Tetrahedron Letters No. 26, pp 2211 - 2214, 1975. Pergamon Press. Printed in Great Britain.

HYDROXYLATION OF PATCHOULOL BY RABBITS. HEMI-SYNTHESIS OF NOR-PATCHOULENOL, THE ODOUR CARRIER OF PATCHOULI OIL.

LUU Bang and Guy OURISSON

Laboratoire de Chimie Organique des Substances Naturelles
associé au CNRS, Institut de Chimie, Université Louis Pasteur,
67008 Strasbourg, France.

and

Paul TEISSEIRE

Centre de Recherche, Roure-Bertrand, 06 Grasse, France.

(Received in UK 21 April 1975; accepted for publication 15 May 1975)

Rabbits can eliminate ingested cedrol by hydroxylating it at one particular non-activated site ; the secondary hydroxyl function thus created is then conjugated to glucuronic acid, thus inducing water-solubility and permitting excretion (1).

We now show that patchoulol 1, the major sesquiterpene component of patchouli oil (40 %) (2), itself one of the more important essential oils of the perfumer industry, is hydroxylated at a primary position in the liver of rabbits or dogs ; this can be used to obtain nor-patchoulenol, the odour carrier of patchouli oil (2).

METHODS.

Patchoulol (1 g) was fed by stomacal tubing to a 3 kg rabbit, and the same procedures were used as in the previous communication, with or without previous induction of hydroxylase activity by barbiturate pre-treatment.

RESULTS.

Column chromatography of the ether extract on SiO_2 gave 20-30 % of a diol 2 and 30-40 % of an acid-alcohol 3 (3). These structures were assigned on the basis of the spectral data, and proved by the reactions of Table 1: the acid-alcohol 3 was reduced to the diol 2, which was further

reduced to the starting material 1. As patchoulol contains only one secondary methyl, the structures indicated are rigorously proved.

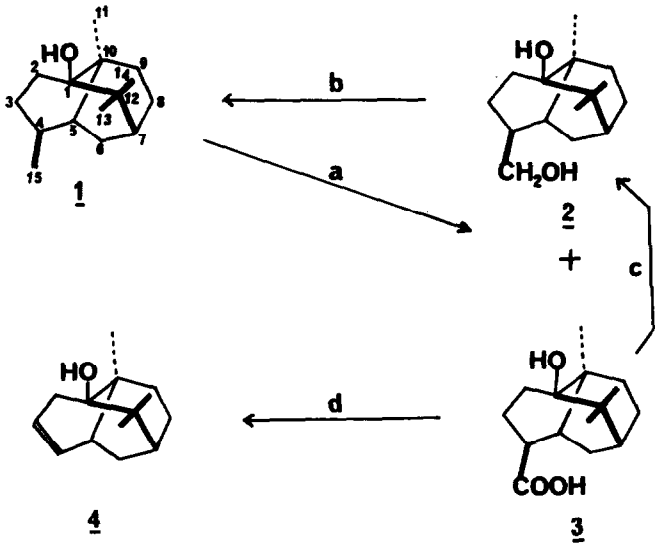
We took advantage of these results to convert patchoulol to nor-patchoulenol 4, a minor constituent of patchouli oil (0.3 %), but its major odour carrier (2): treatment of the acid 3 with lead tetra-acetate (5) gave the desired unsaturated alcohol in 50 % yield ; this was identified by m.p., n.m.r., i.r., $(\alpha)_D$ and by its odour.

SITE OF HYDROXYLATION.

C-15 ^{3}H-labeled patchoulol 1 was obtained by reduction of the acid 3 to the diol 2 with lithium aluminotritide, and further reduction as in Table 1. The labeled patchoulol (55 mCi/mmole) was injected intraperitoneally to three rabbits (1 mg each), which were killed after 10, 12 and 24 hrs. The internal organs were separately treated (6) to obtain their contents in residual patchoulol, and in its oxidation products 2 and another product, an aldehyde-alcohol, as judged from its Rf value. This showed the liver to be the primary site of hydroxylation, as expected (7).

The occurence of nor-patchoulenol in patchouli leaves may be due to the biooxidation of patchoulol in the plant, followed by an elimination reaction which is the biological equivalent of the step 3 → 4 described above. There is therefore apparently an analogy between the oxidative specificity of the plant and of mammals ; quite similarly, with cedrol, the hydroxylated derivatives obtained with rabbits were normal constituents of some plant species. It will be interesting to see whether the parallel selectivity of plant and animal oxidases has some generality.

We thank Professor J. Schwarz and Dr. F. Miesch (Institut de Pharmacologie et de Médecine Expérimentale, Faculté de Médecine, Université Louis Pasteur) and Dr. J. Hoffmann (Institut de Biologie Générale, Université Louis Pasteur) for their gracious help with the animal work.



a) Rabbits or dogs

b) 1, CH_3SO_2Cl, Pyridine ; 2, $LiAlH_4$, Et_2O, 20°

c) 1, CH_2N_2 ; 2, $LiAlH_4$, Et_2O, 20°

d) $(CH_3CO_2)_4Pb$, $(CH_3CO_2)_2Cu/H_2O$, C_5H_5N, C_6H_6 (5)

Diol 2 H_3C-11 : 0,85 (s) ; H_3C-13 and H_3C-14 : 1,1 (s, 6H) ; H_2C-15 (d, J=7.5 Hz). m.p. 104-105°C. $(\alpha)_D$ -120°.

Acidalcohol 3 H_3C-11 : 0,9 (s) ; H_3C-13 and H_3C-14 : 1,1 (s, 6H). m.p. 149-150°C. $(\alpha)_D$ -103°.

Note:

The same as previous article (1).

References

1) LUU Bang and G. OURISSON, Tetrahedron Letters, in press.

2) P. TEISSEIRE, P. MAUPETIT and B. CORBIER, Recherches (R.B.D.), 1974, N° 19, 8 and 36.

3) After induction with barbiturates (4), the yields were slightly increased. With dogs, the same products were obtained but in somewhat lower yields.

4) R. KUNTZMAN, Ann. Rev. Pharmacol., 1969, 9, 21.
A.H. CONNEY, Pharm. Rev., 1967, 19, 317.

5) J.D. BACHA and J.K. KOCHI, Tetrahedron, 1968, 24, 2215.

6) After the sacrifice, liver, spleen, kidneys, guts and lungs were separately homogenized with methanol, centrifuged and filtered. The supernatant liquid was dried, hydrolyzed with snail (D-glucuronide)-glucuronidase ("Suc d'Helix pomatia" of Industrie Biologique Française) and extracted with ether. The ether extract was chromatographied on silica gel plates which were then read with a Berchtold thinlayer scanner ; labeled metabolites were identified by comparison of their Rf values with the reference substances. Blood and urines were treated in the same manner, without homogenization with methanol. One typical result is the presence of diol 2, patchoulol 1 and another product with an Rf value corresponding to an aldehyde alcohol, which was observed in liver in an experiment after 10 hr, though only 1 was present in the blood at this time.

7) D.E. HATHWAY, S.S. BROWN, L.F. CHASSAUD and D.H. HUTSON, "Foreign Compounds Metabolism in Mammals", Chem. Soc., Specialist Report, London 1970, 1, 315.