SYNTHESIS OF 3*a*,6,6,9*a*-TETRAMETHYL-trans-PERHYDRONAPHTHO[2,1-b]FURAN AND 4*a*,7,7,10*a*-TETRAMETHYL-trans-PERHYDRONAPHTHO[2,1-b]PYRAN

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The compounds 3*a*,6,6,9*a*-tetramethyl-trans-perhydronaphtho[2,1-b]furan (ambrox or ambroxide) and 4*a*,7,7,10*a*-tetramethyl-trans-perhydronaphtho[2,1-b]pyran (homofixator) – substances important in the perfume industry – have been synthesized by superacid cyclization of E,E-homofarnesol and E,E-bishomofarnesol or mixtures of the isomeric bicyclohomofarnesenes or bicyclobishomofarnesenols. Superacid cyclization of these alcohols was shown to be an effective structurally selective and stereospecific method of obtaining ambroxide and homofixator.

(3*a*R,9*a*S,9bR)-3*a*,6,6,9*a*-Tetramethyl-trans-perhydronaphtho[2,1-b]furan (I), known as ambrox or ambroxide, and (4*a*R,10*a*S,10bR)-4*a*,7,7,10*a*-tetramethyl-trans-perhydronaphtho[2,1-b]pyran (II) (homofixator) are important in the perfume industry and are widely used as substitutes for ambergris [1, 2].

In all the reported syntheses of both optically active and racemic oxides I and II, the final stage involves the dehydration of the glycols III-V, which are generally obtained by the hydride reduction of the corresponding γ- and δ-lactones [2, 3]. In turn, the optically active forms of the latter were synthesized from naturally occurring diterpenoids and their racemic forms – by catalytic acid cyclization of unsaturated acids. In both cases, the yields of the lactones were often low; in addition, the dehydration of the glycols III-V by certain dehydrating agents gave ambiguous results [2]. Therefore it was of interest to study the possibility of synthesizing the oxides I and II by the cyclization of the corresponding aliphatic and bicyclic unsaturated alcohols: A favorable result from this synthesis would exclude lactonization. The preparation of the oxides I and II by such a route has never been reported.

The tetrahydrofurans and tetrahydropyrans can be obtained from the acid-catalyzed cyclization of Δ^3- and Δ^4-ethylene alcohols [4]. However, in the presence of the usual acids, the yields of the reaction products are often low, because, for the reaction to be successful, the substrate must satisfy certain structural requirements (for example, cyclization takes place only with alcohols that are di- or more highly substituted at the double bond) and, furthermore, side reactions (dehydration, rearrangement, reaction with external nucleophiles, etc.) occur.

In contrast to the standard acids, superacids have been reported [5, 6] to suppress elimination reactions and reactions with external nucleophiles, and should therefore facilitate attack of the carbocation generated by suitably configured intramolecular nucleophilic groups – for example, hydroxyl groups. In fact, the few available examples [7-9] showed that the action of unsaturated alcohols with superacids gave oxides in good yield.

In the present communication, we present results of a study of the reaction of E,E-homofarnesol VI, E,E-bishomofarnesol VII, mixtures of isomeric Δ^7- and Δ^8-bicyclohomofarnesenols VIII, Δ^7- and Δ^8-bicyclobishomofarnesenols IX with fluorosulfonic acid. The alcohols VI and VII were obtained by the reduction of the corresponding acids X and XI using lithium aluminum hydride. The first of these was synthesized by the method given in [10], and the second by a modification of the method of Dietrich and Lederer [11]. E,E-Homofarnesol VI was identified by comparison with a sample obtained by the authors [12].* E,E-Bishomofarnesol VII has not been reported; its structure was confirmed by IR and PMR spectral data. A mixture of isomeric Δ^7- and Δ^8-bicyclohomofarnesenols VIII were isolated from industrial waste from the production of ambroxide [13], and a mixture of Δ^7- and Δ^8-bicyclobishomofarnesenols IX were synthesized by the lithium aluminum hydride reduction of a mixture of bicyclobishomofarnesyl acids XII, obtained as described in [14].

