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CATALYSIS AND THE COURSE OF CYCLISATION IN PHENOLIC TERPENES

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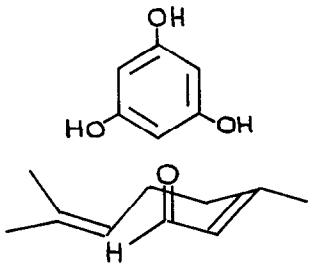
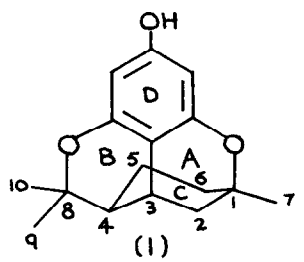
As in the synthesis of deoxybruceol[1] and citrylidene-cannabis (VIII, R=n-C_5H_{11})[2], citral condenses with phloroglucinol (1 mol.) in the presence of pyridine (1 mol.) to give citrylidene-phloroglucinol (I) (40%), m.p. 170°. Pure Z- or E- citral give (I) in identical yield, but on





(I)

the use of more pyridine (3 mol.) yields fall (20%). Using the well-crystallising phloroglucinol series, together with the poorly-crystallising olivetol series, to which the characteristic extractives of Cannabis sativa (hashish) belong, ring rupture, and ring formation connected with terpenic cyclisation have been examined.

Thermal and acid catalysed reactions of (I) lead to products retaining ring A. Thus pyrolysis gives the isopropenyl compound (IXa, R=OH), m.p. 182°, hydrogenated to (IXb, R=OH) m.p. 185°. The former, (IXa, R=OH), was also isolated in 60% yield when citrylidene-phloroglucinol was treated with 5 x 10^{-4} N-hydrochloric acid in tert. butanol, but in similar ethanolic acid the carbonium ion was captured to give (IXd, R=OH) (59%) m.p. 170° and (IXa, R=OH) (23%): acetic acid converted the ethoxy compound into (IXa, R=OH) (90%). Reaction of (I) with boron trifluoride etherate (1%) in benzene solution at 5-10°, or heating with toluene-p sulphonic acid, gave (IXc) (69%) m.p. 133-6° containing some $\Delta^{4(5)}$ impurity (X). With citrylidene-cannabis (VIII, R=n-C_5H_{11}) the situation was similar: 5 x 10^{-4} N-ethanolic hydrochloric acid gave (IXd, R=n-C_5H_{11}) (65%) whilst boron trifluoride etherate (1%) in benzene at 5-10° gave the $\Delta^{4(8)}$ compound (IXc, R=n-C_5H_{11}) (70%). Acetic acid gave (IXa, R=n-C_5H_{11}) (68%).

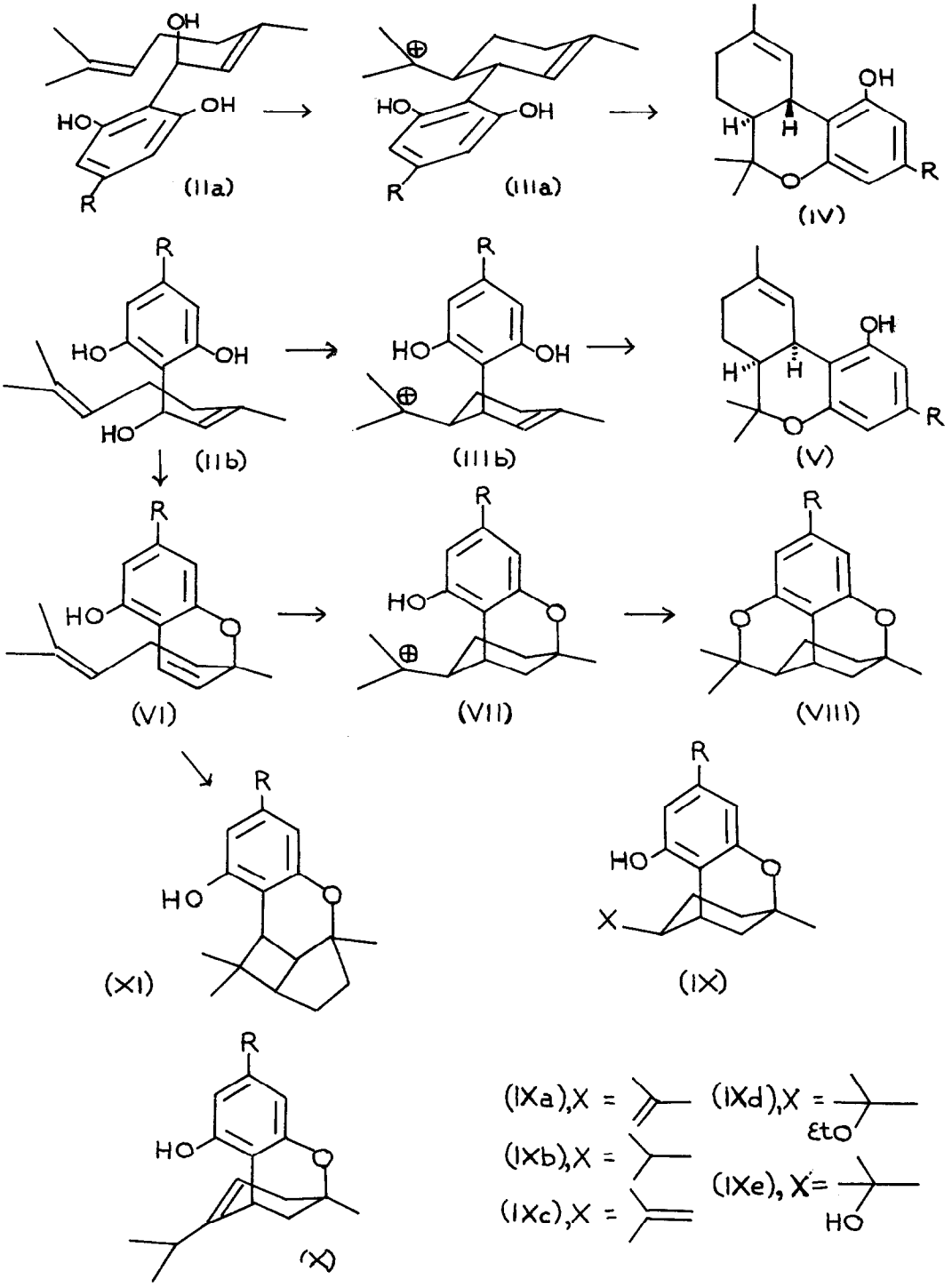
Direct condensation of phloroglucinol and citral in the presence of 5 x 10^{-4} N-ethanolic hydrochloric acid gives, on the other hand, largely the alternative ether series, containing ring B. A mixture of (IV, R=OH) and (V, R=OH) (60: 40 by n.m.r.) (19%) was obtained, from which the pure cis-(V) isomer m.p. 190-1° was isolated: the trans-(IV, R=OH) isomer proved difficult to purify. Minor products were (IXd, R=OH) (2%) and (IXe, R=OH) (4%) m.p. 205°. This behaviour is analogous to the formation of cis and trans- Δ^1-tetrahydrocannabinol (IV, R=n-C_5H_{11}) and (V, R=n-C_5H_{11}), by condensing olivetol with citral in the presence of 5 x 10^{-4} N-hydrochloric acid[3,4]. With boron trifluoride etherate (10%) the products were trans $\Delta^{1(6)}$ - tetrahydrocannabinol and (IXc, R=n-C_5H_{11}).[3,4]

