tion. The assistance of Mr. David Fox in calculating theoretical mass spectra is gratefully expressed.

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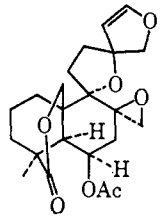
The Structure of Nepetaefolin, a Prefuranoid Diterpene

Sir:

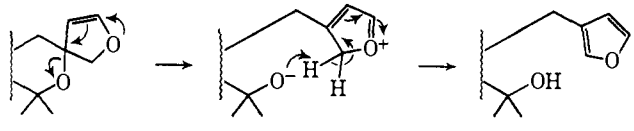
The plant *Leonotis nepetaefolia* R. Br. (family *Labiatae*) is widespread throughout the West Indies, South America, and the African continent, and has attributed to it a variety of salutary physiological effects.[1] In an earlier study of *L. nepetaefolia*, components of the seed oil were characterized,[2] but leaves and stems, wherein the more interesting medicinal properties reside, were not investigated. During a survey of leaf constituents of this plant, we have encountered several diterpenes of novel structure and wish to report evidence leading to stereostructure **1** for one of



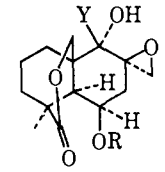
1

these, nepetaefolin.

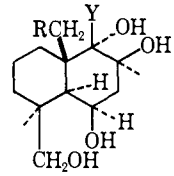
Nepetaefolin, mp 260° dec, $[\alpha]^{25}D$ −14.6° (*c* 0.90, $CHCl_3$), is an unstable substance of composition $C_{22}H_{28}O_7$ and, on warming in $CHCl_3$, isomerizes quantitatively to nepetaefuran (**2**), mp 241–242°, $[\alpha]^{25}D$ +32.3° (*c* 1.35, MeOH), which is also present in the plant extract. The transformation is characterized by disappearance of nmr signals due to a vinyl ether[3] (δ 5.09, 1 H, d, J = 3 Hz; 6.53, 1 H, d, J = 3 Hz) and the appearance of a mono-β-substituted furan (δ 6.29, 1 H, t, J = 0.5 Hz; δ 7.27, 1 H, m; δ 7.38, 1 H, t, J = 1 Hz; mass spectral base peak at *m/e* 81[4]); a hydroxyl group which could not be acetylated was produced concomitantly. The conversion of nepetaefolin (**1**) to nepetaefuran (**2**) thus involves elimination from a 1,2-dihydrofuran, and is rationalized as



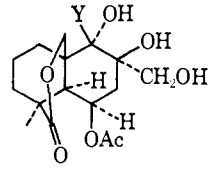
Sharp 3 H singlets at δ 2.07 and 1.96 in the spectra of **1** and **2**, respectively, suggested the presence of acetoxyl groups, and these functionalities were probed



2, R = Ac
3, R = H



4, R = OH
7, R = H



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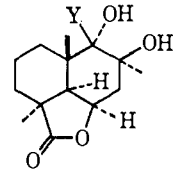

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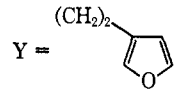
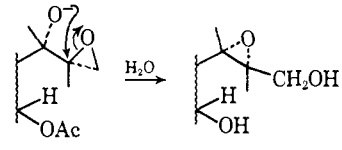


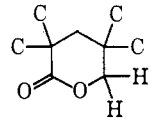
in hydrolytic experiments. Saponification of **1**, followed by acidic work-up, gave a substance (**3**), $C_{20}H_{26}O_6$, mp 202–203°, $[\alpha]^{25}D$ +34.0° (*c* 1.01, MeOH), which, after treatment with Ac_2O–pyridine, afforded nepetaefuran. Base treatment of nepetaefuran, on the other hand, gave a deacetyl compound, mp 196–198°, $[\alpha]^{25}D$ +29.6° (*c*, 1.29 MeOH), which was isomeric with the C_{20} product from **1**; the appearance of a new AB quartet at δ 3.48 and 3.62 indicated that a primary alcohol had been generated in this reaction. Acetylation of this material in the cold gave a primary monoacetate $C_{22}H_{28}O_7$, mp 165–166° (δ 4.06 and 4.18, 2 H, AB quartet, J = 12 Hz); more strenuous acetylation furnished a diacetate which showed no hydroxyl absorption. Since nepetaefuran itself does not contain a primary alcohol and the tertiary hydroxyl initially present has been lost, the transformation occurring upon treatment with base can be formalized as



Proof of the terminal epoxide moiety was obtained by hydrogenolysis of **2** with $LiAlH_4$ in THF, which gave a reduction product (**4**), $C_{20}H_{32}O_6$, mp 137–138°, $[\alpha]^{25}D$ +21.4° (*c* 0.76, MeOH), containing a new CH_3

(1) 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.
(2) C. F. Asenjo, J. A. Goyco, and F. Martinez-Pico, *J. Amer. Chem. Soc.*, 67, 1936 (1945).
(3) L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp 62, 88.
(4) C. R. Enzell and R. Ryhage, *Ark. Kemi*, 23, 367 (1965).

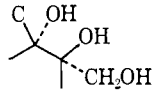
group (δ 1.24, s) in addition to that present originally (δ 1.09, s). Reduction also confirmed the presence of a δ-lactone in nepetaefuran (ν_{max}^{Nujol} 1730 cm^{-1}), a functionality which had been indicated previously by formation of a potassium salt of **2** upon vigorous basic hydrolysis. Acidification of this salt induced immediate relactonization. Part structure A follows



A

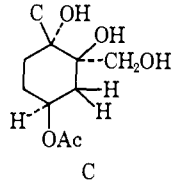
from the observation that the carboxylate cannot be methylated and that the reduction product, **4**, contains two AB quartets at δ 3.27 and 4.19 (J = 11 Hz) and δ 3.88 and 4.29 (J = 13 Hz).

