The Structures of Nepetaefolin, Nepetaefuran, and Nepetaefuranol

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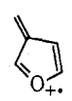
The stereostructures **1**, **2**, and **11** have been deduced for nepetaefolin, nepetaefuran, and nepetaefuranol, respectively, on the basis of chemical evidence, including a correlation *via* leonotin with marrubiin. The facile conversion of **1** to **2** was noted and the interconversion of **2** and **11** was achieved. The spiro epoxide moiety of **1** and **2** was found to undergo anchimerically assisted hydrolysis (*e.g.*, **7**) and hydrochlorination (*e.g.*, **9**), whereas a δ-lactone in these structures remained intact. Metaperiodate oxidation of nepetaefuranol to a nor ketone **16**, followed by elimination to give an α,β-unsaturated ketone **17**, revealed the substitution pattern in the highly functionalized ring B of these labdanoid diterpenes, and pyridine-d_5 shifts assisted configurational assignments. Confirmation of the structural designation was provided by conversion of the reduction product **10** from nepetaefuran to leonotol (**25**), which has also been derived from leonotin (**20**) of established structure and stereochemistry.

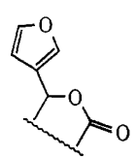
The genus *Leonotis*, frequently associated with *Cannabis* through the colloquial term "dagga," is widely distributed throughout South Africa and tropical regions of America, and is reputed to possess a variety of medicinal properties.[2] Along with a pharmacological study of extracts of the species *Leonotis nepetaefolia R.Br.* (Labiatae),[3] we have pursued chemical investigations of constituents of the leaves and stems of this plant. We now report the structural elucidation of nepetaefolin, an unusual prefuranoid diterpene, together with two closely related diterpenes, nepetaefuran and nepetaefuranol.[4]

Nepetaefolin (1) and Nepetaefuran (2).—Extraction of the dried leaves of *L. nepetaefolia* with acetone, followed by crystallization of the residue from ethanol, furnished crude nepetaefolin (**1**), $C_{22}H_{28}O_7$, in *ca.* 0.2% yield.[5] Rigorous purification of **1** could be effected by chromatography on alumina, which also provided varying amounts of a second diterpene, nepetaefuran (**2**), isomeric with **1**. When methanol was used as the extraction solvent or when extraction was carried out upon plant material which had been stored for an extended period (longer than 6 months), the yield of nepetaefolin was much diminished and that of nepetaefuran correspondingly increased. In fact, it was quickly recognized that nepetaefolin is a somewhat unstable substance and is transformed to **2** under mild conditions, including exposure to ethanolic chloroform. However, nepetaefuran was present in the plant extracts under all extraction conditions and, so far as can be discerned, is an authentic secondary metabolite.

The change **1** → **2** is accompanied by the disappearance of olefinic proton signals at 5.04 and 6.52 ppm in the nmr spectrum of **1** and the emergence of new resonances (1 H each) at 6.29, 7.27, and 7.38 ppm. The latter were recognized as characteristic of a mono-β-substituted furan common to a variety of diterpenes, including members of the labdane group such as lambertianic acid (**3**).[6] Further support for the presence of the furan moiety in **2** came from the mass spectrum, which showed a base peak at *m/e* 81 corresponding to the fragment A.[7] A strong ir absorption at 1612 cm^{-1}



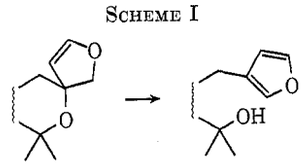
A



D

and an AB quartet at 3.96 and 4.24 ppm (J = 10 Hz) in the nmr spectrum of **1** had also disappeared in this reaction. Moreover, whereas nepetaefolin contained no OH groups, nepetaefuran was found to possess a single hydroxyl function which, from its resistance to acetylation, was judged to be tertiary. The conversion of **1** to **2** thus constitutes elimination from a 3,3-disubstituted 2,3-dihydrofuran, as shown in Scheme I. As expected, acid catalysis greatly facilitates this process.

SCHEME I



B C

In agreement with the partial structures B and C assigned to **1** and **2**, respectively, catalytic hydrogenation of nepetaefolin gave a dihydro derivative **4**, whereas nepetaefuran furnished a tetrahydro compound **5**, corresponding to saturation of the furan ring. In neither case was further hydrogen consumed nor was there any acidic material produced, thus ruling out a partial structure D of the type found in columbin.[8]

Infrared evidence indicated that nepetaefolin and nepetaefuran each contained two carbonyl groups and, in experiments designed to probe the nature of these functions, the basic hydrolysis of **1** and **2** was examined. Treatment of **1** with ethanolic potassium hydroxide, followed by an acidic work-up, afforded a product $C_{20}H_{26}O_6$ (**6**) which, from the disappearance of carbonyl absorption at 1735 cm^{-1} and methyl singlet at 2.02 ppm, was clearly derived by saponification of an acetate.

(1) Address correspondence to Oregon State University.

(2) J. M. Watt and M. G. Breyer-Branwijk, "Medicinal and Poisonous Plants of Southern and Eastern Africa," E. and S. Livingstone, London, 1962, p 520.

(3) We are indebted to Mr. M. Hasmathullah, Warrenville, Trinidad, for the collection of plant materials and to Dr. K. Jewers, Tropical Products Institute, London, for botanical identification.

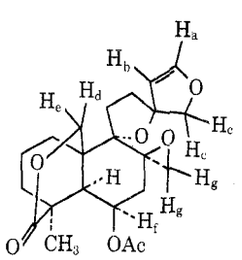
(4) Preliminary communication: J. D. White and P. S. Manchand, *J. Amer. Chem. Soc.*, **92**, 5527 (1970).

(5) A previous investigation of *L. Nepetaefolia* was confined to the seed oil, from which only fatty acids were reported: C. F. Asenjo, J. A. Goyco, and Z. Martinez-Pico, *ibid.*, **67**, 1936 (1945).

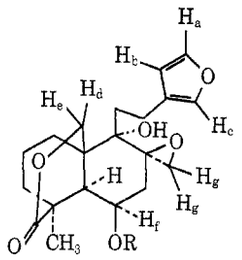
(6) W. G. Dauben and V. F. German, *Tetrahedron*, **22**, 679 (1966).

(7) C. R. Enzell and R. Ryhage, *Ark. Kemi*, **23**, 367 (1965).

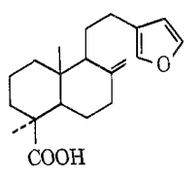
(8) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2090 (1956).



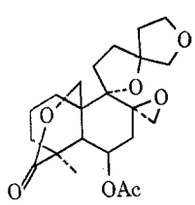
1



2, R = $COCH_3$
6, R = H



3



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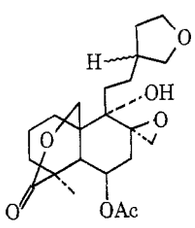
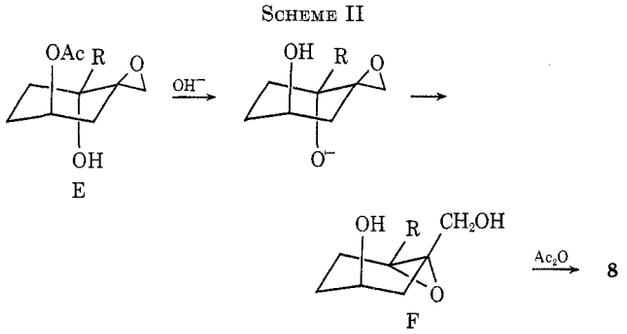


5

As expected, hydrolysis had been accompanied by the spirodihydrofuran–furan rearrangement, and it was also apparent that a carbonyl group (1721 cm^{-1}) had been retained in this process. Deuterium exchange established that **6** was a diol, and, when it was allowed to react with acetic anhydride, nepetaefuran (**2**) was formed in moderate yield. The presence of a one-proton signal at 4.22 ppm in **6**, which shifted downfield to 5.18 ppm in **2**, proved that the acetate group in nepetaefuran was secondary. Unexpectedly, analogous saponification of **2** gave not **6**, but an isomeric product **7**. Apart from loss of the elements of acetic acid, the major change occurring in this process involved the generation of a primary alcohol function (AB quartet at 3.48 and 3.62 ppm); the diminution of signals in the 2.6–3.0-ppm region suggested that this was at the expense of a terminal epoxide. Acetylation of **7** with acetic anhydride in pyridine yielded a primary monoacetate **8** (AB auartet at 4.06 and 4.18 ppm), containing an intact secondary hydroxyl group (ir absorption at 3550 cm^{-1} and a one-proton signal at 4.05 ppm). Although a small amount of a diacetate, showing no hydroxyl absorption, accompanies **8**, it is evident that the secondary hydroxyl group of **7** is appreciably more hindered than that of **6**. The transformation of **2** to its hydrolysis product **7** is well accommodated by a partial structure E in which formation of an alkoxide promotes internal displacement on a terminal epoxide. This is accompanied by straightforward saponification to give F (Scheme II). The

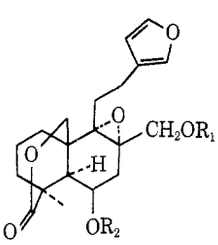
SCHEME II



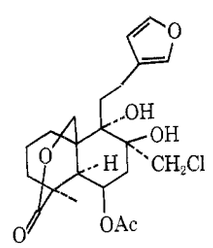
genesis of a new oxirane is feasible only if the participating oxygen functions are arranged trans and diaxially, and this would assure the developing hydroxymethyl group of a pseudoaxial orientation, which could thus provide the source of steric impedance toward acetylation of a neighboring axial hydroxyl function. The failure to observe an analogous epoxide rearrangement in the hydrolysis of **1** implies that the spirodihydrofuran moiety remains intact until acidic work-up, and the 9α alkoxide intermediate is thereby circumvented.

