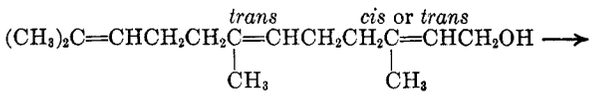
A Convenient Preparation of *trans*-β-Farnesene

GOTTFRIED BRIEGER

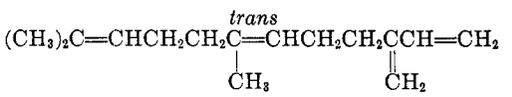
Chemistry Department, Oakland University, Rochester, Michigan

Received May 4, 1967

The dehydration of farnesol has been investigated by several workers, most recently by Naves,[1] who reported that the acid-catalyzed dehydration of farnesol yielded a complex mixture of at least 12 components. The base-catalyzed dehydration of farnesol to give *trans*-β-farnesene has also been reported.[2]



farnesol



trans-β-farnesene

In an effort to obtain larger amounts of pure *trans*-β-farnesene, we have repeated the base-catalyzed dehydration of farnesol. The reaction of farnesol with KOH at 200–210° leads to significant amounts of C_{14} olefins, which are difficult to separate by distillation. Consequently we examined a number of additional methods for dehydration, including the use of iodine, acid anhydrides, acid chlorides, $ZnCl_2$, and hot dimethyl sulfoxide. None of these methods proved satisfactory.

On the other hand, catalytic dehydration by means of activated alumina proved successful. The resulting *trans*-β-farnesene is obtained in 65% yield by passage over activated alumina at 260–270°.

The infrared spectrum of the product so obtained was identical with that of *trans*-β-farnesene isolated from the acid- or base-catalyzed dehydration of farnesol, as was the nmr spectrum.[2] Comparison was also made with a sample of natural *trans*-β-farnesene isolated from *Matricaria matricarioides*. Nerolidol may be similarly dehydrated in comparable yield. The application of this method to other sesquiterpene alcohols is being investigated.

Experimental Section

The dehydration was conducted in a Wilkens A-90 P gas chromatograph, using a 5 ft × 0.25 in. Pyrex column packed with glass beads (60–80 mesh) and 1.0 g of Alcoa F-20 chromatographic alumina. The alumina was activated by heating to 300°. The farnesol (Fluka AG) was injected in 100-μl portions, using a helium flow of 60 ml/min. From 5.0 g of farnesol, 4.26 g of crude product was obtained. The infrared spectrum showed that dehydration was complete at 260–270°. Glpc analysis of the product on a 10 ft × 0.25 in. 25% TCEP/60–80 Chrom W column at 130° showed a purity of 80% *trans*-β-farnesene: $n^{20}D$ 1.4887; $\lambda_{max}^{n\text{-heptane}}$ 224 mμ (ε 14,000); infrared spectrum (0.025-mm cell), 3095 (m), 2970 (s), 2930 (s), 2730 (w), 1790–1820 (w), 1670 (w), 1645 (w), 1630 (w), 1592 (s), *ca.* 1440 (s), 1378 (sh), 1372 (s), 1150 (w), 1105 (m), 990 (s), 900 (sh), 890 (s), 825–835 (m), 740–755 (w), and *ca.* 670 (w).

(1) Y. Naves, *Helv. Chim. Acta*, **49**, 1029 (1966).
(2) A. Bhati, *Perfumery Essent. Oil Record*, **53**, 376 (1962).

Registry No.—*trans*-β-Farnesene, 502-60-3.

Acknowledgment.—Support from the Petroleum Research Fund of the American Chemical Society is acknowledged.

1-(*p*-Chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine

DONG HAN KIM, ARTHUR A. SANTILLI, THEODORE S. SULKOWSKI, AND SCOTT J. CHILDRESS

Research and Development Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania

Received May 31, 1967

The synthesis[1] and pharmacological activity[2] of 1-(*p*-chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (VII) was reported previously from this laboratory. The reaction of 2-(*p*-chlorobenzoyl)benzoic acid with ethylenediamine afforded the tricyclic intermediate (VIII), which upon reaction with lithium aluminum hydride yielded VII. The structural assignment was based on elemental analyses and infrared and nmr spectral data of VII and derivatives. Although a careful examination of these data left little doubt as to the validity of the assigned structure, nonetheless a chemical proof of the structure of VII was desired. This paper describes an unequivocal synthesis of VII. See (Chart I).

Bromination of 4-chloro-2′-methylbenzophenone (I) with N-bromosuccinimide in carbon tetrachloride afforded 2′-bromomethyl-4-chlorobenzophenone (II) as starting material in the synthesis. The reaction of II with N-acetyl-N′-phenylsulfonylethylenediamine in refluxing ethanol containing an equivalent amount of potassium hydroxide gave N-acetyl-N′-(2-*p*-chlorobenzoylbenzyl)-N′-phenylsulfonylethylenediamine (IIIa). Hydrolysis of IIIa with 20% sulfuric acid afforded the amine IVa. Several attempts to cyclize IVa to 1-(*p*-chlorophenyl)-5-phenylsulfonyl-3,4,5,6-tetrahydro-2,5-benzodiazocine (Va) by heating with azeotropic removal of water were unsuccessful. The cyclodehydration was effected by refluxing IVa in pyridine containing a catalytic amount of pyridine hydrochloride. The presence of a small amount of an acid appears to be essential for the ring closure to occur. In the absence of the catalyst only starting material was recovered after 2 days of refluxing.

The formation of Va was accompanied by distinct infrared spectral changes. The amino N–H stretching band (3390 cm^{-1}) and carbonyl absorption peak (1660 cm^{-1}) of N-(2-*p*-chlorobenzoylbenzyl)-N-phenylsulfonylethylenediamine (IVa) were absent in the benzodiazocine Va. The appearance of a new band at 1620 cm^{-1} indicated the development of a >C=N bond.

1-(*p*-Chlorophenyl)-3,4,5,6-tetrahydro-5-(*p*-tolylsulfonyl)-2,5-benzodiazocine (Vb) was prepared by the same reaction sequence used for the synthesis of Va.

(1) T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebold, *J. Org. Chem.*, **32**, 2180 (1967).
(2) (a) M. I. Gluckman, *Pharmacologist*, **7** (2), 146 (1965); (b) T. Baum, *ibid.*, **7** (2), 147 (1965); (c) R. J. Bower and J. B. Kobb, *ibid.*, **7** (2), 147 (1965).