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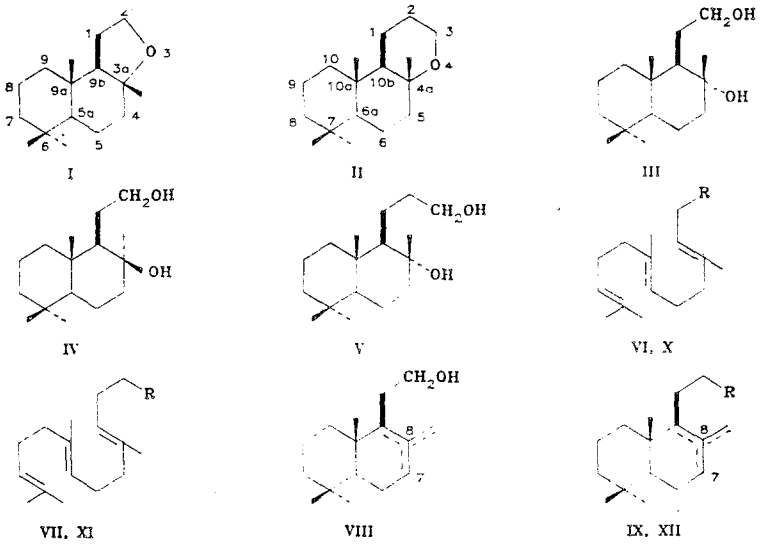

VI, VII, IX R=CH_2OH; X, XI, XII R=CO_2H

As can be seen from Table 1, the main product of the reaction of E,E-homofarnesol VI with fluorosulfonic acid in 2-nitropropane is the racemic ambroxide I. In addition, a hydrocarbon fraction (5-9%), which was not further studied, and a polymeric product were obtained. The amount of the latter increased with increasing temperature and with increasing reaction time (see Table 1), and this occurred even when the ratio of cyclizing agent to alcohol VI was increased. The maximum yield of ambroxide I was obtained when the reaction was carried out at $-80 \pm 2°C$ with a molar ratio of FSO_3H-alcohol VI of 10:1 (Table 1, test 7). At a lower temperature (test 8) the yield of ambroxide decreased, possibly because of the increase in the reaction time necessary for its completion. Basically, the yield and ratio of products depended largely on whether the reaction was carried out at $-70 \pm 2°C$ for the shortest period of time (test 6) or at $-80 \pm 2°C$ for twice the time with half the amount of cyclizing agent (test 5).

The ambroxide I (levorotatory enantiomer) was also formed in good yield (78.5%) by the cyclization of a mixture of bicyclic unsaturated alcohols VIII. In this case the yield of oxide I was greater than from the cyclization of the aliphatic alcohol VI, no hydrocarbons were formed, and the only by-product was polymeric. The best yield of the optically active ambroxide I also was obtained with a 10:1 ratio of FSO_3H-substrate, although when half the amount of fluorosulfonic acid was used, the yield little (76%).

The data given above indicate that superacid cyclization of trans,trans-homofarnesol VI, or a mixture of Δ^7- and Δ^8-bicyclohomofarnesols VII is a structurally selective and stereospecific process.

These results can be used to explain the stereospecific transformation of 8β-bicyclohomofarnesol IV to ambroxide by hydrochloric acid in nitromethane [3]. Apparently, a hydroxyl group splits from the side chain to give a carbocation at $C_{(8)}$ (directly or through the intermediate formation of unsaturated alcohols VIII) and this is followed by stereospecific attack by the hydroxyl group from the side chain.

Cyclization of E,E-bishomofarnesol VII under conditions which are optimum for its lower homolog VI, did not take place satisfactorily; the main reaction product was a mixture of polymeric substances, even when the reaction time was shortened by 2.5 times (Table 2, test 3) the yield of oxide II did not exceed 42%. Under these conditions, a fairly large amount of hydrocarbon and polymer were formed, although the reaction did not go to completion. For the reaction to go to completion in a short time, the temperature of the reaction had to be increased (Table 2, test 1), but the yield of oxide II fell, and more than 40% of polymeric material was formed. A good yield of the oxide II was obtained only when the amount of cyclizing agent was considerably increased (up to 25 moles per mole of substrate) and the reaction time was decreased to 20 min (test 6). When the reaction time was further decreased (test 5) more than 20% of the starting alcohol VII was recovered unchanged.