Chemical evidence for the terminal epoxide in nepetaefolin and nepetaefuran was forthcoming from two sources. First, the reaction of either **1** or **2** with phosphorus oxychloride gave a product **9** containing a chloromethyl group (AB quartet at 3.82 and 3.98 ppm). The infrared spectrum of this product revealed that both acetate (1740 cm^{-1}) and lactone (1720 cm^{-1}) functions were preserved, and nmr evidence as well as polarity according to thin layer chromatography was consistent with a diol. Thus, instead of dehydration, this reaction accomplished formal addition of HCl to the terminal epoxide in the anti-Markovnikov sense. A likely explanation for this unusual process involves participation of the ester G derived from **2** (Scheme III) with intramolecular delivery of the chlorine *via* a SNi′ mechanism.

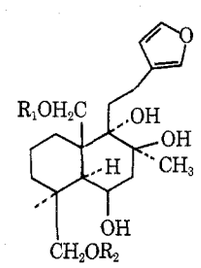
Conclusive proof for the presence of the oxirane in **1** and **2** was obtained when each was reduced with lithium aluminum hydride in tetrahydrofuran. The same pentahydroxy compound **10** was formed from both nepetaefolin and nepetaefuran, and its nmr spectrum clearly displayed a new methyl group with a chemical shift (1.24 ppm) indicative of its placement on a carbon bearing an oxygen function. Lithium aluminum hydride simultaneously accomplished reduction of the acetoxy and δ-lactone functions, thus affording the first



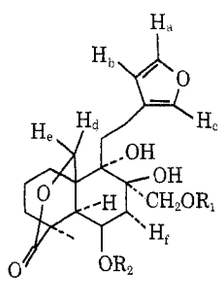
7, $R_1 = R_2 = H$
8, $R_1 = COCH_3$; $R_2 = H$
21, $R_1 = H$; $R_2 = COCH_3$
32, $R_1 = R_2 = COCH_3$



9

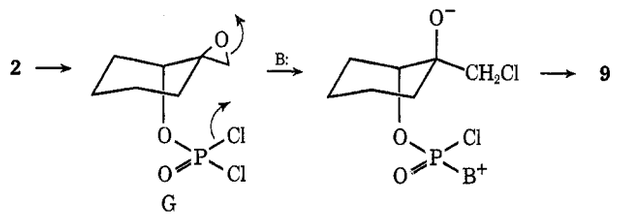


10, $R_1 = R_2 = H$
23, $R_1 = H$; $R_2 = Ts$
24, $R_1 = Ts$; $R_2 = H$

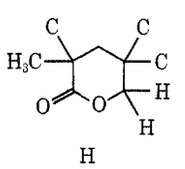


11, $R_1 = H$; $R_2 = COCH_3$
12, $R_1 = R_2 = COCH_3$
13, $R_1 = R_2 = H$
14, $R_1 = COCH_3$; $R_2 = H$
22, $R_1 = Ts$; $R_2 = COCH_3$

SCHEME III



direct chemical evidence for the latter. In hydrolysis studies of **1** and **2** a carboxylate had been isolated but acidification invariably induced immediate relactonization. Moreover, attempts to bring about esterification of the carboxylate were uniformly unsuccessful and suggested that the carboxyl moiety in this system was sterically encumbered. The reduction product **10** showed a new pair of AB quartets (3.26 and 4.19, 3.85 and 4.30 ppm), which therefore requires that the δ-lactone bear a substitution pattern as in H. The presence of a methyl group in nepetaefolin and nepetaefuran was apparent from the three-proton singlet at 1.15 and 1.12 ppm, respectively, with the chemical shift indicative of a placement α to carbonyl.

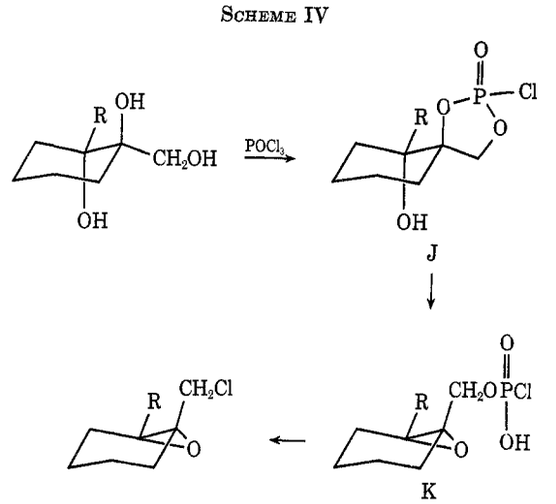


H

Nepetaefuranol.—Further clarification of the structures of nepetaefolin and nepetaefuran became possible with the isolation of a third member of this series, nepetaefuranol (**11**), $C_{22}H_{30}O_8$, differing in composition from **1** and **2** by formal addition of water. Spectral properties as well as the formation of a tetrahydro derivative again pointed to the presence of a β-substituted furan. Deuterium exchange indicated that **11** was a triol, and an AB quartet (3.27 and 3.78 ppm) suggested the presence of a primary alcohol. This was confirmed by formation of a primary acetate **12** (2 H singlet at 4.25 ppm) upon acetylation. Hydrolysis of **11** gave a tetraol **13** derived, as in the case of **2**, by saponification of a secondary acetate; reacetylation gave a primary monoacetate **14**, isomeric with nepetaefuranol. As noted with hydrolysis studies on **2**, the secondary hydroxyl group of **14** is sufficiently hindered to resist acetylation. The second carbonyl functionality due to the δ-lactone had again remained intact throughout these transformations.

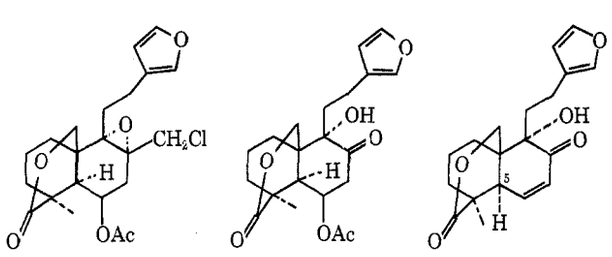
The nature of the hydroxyl substituents in nepetaefuranol was more fully revealed through the action of phosphorus oxychloride, which accomplished chlorinative dehydration to **15**. That this product was a primary halide was clear from the appearance of a new AB quartet at 3.25 and 3.60 ppm, and, since **15** contained neither a hydroxyl group nor unsaturation in the form of an olefinic linkage, an oxirane must have been formed in the dehydration process. On the assumption that a 1,2,3-triol is present in nepetaefuranol, a satisfactory explanation for the phosphorus oxychloride reaction can be found in the formation of the cyclic ester J, which suffers intramolecular displacement to produce the phosphonate ester K. A straightforward SNi transfer of chlorine then gives **15** (Scheme IV). As noted in

SCHEME IV

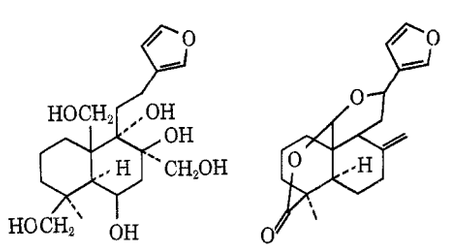


connection with the transformation of **2** to **7** (Scheme II), this mechanism requires a trans-diaxial orientation of tertiary hydroxyl groups, and inversion at the spiro carbon of the cyclic phosponate J converts an initially equatorial primary alcohol to an axial chloromethyl group (*cf.* **9** where the chloromethyl group remains equatorial).

