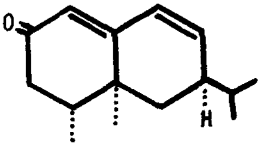
Tetrahedron Letters No. 20, pp 1687 - 1690, 1977. Pergamon Press. Printed in Great Britain.

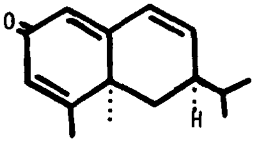
FURTHER STUDIES RELATING TO THE STRUCTURE OF NARDOSTACHONE

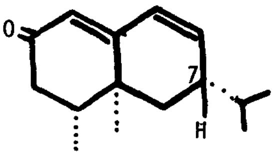
W. D. Saunders and A. R. Pinder*
Department of Chemistry, Clemson University, Clemson, S. Carolina 29631

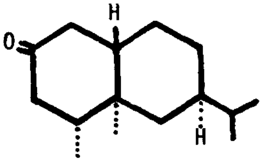
(Received in USA 12 January 1977; received in UK for publication 5 April 1977)

Some time ago one of us demonstrated[1,2] by synthesis that structure 1, assigned to nardostachone[3], a sesquiterpenoid ketone found in Indian spikenard oil, was untenable. We proposed 2 as a possible alternative, but this has been refuted by a group of Naarden workers[4], who have synthesized 2 by dehydrogenation of dienone 1. We have repeated this work and, in agreement, have found that the u.v. spectrum of 2 ($\lambda_{max.}^{EtOH}$ 263.5, 302.5 nm) is not in agreement with the published maxima (235, 298 nm) for nardostachone[3]. Likewise, the n.m.r. spectrum of 2 [δ 0.9d, J=6Hz, 6H, $(CH_3)_2CH$; 1.26s, 3H, angular CH_3; 2.0d, 3H, J = 1Hz, $=CCH_3$; 5.8-6.5, 4H, =CH], in agreement with the published figures[4], is very different from that of nardostachone[3]. We therefore concur that 2 cannot represent nardostachone.

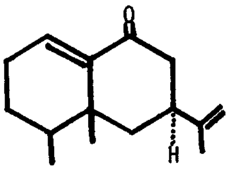

1


2

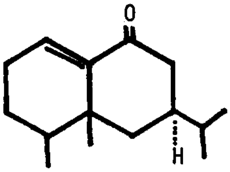

3


4

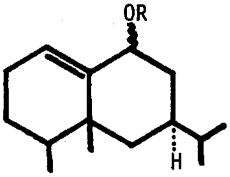
The Dutch workers suggested 3 as a further structural possibility for the ketone, and tried unsuccessfully to synthesize it. This structure is not consistent with the formation of tetrahydronootkatone (4) by sequential catalytic hydrogenation, LAH reduction, and Jones oxidation of nardostachone[3], though the possibility of an axial to equatorial inversion of the isopropyl group at C-7 cannot be ruled out.[5] Nonetheless we aimed at synthesis of 3, and to this end converted eremophilone (5) into 11,12-dihydroeremophilone (6) by homogeneous catalytic hydrogenation[6], thence to 11,12-dihydroeremophilol (7) (LAH) and to the acetate (8) (Ac_2O-pyridine). Hydrogenolysis of 8 (Li-$EtNH_2$) afforded hydrocarbon 9 in 90% yield. However, allylic oxidation of 9 with chromium trioxide-pyridine[7] yielded a complex mixture of products, one of which was the desired enone 10. The last was eventually obtained from 7-epinootkatone (11), which was available by annelation of cis-4-isopropenyl-2-methylcyclohexanone with trans-3-penten-2-one;[2,8] homogeneous catalytic hydrogenation then gave 10. Bromination-dehydrobromination of 10 in our hands yielded a mixture of the desired 3 (as racemate) and unchanged 10 in ratio 3:2. The very closely similar behavior of 3 and 10 on g.l.c. and t.l.c. did not permit them to be separated under a variety of different conditions. Dienone 3 was finally reached by exposure of enone 11 to dilute mineral acid at 55-65°. The major product of this reaction was the desired 3, accompanied by the epimeric 1 (ratio about 9:1), the latter being the result of simultaneous inversion at C-7. The two dienones were separated by fractional crystallization of the mixed semicarbazones. Hydrolysis of the two fractions afforded pure 3 and 1, the latter being identical with the product obtained earlier by bromination-dehydrobromination of 11,12-dihydronootkatone[1,2], or by acid-catalyzed rearrangement of nootkatone[4]. The major dienone 3 had a single well-defined u.v. maximum at 286 nm in ethanol, in reasonable agreement with the value (280 nm) calculated from Woodward's rules.[9] Its semicarbazone had the same m.p. [214° (decomp.)] as that of 1 [213° (decomp.)],[1,2] but the two derivatives were clearly different, as evidenced by mixed m.p.



