from 50 mg of sodium. The suspension was refluxed for 1 hr. Water was added dropwise with stirring and the suspension was neutralized with dilute hydrochloric acid. Extraction with ether gave an oil which was chromatographed on alumina. The pale yellow oil obtained in intermediate fractions was crystallized from ligroin (30–60°) to give a white substance. Further recrystallization from ligroin yielded 7 mg (29% yield) of white crystals, mp 246–246.5°. Spectral data gave $\nu_{max}^{CHCl_3}$ 2245, 1725, 1658, and 1602 cm^{-1}; λ_{max}^{EtOH} 246 mμ (log ε 3.83).

Anal. Calcd for $C_{32}H_{51}O_3N$: C, 77.21; H, 10.33; N, 2.82. Found: C, 77.46; H, 10.51; N, 3.04.

A Stereoselective Synthesis of α- and β-Agarofuran

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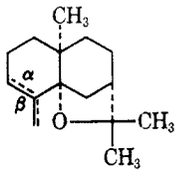
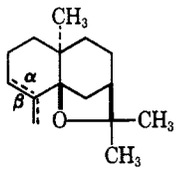
Bhattacharyya and coworkers[3] isolated α- and β-agarofuran from agarwood oil and, on the basis of chemical degradation and spectroscopic evidence, assigned the structures depicted by I to these compounds.[4]

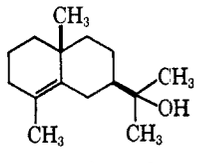


I

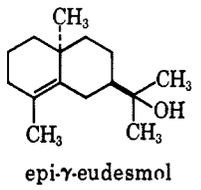


II

Barrett and Büchi[5] deduced that the isopropoxy bridge of the agarofurans was more likely β-oriented as shown in II and supported their conclusion by synthesizing α-agarofuran. During the past year we have been working on potential synthetic routes to the agarofurans. Our initial plans along these lines called for the use of γ-eudesmol[6] as the starting material, but many of our early studies were conducted with the more accessible isomer, 10-epi-γ-eudesmol. The recent structure revision of the agarofurans[5] prompted us to continue our early work in the epi series where certain promising intermediates had been prepared. Consequently, we can now report a stereoselective synthesis of α- and β-agarofuran which fully supports the structures proposed by Barrett and Büchi.



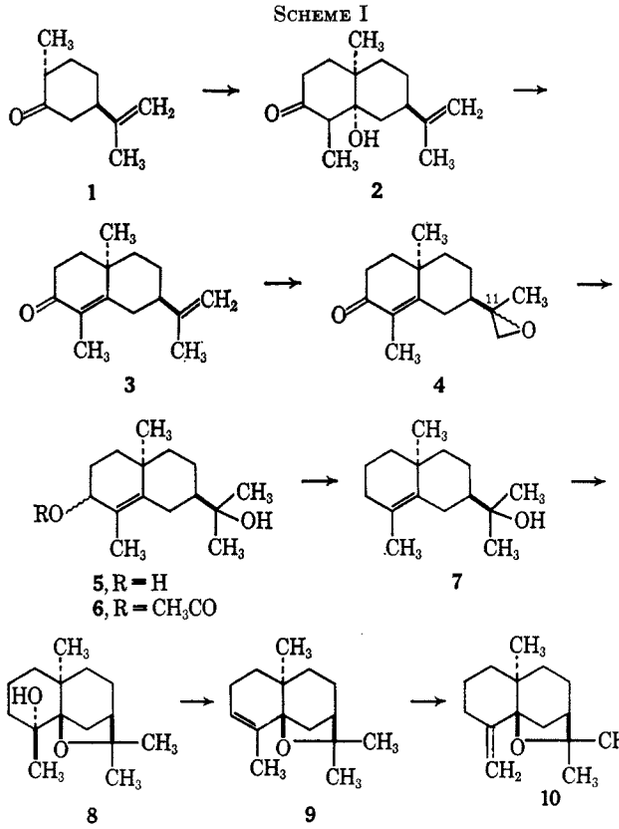
γ-eudesmol



epi-γ-eudesmol

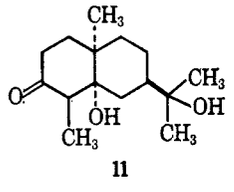
(−)-10-Epi-α-cyperone (**3**)[7] was prepared *via* condensation of (+)-dihydrocarvone (**1**) with ethyl vinyl ketone and dehydration of the resulting crystalline ketol **2**[8] with aqueous base (Scheme I). Conversion to

