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STEREOSELECTIVE CYCLIZATIONS OF CANNABINOID 1,5 DIENES.

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The biosynthesis of many steroids and some triterpenoids procceeds via cyclization of 2,3 - oxidosqualene (1). Work on carefully chosen non-enzymic models has demonstrated that this reaction is strongly based on organic chemical foundations (2). Some terpenoids, which do not possess an oxygen at C_3 have been shown to be formed in Nature by cyclization of geranyl-geranyl pyrophosphate or squalene (3). These processes probably procceed by direct proton addition to the terminal double bond of a suitable polyene systerm, thereby initiating a stereoselective cyclization reaction. This concept was developed by Eschenmoser (4a) and by Stork (4b) more than a decade ago and organic models of synchronous stereoselective production of cyclic materials from acyclic substrates via suitable sulfonate esters, olefinic acetals etc. according to this hypothesis have been reported (5). We wish to report now a bicyclization, which is initiated by a direct proton addition to the terminal double bond of a 1,5-diene and terminated by a phenolic group within the same molecule in a stereoselective fashion (cf 5b).

Cannabigerol (I) was prepared by condensation of geraniol and olivetol in methylene chloride in the presence of p-toluenesulfonic acid at 20° to yield 52% crystalline material, m.p. 49 -50 , identical with the natural product (6). None of the 6-cis isomer (cannabinerol, II) could be isolated, though on vpc a peak corresponding to this isomer (2%) was observed.

The cis isomer (II) was prepared in 39% yield by the same procedure starting from nerol and olivetol. In this reaction 5% of the trans isomer (I) was detected by vpc and isolated. While cannabigerol (I) could be crystallized directly after chromatography, the cis isomer (II) had to be purified by repeated chromatographies to yield a colorless oil (7,8). The dinitrozenzoate of II melts at 76°.

The above syntheses confirm the geometry of the C_6- C_7 bond in cannabigerol. The high retention of double bond configuration in the synthesis of I and II is in accord with published data on the stability of short-lived primary allylic cations (9). Alternatively, these reactions can be viewed as having S_N2 like characteristics.

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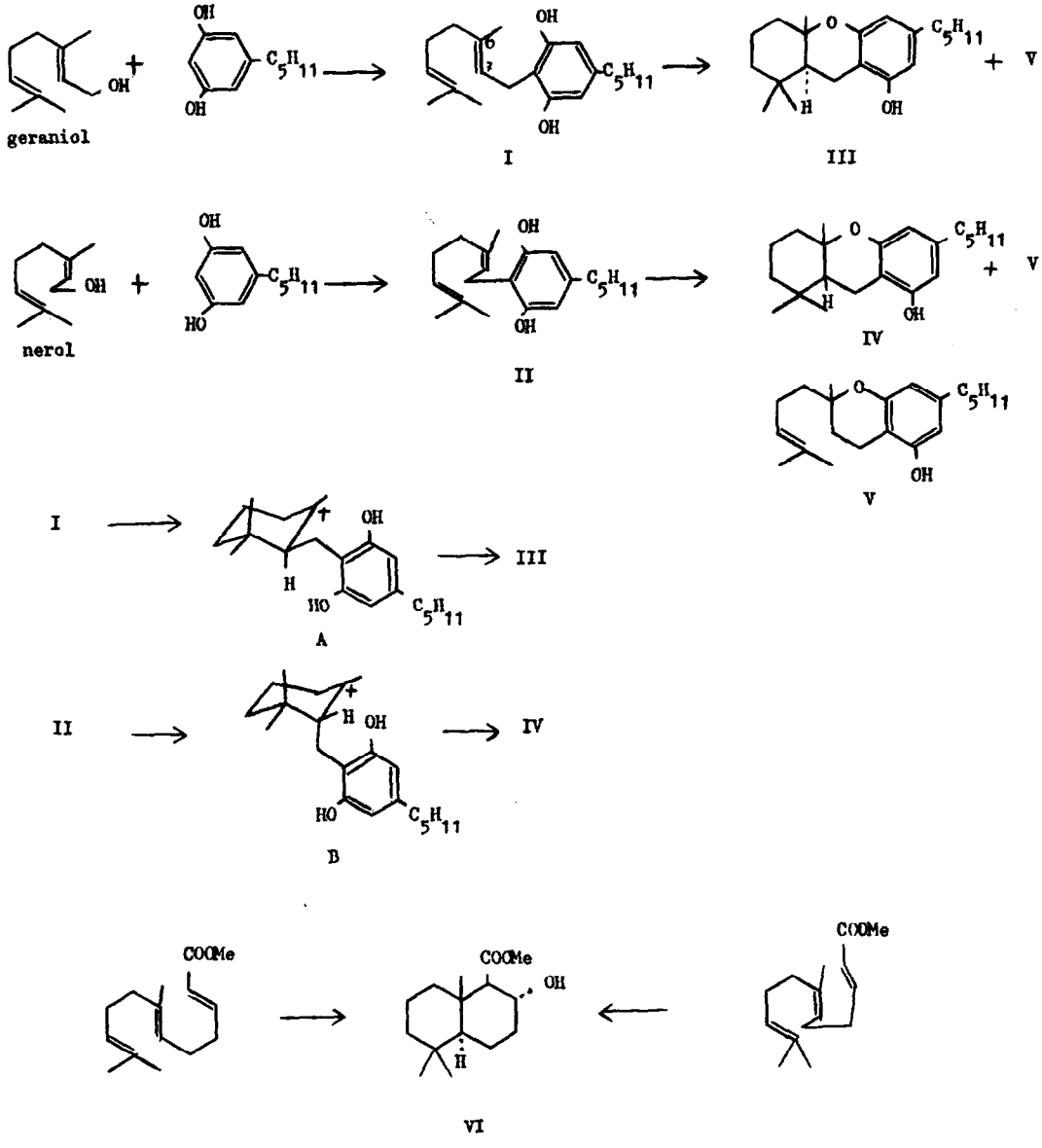
geraniol
nerol
I
II
III
IV
V
A
B
VI
COOMe
OH
HO
H