When the ratio of fluorosulfonic acid to alcohol VII was decreased (test 4), or increased (test 9), other conditions being the same, the yield of oxide II decreased, while the amount of polymeric product increased.

The heterocyclization of a mixture of the bicyclic alcohols IX to the oxide II went successfully under conditions (alcohol IX-FXO_3H, 1:10, -75 to $-80°C$, 20 min), considerably milder than those needed for the cyclization of the aliphatic alcohol VII, and a higher yield of oxide II was obtained. The best results were obtained with a 10:1 ratio of fluorosulfonic acid to substrate.

TABLE 1. Cyclization of E,E-Homofarnesol VI with Fluorosulfonic Acid in 2-Nitropropane

Test	Alcohol VI:FSO_3H, mole/mole	Temperature of reaction, °C	Time of reaction, h	Yield, %		
				(±) Ambroxide I	hydrocarbons	polymeric materials
1	1 : 1	−40±2	1,0	55,2	8,9	30,7
2	1 : 5	−32±2	0,12	50	9,3	37,5
3	1 : 5	−50±2	1,0	51,1	8,5	37,0
4	1 : 5	−60±2	1,0	57,7	7,5	32,4
5	1 : 5	−80±2	3,5	70,8	4,7	20,1
6	1 : 10	−70±2	1,7	71,3	6,2	18,2
7	1 : 10	−80±2	2,5	72,7	5,5	17,0
8	1 : 10	−90±2	3,2	70,4	4,5	19,8
9	1 : 15	−80±2	2,0	69,8	6,3	20,3

TABLE 2. Cyclization of E,E-Bishomofarnesol VII with Fluorosulfonic Acid in 2-Nitropropane

Test*	Alcohol VII:FSO_3H, mole/mole	Temperature of reaction, h	Reaction time, minutes	Yield, %		
				(±) oxide II	hydrocarbon	polymer substances
1	1 : 10	−32±2	30	34,7	17,7	44,0
2	1 : 10	−42±2	30	42,5	12,8	40,9
3	1 : 10	−82±2	54	41,8	18,7	26,3
4	1 : 15	−47±2	20	57,7	9,1	28,6
5	1 : 25	−47±2	10	72,5	6,4	17,9
6	1 : 25	−47±2	20	69,6	7,4	19,2
7	1 : 25	−50±2	15	62,8	8,4	23,6
8	1 : 25	−47±2	120	17,3	11,7	65,7
9	1 : 30	−47±2	20	53,3	12,0	31,4

*In tests 2-5 the amount of the starting alcohol recovered was 42.3, 60.0, 12.5, and 23.3%, respectively. Yields of reaction products under these conditions are given based on the alcohol VII reacted.

alcohol VII, and a higher yield of oxide II was obtained. The best results were obtained with a 10:1 ratio of fluorosulfonic acid to substrate.

These results show that the superacid cyclization of the unsaturated alcohols VI-IX is an effective structurally selective and stereospecific method of obtaining ambroxide I and homofixator II, compounds which are important in the perfume industry.

EXPERIMENTAL

Melting points were determined with a Boetius apparatus. IR spectra of solutions of the compounds in CCl_4 were taken on a Specord IR-74. PMR were recorded on a Tesla BS-467 (60 MHz), internal standard TMS. Solutions of the substances in organic solvents were dried over anhydrous sodium sulfate. Petroleum ether bp 40-60°C was used. For the column we used silica gel L 100/160 μm; for TLC, LS 5/40 μm. Fluorosulfonic acid was purified by double distillation. 2-Nitropropane was purified by distillation over anhydrous potassium chloride. Triethylamine was twice distilled over potassium hydroxide.

Elemental analysis data (C, H) were in good agreement with calculated values.