SCHEME I

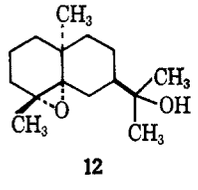


the oxirane derivative **4** (undoubtedly a mixture of diastereoisomers at C-11) was effected using 1 equiv of *m*-chloroperoxybenzoic acid.[9] Reduction of **4** with lithium aluminum hydride afforded the diol **5** which was directly acetylated and reduced with lithium in ammonia[10] to give 10-epi-γ-eudesmol (**7**) in nearly 70% over-all yield based on the ketol **2**.

An alternative route to diol **5** involving oxymercuration[11] of epi-α-cyperone (**3**) was examined and abandoned when difficulty was encountered in reducing the organomercury intermediate. Perhaps for the same reason, the crystalline keto diol **11** could be prepared in only 40% yield from ketol **2** using the oxymercuration procedure.



11



12

Epoxidation of 10-epi-γ-eudesmol (**7**) with *m*-chloroperoxybenzoic acid did not afford the expected oxirane **12**, but gave instead the naturally occurring[4] tetrahydrofuran derivative, 4-hydroxydihydroagarofuran

(1) Fellow of the Alfred P. Sloan Foundation, 1966–1968.

(2) National Institutes of Health Predoctoral Fellow, 1965–1967.

(3) T. C. Jain, M. L. Maheshwari, and S. C. Bhattacharyya, *Perfumery Essent. Oil Record*, **53**, 294 (1962).

(4) M. L. Maheshwari, T. C. Jain, R. B. Bates, and S. C. Bhattacharyya, *Tetrahedron*, **19**, 1079 (1963); M. L. Maheshwari, K. R. Varma, and S. C. Bhattacharyya, *ibid.*, **19**, 1519 (1963).

(5) H. C. Barrett and G. Büchi, *J. Am. Chem. Soc.*, **89**, 5665 (1967). We are grateful to Professor Büchi for disclosing his results to us prior to publication.

(6) J. A. Marshall and M. T. Pike, *Tetrahedron Letters*, 4989 (1966), and references therein.

(7) R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2423 (1955).

(8) *Cf.* J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).

(9) *Cf.* A. R. Pinder and R. A. Williams, *J. Chem. Soc.*, 2773 (1963).

(10) *Cf.* A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *ibid.*, 1969 (1957).

(11) H. C. Brown and P. Geoghegan, Jr., *J. Am. Chem. Soc.*, **89**, 1522 (1967).

(8), directly. Undoubtedly oxirane 12 is initially formed but the geometry of this intermediate renders subsequent acid-catalyzed cyclization to 8 an exceedingly favorable process. Related cyclizations have been observed with acyclic epoxy alcohols.[12] The synthesis of alcohol 8 by the above route constitutes an unequivocal structure proof of 4-hydroxydihydroagarofuran.

Dehydration of alcohol 8 with thionyl chloride in pyridine yielded α-agarofuran (9). The identity of this substance was ascertained by comparison of its infrared and nmr spectra with the published spectra[4] of natural material. Irradiation of α-agarofuran in isopropyl alcohol containing xylene as a photosensitizer[13] effected its isomerization to β-agarofuran (10). The spectral properties of this material matched those of natural β-agarofuran.

