid, but the formation also of spiro- $\delta$ lactone VII was noted in this case [20] (see scheme on page 247).

Norambreinolide (IX) — an important intermediate in the manufacture of perfumes with the smell of amber — was obtained in excellent yield (93%) by cyclization of E,E-homofarnesylic acid (VIII) with fluorosulfonic acid under the same conditions. In addition, a small amount (~4%) of an acidic fraction was isolated. The effect of the reaction conditions on the yield of lactone IX was investigated in greater detail in the case of acid VIII (see Table 1). It was found that the yield decreases by only 5% when the reaction temperature is increased to  $-55^{\circ}$ C, but only 40 min are required for completion of the reaction. The 2 reaction also proceeds successfully at a cyclizing agent:substrate ratio of 1:1 and is complete after 2.5 h.

Institute of Chemistry, Academy of Sciences of Moldavia, Kishinev 277028. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 305-309, March, 1991. Original article submitted July 27, 1989. Let us note that the cyclization of homofarnesylic acid (VIII) with a mixture of concentrated sulfuric acid and 100% formic acid gives not norambreinolide (IX) but rather a small amount of its epimer X with cis-fused lactone and cyclohexane rings [21], whereas a mixture of lactones IX and X in a ratio of ~1:1 is obtained in 50% yield in the case of cyclization with 100% sulfuric acid in acetic acid [22]. Acid VIII reacts with boron trifluoride etherate to give a complex mixture of substances, from which lactone IX was isolated in ~38% yield [23]. According to a patent [24], stannic chloride in methylene chloride is an effective cyclizing agent for acid VIII (the yield of unpurified lactone IX is ~91%). In addition, the data in this patent contradict the results of Saito and coworkers [23], who, in the cyclization of homofarnesylic acid (VIII) with the same reagent, isolated a mixture of lactones IX and X in low yield.



The production of norambreinolide (IX) in the same yield (93%) also in the superacid lactonization of a mixture of isomeric bicyclohomofarnesenic acids XI possibly indicates that the overall result of the cyclization of homofarnesylic acid (VIII) is determined by the effective formation, under the reaction conditions, of bicyclic carbonium ion intermediate XII.

The lactonization of a mixture of acids XI with ordinary acids (a mixture of concentrated sulfuric and nitric acids) proceeds structurally unselectively and leads to a mixture of substances (the yield of lactone IX is 35%) [25].

(+)-Ambreinolide (XIV) (85% yield), which is a valuable intermediate in the manufacture of perfumes — substitutes for ambergris — is formed in the superacid cyclization of E,E-farnesylic acid (XIII) [26]. Let us note that the yield of lactone XIV in the cyclization of acid XIII with a mixture of concentrated sulfuric and acetic acids is ~14% [27]. The superacid lactonization of a mixture of isomeric bicyclofarnesylic acids XV to (+)-ambreinolide (XIV) (92% yield) also proceeds smoothly, although a mixture of concentrated sulfuric and acetic acids is also a good catalyst for this reaction (85%) [28] (see scheme on page 248).

TABLE 1. Results of Cyclization of E,E-Homofarnesylic Acid (VIII) by Means of	of
Fluorosulfonic Acid	

Reactio	n condit	ions	Vield of	React			
substrate VIII:FSO <sub>3</sub> H, moles	<i>T</i> ±2 ℃	t, h	(±)-IX, %	substrate VIII:FSO <sub>3</sub> H, moles	T ±2 ℃	<sup>t,</sup> h	Yield of (±)-IX, %
1:5 1:5 1:5 1:5	78 72 88 55	1.5 1.5 1.5 0.7	93 88 91 88	1:10 1:10 1:15 1:1	-68 -78 -78 -78 -78	0,5 0,8 1,5 2,5	86 87 91 71*

\*Taking into account unchanged starting acid VIII (24%).