Confirmation of a glycol functionality in **11** was acquired from its reaction with sodium metaperiodate, which gave cleanly a nor ketone **16**. Upon chromatography over alumina, **16** underwent elimination of acetic acid to yield quantitatively a pair of α,β-unsaturated ketones (1670 cm^{-1}) in the ratio 5:1. The major isomer **17** displayed olefinic proton signals at 6.41 and 6.81 ppm corresponding to α and β protons of the enone, respectively, with a cisoid olefinic coupling of 10 Hz. The minor isomer is believed to be epimeric with **17** at C-5, but this material was not fully characterized. The facile elimination of acetic acid from **16** is anticipated from a structure which contains an axial acetoxyl group β to a carbonyl group,[9] and this result serves to complete the placement of functionality in one carbocyclic ring of nepetaefuranol.



15 **16** **17**



18 **19**

(9) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 227.

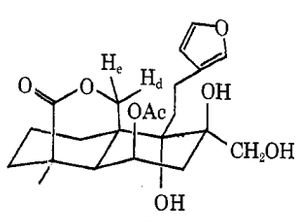
TABLE I

CHEMICAL SHIFTS (δ, PPM) AND PROTON COUPLING CONSTANTS (J, Hz)[a] FOR NEPETAEFOLIN, NEPETAEFURAN, NEPETAEFURANOL, AND LEONOTIN

Compd	Solvent	H_a	H_b	H_c	H_d	H_e	H_f	H_g	CH_3CO	CH_3
1	$CDCl_3$	6.52 (d, J = 3)	5.04 (d, J = 3)	3.97 4.24 (d, J = 10)	5.07 (d, J = 11)	3.96 (d, J = 11)	5.18 (d of t)	2.35 2.58 (d of d, J = 4, 14)	2.02 (s)	1.15 (s)
2	DMSO-d_6–$CDCl_3$ (10:1)	7.38 (t, J = 1)	6.27 (m)	7.27 (s)	5.02 (d, J = 12)	4.05 (d, J = 12)	5.18 (d of t)	2.32 2.70 (d of d, J = 4, 13)	1.96 (s)	1.12 (s)
11	DMSO-d_6–$CDCl_3$ (10:1)	7.38 (t, J = 1)	6.34 (m)	7.28 (s)	5.90 (d, J = 12)	4.04 (d, J = 12)	5.22 (m)	3.27[b] 3.78 (d of d, J = 4, 11)	1.96 (s)	1.10 (s)
20	DMSO-d_6–$CDCl_3$	7.35 (t, J = 1)	6.32 (m)	7.25 (s)			4.75 (d of t, J = 6, 8)			1.02 (s) 1.22 (s) 1.30 (s)

[a] Coupling assignments were checked by double resonance (except for H_f). [b] Collapses to a doublet (J = 11) upon addition of D_2O.

Reduction of nepetaefuranol with lithium aluminum hydride yielded an amorphous hexahydroxy compound **18**, and evidence similar to that cited for the case of nepetaefuran supports a δ-lactone corresponding to part structure H for **11** also. Placement of this lactone within the framework of the three diterpenes is dictated by the fact that its reduction generates two primary alcohol groups and the recognition that all but one of the isoprenoid *C*-methyl groups have been oxidized. Thus, assuming a skeleton of the normal labdane type,[10] a lactone bridge spanning the C-5 and C-10 positions similar to that in sciadin (**19**)[11] provides a full account of the experimental evidence and explains serendipitously the widely divergent chemical shifts of protons H_d and H_e in these diterpenes and several derivatives (Table I). A three-dimensional representation L of **11**



L

shows that H_d is subject to the deshielding influence of both the axial hydroxyl at C-8 and the axial acetoxy group at C-6, whereas in nepetaefolin and nepetaefuran, both containing the spiro epoxide at C-8, the effect is less pronounced. When nmr spectra of **2** and **11** were measured in pyridine-d_5 solution, a further downfield shift of H_d and H_e was observed (Table II). The relatively large shift (0.39 ppm) observed for H_d in **11** accords with the explanation proposed by Demarco, *et al.*, for this phenomenon, involving anisotropic effects arising from coordination of pyridine with a neighboring, axially situated hydroxyl group.[12] As expected, the effect on the more remote proton H_e is smaller. A

TABLE II

PYRIDINE-d_5 CHEMICAL SHIFTS (δ, PPM) OF NEPETAEFURAN AND NEPETAEFURANOL

Compd	H_d	$\Delta\delta$[a]	H_e	$\Delta\delta$[a]	H_g	$\Delta\delta$[a]
2	5.31	0.29	4.20	0.15	2.30	−0.02
					2.93	0.23
11	6.29	0.39	4.22	0.18	3.70	0.43
					4.22	0.44

[a] Chemical-shift differences are calculated with reference to the solvent system of Table I.

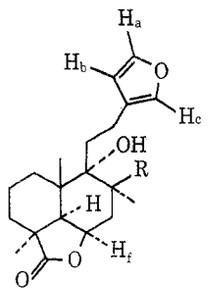
similar deshielding due to solvent pyridine was noted in the case of the angular methyl group of leonotin (**20**).[13]

The structural and stereochemical relationship between nepetaefuran (**2**) and nepetaefuranol (**11**) was confirmed by means of direct interconversion of these two substances. First, the hydrolysis of **2** with aqueous perchloric acid in tetrahydrofuran was found to yield **11**, in addition to products derived from cleavage of the acetate. This result is anticipated, assuming participation of the hydroxyl at C-9 in the opening of the spiro epoxide (*cf.* Scheme II), so that hydrolytic opening of epoxy alcohol **21**, an isolable intermediate in this reaction, assures overall retention (*via* double inversion) at C-8. Furthermore, a product formed in the prolonged treatment of nepetaefuran with phosphorus oxychloride and pyridine or upon similar treatment of **9** was found to be identical with the dehydration product **15** from nepetaefuranol. This quite clearly is the result of a subsequent dehydration of the trans-diaxial glycol **9** with elimination of the oxygen function at C-8. Finally, the reverse correlation of nepetaefuranol with a derivative of **2** was accomplished by conversion of **11** to an unstable, primary tosylate **22** with *p*-toluenesulfonyl chloride in pyridine, followed by treatment with potassium hydroxide. Among other products, a substance identical with the hydrolysis product **7** of nepetaefuran was formed.

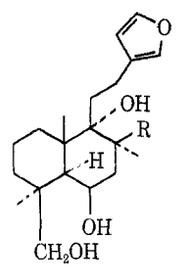
Correlation with Leonotin (20).—The structural hypotheses put forward for nepetaefolin, nepetaefuran,

(10) R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965).
(11) M. Sumimoto, *Tetrahedron*, **19**, 643 (1963).
(12) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).
(13) J. D. White, P. S. Manchand, and W. B. Whalley, *Chem. Commun.*, 1315 (1969).

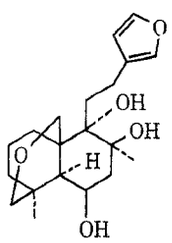
and nepetaefuranol were placed on a firm foundation by a direct interrelation with leonotin (**20**), of established structure and stereochemistry.[13] The reduction product **10** from nepetaefuran (or nepetaefolin), upon treatment with *p*-toluenesulfonyl chloride in pyridine, yielded a crystalline mixture consisting of two primary monotosylates, **23** and **24**. Without purification, this mixture was subjected to hydrogenolysis with lithium aluminum hydride in tetrahydrofuran to give leonotol (**25**), previously prepared by reduction of leonotin (**20**) with lithium aluminum hydride. A relatively fast-moving component in the reduction mixture is believed to be the cyclic ether **26**,[14] since, upon prolonged treatment with lithium aluminum hydride, this material also gave leonotol. Leonotin (8β-hydroxymarrubiin)[15] has, in turn, been correlated with marrubiin (**29**), of



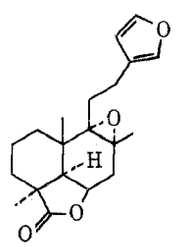
20, R = OH
29, R = H



25, R = OH
28, R = H



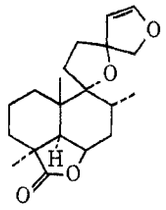
26



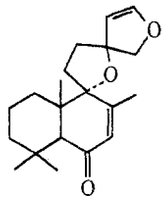
27

established structure and absolute stereochemistry,[16] by dehydration to epoxide **27**, followed by reduction with lithium aluminum hydride to give marrubenol (**28**). The latter has been previously prepared by lithium aluminum hydride reduction of marrubiin,[17] and, when a sample obtained by this method[18] was compared with material acquired from leonotin, they were found to be identical in all respects. Thus, correlation of the nepetaefolin series with a substance of independently ascertained structure is complete; this serves to confirm the stereochemistry at all six chiral centers of nepetaefuran (**2**) and nepetaefuranol (**11**), as well as the corresponding centers in nepetaefolin (**1**). The configuration of the additional spiro carbon in **1** remains undefined.