Experimental Section[14]

(−)-10-Epi-α-cyperone (3) was prepared in 95% yield from the crystalline ketol 2, mp 97–106° (lit.[7] mp 106°), as previously described for the (+) enantiomer.[8] Material thereby obtained exhibited bp 90–92° (0.03 mm), $n^{20}D$ 1.5335 (lit.[7] $n^{20}D$ 1.5340); 2,4-dinitrophenylhydrazone, mp 203–204° (lit.[7] mp 202°).

11,12-Oxido-10-epi-α-cyperone (4).—A solution containing 5.0 g of (−)-10-epi-α-cyperone 3[7,8] and 4.6 g of *m*-chloroperoxybenzoic acid (86% by titration) in 75 ml of chloroform was stirred at room temperature for 4.5 hr. The reaction mixture was diluted with ether, washed with 5% aqueous sodium hydroxide and brine, and dried over anhydrous magnesium sulfate. Distillation afforded 5.2 g (98%) of colorless oil: bp 110–118° (0.05–0.02 mm); λ_{max}^{film} 6.02 (CO), 6.22 (C=C), 8.32, 9.03, 9.07, 9.79, 12.15, 12.77, and 13.09 μ; $n^{20}D$ 1.5305. The analytical sample was secured after an additional distillation.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 77.1; H, 9.4.

10-Epi-γ-eudesmol (7).—A 4.0-g sample of oxido ketone 4 in 25 ml of ether was added to a stirred mixture containing 1.70 g of lithium aluminum hydride in 150 ml of ether at 0°. After 6.5 hr at room temperature, water (3.4 ml) and 10% aqueous sodium hydroxide (2.7 ml) were added and stirring was continued overnight. The mixture was filtered and the ether was removed from the filtrate under reduced pressure affording 4.3 g of viscous colorless diol 5: λ_{max}^{film} 2.99 (OH), 9.25, 9.37, 9.48, 9.77, and 10.72 μ.

A 3.85-g sample of the above diol in 25 ml of pyridine was treated with 4.95 g of acetic anhydride at room temperature for 22 hr.[14a] The solution was diluted with water and thoroughly extracted with ether. The combined extracts were washed with water, 5% aqueous sulfuric acid, saturated brine, and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure affording 4.4 g of hydroxy acetate 6 as a yellow oil: λ_{max}^{film} 2.87 (OH), 5.78 (CO), 8.02, 9.75, 10.18, 10.95, and 11.50 μ; $\delta_{TMS}^{CCl_4}$ 5.25–4.85, 4.70–4.50 (epimeric H-3's), 1.92 (CH_3CO), 1.93 (vinyl CH_3), 1.20 (angular CH_3), and 1.11 ppm [$(CH_3)_2$ C–O–].

A 3.87-g sample of the above hydroxy acetate in 140 ml of ether was added during 10 min to a stirred mixture containing 0.7 g of lithium wire in 280 ml of liquid ammonia. Stirring was continued for 20 min and 6 g of ammonium chloride was carefully added. The ammonia was allowed to evaporate and the residue was diluted with water and extracted with ether. After drying, the ether extract was distilled affording 2.60 g (83% based on epi-α-cyperone) of epi-γ-eudesmol (7), bp 105–110° (bath temperature) at 0.1 mm. The gas chromatogram revealed the presence of impurities (~15%) at short retention times, presumably dehydration products of 7. The analytical sample, $n^{20}D$ 1.5110, was secured by preparative gas chromatography:[15] λ_{max}^{film} 2.99 (OH), 8.78, 10.53, 10.74, and 11.84 μ; $\delta_{TMS}^{CCl_4}$ 2.25 (OH), 1.64 (vinyl CH_3), 1.19, 1.13, and 1.07 ppm (three CH_3's).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.79. Found: C, 80.8; H, 11.7.