Cannabichromene (VI), the first formed product in the pyridine reaction, appears to be the key to the dichotomy between the mineral acid or BF_3 catalysed reactions on the one hand, and the pyridine reaction on the other. When treated with 5 x 10^{-4} N-hydrochloric acid in ethanol, the 8-ethoxy compound (IXd, R=n-C_5H_{11}) (50%) is obtained from (VI). Boron trifluoride etherate (1%) gives the $\Delta^{4(8)}$-compound (IXc, R=n-C_5H_{11}) (48%), whilst acetic acid gives the Δ^8 isomer (IXa, R=n-C_5H_{11}) (60%). Ring A is retained throughout.

A scheme for the formation of cannabinoids by terpenic cyclisation may now be drawn up. In the presence of pyridine (1 mol.), olivetol forms cannabichromene (VI) from Z- or E- citral, catalysed by pyridinium or related electron acceptor. This may now undergo further acid-catalysed cyclisation in conformation (VI) to give (VII) and hence (VIII): the geometry does not sustain a fully concerted process. Cannabicyclol (cannabipinol) (XI) is formed by 1,2-cyclisation. Under proton or BF_3 catalysis, cannabichromene gives (VII), which may be captured to give (VIII), but which eventually gives the same type of products as does treatment of (VIII) with the catalyst being employed. Once ring A is formed at the chromene stage, it remains.

In the BF_3 and mineral-acid catalysed reaction of citral with olivetol, terpenic cyclisation involving the carbonium ion generated from conformation (IIa) or (IIb) i.e. (IIIa) or (IIIb) characteristically precedes ether-formation, and on ether-formation both trans-(IV) and cis-(V) fused B/C systems form. The by-products of type (IXc)-(IXe) encountered may derive from competing formation of (VI). The transition states leading to (IIIa) and (IIIb) demand Z- geometry: actually Z- and E- citral cyclise but there is opportunity for stereomutation.

Customarily, the biosynthesis of cannabinoids such as cannabichromene, cannabicyclol, tetrahydrocannabinols and their relatives are discussed in terms of alkylation of olivetol by geranyl pyrophosphate to give cannabigerol (or the same sequence on olivetolic acid).[5]


(IIa)
(IIIa)
(IV)
(IIb)
(IIIb)
(V)
(VI)
(VII)
(VIII)
(XI)
(IX)
(X)
(IXa), X =
(IXb), X =
(IXc), X =
(IXd), X =
EtO
(IXe), X =
HO

Oxidation at the benzylic position is then postulated.[6] Clearly the intermediate (IIa)-(IIb) could arise at the correct oxidation level if condensation with citral or its equivalent is involved. Biogenetic information on these alternative pathways is not available, and there is uncertainty as to the status of cannabichromene and cannabicyclol as natural products because of their apparent optical inactivity.[7]

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