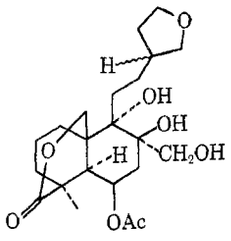
Identification of the structure of nepetaefolin as **1** places it in a select group of spiro dihydrofuranoid diterpenes comprising, to date, two other members, premarrubiin (**30**)[19] and presolidagenone (**31**).[20] Interestingly, the traditional source of marrubiin (**29**), white horehound (*Marrubium vulgare L.*), was found to produce no trace of **29** when extraction was carried out with cold acetone, and the evidence now clearly points to marrubiin as an artifact arising from **30** *via* a process which has an obvious parallel in the nepetaefolin → nepetaefuran conversion.



30



31



32

Experimental Section

General Techniques.—Melting points were determined on a Kofler heating stage or in capillaries on a Büchi melting point apparatus, and are uncorrected. Infrared spectra (ir) were determined as Nujol mulls except where otherwise stated on Perkin-Elmer 237 or 257 spectrometers. Nuclear magnetic resonance spectra (nmr) were recorded on a Varian HA-100 spectrometer with tetramethylsilane as internal standard. Chemical shifts are expressed in δ units (parts per million) and coupling constants (J) in hertz. Mass spectra were determined on an Associated Electronics Industries MS-9 spectrometer, using a direct inlet system with ionization energy of 70 eV; m/e values are given with relative intensities (%) in parentheses. Thin layer chromatograms (tlc) were made from Merck (Darmstadt) silica gel G; spots were made visible by spraying with a 10% solution of ceric sulfate and heating the plates to 110°. Elemental analyses were carried out by Micro-Tech Laboratories, Inc., Skokie, Ill., or by the microanalytical department, Hoffmann-La Roche, Inc., Nutley, N. J.

Isolation of Nepetaefolin (1).—One kilogram of the dried leaves of *Leonotis nepetaefolia R.Br.* was steeped in 10 l. of acetone at room temperature for 3 days and the mixture was decanted through a filter funnel. The filtrate was evaporated *in vacuo* at 40° and the residue was dissolved in 800 ml of ethyl acetate. The mixture was stirred with 50 g of decolorizing charcoal ("Norit A") at 45° for 10 min, cooled, and filtered (this process was repeated until the filtrate was virtually colorless). Evaporation of the filtrate gave 20.3 g of a gum, which was taken up into 150 ml of warm ethanol and allowed to stand at 0° for 3 hr. The crystals of crude nepetaefolin were filtered, washed with 10 ml of cold ethanol, and dried *in vacuo* at 45° to give 1.74 g of colorless needles, mp 250–255°. Repeated crystallizations from acetone–methanol gave analytically pure nepetaefolin: mp 260° dec; $[\alpha]^{25}D$ −14.6° (c 0.90, chloroform); ir 1740, 1722, 1612, 1380, 1242, 1140, and 750 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (3 H, s), 2.02 (3 H, s), 2.35 (1 H, d, J = 4 Hz), 2.58 (1 H, d, J = 4 Hz), 3.96 (1 H, d, J = 10 Hz), 3.97 (1 H, d, J = 11 Hz), 4.24 (1 H, d, J = 10 Hz), 5.04 (1 H, d, J = 3 Hz), 5.07 (1 H, d, J = 11 Hz), 5.18 (1 H, d, of t), and 6.52 (1 H, d, J = 3 Hz); mass spectrum m/e (rel intensity) 404 (M^+, 52), 344 (100).

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.20; H, 6.98.

Isolation of Nepetaefuran (2) and Nepetaefuranol (11).—One kilogram of the dried leaves of *L. nepetaefolia* was steeped in 10 l. of methanol for 10 days. The mixture was decanted through a filter funnel and the filtrate was concentrated to 1 l., diluted with 100 ml of water, and extracted with 1.5 l. of ligroin (bp 60–70°). The extract was dried ($MgSO_4$), concentrated to 750 ml, and treated with decolorizing charcoal as described for the

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(14) E. R. Kaplan, K. Naidu, and D. E. A. Rivett, *J. Chem. Soc. C*, 1656 (1970).
(15) R. A. Appleton, J. W. B. Fulke, M. S. Henderson, and R. McCrindle, *ibid.*, 1943 (1967); D. M. S. Wheeler, M. M. Wheeler, M. Fetizon, and W. H. Castine, *Tetrahedron*, **23**, 3909 (1967). Total synthesis of marrubiin: L. Mangoni, M. Adinolfi, G. Laonigro, and R. Caputo, *ibid.*, **28**, 611 (1972).
(16) W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward, and T. F. Holley, *J. Chem. Soc.*, 2540 (1953).
(17) Samples of marrubiin were kindly provided by Professor D. M. S. Wheeler, University of Nebraska, and by Dr. D. E. A. Rivett, Rhodes University, Grahamstown, South Africa.
(19) M. S. Henderson and R. McCrindle, *J. Chem. Soc. C*, 2014 (1969).
(20) T. Anthonsen, P. H. McCabe, R. McCrindle, and R. D. H. Murray, *Tetrahedron*, **25**, 2233 (1969).

isolation of **1**. Removal of the charcoal and solvent gave 11.0 g of an oil. The aqueous phase from the above partition was diluted with 1 l. of saturated brine and extracted with two 1.5-l. portions of ethyl acetate. The extract was concentrated to *ca.* 750 ml, dried ($MgSO_4$), decolorized with charcoal ("Norit A"), and evaporated to give 12.8 g of a gum. This was chromatographed on 500 g of neutral alumina (Woelm, activity II), with increasing percentages of ethyl acetate in benzene as eluent. Fractions of similar composition (ascertained by tlc, 40% ethyl acetate in benzene) were combined, evaporated, and treated as follows to give the individual diterpenes.

A. Nepetaefuran (2).—A mixture of nepetaefuran and leonotin, eluted with 20–25% ethyl acetate in benzene, was fractionally crystallized from methylene chloride–hexane to give 418 mg of leonotin (**20**) as plates, mp 175°. The mother liquors from these crystallizations were combined and chromatographed on 150 g of neutral alumina (Woelm, activity II) with 15% ethyl acetate in benzene as eluent. Removal of the solvents and repeated crystallizations of the residue from ethyl acetate–hexane gave nepetaefuran, mp 233–235°. A further crystallization from aqueous ethanol produced large, colorless needles which were dried *in vacuo* at 56° to give 160 mg of nepetaefuran (**2**): mp 241–242°; $[\alpha]D^{25}$ +32.3° (*c* 1.35, CH_3OH); ir 3500, 1735, 1730, 1380, 1240, 1145, 1025–1045, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 10:1) δ 1.12 (3 H, s), 1.2–1.85 (m), 1.96 (3 H, s), 2.2–2.85 (m), 2.32 (1 H, d, J = 4 Hz), 2.70 (1 H, d, J = 4 Hz), 4.05 (1 H, d, J = 12 Hz), 4.87 (1 H, s, disappears on addition of D_2O), 5.02 (1 H, d, J = 12 Hz), 5.18 (1 H, d, of t), 6.27 (1 H, m), 7.27 (1 H, s), 7.38 (1 H, 5, J = 1 Hz); mass spectrum m/e (rel intensity) 404 (M^+, 4) and 81 (100).

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.30; H, 6.99.

B. Nepetaefolin (1).—A mixture of nepetaefolin and nepetaefuran was eluted with 25–30% ethyl acetate in benzene. The solvents were removed and the residue was dissolved in 5 ml of warm ethanol and allowed to stand at 0° overnight. Filtration gave 103 mg of nepetaefolin, mp 260° (from acetone–methanol). The mother liquor was evaporated and the residue was repeatedly crystallized from ethyl acetate–hexane to give 74 mg of nepetaefuran, mp 235–238°.

C. Nepetaefuranol (11).—Crude nepetaefuranol was eluted with 70–80% ethyl acetate in benzene. Removal of the solvents left a gum which was dissolved in 15 ml of hot methylene chloride, and the mixture was left at 0° overnight. The crystals were filtered, washed with a little cold methylene chloride, and dried *in vacuo* at 56° to give 800 mg of nepetaefuranol (**11**) as colorless needles: mp 253–255°; $[\alpha]D^{25}$ +17.2° (*c* 1.053, CH_3OH); ir 3550 (broad), 1735, 1720, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 10:1) δ 1.10 (3 H, s), 1.6–1.9 (m), 1.96 (3 H, s), 2.1–2.65 (m), 3.27 (1 H, d, J = 11 Hz), 3.78 (1 H, d of d, J = 3 and 11 Hz, becomes d, J = 11 Hz, on addition of D_2O), 4.04 (1 H, d, J = 11 Hz), 4.36 (1 H, disappears on addition of D_2O), 5.20 (1 H, d of t), 5.20 (1 H, s, disappears on addition of D_2O), 5.70 (1 H, t, J = 3 Hz, disappears on addition of D_2O), 5.90 (1 H, d, J = 11 Hz), 6.34 (1 H, m), 7.28 (1 H, s), and 7.38 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 422 (M^+, 5), and 81 (100).

Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.62; H, 7.21.

Conversion of Nepetaefolin (1) into Nepetaefuran (2).—A solution of 40.4 mg (0.10 mmol) of nepetaefolin in 10 ml of chloroform and 10 ml of ethanol was heated under reflux for 5 hr. The solvents were evaporated and the solid residue was crystallized from ethyl acetate–hexane to give 36 mg of **2** as colorless needles, mp 236–238°, $[\alpha]D^{25}$ +31.4° (*c* 1.120, CH_3OH). This compound was identical in all respects with natural nepetaefuran [mixture melting point, mixed tlc (40% ethyl acetate in benzene), ir, nmr, and mass spectra].

Dihydronepetaefolin (4).—A solution of 40.4 mg (0.10 mmol) of nepetaefolin (**1**) in 25 ml of ethyl acetate was hydrogenated, at ambient temperature and pressure, over 25 mg of 5% palladium on charcoal until hydrogen absorption ceased; 3.5 ml was absorbed during *ca.* 4 min. The mixture was filtered and the catalyst was washed with 15 ml of ethyl acetate. The filtrate and washings were combined and evaporated to leave 40 mg of a colorless solid, which was crystallized from methylene chloride–hexane to give 33 mg of **4**: mp 285–286° dec; $[\alpha]D^{25}$ +34.4° (*c* 1.236, $CHCl_3$); ir 1740, 1717, 1320, 1247, 1160, and 1030 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:1) δ 1.14 (3 H, s), 2.00 (3 H, s), 2.36 (1 H, d, J = 4 Hz), 2.63 (1 H, d, J = 4 Hz), 3.61 (2 H, q, J = 9 Hz), 3.94 (3 H, m), 5.09 (1 H, d, J = 11 Hz), 5.19 (1 H, d of t); mass spectrum m/e (rel intensity) 406 (M^+, 1) and 83 (100).

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.08; H, 7.54.

Tetrahydronepetaefuran (5).—A solution of 80.8 mg (0.20 mmol) of nepetaefuran (**2**) in 20 ml of 95% ethanol was hydrogenated over 100 mg of 10% palladium on charcoal at atmospheric pressure and room temperature until hydrogen absorption (*ca.* 12 ml) ceased. Removal of the catalyst and solvent yielded 80 mg of a colorless, crystalline solid which was recrystallized from ethanol to give **5** as plates: mp 222°; $[\alpha]D^{25}$ +29.6° (*c* 1.08, CH_3OH); ir 3400, 1740, and 1725 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:1) δ 1.12 (3 H, s), 1.2–1.9 (m), 1.96 (3 H, s), 2.29 (1 H, d, J = 3 Hz), 2.66 (1 H, s, J = 3 Hz), 3.28 (2 H, overlapping t), 3.76 (4 H, m), 4.05 (1 H, d, J = 11 Hz), 4.71 (1 H, s, disappears on addition of D_2O), 5.00 (1 H, d, J = 11 Hz), and 5.17 (1 H, d of t); mass spectrum m/e (rel intensity) 408 (M^+, 2).

Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.44; H, 8.03. Found: C, 64.69; H, 7.90.

Hydrogenation of nepetaefuran in glacial acetic acid with Adams platinum oxide catalyst at room temperature and atmospheric pressure also gave the tetrahydro derivative **5**.

Alkaline Hydrolysis of Nepetaefolin (1).—A mixture of 40.4 mg (0.10 mmol) of nepetaefolin and 10 ml of 95% ethanol was stirred at *ca.* 40° for 30 min. The mixture was cooled to room temperature, treated with 5 ml of 10% ethanolic potassium hydroxide, and stirred for a further 1 hr. The solution was diluted with 40 ml of water, acidified with ice-cold 2 *N* hydrochloric acid, and extracted with two 100-ml portions of ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a gum which was crystallized from methylene chloride–hexane to give 28.1 mg of **6**: mp 202–203°; $[\alpha]D^{25}$ + 34° (*c* 1.01, CH_3OH); ir 3450, 1721, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:1) δ 1.28 (3 H, s), 1.5–2.0 (m), 2.35 (1 H, d, J = 3 Hz), 2.70 (1 H, d, J = 3 Hz), 3.91 (1 H, disappears on addition of D_2O), 3.98 (1 H, d, J = 11 Hz), 4.22 (1 H, broad s), 5.43 (1 H, s, disappears on addition of D_2O), 5.09 (1 H, d, J = 11 Hz), 6.25 (1 H, m), 7.22 (1 H, s), and 7.35 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 362 (M^+, 4) and 81 (100).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.29; H, 7.11.

Acetylation of 20.2 mg of **6** with 1.0 ml of acetic anhydride and 1 ml of anhydrous pyridine during 16 hr at room temperature gave 12 mg of nepetaefuran (**2**), identified by melting point, ir, and tlc properties.

Alkaline Hydrolysis of Nepetaefuran.—A solution of 80.0 mg (0.20 mmol) of nepetaefuran (**2**) in 10 ml of 95% ethanol was stirred with 10 ml of 10% ethanolic potassium hydroxide at room temperature for 1 hr. The solution was diluted with 50-ml of water, acidified with ice-cold 5% hydrochloric acid, and extracted with 150 ml of ethyl acetate. The extract was washed with two 125-ml portions of water, dried ($MgSO_4$), and evaporated to give 75 mg of a crystalline solid. Recrystallization from ethyl acetate–hexane gave 72 mg of **7** as colorless prisms: mp 196–198°; $[\alpha]D^{25}$ +29.6° (*c* 1.287, CH_3OH); ir 3500, 1715, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$) δ 1.27 (3 H, s), 3.48 (1 H, d, J = 12 Hz), 3.62 (1 H, d, J = 12 Hz), 5.08 (1 H, m), 5.29 (1 H, d, J = 11 Hz), 5.89 (1 H, J = 11 Hz), 6.30 (1 H, m), 7.29 (1 H, s), 7.38 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 362 (M^+, 3) and 81 (100).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.30; H, 7.28.

A mixed tlc (55% ethyl acetate in benzene) of this material with a sample of **6** from the preceding experiment did not show a clear separation, but the mixture melting point showed a depression (mmp 170–180°); the ir, nmr, and mass spectra of the two samples were clearly different.

Acetylation of 7.—To a mixture of 50 mg (0.12 mmol) of hydrolyzed nepetaefuran (**7**) and 2 ml of anhydrous acetic anhydride (warming was necessary to obtain a solution) was added 1 drop of anhydrous pyridine. The mixture was allowed to stand at 0° for 16 hr. The solution was added to 100 ml of ice-cold water and extracted with 150 ml of ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated to give a colorless solid. Tlc (40% ethyl acetate in benzene) and mass spectral data (M^+ at 404 and 446) indicated that the major product was the monoacetate **8**, with 10–15% of the diacetate also present. Crystallization of the solid from ethyl acetate–hexane furnished 34 mg of **8** as colorless needles: mp 165–166°;

$[\alpha]^{25}D$ +23° (*c* 1.319, $CHCl_3$); ir 3550, 1740–1720 (broad), 1380, 1210–1240, 1165, 1045 and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:5) δ 1.23 (3 H, s), 1.5–2.0 (m), 2.12 (3 H, s), 2.50 (2 H, t, J = 7 Hz), 4.05 (1 H, d of t), 4.06 (1 H, d, J = 12 Hz), 4.18 (1 H, d, J = 12 Hz), 4.28 (1 H, d, J = 11 Hz), 4.86 (1 H, d, J = 11 Hz), 4.86 (1 H, disappears on addition of D_2O), 6.30 (1 H, m), 7.27 (1 H, s), and 7.37 (1 H, t, J = 1 Hz); mass spectrum *m/e* (rel intensity) 404 (M^+, 5).

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.11; H, 7.07.

In a mixed tlc (40% ethyl acetate in benzene), **8** (R_f 0.41) was readily separated from nepetaefuran (R_f 0.50). The mother liquor from the above crystallization was evaporated and the residue was dissolved in 2 ml of pyridine, to which was added 2 ml of anhydrous acetic anhydride. The mixture was allowed to stand at room temperature for 24 hr, and then added to 50 ml of ice-cold water and extracted with two 50-ml portions of ethyl acetate. The extract was washed, dried (Na_2SO_4), evaporated, and filtered through 25 g of neutral alumina (Woelm, activity II) with 15% ethyl acetate in benzene as eluent. Removal of the solvents gave 19 mg of **32** as a colorless gum which, although homogeneous by tlc (15% ethyl acetate in benzene), could not be induced to crystallize: $[\alpha]^{25}D$ −4.2° (*c* 1.120, $CHCl_3$); ir ($CHCl_3$) 1741, 1730, 1380, 1240–1210, 1160, 1050–1035, and 878 cm^{-1}; nmr ($CDCl_3$) δ 1.19 (3 H, s), 1.7–2.7 (m), 2.08 (3 H, s), 2.15 (3 H, s), 4.10 (2 H, s), 4.44 (1 H, d, J = 12 Hz), 4.68 (1 H, d, J = 12 Hz), 5.13 (1 H, m), 6.26 (1 H, m), 7.21 (1 H, s), 7.34 (1 H, s); mass spectrum *m/e* (rel intensity) 446 (M^+, 4).

