Tetrahedron Letters No. 36, pp 3175 - 3178, 1976. Pergamon Press. Printed in Great Britain.

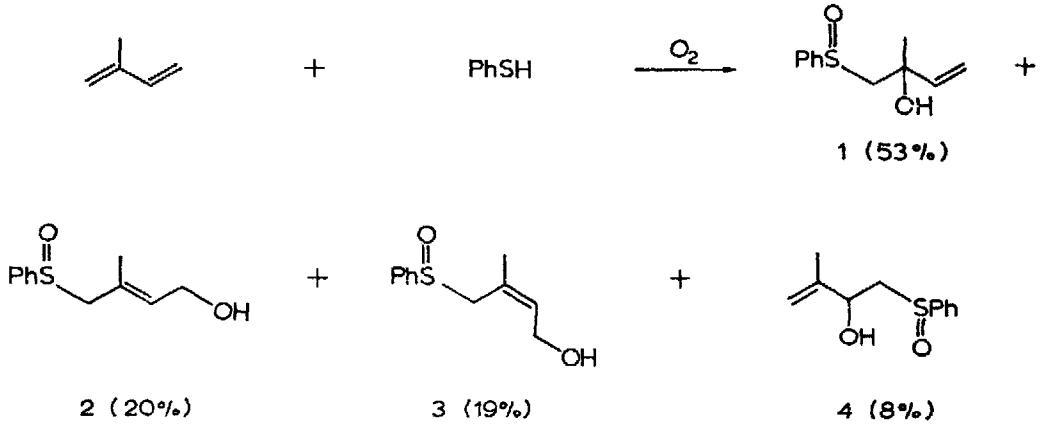
ISOPRENE FUNCTIONALIZATION; HYDROXY SULFOXIDE TERPENE BUILDING BLOCKS

P.J.R. Nederlof, M.J. Moolenaar, E.R. de Waard* and H.O. Huisman,
Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

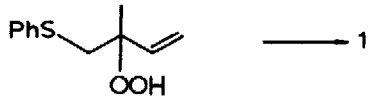
(Received in UK 23 April 1976; accepted for publication 16 July 1976)

The ready availability of isoprene from petrochemical sources has considerably stimulated the search for isoprene derivatives which can be used as five-carbon synthons in terpene synthesis. Many elegant isoprene homologations have been added to the armoury of synthetic methods during recent years[1]. However very few of the intermediates published thusfar can be directly synthesized from isoprene itself. We wish to report a convenient conversion of isoprene into a mixture of the functionalized derivatives 1-4. The components can be easily obtained in a pure form on a practical scale and preliminary experiments have shown that each of these five-carbon synthons can serve as a versatile reagent in the total synthesis of terpenoid compounds[2].

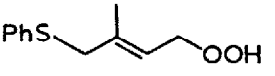
Isoprene[3] is readily co-oxidized with thiophenol by molecular oxygen at roomtemperature to give a mixture consisting of the hydroxysulfoxides 1, 2, 3 and 4[4] in 96% conversion based on thiophenol; 4% of the thiophenol is recovered in the form of diphenyl disulfide.



The first mention of this type of co-oxidation of olefins with thiols was made by Kharasch c.s.[5] Later investigations have revealed[6-9] this radical chain reaction to lead to β-hydroxyperoxy sulfides which may be isolated at temperatures below 5°C and have been shown to give the corresponding hydroxy sulfoxides at room temperature[6,7,9]. The radical process is considerably accelerated by the addition of finely powdered sodium chloride[7].
The low temperature co-oxidation of isoprene with thiophenol leading to the hydroperoxysulfides 5 and 6 is described in the literature[10] as part of a synthesis of the corresponding hydroxysulfides which are formed upon reduction of the hydroperoxy group by excess of thiophenol in the presence of an amine as a catalyst. Surprisingly no mention is made of the products 1 and 2 which are readily formed at room temperature from 5 and 6.



5 ——→ 1



6 ——→ 2

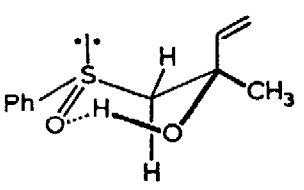
The co-oxidation is essentially performed as described in the literature[10], but for the addition of powdered sodium chloride and the absence of external cooling. The greater part of the hydroxy sulfoxide 1 crystallizes slowly as a mixture of the two diastereoisomeric racemates in a 1:1 ratio. The crystalline fraction can be readily separated into the components. The isomer 1a (mp. 93-96°C) is obtained by crystallization from acetone; the diastereoisomer 1b (mp. 110-112°C) crystallizes faster from ethyl acetate.
1a: δ $\overset{CDCl_3}{TMS}$ (60 MHz) 7.8-7.3 (m, 5H, phenyl), 6.4-5.2 (m, 3H, vinyl), 4.4 (broad s, 1H, hydroxyl), 3.0 and 2.8 (AB-pattern, J_{AB} 13.5 Hz, methylene), 1.38 (s, 3H, methyl); ν $\overset{CHCl_3}{max}$ 3400 and 1020 cm^{-1} (OH and SO).
1b: δ $\overset{CDCl_3}{TMS}$ (100 MHz) 7.8-7.4 (m, 5H, phenyl), 6.1-5.0 (m, 3H, vinyl), 4.4 (s, 1H, hydroxyl), 3.00 and 2.88 (AB-pattern, J_{AB} 13.6 Hz, methylene), 1.57 (s, 3H, methyl); ν $\overset{CHCl_3}{max}$ 3400 and 1020 cm^{-1} (OH and SO).