E,E-Homofarnesol (VI). Lithium aluminum hydride (240 mg, 6.3 mmoles) was added to a solution of E,E-homofarnesyl acid X (800 mg, 3.2 mmoles) in absolute ether (10 ml) and the mixture heated under reflux for 3 h. Excess lithium

aluminum hydride was decomposed with ethyl acetate (5 ml), 10% sulfuric acid (15 ml) was then added and the mixture extracted with ether (3 × 10 ml). The ether extract was washed with water (2 × 10 ml), saturated $NaHCO_3$ solution (10 ml), water (10 ml), dried, filtered, and the solvent evaporated in vacuum to give 702 ml (93%) of E,E-homofarnesol VI, identified by comparison with a known sample [12]: n_D^{22} 1.4852; IR spectrum: 1050, 3460 cm^{-1} (OH).

Cyclization of E,E-Homofarnesol (VI). To a solution of E,E-homofarnesol VI (33 mg, 0.14 mmoles) in 2-nitropropane (0.3 ml) at –80 ± 2°C was added with mixing fluorosulfonic acid (140 mg, 1.4 mmoles) in 2-nitropropane (0.2 ml) cooled to the same temperature. The solution was mixed for 2.5 h at this temperature, triethylamine (0.28 ml) and water (10 ml) added, and the mixture extracted with petroleum ether (3 × 5 ml). The ether extract was washed with water to neutral reaction, dried, filtered, and the solvent evaporated. The residue (31.4 mg) was chromatographed on a column with 0.7 g silica gel. The hydrocarbon fraction (1.8 mg) was washed with petroleum ether, and a 19:1 mixture of petroleum ether and ethyl acetate to give 24 mg (~73%) of (±)-3*a*,6,6,9*a*-tetramethyl-trans-perhydronaphtho[2,1-b]furan I with mp 70.5-73°C (from methanol), identified by chromatography and by spectral comparison with an optically active sample. In this example, the optimum conditions for cyclization are described (Table 1, experiment 7). The conditions and results for the remaining experiments are given in Table 1.

Cyclization of a Mixture of Δ^7- and Δ^8-Bicyclohomofarnesenols (VIII). A. To a solution of fluorosulfonic acid (850 mg, 8.5 mmoles) in 2-nitropropane (2.3 ml) at –75 to –78°C was added a solution of a mixture of alcohols VIII (200 mg, 0.84 mmole) in 2-nitropropane (1.5 ml) at the same temperature. The mixture was held at this temperature and stirred for 1.5 h. Triethylamine (1.7 ml) was then added, followed by water (15 ml) and the mixture extracted with ether (3 × 10 ml). The ether extract was washed with water to neutral reaction, dried, filtered, the solvent evaporated in vacuum and the residue (182 mg) chromatographed on a column of 3.5 g of silica gel. Washing with a mixture of petroleum ether and ethyl acetate (19:1) gave (–)-ambroxide (157 mg, 78.5%) with mp 72.5-74°C (from methanol); $[\alpha]_D^{22}$ –26.2°C (c = 1.8, $CHCl_3$). The compound gave no depression of melting point when mixed with an authentic sample, and the IR spectrum was also identical with that of the known material.

B. To a mixture of alcohols VIII (150 mg, 0.64 mmole) was added fluorosulfonic acid (320 mg, 3.17 mmoles) in 2-nitropropane (3.3 ml). The mixture was worked up and purified as described in method A to give (–)-ambroxide I (114 mg, 76%) with mp 73-74°C (from methanol).

E,E-Bishomofarnesol (VII, $C_{17}H_{30}O$). To a solution of farnesylacetic acid XI (560 mg, 2.12 mmoles) [11] in absolute ether (10 ml) was added lithium aluminum hydride (120 mg, 3.16 mmoles) and the mixture heated under reflux for 3.5 h. The mixture was worked up as described above for the synthesis of homofarnesol VI to give 498.5 mg, 94% of E,E-bishomofarnesol VII as a colorless viscous liquid with n_D^{19} 1.4880. IR spectrum: 835, 1662 (>C=C<$_H$), 3334, 3630 cm^{-1} (OH). PMR spectrum (CCl_4): 1.55 (9H, s, 3 CH_3); 1.63 (3H, s, CH_3); 3.43 (2H, m, CH_2–O–); 5.05 ppm (m, 3H, vinyl H).