Reaction of Nepetaefuran (2) with Phosphorus Oxychloride.—To a solution of 50 mg (0.12 mmol) of nepetaefuran (**2**) in 5 ml of anhydrous pyridine was added 1.5 ml of freshly distilled, anhydrous phosphorus oxychloride. The mixture was stirred at 100° for 4 hr, cooled to *ca.* 10°, and added to crushed ice (200 g). The mixture was extracted with 200 ml of ether, and the extract was washed with three 200-ml portions of water, dried ($MgSO_4$), and evaporated. Crystallization of the residue from ethyl acetate–hexane gave 44 mg of **9** as colorless needles, mp 209–211°. This sample was dried *in vacuo* to give 38 mg of pure **9**: mp 211–212°; $[\alpha]^{25}D$ −1.60° (*c* 1.14, $CHCl_3$); ir 3650, 3500, 1740, 1720, and 872 cm^{-1}; nmr (DMSO-d_6–acetone-d_6) δ 1.12 (3 H, s), 1.98 (3 H, s), 2.1–2.6 (m), 3.82 (1 H, d, J = 11 Hz), 3.98 (1 H, d, J = 11 Hz), 4.14 (1 H, d, J = 11 Hz), 5.21 (1 H, d of t), 5.94 (1 H, d, J = 11 Hz), 6.37 (1 H, m), 7.31 (1 H, s), and 7.39 (1 H, t, J = 1 Hz); mass spectrum *m/e* (rel intensity) 442 (M^+, 3), 81 (100).

Anal. Calcd for $C_{22}H_{29}O_7Cl$: C, 59.93; H, 6.63; Cl, 8.08. Found: C, 60.00; H, 6.84; Cl, 8.12.

Reaction of Nepetaefolin (1) with Phosphorus Oxychloride.—Nepetaefolin (**1**) was treated under conditions identical with respect to quantities, reaction time, and work-up with those previously described for nepetaefuran. Crystallization of the product from ethyl acetate–hexane gave colorless needles, mp 210–211°. This product was identical in all respects with the product obtained from nepetaefuran [mmp 210–211°; mixed tlc (40% ethyl acetate in benzene), ir, nmr, and mass spectra].

Lithium Aluminum Hydride Reduction of Nepetaefuran.—A solution of 40.4 mg (0.10 mmol) of nepetaefuran (**2**) in 1 ml of anhydrous tetrahydrofuran was added to a stirred suspension of 200 mg of lithium aluminum hydride in 5 ml of anhydrous tetrahydrofuran. The mixture was heated under reflux with stirring for 3.5 hr, cooled to 0–5°, and treated with ethyl acetate to destroy excess hydride reagent. The slurry was added to 100 ml of ice-cold 5% sulfuric acid and extracted with two 100-ml portions of ethyl acetate. The extract was washed with saturated brine until it was neutral, dried ($MgSO_4$), and evaporated. Crystallization of the residue from methylene chloride gave 34 mg of colorless prisms, mp 124–127°. Further crystallizations from ethyl acetate–hexane and acetone–hexane gave an analytical sample of **10**: mp 137–138°; $[\alpha]^{25}D$ +21.4° (*c* 0.761, CH_3OH); ir 3425, 3340, 3160, and 875 cm^{-1}; nmr (DMSO-d_6–acetone-d_6) δ 1.09 (3 H, s), 1.24 (3 H, s), 3.26 (1 H, d, J = 12 Hz), 3.85 (1 H, d, J = 13 Hz), 4.19 (1 H, d, J = 12 Hz), 4.30 (1 H, d, J = 13 Hz), 6.42 (1 H, m), 7.39 (1 H), and 7.49 (1 H, t, J = 1 Hz); mass spectrum *m/e* (rel intensity) 368 (M^+, 1) and 81 (100).

Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.00; H, 8.61.

Lithium Aluminum Hydride Reduction of Nepetaefolin.—Nepetaefolin (**1**) was reduced under the conditions described for nepetaefuran. Acid work-up of the reaction mixture gave a product which was identical in all respects with the product obtained from the hydride reduction of nepetaefuran [mixture melting points, mixed tlc (80% ethyl acetate in benzene), ir, nmr, and mass spectra].

Acetylation of Nepetaefuranol (11).—A mixture of 65 mg (0.13 mmol) of nepetaefuranol (**11**) in 4.0 ml of anhydrous acetic anhydride was warmed to obtain a solution and, after cooling to room temperature, the solution was treated with 2 drops of anhydrous pyridine. The solution was allowed to stand at room temperature for 17 hr, added to 50 ml of ice-cold water, allowed to stand for 1.5 hr, and extracted with two 100-ml portions of ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated with addition of benzene to effect azeotropic removal of traces of acetic acid. Crystallization of the residue from ethyl acetate–hexane gave 60 mg of **12** as colorless crystals: mp 185–186°; ir ($CHCl_3$), 3500, 1735, 1715, and 872 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (3 H, s), 1.6–1.95 (m), 2.03 (3 H, s), 2.12 (3 H, s), 2.55 (1 H, disappears on addition of D_2O), 2.86 (1 H, disappears on addition of D_2O), 4.14 (1 H, d, J = 11 Hz), 4.25 (2 H, s), 5.25 (1 H, d of t), 5.78 (1 H, d, J = 11 Hz), 6.32 (1 H, m), 7.28 (1 H, s), and 7.38 (1 H, t, J = 1 Hz); mass spectrum *m/e* (rel intensity) 464 (M^+, 10), 344 (100), and 81 (95).

Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.06; H, 6.94. Found: C, 61.91; H, 7.02.

Alkaline Hydrolysis of Nepetaefuranol (11).—To a solution of 84.4 mg (0.20 mmol) of nepetaefuranol (**11**) in 20 ml of 95% ethanol was added 5.0 ml of a 10% solution of ethanolic potassium hydroxide. The solution was allowed to stand at room temperature for 1.0 hr, diluted with 50 ml of water, slowly acidified with ice-cold dilute sulfuric acid, and extracted with two 100-ml portions of ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated to give colorless crystals. Recrystallization from ethyl acetate–hexane gave 68 of large, colorless prisms: mp 196–197°; $[\alpha]^{25}D$ +22.5° (*c* 1.080, CH_3OH); ir 3650, 3460, 1735, and 874 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 10:1) δ 1.23 (3 H, s), 1.5–2.0 (m), 2.4–2.7 (m), 3.30 (1 H, d of d, J = 11 and 3 Hz; collapses to d on addition of D_2O, J = 11 Hz), 3.76 (1 H, d of d, J = 3, 11 Hz; collapses to d on addition of D_2O, J = 11 Hz), 4.03 (1 H, d, J = 11 Hz), 4.30 (1 H, broad s), 5.10 (1 H, disappears on addition of D_2O), 5.18 (1 H, disappears on addition of D_2O), 5.28 (1 H, d, J = 5 Hz, disappears on addition of D_2O), 5.40 (1 H, d, J = 11 Hz), 5.68 (1 H, broad t, J = 4 Hz, disappears on addition of D_2O), 6.32 (1 H, m), 7.30 (1 H, s), and 7.39 (1 H, t, J = 1 Hz); mass spectrum *m/e* (rel intensity) 380 (M^+, 4) and 81 (100).

Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.15; H, 7.31.

Acetylation of Hydrolyzed Nepetaefuranol (13).—A mixture of 38.0 mg (0.10 mmol) of the tetraol **13** in 1.0 ml of acetic anhydride was warmed (to dissolve), cooled to room temperature, and treated with 1 drop of anhydrous pyridine. The mixture was allowed to stand at room temperature for 16 hr, added to 100 ml of ice-cold water, allowed to stand at room temperature for 1.5 hr, and extracted with two 100-ml portions of ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated to give 37 mg of a gum: ir ($CHCl_3$) 3600, 1740, 1725, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:1) δ 1.16 (3 H, s), 2.13 (3 H, s), 4.14 (1 H, d, J = 11 Hz), 4.20 (2 H, s), 4.35 (1 H, broad s), 5.40 (1 H, d, J = 11 Hz), 6.33 (1 H, m), 7.30 (1 H, s), and 7.35 (1 H, t, J = 1 Hz); mass spectrum *m/e* (rel intensity) 422 (M^+, 5) and 81 (100). This compound (R_f 0.39) was readily separated from nepetaefuranol (**11**, R_f 0.52) in a mixed tlc (50% ethyl acetate in benzene).