## TABLE 2. Results of Cyclization of Homo- and Bishomoisoprenoid Acids by Means of Fluorosulfonic Acid

Substrate	t,* h	Reaction product	mp, °C	Yield,%	Literature
Homogeranic acid (I) Geranylacetic acid (V) Isomeric mixture of $\Delta^{7(\cdot 8)}$ -, $\Delta^{8(9)}$ -, and $\Delta^{8(20)}$ -bicyclohomofarnesylic acids XI	1,5 0,75 1,5	Lactone II Lactone VI Norambreinolide (IX)	7073 4445,5 122124	81 96 93	[20] [18] [25]
E,E-Bishomofarnesylic acid (XIII)	1,5	(±)-Ambreinolide	130 132	85	[27]
Isomeric mixture of $\Delta^{7(8)}$ -, $\Delta^{8(9)}$ - and $\Delta^{8(20)}$ -bycyclobishomofarnesylic acids	1,5	(XIV) (±)-Ambreinolide (XIV)	131 132,5	92	[28]
Isometric mixture of bicylogeranyl- geranylacetic acids XVI	0,33	Mixture of lactones XVII and XVIII	132 133 34 36,5	79 (XVII) 16 (XVIII)	[29]

\*t is the reaction time.

We established that a mixture (~5:1) of  $\delta$ -lactones XVII and XVIII, the structures of which were proved on the basis of spectral data and chemical transformations [29], is formed in 95% yield in the superacid cyclization of a mixture of isomeric bicyclogeranylgeranylacetic acids XVI. These lactones are valuable intermediates for the synthesis of tri- and tetracyclic sesterterpenoids.

Thus, according to our studies, the cyclization of homo- and bishomoisoprenoid acids to  $\gamma$ - and  $\delta$ -lactones by means of superacids proceeds stereospecifically, chemically selectively, structurally selectively, is general in character, and ensures high yields of the desired products. In contrast to this, cyclization of the indicated substances by ordinary and Lewis acids proceeds structurally unselectively and, consequently, ineffectively: the yields of the desired products are low, complex mixtures of substances are formed, and in each specific case it is necessary to carry out an empirical search for the reagents and cyclization conditions.



## **EXPERIMENTAL**

See [4] for the general part.

The results of elementary analysis for C and H correspond to the calculated values.

Cyclization of Homo- or Bishomoisoprenoid Acids by Means of Fluorosulfonic Acid (General Method). A solution of 0.67 mmole of the homo- or bishomoisoprenoid acid in 2 ml of 2-nitropropane cooled to  $-78^{\circ}$ C was added with stirring at the same temperature to a solution of 3.3 mmole of fluorosulfonic acid in 2.5 ml of 2-nitropropane, after which the mixture was stirred for the necessary time (monitoring by TLC; see Table 2). A 0.65-ml sample of triethylamine and 5 ml of water were added to the solution, and the product was extracted with ether (three 10-ml portions). The extract was washed successively with water (two 10-ml portions), a saturated solution of sodium bicarbonate (10 ml), and water (two 10-ml portions), dried, and filtered, and the solvent was removed by vacuum distillation. The known substances were identified by comparison with authentic samples.

**Lactone XVII** ( $C_{22}H_{36}O_2$ ). This compound had mp 132-133°C (from petroleum ether) and  $[\alpha]_D^{20} + 12.8°$  (c 1.1, CHCl<sub>3</sub>). IR spectrum: 1708 cm<sup>-1</sup> ( $\delta$ -lactone). PMR spectrum (CCl<sub>4</sub>),  $\delta$ , ppm: 0.80 (9H, s, 3CH<sub>3</sub>), 0.85 (3H, s, CH<sub>3</sub>), 1.15 (3H, s, CH<sub>3</sub>), 2.33 (2H, m, CH<sub>2</sub>COO). Mass spectrum, m/z (%): 332 (M<sup>+</sup>, 31), 317 (29), 260 (62), 245 (18), 204 (29), 191 (63), 136 (96), 123 (44), 104 (47), 69 (100).

**Lactone XVIII** ( $C_{22}H_{36}O_2$ ). This compound had mp 34-36.5°C (from petroleum ether) and  $[\alpha]_D^{22} - 23.5°$  (c 1.9; CHCl<sub>3</sub>). IR spectrum: 1740 cm<sup>-1</sup> ( $\delta$ -lactone). PMR spectrum (CCl<sub>4</sub>),  $\delta$ , ppm: 0.77 (6H, s, two CH<sub>3</sub>), 0.92 (6H, s, two CH<sub>3</sub>), 1.25 (3H, s, CH<sub>3</sub>), 2.33 (2H, m, CH<sub>2</sub>COO).

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