4α-Hydroxydihydroagarofuran (8).—A mixture containing 1.04 g of 10-epi-γ-eudesmol (7) and 1.52 g of *m*-chloroperoxybenzoic acid (80% by titration) in 12 ml of benzene was stirred at room temperature for 10 hr. The mixture was diluted with ether and washed with 5% aqueous sodium hydroxide, saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the solid residue was recrystallized from hexane affording 0.48 g of hydroxy ether 8: mp 128–129° (lit.[4] mp 130–131°); λ_{max}^{film} 2.91 (OH), 7.98, 8.06, 8.30, 8.64, 8.90, 9.17, 9.40, 9.66, 9.90, 10.69, 11.36, and 12.29 μ; $\delta_{TMS}^{CCl_4}$ 1.32, 1.25 (two CH_3's), and 1.17 ppm (two CH_3's). A second and third crop afforded an additional 0.12 g of crystalline material (54.5% total yield). The infrared and nmr spectra of this material were identical with the published spectra[4] of the naturally derived hydroxy ether 8.

The residue (0.43 g) contained 30–40% of hydroxy ether 8 along with a number of unidentified components according to the gas chromatogram. The analytical sample, mp 128–129°, was obtained by sublimation.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.6; H, 10.9.

α-Agarofuran (9).—A solution of 0.48 g of alcohol 8, 1.3 ml of thionyl chloride, and 13 ml of pyridine was stirred at 0° for 1.5 hr,[14a] poured onto crushed ice, acidified with cold concentrated hydrochloric acid, and thoroughly extracted with ether. The combined extracts were washed with water, aqueous sodium bicarbonate, saturated brine, and dried over anhydrous magnesium sulfate. Distillation afforded 0.42 g (94%) of colorless α-agarofuran (9). The infrared and nmr spectra of this material were identical with the published spectra[4] of α-agarofuran derived from agarwood oil.

β-Agarofuran (10).—A solution containing 140 mg of α-agarofuran (9) and 1 ml of xylene in 100 ml of isopropyl alcohol was irradiated using a Hanovia 450-w high-pressure mercury vapor lamp (Type L) equipped with a water-jacketed Vycor immersion well. A slow stream of nitrogen was admitted during the irradiation. After 4.5 hr, the reaction mixture was distilled affording 185 mg of oil, bp 110° (bath temperature) at 0.02 mm. Material thus secured contained β-agarofuran (10) and unreacted α-agarofuran (9) in the ratio 7:3. Preparative gas chromatography[16] afforded a sample of β-agarofuran with infrared and nmr curves identical with the published spectra.[4]

5α,11-Dihydroxy-10-epieudesman-3-one (11).—To a well-stirred suspension prepared from 100 ml of tetrahydrofuran and 32.4 g (0.102 mole) of mercuric acetate in 100 ml of water was added a solution containing 12.0 g (0.051 mole) of ketol 2 in 25 ml of tetrahydrofuran.[11] The mixture was stirred at room temperature for 2 hr and maintained at 20–25° while 100 ml of 3 *M* aqueous sodium hydroxide followed by 82 ml of 0.5 *M* sodium borohydride in 3 *M* sodium hydroxide was added. The mixture was filtered through Supercel using ethyl acetate to wash the filter cake, saturated brine was added to the filtrate, and the mixture was thoroughly extracted with ethyl acetate. Evaporation of the solvent from the dried ($MgSO_4$) extracts yielded 10.6 g of gray-white solid. This material was recrystallized from ethyl acetate affording 4.80 g of white needles: mp 192–194°; λ_{max}^{KBr} 2.93 (OH), 5.90 (CO), 7.88, 8.78, 9.45, 10.03, 10.65, 11.50, and 12.70 μ. A second crop of 0.29 g (40% total yield) was obtained from ethyl acetate–heptane. The analytical sample, mp 195–196°, was obtained after two recrystallizations of first crop material from ethyl acetate.

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.6; H, 10.2.

Attempted Hydration of 10-Epi-α-cyperone *via* Oxymercuration.—To a well-stirred suspension prepared from 13 ml of tetrahydrofuran and 4.00 g (13.0 mmoles) of mercuric acetate in 13 ml of water was added a solution containing 2.50 g (11.5 mmoles) of epi-α-cyperone (3) in 2 ml of tetrahydrofuran.