Hydrogenation of Nepetaefuranol (11).—A solution of 84.4 mg (0.20 mmol) of nepetaefuranol (**11**) in 15 ml of 95% ethanol was hydrogenated over 90 mg of prereduced 10% palladium on charcoal at atmospheric pressure and room temperature until absorption ceased; 12 ml of hydrogen was absorbed during 10 min. Removal of the catalyst and solvent gave a solid which was crystallized from acetone–hexane and then from ethyl acetate–hexane to give 53 mg of **32** as colorless plates, mp 234–236°, mass spectrum *m/e* (rel intensity) 426 (M^+, 1) and 348 (60).

Reaction of Nepetaefuranol with Phosphorus Oxychloride.—To a solution of 84.4 mg (0.20 mmol) of **11** in 10 ml of anhydrous pyridine was added 1.0 ml of redistilled, anhydrous phosphorus oxychloride. The mixture was then stirred at 100° for 4 hr, cooled to *ca.* 10°, poured into 100 g of crushed ice, and extracted with 150 ml of ether. The extract was washed with two 125-ml portions of water, dried (Na_2SO_4), and evaporated.

The residue was further dried at 40° *in vacuo* (0.10 mm) to yield 43 mg of a gum which was crystallized from methylene chloride–hexane (at 0°) to give **15** as needles: mp 65–68°; ir ($CHCl_3$) 1740, 1725, 1340, and 875 cm^{-1}; nmr ($CDCl_3$) δ 1.16 (3 H), 2.04 (3 H, s), 3.25 (1 H, d, J = 10 Hz), 3.60 (1 H, d, J = 10 Hz), 4.30 (1 H, d, J = 11 Hz), 4.67 (1 H, d, J = 11 Hz), 5.11 (1 H, d of t), 6.26 (1 H, m), 7.26 (1 H, s), and 7.40 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 424 (M^+, 12) and 81 (100). This unstable compound gave a persistent green color in the Beilstein test.

Reduction of Nepetaefuranol with Lithium Aluminum Hydride.—A solution of 84.4 mg (0.20 mmol) of **11** in 5 ml of anhydrous tetrahydrofuran was added to a stirred suspension of 400 mg of lithium aluminum hydride in 10 ml of anhydrous tetrahydrofuran. The mixture was heated under reflux with stirring for 3 hr, cooled with an ice bath, and treated with ethyl acetate to destroy excess reagent. The cold mixture was added to 10 ml of ice-cold, 5% sulfuric acid, and extracted with two 50-ml portions of ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and evaporated to give a gum which, on addition of hexane, gave 72 mg of **18** as an amorphous solid: mp 108–113°; ir 3600 and 3500 cm^{-1}, with no carbonyl absorptions; nmr (DMSO-d_6–$CDCl_3$, 3:1) δ 1.03 (3 H, s), 3.30 (1, H, d, J = 11 Hz), 3.35 (1 H, d, J = 11 Hz), 3.74 (2 H, m), 4.07 (2 H, m), 4.30 (1 H, m), 6.35 (1 H, m), 7.33 (1 H, s), and 7.42 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 384 (M^+, 4) and 81 (100).

Reaction of Nepetaefuranol (11) with Sodium Periodate (Norketone 16).—To a stirred solution of 42.2 mg (0.10 mmol) of **11** in 8 ml of ethanol and 8 ml of water was added a solution of 120 mg of sodium acetate in 1.0 ml of water, followed by 110 mg of sodium metaperiodate in 2 ml of water during 5 min. The mixture was stirred at room temperature for a further 1 hr, diluted with 25 ml of water, and extracted with 100 ml of ethyl acetate. The extract was washed with 100 ml of saturated brine followed by 100 ml of water, dried ($MgSO_4$), and evaporated to give a gum. Crystallization of this material from methylene chloride–hexane gave 33 mg of nor ketone **16** as colorless needles: mp 188–189°; ir 3450, 1740–1720 (broad), and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:5) δ 1.16 (3 H, s), 1.5–1.9 (m), 1.98 (3 H, s), 2.3–2.6 (m), 3.58 (2 H, d of d, J = 13 and 4 Hz), 4.07 (2 H, d, J = 12 Hz), 4.27 (2 H, d, J = 12 Hz), 5.20 (1 H, s, disappears on addition of D_2O), 5.50 (1 H, d of t), 6.30 (1 H, m), 7.24 (1 H, s), and 7.36 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 390 (M^+, 13), 236 (100), and 81 (95).

Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.83; H, 6.72.

Elimination of Acetic Acid from 16 (α,β-Unsaturated Ketone 17).—A solution of 30 mg (0.077 mmol) of **16** in ethyl acetate–benzene (1:10) was chromatographed on 100 g of neutral alumina (Woelm, activity I) with 15% ethyl acetate in benzene as eluent. The main fraction was collected (as shown by tlc, 20% ethyl acetate in benzene), and the solvents were removed, leaving 24 mg of a gum. Preparative scale tlc (1 mm thick plates, 10% ethyl acetate in benzene) separated this material into two components and the major component (**17**, 17 mg) solidified: mp 175–177°; ir ($CHCl_3$) 3450, 1720, 1670, 1630, and 870 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (3 H, s), 3.92 (1 H, d, J = 9 Hz), 4.54 (1 H, d, J = 9 Hz), 6.25 (1 H, m), 6.41 (1 H, d, J = 9) Hz), 6.81 (1 H, d, J = 9 Hz), 7.16 (1 H, s), and 7.35 (1 H, s); mass spectrum m/e (rel intensity) 330 (M^+, 50) and 81 (100). The minor component (5 mg) had a mass spectrum virtually identical with that of **17**.

Reaction of Nepetaefuran (2) with Perchloric Acid.—To a solution of 40.4 mg of nepetaefuran in 4 ml of tetrahydrofuran was added to 0.4 ml of perchloric acid, and the mixture was allowed to stand at room temperature for 15 hr. The mixture was diluted with 50 ml of saturated brine and extracted with 50 ml of ethyl acetate. The extract was washed with 50 ml of 1% $NaHCO_3$ solution followed by two 50-ml portions of saturated brine, dried (Na_2SO_4), and evaporated to leave a gum. Tlc (40% ethyl acetate in benzene) showed the product to be a complex mixture containing compounds **7**, **11**, **13**, and **21**. Chromatography of the mixture on neutral alumina (Woelm, activity II) with 75–80% ethyl acetate in benzene gave 11 mg of nepetaefuranol (**11**) (identified by melting point, mixed tlc, and ir spectrum). Reaction of nepetaefolin (**1**) under the above conditions gave an identical result.

Conversion of Nepetaefuranol (11) into 7.—A solution of 42.2 mg (0.10 mmol) of **11** in 5 ml of anhydrous pyridine containing 20 mg of *p*-toluenesulfonyl chloride was allowed to stand at 0° overnight. The solution was diluted with 75 ml of saturated brine and extracted with 75 ml of ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated at 30° to give a gum which was dried *in vacuo* (0.02 mm) for 3 hr. This material was dissolved in 5 ml of 90% ethanol, treated with 5 ml of 10% potassium hydroxide, and allowed to stand at room temperature for 2 hr. After dilution with 50 ml of saturated brine, the mixture was extracted with 100 ml of ethyl acetate, and the extract was dried (Na_2SO_4) and evaporated, leaving 32 mg of a gum, which was chromatographed over 25 g of neutral alumina (Woelm, grade II) with 80% ethyl acetate in benzene to give 14 mg of **7** (identified by mixture melting point, mixed glc, and ir spectrum).

Reaction of 10 with *p*-Toluenesulfonyl Chloride (Tosylates 23 and 24).—A solution of 28 mg (0.076 mmol) of **10** in 1.5 ml of anhydrous pyridine containing 35 mg of *p*-toluenesulfonyl chloride was allowed to stand at room temperature for 14 hr. The mixture was diluted with 5 ml of water and extracted with two 10-ml portions of ethyl acetate. The extract was washed twice with a saturated solution of $CuSO_4$ and once with saturated $NaHCO_3$ solution, and dried (Na_2SO_4). Evaporation of the solvent gave 33 mg of a residue which crystallized, and which was shown by tlc (3% methanol in benzene) to consist of two closely related compounds (**23** and **24**); mass spectrum m/e 522 (M^+).

