Synthesis of Hashish Cannabinoids by Terpenic Cyclisation

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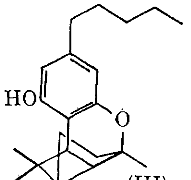
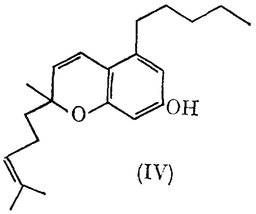
IT has recently been shown[1] that condensation of 5,7-dihydroxycoumarin with citral (1 mol.) in the presence of pyridine (1 mol.) gives deoxybruceol and related chromenes. Similar reaction with olivetol as the phenol should lead to structures having the correct oxidation level of the major hashish cannabinoids and is clearly of biogenetic relevance. An acid-catalysed reaction of this type has been examined[2,3] but none of the reported products are the same as from our system.

Chromatography (Florisil, petrol–benzene) of the reaction product (7 hr./110°) gave cannabichromene[4,5] (I) (15%) citrylidene-cannabis (II) (26%) and cannabicyclol[6] (cannabipinol)[7] (III) (1%, m.p. 146°), together with isocannabichromene (IV) (3%) and isocannabicyclol (V) (3%). Also isolated were two bis-citral condensation products, the bis-chromene (VI) (6%) and the bis-cyclobutane type (VII) (1·5%, m.p. 122—123°).† The overall recovery of products (55%) fell to 44% when 3 mol. of pyridine was used under identical conditions: more cannabichromene and less citrylidene-cannabis were present (I) (20%), (II) (7%), (III) (2%), (IV) (8%), (V) (2%), (VI) (3%), (VII) (0·5%). Using 6 mol. pyridine and 24 hr. heating, reaction was slower, giving only 8% of products made up mostly of mono-chromene [(I) (5%), (IV) (2%), (VI) (1%)].

On heating cannabichromene with pyridine (1 mol.), citrylidene-cannabis (34%) and cannabicyclol (5%) were isolated, suggesting that the chromenes were formed first and then converted into citrylidene and cyclobutane types, conformation (IX) being involved. Similarly chromene (IV) gave (V) and bis-chromene (VI) gave (VII).



(III)



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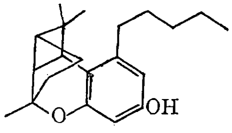
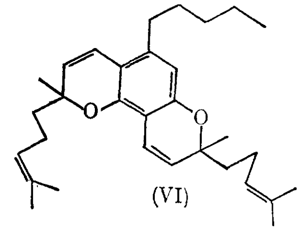
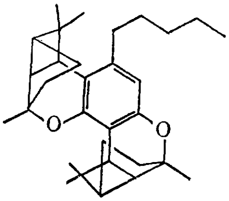


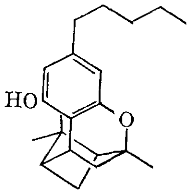
(V)



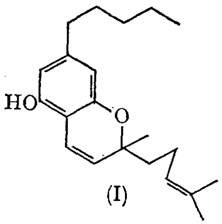
(VI)



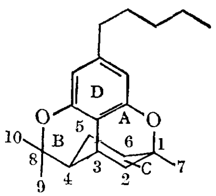
(VII)



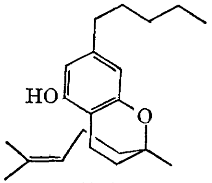
(VIII)



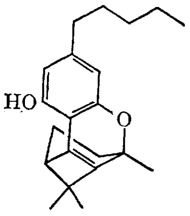
(I)



(II)



(IX)



(X)

Spectral data (including full i.r. traces) for cannabichromene and cannabicyclol, which have not previously been synthesised,‡ are identical

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† All synthetic structures refer to (±)-compounds: they are based on analytical, mass spectral, n.m.r., i.r., and u.v. data.

‡ Since submission, reports of the dehydrogenation of cannabigerol to cannabichromene have appeared (R. Mechoulam, B. Yagintsky, and Y. Gaoni, *J. Amer. Chem. Soc.*, 1968, **90**, 2418; G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1968, **24**, 4825).

with those published for the natural hashish compounds.[6] We are not, however, content with structure (VIII) suggested recently by two groups[6,7] for the latter. On the grounds of its formation from (I) revision to (III) or (X) is suggested: the appearance of a benzylic 3-proton doublet (τ 6·93, J 9·5 c./sec.) appears more reconcilable with (III) than (X) or (VIII). Thus far, citrylidenecannabis (II) has not been reported as a component of hashish, but in view of the occurrence of this structure-type elsewhere in Nature,[1,8] search is required.

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[1] L. Crombie and R. Ponsford, *Chem. Comm.*, 1968, 368.
[2] E. C. Taylor, K. Lenard, and Y. Shvo, *J. Amer. Chem. Soc.*, 1966, **88**, 367.
[3] Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, 1966, **88**, 5673.
[4] U. Claussen, F. von Spulak, and F. Korte, *Tetrahedron*, 1966, **22**, 1477.
[5] Y. Gaoni and R. Mechoulam, *Chem. Comm.*, 1966. 20.
[6] R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturstoffe*, 1967, **25**, 175.
[7] U. Claussen, F. von Spulak, and F. Korte, *Tetrahedron*, 1968, **24**, 1021.
[8] A. M. Duffield, P. R. Jeffries, E. N. Maslen, and A. I. M. Rae, *Tetrahedron*, 1963, **19**, 593.