(12) *Cf.* M. Mousseron-Canet, C. Levallois, and H. Huerre, *Bull. Soc. Chim. France*, 658 (1966); H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959).

(13) *Cf.* F. J. McQuillin and J. D. Parrack, *ibid.*, 2973 (1956); P. J. Kropp, *J. Am. Chem. Soc.*, **88**, 4091 (1966); J. A. Marshall and R. D. Carroll, *ibid.*, **88**, 4092 (1966).

(14) (a) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Syn.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere over reaction mixtures; (b) melting points were taken on a Fisher-Johns hot stage; (c) microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

(15) A 0.5 in. × 11 ft column of 24% 4:1 Carbowax 20M–KOH on Chromosorb W was employed.

(16) A 0.5 in. × 10 ft column of 15% silicone gum rubber GE SE 30 on Chromosorb W was employed at 200°.

The yellow color of the reagent was discharged within several seconds. The resulting solution was stirred at room temperature for 0.5 hr, 13 ml of 3 *M* aqueous sodium hydroxide and 26 ml of 0.5 *M* sodium borohydride in 3 *M* sodium hydroxide were added, and stirring was continued for 6 hr. The mixture was decanted away from the mercury, diluted with saturated brine, and thoroughly extracted with ethyl acetate. Evaporation of the solvent afforded 3.45 g of oil: λ_{max}^{film} 2.92 (OH), 6.05 (CO), and 6.19 μ (C=C). This material decomposed with the appearance of metallic mercury during attempted distillation at 110° (0.01 mm).

Registry No.—**4**, 15051-78-2; **5**, 15051-79-3; **6**, 15051-80-6; **7**, 15051-81-7; **8**, 15052-76-3; **9**, 5956-12-7; **10**, 6040-08-0; **11**, 15051-82-8.

Acknowledgments.—We are grateful to the Public Health Service, Division of Allergy and Infectious Diseases, for supporting this work (Research Grant AI 04965).

The Reversible Removal of Carbon 2 of 3-Substituted 4-Hydroxycoumarins

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The need for isotopically labeled, optically active 4-hydroxycoumarin anticoagulants prompted the investigation of methods of inserting a radiocarbon atom into the preresolved cold molecule. This approach seemed attractive because of the problems involved in a classical resolution by fractional crystallization of necessarily small quantities of radioactive diastereomers.

The synthetic route taken involves hydrolytic removal and subsequent reinsertion (with labeling) of the 2 carbon of the 4-hydroxycoumarin lactone ring. Methods for performing both of these transformations have been improved. We have also shown that the decarboxylation–carboxylation cycle does not involve racemization of a center attached at position 3 of the 4-hydroxycoumarin.

We also wish to suggest 3 substitution and hydrolytic decarboxylation of 4-hydroxycoumarins as an effective synthetic route to pure *o*-hydroxy ketones with complex side chains.

4-Hydroxycoumarin can be substituted in the 3 position with wide variety of groups. Most useful appear to be the Michael reaction[1] and the displacement reactions described by Ziegler[2] and by Schroeder.[3] In addition the cyclization of substituted phenyl malonates[4] yields a wide variety of 3-substituted 4-hydroxycoumarins. Van Zanten[5] has reveiwed the methods available.

Lactone opening and decarboxylation of 4-hydroxycoumarins has been reported.[6] The use of strongly alkaline solutions leads in some cases to extensive degradation as a side reaction, even as far as to salicylic acid. We have found that decarboxylation is accomplished better by heating pH 9 solutions of the sodium enolates of the 4-hydroxycoumarins to *ca.* 150° in sealed tubes. Wildi[7] has described the stability of the 3-phenyl-4-hydroxycoumarin anion to hydrolysis: we feel that in our procedure hydroxide ion attacks the uncharged 4-hydroxycoumarin since more strongly basic solutions are slower to react. Attempts at decarboxylations in neutral and acid solutions failed, as did attempts to decarboxylate 3-acetyl-4-hydroxycoumarin under any conditions.