Further clarification of the structures of these diterpenoids became possible with the discovery of a third substance, nepetaefuranol (**5**), $C_{22}H_{30}O_8$, mp 253–255°, $[\alpha]^{25}D$ +17.2° (c 1.05, MeOH), in the extract from *L. nepetaefolia*. Nepetaefuranol contained a primary alcohol (δ 3.30 and 3.79, 2 H, AB quartet, J = 11 Hz) and furnished a monoacetate, mp 185–186°, containing two hydroxyl groups. Its relationship with **2** was established by treatment of the latter with perchloric acid, which gave **5**; the reverse transformation was accomplished by treatment of the tosylate of **5** with base. Nepetaefuranol therefore contains the part structure represented as B. Oxidation of **5** with sodium meta-



B

periodate yielded a norketone, $C_{21}H_{22}O_7$, mp 188–189°, ν_{max}^{Nujol} 1720–1740 cm^{-1} (broad), from which acetic acid was eliminated on alumina to give an α,β-unsaturated cyclohexenone, mp 175–177°, m/e 330, ν_{max}^{Nujol} 1670 cm^{-1}, δ 6.41 (1 H, d, J = 10 Hz) and 6.81 (1 H, d, J = 10 Hz). This allows extension of part structure B to C.



C

Structural features uncovered in the course of degradative work suggest that **1**, **2**, and **5** are diterpenes of the labdane type,[5] and chemical data as well as biogenetic theory are accommodated uniquely in these formulas. The position and orientation of the lactone are dictated by the conspicuous AB pattern of the lactone methylene protons in **5** (δ 4.03 and 5.88, J = 12 Hz) and degradation products containing an 8-β-OH function, where a pronounced downfield shift occurs due to a 1,3-diaxial relationship.[6] Unambiguous proof of the structure of nepetaefuran, and hence of nepetaefolin and nepetaefuranol, was obtained by correlation with leonotin (**6**) of known structure and relative stereochemistry.[7] Treatment of **4** with tosyl chloride in pyridine gave a mixture of the two primary monotosylates which, upon hydrogenolysis with $LiAlH_4$ in THF, afforded leonotol (**7**), mp 136–138°, probably by way of an intermediate cyclic ether.[8] Leonotol had previously been acquired by reduction of **6** and the latter, in turn, has been correlated with marrubiin.[9] The relative stereochemistry at all six chiral centers of **2** and **5** are thereby defined, as are the corresponding centers in nepetaefolin (**1**), but configuration at the additional spirocarbon of the latter remains unspecified.

The biogenetic implication that **1** is the immediate precursor of **2** in *L. nepetaefolia* is upheld by isolation studies to be reported subsequently, but it may be noted that observations in parallel with ours have recently been made in the marrubiin series.[10] Details of the biosynthetic processes leading from the isoprenoid skeleton to the spirodihydrofuran system, however, are as yet obscure.

Acknowledgments. We are grateful to Mr. M. Hasmathullah, Warrenville, Trinidad, for a supply of *Leonotis nepetaefolia*. Generous financial support was provided by the National Science Foundation (Grant No. GP-15,331) and by Hoffmann-LaRoche, Inc.

(5) R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965).

(6) Measurement of nmr spectra in pyridine-d_5 produces an even larger displacement downfield [see P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968)].

(7) J. D. White, P. S. Manchand, and W. B. Whalley, *Chem. Commun.*, 1315 (1969).

(8) H. L. Goering and C. Serres, *J. Amer. Chem. Soc.*, **74**, 5908 (1952).

(9) D. M. S. Wheeler, M. M. Wheeler, M. Fetizon, and W. H. Castine, *Tetrahedron*, **23**, 3909 (1967).

(10) M. S. Henderson and R. McCrindle, *J. Chem. Soc. C*, 2014 (1969).

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Incorporation of 1,3-Dimethyl-1-pyrrolinium Chloride in *Nicotiana glutinosa*. Biosynthesis of a Substituted Nicotine[1]

Sir:

The study of the biosynthesis of natural products in plants has been carried out almost exclusively by means of precursor feeding experiments, although the importance of alternate methods such as short-term biosynthesis with $^{14}CO_2$ has been stressed.[2] Ideally, only the natural precursor should be incorporated efficiently into the natural product; however, incorporation of an unnatural precursor into a natural product is well documented.[3] Although theoretically possible, neither the incorporation of a natural precursor into an unnatural product[4] nor the incorporation

(1) This investigation was supported in part by Grant No. MH 12797 from the National Institute of Mental Health, U. S. Public Health Service, and the U. S. Atomic Energy Commission. Dedicated to Professor Kurt Mothes on the occasion of his 70th birthday.

(2) A. A. Liebman, B. P. Mundy, and H. Rapoport, *J. Amer. Chem. Soc.*, **89**, 664 (1967).

(3) G. Blaschke, H. I. Parker, and H. Rapoport, *ibid.*, **89**, 1540 (1967); T. J. Gilbertson and E. Leete, *ibid.*, **89**, 7085 (1967).

(4) Preliminary results indicate that examples of this type have been observed in studies on nicotine and morphine metabolism.