Cyclization of E,E-Bishomofarnesol (VII). To a solution of fluorosulfonic acid (230 mg, 2.3 mmoles) in 2-nitropropane (0.5 ml) at –47 ± 2°C was added a solution of E,E-bishomofarnesol VII (23 mg, 0.09 mmole) in 2-nitropropane (0.3 ml) cooled to the same temperature. The solution was stirred for 20 min at this temperature and potassium hydroxide solution (1.5 ml, 20%) then added. The mixture was diluted with water (5 ml) and extracted with petroleum ether (3 × 5 ml). The extract was washed with water to neutral reaction, dried, filtered, and the solvent evaporated in vacuum. The residue (22.1 mg) was chromatographed on a column of 0.4 g of silica gel. The hydrocarbon fraction (1.7 mg) was washed with petroleum ether, and a 19:1 mixture of petroleum ether and ethyl acetate, to give (16 mg, 69.6%) (±)-4*a*,7,7,10*a*-tetramethyl-trans-perhydronaphtho[2,1-b]pyran II with mp 79-82.5°C (from ethanol), which was identified by comparison with a sample of the optically active form of the oxide II. In this example, the optimum conditions for cyclization are given (Table 2, test 6). The conditions and results of the remaining tests are given in Table 2.

A Mixture of Δ^7- and Δ^8-Bicyclobishomofarnesenols (IX). To a solution of a mixture of Δ^7- and Δ^8-bicyclobishomofarnesyl acids XII [14] (300 mg, 1.14 mmoles) in 20 ml absolute ether was added lithium aluminum hydride (200 mg). The mixture was heated under reflux for 2 h and treated as described for the preparation of compound VI, to give a mixture of Δ^7- and Δ^8-bicyclobishomofarnesenols IX (271 mg, 95.4%) as a viscous liquid which was identified by comparison with a known sample [15].

Cyclization of a Mixture of Δ^7- and Δ^8-Bicyclobishomofarnesenols (IX). A. To a solution of fluorosulfonic acid (260 mg, 2.6 mmoles) in 2-nitropropane (2.5 ml) was added with mixing at –75 to –78°C a mixture of the alcohols IX (65 mg, 0.26 mmoles) in 2-nitropropane (0.8 ml) cooled to the same temperature. The mixture was stirred at this temperature for 20 min, triethylamine (0.45 ml) added, and the mixture extracted with ether (3 × 10 ml). The extract was washed with water to neutral reaction, dried, filtered, and the solvent evaporated. The residue (61.4 mg) was chromatographed on a column of 1.1 g of silica gel. The hydrocarbon fraction (3.4 mg) was washed with petroleum ether and a 97:3 mixture

of petroleum ether and ethyl acetate to give the oxide II (51 mg, 78.4%) with mp 80.5-82°C (from ethanol); $[\alpha]_D^{22}$ –8.7° (c = 1.3, $CHCl_3$). The compound was identified by spectral and chromatographic comparison of an authentic sample [15].

B. Using conditions described in method **A**, fluorosulfonic acid (175 mg, 1.75 mmoles) was added to a mixture of the alcohols IX (87 mg, 0.35 mmole). Treatment as before, and chromatography gave oxide II (64 mg, 73.6%).

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PYRYLOCYANINS.

26.* SYMMETRICAL DI-tert-BUTYLDIPHENYL-SUBSTITUTED PYRYLO-2-CYANINS

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Isomeric 2-methyl-4-phenyl-6-tert-butylpyrylium and 2-methyl-4-tert-butyl-6-phenylpyrylium salts and their sulfur analogs were synthesized. From these, symmetrical α-pyrylium and α-thiopyrylium carbo- and dicarbocyanins were obtained. α-Pyrylocyanins were converted into symmetrical α-pyridocyanins. From a comparison of the experimental spectral characteristics of the above dyes with the results of quantum-chemical calculations of the average positions of the absorption bands and the quadratic changes of the bond orders during excitation, the influence of the phenyl substituent in the 2- and 4-positions of the heteroresidue on the color was analyzed.

We have previously described [2, 3] the synthesis and studied the patterns of color formation of symmetrical tetraphenyl- and tetra-tert-butyl-substituted pyrylo-2-cyanins and their heteroanalogs. The aim of the present work was to study similar

*See [1] for Communication 25.

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