Recarboxylation of ring-substituted *o*-hydroxyacetophenones has been discussed by Desai and Sethna.[8] We have found that the presence of α-substituents as large as diphenylmethyl on the acetophenone methyl group do not interfere with base-catalyzed carboxylative cyclization with alkyl carbonates. It appears that this route to 3-substituted 4-hydroxycoumarins is a favorable one provided the *o*-hydroxy ketone is available.

Experimental Section

Decarboxylation. General Procedure.—The 3-substituted 4-hydroxycoumarin was dissolved in a very small excess of 5% aqueous sodium hydroxide and the solution was sealed in a heavy walled Pyrex tube. The tube was heated to 150° in a capped iron pipe in an oven for 48 hr. The reaction mixture was extracted with chloroform and the chloroform was freed of traces of starting material or salicylic acid by washing with aqueous sodium carbonate. The chloroform solution was evaporated. All products except where R = 1-phenyl-2-carboxyethyl were distilled at reduced pressure; when products solidified after distillation, uncorrected melting points are given.

An exception to the general scheme given in Table I was the decarboxylation of warfarin, 3-(α-acetonylbenzyl)-4-hydroxycoumarin.[9] The product of this decarboxylation was 3-(*o*-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one, as was first shown by Robertson[10] and Link.[11] The decarboxylation was done as above, except that the solid product was filtered from the reaction mixture and crystallized first from acetic acid, then from benzene, mp 161–163°.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.9; H, 6.10. Found: C, 82.3; H, 6.00.

The same reaction, carried out with (−)(*S*)-warfarin,[11] $[\alpha]^{25}D$ −148° (*c* 2, 0.5 *N* NaOH), yielded the (+) isomer of the above ketone, $[\alpha]^{23}D$ +100° (*c* 0.8, 0.5 *N* NaOH), mp 145–146°.

Carboxylative Cyclization of *o*-Hydroxy Ketones.—Approximately 1 g of the *o*-hydroxy ketone was added to 1 g of sodium dispersion in 100 ml of benzene. After the evolution of hydrogen had ceased, 6 ml of dimethyl carbonate was added and the mixture was refluxed with stirring until thin layer chromatography on fluorescent silica gel plates showed absence of starting material. The time varied from 24 to 48 hr. The tlc solvent system was in all cases 3:1 v/v of toluene–glacial acetic acid. Excess sodium was consumed with ethyl alcohol and water was added. The aqueous layer was separated and poured into excess dilute

(1) M. Ikawa, M. A. Stahmann, and K. P. Link, *J. Am. Chem. Soc.*, **66**, 902 (1944).
(2) E. Ziegler, V. Roszmann, and F. Litvan, *Monatsh*, **88**, 587 (1957).
(3) C. H. Schroeder, E. D. Titus, and K. P. Link, *J. Am. Chem. Soc.*, **79**, 3291 (1957).
(4) H. Junek and E. Ziegler, *Monatsh*, **87**, 218 (1956).
(5) B. Van Zanten and W. T. Nauta, *Rec. Trav. Chim.*, **79**, 1211 (1960).
(6) M. A. Stahmann, C. F. Huebner, and K. P. Link, *J. Biol. Chem.*, **138**, 513 (1941).
(7) B. S. Wildi, *J. Org. Chem.*, **16**, 407 (1951).
(8) N. J. Desai and S. Sethna, *ibid.*, **22**, 388 (1957).
(9) C. H. Schroeder, S. Preis, and K. P. Link, *Tetrahedron Letters*, No. 13, 23 (1960).
(10) A. O. Robertson, Ph.D. Thesis, University of Wisconsin, Madison, Wis., 1953.
(11) B. D. West, S. Preis, C. H. Schroeder, and K. P. Link, *J. Am. Chem. Soc.*, **83**, 2676 (1961).