Reaction of cannabigerol (250mg.) with 0.2ml. 100% sulfuric acid in 16 ml. nitromethane at -30° for 15 min. gave, after purification by column chromatography (Florisil), 88% of the trans tricyclic compound III (7,8), 3% of the cis tricyclic compound IV (7,8), and 5% of the bicyclic compound V (6, 7,8). Under the same conditions II gave 71% of IV, 8.8% III and 20.7% V. Compounds III, IV and V are recovered unchanged when submitted to the same reaction conditions.

These results are in sharp contrast to those obtained (under somewhat different experimental conditions) for the acid catalysed cyclizations of trans and cis-desmethyl farnesic esters, both of which give the same trans product VI (10). It can be argued that in our case the reactions are concerted while in that of the desmethyl farnesic esters they proceed via a common monocyclic olefinic intermediate (as shown by Stork (4b) for the related farnesic acid.) In view of the close chemical relationship of the reactions in both series, however, we believe that the observed stereochemical variations are due not to any basic mechanistic difference but to the rate of ring closure of the hypothetical intermediate cations (A and B) at the monocyclic state. The nucleophilic phenolic group apparently reacts with the monocyclic carbonium ions (which may be partially "frozen") before the achievement of conformational equilibration or the elimination of a proton (5). A certain support to this view is to be found in the fact that with the cis compound (II) the stereospecificity is somewhat lower than with the trans compound. In the case of II the bulky benzylic moiety adjacent to the cationic site will be in a pseudoaxial conformation and will tend to equilibrate faster than in the case of trans I.

When the temperature of the reaction is increased there is slight decrease in stereospecificity as well as increase in the amount of bicyclic material. Thus I at 0° gives 79% III, 5% IV and 15% V and at 20° gives 73% III, 6% IV and 21% V. The increase of V can be explained by a change in the conformation of I, from a more folded to a less folded one, thus allowing for an increased possibility of attack at the non-terminal double bond (2b,c).

Whatever is the detailed mechanism, the above reactions show that high stereospecificity can be obtained by direct proton addition to the terminal double bond of a suitable polyene system. Hence these reactions may represent an organic model for related biochemical cyclizations.

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REFERENCES

1. E.E. van Tamelen, J.D. Willett, R.B. Clayton, and K.E. Lord, J. Am. Chem. Soc., 88, 4752 (1966); E.J. Corey, W.E. Russey and P.R. Ortiz de Montellano, ibid., 88, 4750 (1966); E.J. Corey and P.R. Ortiz de Montellano, ibid., 89, 3362 (1967); H.H. Rees, L.J. Goad, and T.W. Goodwin, Tetrahedron Letters, 723 (1968); D.H.R. Barton, A.F. Gosden, G. Mellows, and D.A. Widdowson, Chem. Commun., 1067 (1968).

