BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 3947—3948 (1970)

The Occurrence of (−)-(2R : 5R)-*trans*-2,5-Diethyltetrahydrofuran in "Hōyō" Mint Oil

Yasuaki ITAHARA, Hajime WATANABE and Jun KATSUHARA
Sun Star Dentifrice Company, Research Laboratory, Takatsuki, Osaka

(Received July 2, 1970)

To data, more than fourteen kinds of low-boiling, oxygenated non-terpenoidal compounds have been isolated from the essential oil of *Mentha* genus.

We have recently isolated (−)-*trans*-2,5-diethyltetrahydrofuran (I) as a novel component of the *Mentha* essential oil. To our knowledge, this is the first example of the occurrence of (−)-I in the vegetable kingdom. We wish, at this time, to report on the isolation, structure elucidation, assignment of absolute configuration, and confirmation of this substance by means of the synthesis of enantiomeric (+)-I.

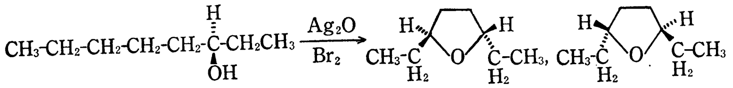
The low-boiling fraction of a "Hōyō" dementholized mint oil was rectified on a helix-packed column to give several fractions, from among which the cut distilling over the range from 131.5 through 152.0°C was further purified by means of preparative vpc to afford a liquid, boiling at 143—144°C, in an over-all yield of 0.009% (based on the crude oil used). The purity of this sample was demonstrated by the sharp single peak in the vapor-phase chromatogram. The molecular ion peak at *m/e* 128 in the mass spectrum, coupled with the results of the elemental analysis, showed the molecular formula of this compound to be $C_8H_{16}O$. The absence of hydroxyl, carbonyl, isopropyl, and geminal dimethyl groups and a double bond were indicated by the IR analysis, the results of which suggested a saturated cyclic ether structure. Similarly, the NMR spectrum showed a methin proton signal centered at τ 6.2 (2H; $>\mathrm{C}\underline{\mathrm{H}}\text{–O–}\mathrm{C}\underline{\mathrm{H}}<$), methylene proton signals at τ 7.9—8.9 (8H), and methyl proton signals at τ 9.1 (6H triplet, J= 6 Hz). The oxiran structure was precluded by the complete inertness of (−)-I toward lithium aluminum hydride. The NMR spectral data, when combined with the intense fragment ion peaks at *m/e* 99 (M-29) and *m/e* 29 (C_2H_5), led us to the convincing deduction of the structure as 2,5-diethyltetrahydrofuran. Moreover, in *a priori* symmetry considerations, the optical activity as manifested in the levorotation found for I, $[\alpha]_D^{24}$ −9.9°, logically necessitates the point group C_2 for this molecule, thus enabling us reasonably to assign the *trans*-geometry.

In order to confirm this deduction, to establish the absolute configuration, and also to ascertain whether or not (+)-(3S)-octanol (II), a constituent of very frequent occurrence in mint oil, is a biogenetic precursor of (−)-I, the oxidative cyclization of (+)-II with silver oxide and bromine was carried out according to the Mihailovic procedure[1] in the following manner (Scheme 1). The structure of the resulting (+)-I was fully substantiated by a comparison of its physical properties, and IR and mass spectra with those of the authentic specimen described in the literature.[2] The IR and mass spectral comparisons gave unambiguous evidence that the naturally-derived (−)-I is the enantiomer of the synthetic (+)-I. The conversion of the (+)-II with the well-defined S-configuration into (+)-I *via* the present process, which does not jeopardize the chiral carbon, permits us to identify the (2S : 5S)-configuration as

---

[1] M. Lj. Mihailovic, Z. Cekovic and J. Stankovic, *Chem. Commun.*, **1969**, 981.

[2] M. Lj. Mihailovic, R. I. Mamuzic, Lj. Zigic-Mamuzic, J. Bosnjak and Z. Cekovic, *Tetrahedron*, **23**, 215 (1967).



(+)−(3S)-II (+)-(2S : 5S)-III (−)-(2R : 5R)-I

Scheme 1

the synthetic (+)-I and, consequently, the (2R : 5R)-configuration as the naturally-derived enantiomer, (−)-I. This implies also that, in contrast to expectation, the naturally-occurring (−)-(2R : 5R)-I can not find its genetic origin in (+)-(3S)-II in the biosynthesis of *Mentha* plants.

Experimental

Isolation of (−)-*trans*-2,5-Diethyltetrahydrofuran (—)-(I). A forerun (5 kg) obtained by the steam-distillation of "Hōyō" dementholized mint oil (300 kg) was redistilled under reduced pressure to yield a low-boiling fraction (420 g). A part of this fraction (300 g) was rectified on a Helipack-type precision still to give a fraction distilling over the range from 131.5 through 150.0°C (23.5 g); this fraction was further purified by means of preparative vpc to yield I; bp 143—144°C; n_D^{24} 1.4201, $[\alpha]_D^{24}$ $-9.9° \pm 0.1°$ (c 2.0, ethanol). Fragment ion peaks in the mass spectrum: *m/e* 128 (molecular ion; 3.5%), 99 (24), 81 (100), 59 (21), 57 (45), 55 (100), 43 (63), 42 (53), 41 (45), 39 (27), 31 (11), 29 (68), 28 (15), 27 (39).

Found: C, 74.94; H, 12.65%. Calcd for $C_8H_{16}O$: C, 75.00; H, 12.50%. IR Spectrum: 2980 s, 2950 sh, 2890 sh, 1470 s, 1380 m, 1110 s, 1090 s, 1020 s, 990 sh, 930 m, 875 m cm^{-1}.

Synthesis of (+)-(2S : 5S)-*trans*-2,5-Diethyltetrahydrofuran (+)-(I). Bromine (7.5 g) was stirred, drop by drop, into a mixture of (+)-3-octanol (II) ($[\alpha]_D^{24}$ $+9.0 \pm 0.2°$ (*c* 1.2, ethanol), 96.5% optical purity (3.0 g)) and silver oxide (5.7 g) in 80 m*l* of *n*-pentane in a nitrogen atmosphere over a 3-hr period. The reaction mixture was kept at 18—20°C during the addition, and then the stirring was continued for a further 2 hr. After this period, the reaction mixture was filtered to remove the silver bromide, the filtrate was washed successively with a 10% sodium thiosulfate solution, a 10% sodium hydrogencarbonate solution and water, dried over anhydrous sodium sulfate, and concentrated until a *n*-pentane-free residue was obtained (2.6 g). This residue was further purified by means of vpc to give (+)-I; bp 142—144°C, n_D^{24} 1.4188, $[\alpha]_D^{24}$ $+4.4 \pm 0.3°$ (c 1.2, ethanol). The IR and mass spectra of (+)-I were identical in every respect with those of the authentic specimen described in the literature[2] and also with those of the naturally-derived (—)-I.

The authors wish to thank Professor Yūzō Inouye of Kyoto University for many helpful discussions during the course of this work and Dr. Hideo Urushido of Hokuren for his generous gift of a sample. Thanks are also due to Dr. Shigeru Muraki of the Takasago Perfumery Co., for his measurements of the NMR and mass spectra, and to Dr. Tsutomu Sakai and his staff of the Institute of Food Chemistry for their measurement of the optical rotation.