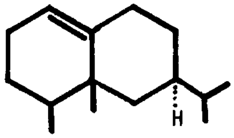
5



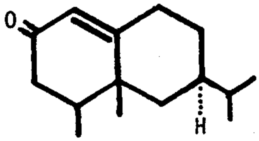
6



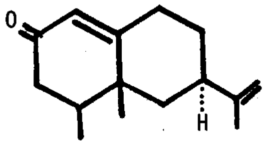
7 R = H
8 R = Ac



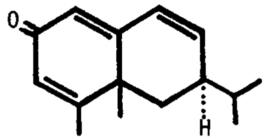
9



10



11



12

comparison (large depression), by the observation that the semicarbazone of **3** is not photochromic in contrast to that of **1**[1,2], and by the difference in their u.v. maxima [respectively 301 nm (ε 38,000) and 311 nm (ε 18,000)]. There were also significant small differences in the fingerprint i.r. region of the two ketones. The n.m.r. spectrum of **3** showed the same simplicity in the olefinic-H region as **1**[1,2] (singlets at δ5.7 and 6.1, 1H and 2H respectively), but some chemical shift differences were noted in the high field area due to the various methyl groups. These various spectra are very different from those reported for nardostachone.[3]

We next turned our attention to a synthesis of the 7-epimer, **12**, of trienone **2**. Dehydrogenation of dienone **3** with DDQ in refluxing benzene[10] somewhat surprisingly yielded trienone **2** in poor yield, the reaction being accompanied by total epimerization at C-7.[11]

It must be concluded that none of the structures **1**, **2**, or **3** can represent nardostachone. Trienone **12** remains a possibility, but we do not anticipate that the spectral properties of **12** will be very different from those of **2**, and feel justified in ruling out this structure as well. We have been unable to obtain any authentic nardostachone for structural study, and are currently proposing to re-isolate the compound from *Nardostachys jatamansi* roots.

References and Notes

[1] A. R. Pinder, *Tetrahedron Letters*, 413 (1970).

[2] H. C. Odom and A. R. Pinder, *J. Chem. Soc. Perkin Trans. I*, 2193 (1972).

[3] S. D. Sastry, M. L. Maheswari, K. K. Chakravarti and S. C. Bhattacharyya, *Perf. Essent. Oil Record*, **58**, 154 (1967); *Tetrahedron*, **23**, 2491 (1967).

[4] W. M. B. Könst, L. M. van der Linde and J. G. Witteveen, *Internat. Flavours and Food Additives*, **6**, 121 (1975).

[5] Such an inversion occurs in part when intermedeol is reduced

using a Pd-C catalyst: G. L. Chetty, V. B. Zalkow and L. H. Zalkow, Tetrahedron Letters, 3223 (1968); S. Sulser, J. R. Scherer and K. L. Stevens, J. Org. Chem., 36, 2422 (1971). Other examples are to be found among steroids.

[6] M. Brown and L. W. Piszkiewicz, J. Org. Chem., 32, 2113 (1967).

[7] Cf. W. G. Dauben, M. Lorber and D. S. Fullerton, J. Org. Chem., 34, 3587 (1969).

[8] A. van der Gen, L. M. van der Linde, J. G. Witteveen and H. Boelens, Rec. Trav. Chim., 90, 1034 (1971).

[9] R. B. Woodward, J. Amer. Chem. Soc., 63, 1123 (1941); 64, 76 (1942).

[10] Cf. A. B. Turner, Chem. Commun., 845 (1966).

[11] Satisfactory analyses have been obtained for all new compounds.