2.(a) D.J. Goldsmith, J. Am. Chem. Soc., 84, 3913 (1962)b. E.E. van Tamelen Accounts Chem. Res., 1, 111 (1968);c. E.E. van Tamelen and J.P. McCormick, J. Am. Chem. Soc., 91, 1847 (1969).

3. D. Arigoni in "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols", G.E. Wolstenholme and M. O'Conner, Ed., J. and A. Churchill Ltd., London, 1959, p. 231 and

references cited therein; A.J. Birch and H. Smith, ibid., p. 245; E. Caspi, J.B. Creig, J.M. Zander and A. Mandelbaum, Chem. Commun., 28, (1969); D.H.R. Barton, A.F. Gosden, G. Mellows and D.A. Widdowson ibid., 184 (1969).

4.(a) A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, Helv. Chim. Acta., 38, 1890 (1955); (b) G. Stork and A.W. Burgstahler, J. Am.Chem. Soc., 77, 5068 (1955).

5. (a) W.S. Johnson, Accounts Chem. Res. 1, 1 (1968); (b) see the impressive series of papers on the stereospecificity of acid catalysed cyclizations of geranylacetone, farnesylacetone and related compounds by a group at the USSR Academy of Science in Moscow. M.Z. Krimer, W.A. Smit, A.V. Semenovsky and V.F. Kucherov, Izvestia Acad. Nauk SSSR, Otd. Chim. Nauk, 1590 (1968) and previous papers.

6. Y. Gaoni and R. Mechoulam, Proc. Chem. Soc. 82 (1964).

7. Elemental analytical data in accord with theory were obtained for this substance.

8. The supporting physical data for II, III, IV and V are as follows: λ_{max}^{EtOH} 272 mμ (ε 1080) and 282 mμ (ε 1050); δ (CCl_4) 0.88 (tr., $-CH_3$), 1.60, 1.68 (3 olefinic - CH_3), 3.30 (d., J=6cps) (C-8 protons), 4.90-5.60 (2 olefinic protons), 6.05 (2 aromatic protons), mol. weight (mass spectrum) 316; rt on vps (of the bis(trimethyl) silyl ether) 76 min.; Column: 10% Apiezon L on Chromosorb W, 80-100 mesh; N_2 flow; 20ml/min.; T. 230°; The bis-(trimethyl)-silyl ether of cannabigerol under the same conditions has rt of 83 min. Compounds I and II as such are difficult to distinguish on vpc or tlc; III, λ_{max}^{EtOH} 274 mμ (ε 1060) and 281 mμ (ε 1050); δ (CCl_4) 0.95, 1.05, 1.24 (four $-CH_3$), 2.2-2.8 (mult., 4 benzylic protons), 6.1, 6.2, (2 aromatic protons); IV, λ_{max}^{EtOH} 273 mμ (ε 1080), 282 mμ (ε 890); δ (CCl_4) 0.65, 0.95, 1.14 (four $-CH_3$), 2.65 (d., J = 6cps) (2 benzylic protons); 5.98, 6.08 (2 aromatic protons) and V, λ max 276 mμ (ε 1010) and 282 mμ (ε 1030); δ (CCl_4) 0.88, 1.24 (two-CH_3), 1.60, 1.65 (2 olefinic $-CH_3$), 2.25-2.75 (benzylic & allylic protons), 5.0 (1 olefinic protons), 5.98, 6.16 (2 aromatic protons).

9. W.G. Young, S.H. Sharman and S. Winstein J. Am. Chem. Soc., 82, 1376 (1960). L.M. Jackman, R. Ruegg, G. Ryser, C. von Planta, U. Gloor, H. Mayer, P. Schudel, M. Kofler and O. Isler, Helv. Chim. Acta, 48, 1332 (1965); W. Rittersdorf and F. Cramer, Tetrahedron, 23, 3023 (1967).

10. P.A. Stadler, A. Nechvatal, A.J. Frey and A. Eschenmoser, Helv. Chim. Acta, 40, 1373 (1957); A. Eschenmoser, D. Felix, M. Gut, J. Meier and P. Stadler in "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," G.E. Wostenholme and M. O'Conner, Ed. J. and A. Churchill, Ltd. London, 1959, p.217.