[CONTRIBUTION FROM THE TRUBEK LABORATORIES]

Structure of Hydroxycitronellal

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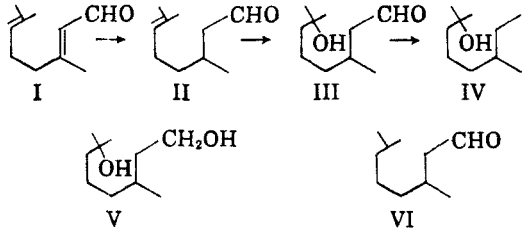
The structure of hydroxycitronellal has been shown to be 3,7-dimethyl-7-hydroxyoctanal by relating it to the known 2,6-dimethyl-2-octanol. The synthesis of DL-hydroxycitronellal is also reported.

The acidic or basic decomposition of the bisulfite adduct of citronellal (II) is reported[2] to give hydroxycitronellal which has been assigned structure III. The evidence for this structure[3] is due mainly to the work of Palfray *et al.*[4] These workers reduced hydroxycitronellal to a hydroxycitronellol and studied the behavior of this diol to formylation, acetylation, and tritylation. From their results they concluded that the diol contained a primary and a tertiary hydroxyl group and was best represented as V. They also concluded that III was the structure of hydroxycitronellal.

In the present work it was desired to establish a direct relationship between the known 2,6-dimethyl-2-octanol (IV) and hydroxycitronellal, thereby fixing the position of the hydroxy group.

The partial low pressure hydrogenation of citral (I) with a 5% palladium-carbon catalyst[5] gives DL-citronellal (II) together with *ca.* 6–7% DL-dihydrocitronellal (VI). The infrared spectrum of this material showed no hydroxyl bands, indicating that only the carbon-carbon double bonds had been affected. The conversion of II to its sodium bisulfite addition product followed by acid hydrolysis gave a 30% yield of DL-hydroxycitronellal (III). The Wolff-Kishner reduction of III gave a 75%



I II III IV V VI

yield of a tertiary alcohol that was shown by its infrared spectrum and derivatives to be identical with the known DL-2,6-dimethyl-2-octanol[6] (IV).

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(2) A. Verley, *Bull. soc. chim.*, [IV] **43**, 849 (1928).

(3) Several other structures have been postulated for hydroxycitronellal. For a discussion of these see P. Z. Bedoukian, *Perfumery Synthetics and Isolates*, D. Van Nostrand Co., Inc., New York, 1951, pp. 231–237.

(4) L. Palfray, S. Sabetay, and A. Rangel, *Compt. rend.*, **212**, 911 (1941).

(5) The reduction of citral has been studied under a wide variety of conditions and catalysts. For a summary see J. L. Simonsen, *The Terpenes*, Cambridge Press, 1947, Vol. I, pp. 90–1.

EXPERIMENTAL[7,8]

DL-*Citronellal.* Citral (247 g., 1.62 moles) in absolute ethanol (100 ml.) was treated with 5% palladium-carbon (3.0 g.) and hydrogenated at room temperature at an initial pressure of 51.0 p.s.i. The theoretical amount of hydrogen for one double bond was absorbed in 8 hr. The catalyst was removed by filtration. The filtrate was added to 2% sodium carbonate (200 ml.) and the mixture was refluxed for 2.5 hr. The organic layer was separated and distilled through a 10-in. packed column. The main fractions (202 g.) consisted largely of DL-citronellal,[9,10] b.p. 78–78.5° (6.0 mm.), n_D^{20} 1.4434–1.4443, d_{20}^{20} 0.8505. The presence of dihydrocitronellal in *ca.* 6–7% was confirmed during the preparation of hydroxycitronellal.

The product yielded an orange 2,4-dinitrophenylhydrazone, m.p. 82° (ethanol), (lit.[11] m.p. 89–90°).

Anal. Calcd. for $C_{16}H_{23}N_4O_4$: C, 57.47; H, 6.63; N, 16.74. Found: C, 57.52; H, 6.12; N, 16.94.