Reduction of Tosylates 23 and 24 with Lithium Aluminum Hydride. Leonotol (25).—To a solution of 33 mg (0.063 mmol) of **23** and **24** in 10 ml of anhydrous tetrahydrofuran was added 15 mg of lithium aluminum hydride and the mixture was heated under reflux for 4 hr. The mixture was treated cautiously with water to decompose excess reagent and extracted with ether. The extract was dried (Na_2SO_4) and the solvent was evaporated to leave a gum which, according to tlc, contained leonotol (**25**) in admixture with several other components. Preparative layer chromatography (2% methanol in benzene) with methanol as eluent, followed by crystallization from chloroform–hexane, afforded 8 mg of **25**, mp 139–140°, identified with leonotol by mixture melting point, ir spectrum, mixed tlc, and mass spectrum.

Epoxy Alcohol (21).—To a stirred solution of 40.4 mg (0.10 mmol) of nepetaefolin (**1**) in a 4 ml of tetrahydrofuran was added 0.4 ml of 60% perchloric acid. A slightly exothermic reaction ensued, after which the mixture was stirred at room temperature for 2.25 hr and then added to 40 ml of saturated brine and extracted with 50 ml of ethyl acetate. The extract was washed with 40 ml of 1% sodium bicarbonate solution and with two 40-ml portions of saturated brine, and dried (Na_2SO_4). Evaporation of the solvent left 38 mg of a gum, which was chromatographed on 20 g of neutral alumina (Woelm, activity II) with 40% ethyl acetate in benzene as eluent. The major fraction gave, after evaporation of the solvents, a colorless gum which solidified *in vacuo* during 4 hr to give 27 mg of **21** in a semicrystalline state: mp 146–149°; $[\alpha]^{25}D$ −4.4° (c 1.45, $CHCl_3$); ir 3330, 1740, 1700, 1380, 1240, 1040, and 875 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (3 H, s), 1.96 (3 H, s), 3.52 (1 H, d, J = 11 Hz), 3.66 (1 H, d, J = 11 Hz), 4.36 (1 H, d J = 11 Hz), 4.70 (1 H, d, J = 11 Hz), 5.07 (1 H, d of t), 6.24 (1 H, m), 7.19 (1 H, s), and 7.31 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 404 (M^+, 4) and 81 (100).

Anal. Calcd for $C_{22}H_{28}O_7$; C, 65.33; H, 6.98. Found: C, 64.97; H, 7.01.

Treatment of nepetaefuran (**2**) under the above conditions also gave **21**. Acetylation of **21** as described for **7** gave diacetate **32**, identical with material obtained previously.

Reduction of Leonotin. Leonontol (25).—A solution of 34.8 mg (0.01 mmol) of leonotin (**20**) in 1.0 ml of anhydrous tetrahydrofuran was added to a stirred suspension of 50 mg of lithium aluminum hydride in 3.0 ml of tetrahydrofuran. The mixture was heated under reflux with stirring for 4 hr, cooled (ice bath), and treated slowly with 10 ml of ethyl acetate. The resulting slurry was added to 50 ml of ice-cold, 5% sulfuric acid and the mixture was extracted with two 50-ml portions of ethyl acetate. The extract was washed with saturated brine until it was neutral, dried (Na_2SO_4), and evaporated to give 32 mg of a gum. Crystallization from ethyl acetate–hexane (1:5) gave **25** as colorless prisms: mp 136–138°; $[\alpha]^{25}D$ +32.0° (c 1.07, $CHCl_3$); ir ($CHCl_3$) 3600, 3300, 1021, and 873 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (3 H, s), 1.25 (3 H, s), 1.42 (3 H, s), 3.18 (1 H, d, J = 11 Hz), 4.12 (1 H, d of t), 4.22 (1 H, d, J = 11 Hz), 5.0–5.6 (broad, disappears on addition of D_2O), 6.35 (1 H, m), 7.27 (1 H, s), 7.36 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 352 (M^+, 2).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.44; H, 9.32.

Registry No.—**1**, 29606-32-4; **2**, 29461-24-3; **4**, 37705-47-8; **5**, 37759-46-9; **6**, 29606-33-5; **7**, 37759-48-1; **8**, 37759-49-2; **9**, 37705-50-3; **10**, 29461-38-9; **11**, 29722-58-5; **12**, 37759-52-7; **13**, 37759-53-8; **15**, 37759-54-9; **16**, 37759-55-0; **17**, 37759-56-1; **18**, 37705-51-4; **20**, 26549-00-8; **21**, 37759-57-2; **23**, 37759-58-3; **24**, 37759-59-4; **25**, 29389-54-6; **32**, 37759-61-8.

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Biogenetically Patterned Total Syntheses of (+)-Occidentalol and 7-Epi-(−)-occidentalol[1,2]

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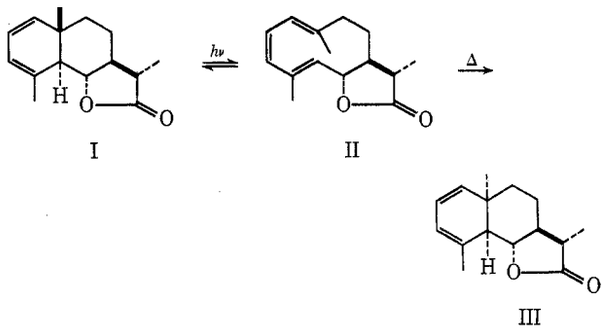
Diene (−)-**9** was prepared from (−)-**3** by standard procedures. Irradiation of **9** at −78° led to a probable photoequilibrium between **9** and an unstable intermediate believed to be **10**. Cyclodecatriene **10** underwent thermally induced cyclization at > −30° to yield cis-fused dienes (−)-**11** and (+)-**12** in a 2:1 ratio. The stereostructures assigned to the cis-fused dienes were based on conformational analysis, nmr, ORD, and CD data, and the finding that (−)-**11** is converted to (−)-**12** by base-catalyzed epimerization at C-7. Treatment of (+)-**12** with CH_3Li afforded (+)-occidentalol [(+)-**2**], thereby establishing the absolute stereostructure of this natural product. Similarly, (−)-**12** gave (−)-occidentalol [(−)-**2**] and (−)-**11** gave 7-epi-(−)-occidentalol [(+)-**1**]. A hypothetical biosynthetic scheme is outlined for the formation of (+)-occidentalol and some other known cis-fused eudesmanes by disrotatory cyclization of *trans,cis,trans*-cyclodecatrienes derivable from farnesol. A biogenetic-type synthesis of (+)-**2** and (+)-**1** *via* thermally induced cyclization of **15**, presumed to be generated during irradiation of (−)-**14**, is also described.

(+)-Occidentalol, a eudesmane-type sesquiterpene alcohol isolated from the wood of *Thuja occidentalis* L.[3,4] and *T. koraiensis* Nakai,[5] has been shown to have stereostructure (+)-**2**.[6] The coincident presence of a rarely occurring cis ring junction and a 1,3-diene system in occidentalol suggests that a unique biosynthetic pathway[7] involving disrotatory thermal cyclization[8] of a *trans,cis,trans*-cyclodecatriene intermediate derivable from farnesol may be operative in the formation of (+)-**2** and related cis-fused eudesmanes. We report here two total syntheses of (+)-**2** and (+)-**1** by routes (see Scheme I) which parallel the presumed biogenesis[7] and would seem to be generally applicable to the synthesis of other polyfunctionally substituted cis-fused decalins. A preparation of (−)-**2** from a common intermediate is also described.[9-11]

Total Synthesis and Stereochemistry of (+)-Occidentalol, (−)-Occidentalol, and 7-Epi-(−)-occidentalol



I II III

[(+)-**2**, (−)-**2**, and (+)-**1**].—The observation that thermally induced cyclization of cyclodecatriene II (generated by photolysis of I) affords cis-fused diene III[12] provided and experimental basis for the hypothetical biosynthetic scheme for (+)-**2** already outlined[7] as well as the biogenetically patterned syntheses of (+)-**2** shown in Scheme I.

Thus, keto ester (−)-**3**, prepared from (+)-carvone,[13] was brominated to yield the 2α-bromo derivative **4**. Dehydrobromination of crude **4** with LiBr and $LiCO_3$ in DMF at 120° gave the olefinic keto ester **5**, which could be purified by recrystallization of the corresponding acid, **6**, followed by remethylation of **6** with CH_2N_2 in ether. Reduction of either **5** or **6** with aluminum isopropoxide gave a mixture of olefinic hydroxy esters, **7** and **8**, *via* hydrolysis of the intermediate isopropyl ester analogs. Dehydration of the oily mixture of epimeric alcohols **7** and **8** by heating at 220° in the presence of alumina containing 2% pyridine[12] afforded the trans-fused diene **9** in ~25% yield. The diene **9** analyzed correctly for $C_{14}H_{20}O_2$ but contained 8–10%

(1) We thank the National Institutes of Health for financial support of this research (Grant GM13441).

(2) Reported in part at the 4th Midwest Regional Meeting of the American Chemical Society, Manhattan, Kans., Nov 1, 1968.

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