When the non-crystalline fraction of the reaction mixture is extracted with water the E-hydroxysulfoxide 2 can be obtained without noticeable 2,3-sigmatropic shift[11] from the aqueous solution by extraction with chloroform. Recrystallization from ether gives 2 in a pure state (m.p. 28-30°C).
2: δ $\overset{CDCl_3}{TMS}$ (100 MHz) 7.75-7.45 (m, 5H, phenyl), 5.52 (t, 1H, vinyl), 4.15 (t, 2H, $-CH_2O-$), 3.48 and 3.43 (AB-pattern, J_{AB} 12 Hz, $-CH_2SO-$), 2.4 (s, 1H, hydroxyl), 1.78 (s, 1H, methyl).

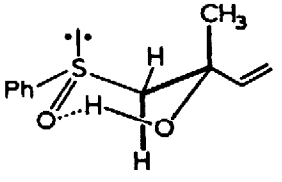
Column chromatography of the combined remaining fractions gives additional quantities of pure 1a, 1b and 2 along with two other fractions consisting of the Z-hydroxysulfoxide 3, and a mixture of presumable both diastereoisomeric hydroxysulfoxides 4, respectively.

3: $\delta \overset{CDCl_3}{TMS}$ (60 MHz) 7.6-7.3 (m, 5H, phenyl), 5.9 (t, 1H, vinyl), 3.8 (d, 2H, $-CH_2O-$), 3.72 and 3.37 (AB-pattern, J_{AB} 12 Hz, $-CH_2SO-$), 3.2 (broad s, 1H, hydroxyl), 1.7 (s, 3H, methyl).

The relative configuration of 1a and 1b can be derived from the NMR spectra. Multiple resonance reveals that the methyl signal of 1a exhibits a long range coupling (0.8 Hz) in chloroform with the hydroxylic hydrogen; the methyl signal of 1b, however, is coupled (0.6 Hz) to one of the methylene hydrogens. These long range effects disappear completely in d_6-DMSO, indicating that they originate from hydrogen bonding. We assume that 1a and 1b have a small preference in chloroform solution for the quasi-chair hydrogen-bonded conformations 7 and 8[12], since the quasi-equatorial position of the phenyl group minimizes the non-bonded interactions. These conformations 7 and 8 would explain the observed long range effects and correspond to the RS/SR-configuration for the racemate 1a and the RR/SS-configuration for 1b[13].



7



8

REFERENCES AND NOTES

*To whom all correspondence should be addressed.

1. See e.g.: M. Julia and D. Arnould, Bull. Soc. Chim. France, 743 (1973); G. Cardillo, M. Contento and S. Sandri, Tetrahedron Letters, 2215 (1974); S. Kobayashi and T. Mukaiyama, Chem. Letters, 705 (1974); L.J. Altman, L. Ash and S. Marson, Synthesis, 129 (1974); K. Takabe, T. Katagiri and J. Tanaka, Tetrahedron Letters, 3005 (1975); K. Sato, S. Inoue and S. Morii, Chem. Letters, 747 (1975); J.H. Babler and W.J. Buttner, Tetrahedron Letters, 239 (1976) and references cited therein.

2. The various applications will be published in due course.

3. Similar results have been obtained with butadiene and with 3-methylidene-pentene (2-ethyl-1,3-butadiene).

4. The ratio of the products is slightly dependant on the reaction conditions.

5. M.S. Kharasch, W. Nudenberg and G.J. Mantell, J. Org. Chem. 16, 524 (1951).

6. A.A. Oswald, J. Org. Chem. 24, 443 (1959).

7. H. Bredereck, A. Wagner and A. Kottenhahn, Chem. Ber. 93, 2415 (1960).

8. A.A. Oswald and T.J. Wallace in: "The Chemistry of Organic Sulfur Compounds", vol. 2, N. Kharasch and C.Y. Meyers, Editors, Pergamon Press, Oxford, 1966.

9. S. Iriuchijima, K. Maniwa, T. Sakakibara and G. Tsuchihashi, J. Org. Chem., 39, 1170 (1974).

10. A.A. Oswald, K. Griesbaum and B.E. Hudson Jr., J. Org. Chem., 28, 2355 (1963).

11. D.A. Evans and G.C. Andrews, Acc. Chem. Res. 7, 147 (1974).

12. Only one enantiomer is shown for each racemate.

13. An X-ray analysis is under performance.