DL-*Hydroxycitronellal.* The procedure of Verley[2] was followed.

From DL-citronellal (165 g., 1.08 moles) there was obtained 56 g. (30%) of DL-hydroxycitronellal, b.p. 106–107.5° (4.0 mm.), n_D^{20} 1.4482, d_{20}^{20} 0.9220, M_{obs}^R 49.78, M_{calcd}^R 49.90. This showed characteristic aldehyde bands at 3.65 μ and 5.80 μ. A tertiary C—O stretching band[12] was observed at 8.70 μ. The literature[13] reports n_D^{20} 1.4494, d_{20} 0.9220 for the (+)-isomer.

An insoluble bisulfite fraction was obtained while working up the product. The treatment of this material with saturated sodium carbonate followed by steam distillation gave 10 g. of liquid. Distillation gave 9.1 g. of material boiling at 60–61° (4.0 mm.) n_D^{20} 1.4310, d_{20}^{20} 0.8584. The infrared showed an unconjugated aldehyde carbonyl at 5.78 μ.

Anal. Calcd. for $C_{10}H_{20}O$: C, 77.56; H, 12.82, for $C_{10}H_{16}O$: C, 80.00; H, 10.52. Found: C, 78.37; H, 11.89.

(6) The synthesis of DL-2,6-dimethyl-2-octanol will be reported in a forthcoming publication by W. J. Houlihan, J. Levy, and J. Meyer.

(7) All melting points are uncorrected.

(8) The microanalyses were performed by the Schwarzkoff Microanalytical Laboratory, 56–19 37th Avenue, Woodside 77, N. Y.

(9) The citronellal obtained by this procedure contained some unreduced citral or other α,β-unsaturated aldehyde (as indicated by the ultraviolet spectrum) and dihydrocitronellal. If it is assumed that the ultraviolet maximum is caused by citral alone then there is 1.1% of this material present—calculated on the starting citral with λ_{max}^{EtOH} 240 mμ, ϵ 14,288.

(10) The physical constants reported in the literature for (+)-, (−)-, and DL-citronellal vary widely. For some more recent constants see: A. Tauchenauer and H. Schinz, *Helv. Chim. Acta*, **32**, 1269 (1949); C. Grundmann, *Ann.*, **524**, 31 (1936); and ref. 2.

(11) Y. R. Naves, L. Desalbres, and P. Ardizio, *Bull. soc. chim. France*, **1956**, 1768.

(12) H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, **75**, 897 (1953).

(13) A. Muller, *Ber.*, **74**, 1745 (1941).

This material gave a yellow 2,4-dinitrophenylhydrazone, m.p. 89–89.5° (ethanol) and a semicarbazone, m.p. 91–92° (ethanol).

From the above constants and derivatives it is believed that the above material is DL-dihydrocitronellal (VI) contaminated with some citral.

The literature[11] reports for VI, b.p. 81° (12 mm.), n_D^{20} 1.4257, d_4^{20} 0.8253, 2,4-dinitrophenylhydrazone, m.p. 93.5°, semicarbazone, m.p. 91–92°.

Wolff-Kishner reduction of DL-*hydroxycitronellal.* Hydrazine hydrate (85%; 44 g., 0.76 mole) was added in 1 hr. to a solution of DL-hydroxycitronellal (43 g., 0.25 mole) in diethylene glycol (200 ml.). The temperature rose to 52° during the addition. Potassium hydroxide (15 g., 0.27 mole) was added and the temperature slowly raised so that 45 g. of azeotrope (33 g. of water) b.p. 105–115° was collected over 2 hr. Water (200 ml.) was added to the residue in the flask. The organic layer was separated and the water layer was washed with benzene (75 ml., twice). The combined organic layers (including that from the azeotrope) were distilled through a 6-in. packed column. There was obtained 29.7 g. (75.2%) of DL-2,6-dimethyl-2-octanol (IV), b.p. 69.0–69.5° (4.0 mm.), n_D^{20} 1.4338, d_{20}^{20} 0.8275. Authentic[6] IV has a b.p. 75–76° (7.0 mm.), n_D^{20} 1.4336, d_{20}^{20} 0.8273.

The infrared spectrum of the above alcohol was identical with the known 2,6-dimethyl-2-octanol.

This gave a phenylurethane, m.p. 84.8–85.2° which failed to depress the melting point of the phenylurethane obtained from an authentic sample[6] of DL-2,6-dimethyl-2-octanol.

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[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XV.[1] Preparation of *trans*- and *cis*-4,9-Dimethyl-Δ^4-3-octalon-6-acetic Acids[2]

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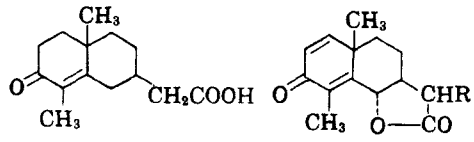
The Michael addition of diethyl malonate to 3-keto-4,9-dimethyl-$\Delta^{4,5}$-hexahydronaphthalene (III) with sodium *tert*-butoxide gave two stereoisomers of the adduct (IV). The relative yield of these isomers depended on the conditions employed. One isomer, which was predominantly obtained on prolonged reaction at room temperature, may be assigned the *trans*-structure (IVA) with the malonate side chain at an axial position. Another isomer, formed chiefly under more severe conditions, must possess the *cis*-structure (IVB). Hydrolysis and decarboxylation of each isomer of the substituted malonate (IV) gave, respectively, the corresponding monoacid (IA or IB) through the diacid (V). The formation of two isomers on Michael addition does not conform to the earlier belief. From this view, the Michael reactions in the same or closely related systems reported previously were examined. It was reported that addition of diethyl methylmalonate to III under similar conditions gave exclusively the stable *cis*-adduct even at room temperature. An alternative route to the monoacid (I) involved the Robinson reaction of 4-methylcyclohexan-3-one-1-acetate (VIII, R=CH_3) with the Mannich base (VII), giving chiefly the ester of the *trans*-acid (IA). This aspect of the stereochemistry agrees with the earlier postulates. A possible mechanism is offered for explanation of the steric course of Robinson reactions of this type.

From the viewpoint of stereochemical research on the α-propionic acid side chain of the lactone ring in the santonin molecule (II, R = CH_3), it was desirable to prepare, as a model compound, 4,9-dimethyl-Δ^4-3-octalon-6-acetic acid (I) in a state of stereochemical purity. This acid, moreover, will represent a useful intermediate for the synthesis of a simple santonin analog such as II



I II

(R = H). Since this work was initiated, certain papers[3–6] have appeared in which the same ground is covered. Abe, *et al.*[7] announced the total synthesis of natural santonins and of their stereoisomers, which provided the basis for discussion of configuration at the asymmetric centers in santonin (II, R = CH_3).

A route to the acid (I) involving the reaction sequence III → IV → V was first disclosed by Matsui, *et al.*[3] The Michael addition of diethyl malonate to the $\Delta^{4,5}$-dienone (III) was effected at relatively low temperature, and a semisolid product (IV) on hydrolysis was said to give two acids (V), a solid and a liquid, which were each decarboxylated

(1) Paper XIV, R. Futaki, *J. Org. Chem.*, **23**, 451 (1958).

(2) This work was supported in part by the Grant in Aid for Scientific Research from the Japanese Ministry of Education.

(3) M. Matsui, K. Toki, S. Kitamura, Y. Suzuki, and M. Hamuro, *Bull. Chem. Soc. Japan*, **27**, 7 (1954).

(4) F. J. McQuillin, *Chem. & Ind. (London)*, 311 (1954).

(5) T. Miki, *J. Pharm. Soc. Japan*, **75**, 395 (1955).

(6) F. D. Gunstone and A. P. Tulloch, *J. Chem. Soc.*, 1130 (1955).

(7) (a) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **75**, 2567 (1953). (b) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1416 (1956). (c) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956). *Cf.*, reference 3 and J. K. Chakrabarti, P. Dutt, and P. C. Dutta, *J. Chem. Soc.*, 4978 (1956).