Tetrahedron Letters No. 10, pp 945 - 948, 1972. Pergamon Press. Printed in Great Britain.

ALKYLATION OF RESORCINOLS WITH MONOTERPENOID ALLYLIC ALCOHOLS IN AQUEOUS ACID: SYNTHESIS OF NEW CANNABINOID DERIVATIVES

B. Cardillo, L. Merlini and S. Servi

Politecnico, Istituto di Chimica[+], 20133 Milano, Italy

(Received in UK 21 January 1972; accepted for publication 2 February 1972)

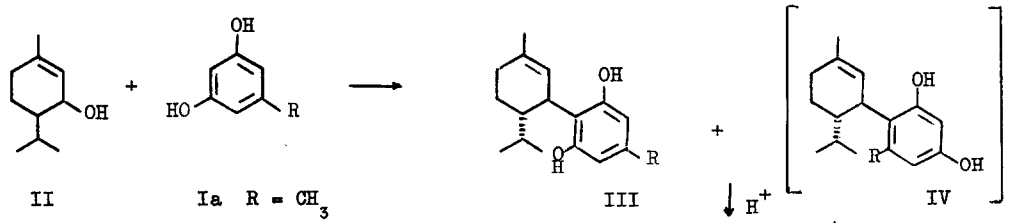
The proposal[1] that the biogenesis of natural ortho-γ,γ-dimethylallylphenols, cinnamylphenols and neoflavanoids involves the attack of a phenol or its poly-β-ketonic precursor by an activated allylic alcohol derivative has found recently large support by successful biomimetic experiments. Thus the alkylation of phenols has been performed with allylic pirophosphates in buffers[2], with allylic alcohols in aqueous acid[3] and with allylic bromides in buffers[4].

We wish to report here another development of this method, viz. the alkylation of 5-alkylresorcinols with monoterpenoid allylic alcohols in acid aqueous medium, to synthesize new derivatives of cannabinoids[5]. The novelty of this approach to hashish derivatives concerns: i) the use of some easily available menthen-3-ols or menthadien-3-ols, never employed before; ii) the low acidity of the medium, enough to allow the isolation of cannabidiol-like compounds, which are usually readily cyclized in the strong acid conditions used in the previous attempts to obtain this alkylation. Although the potentiality of this approach has not yet been fully explored, continuous interest in this field[6] prompts us to communicate our preliminary results.

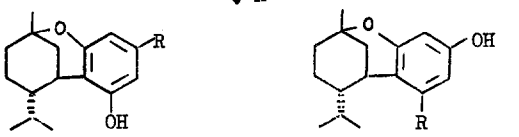
The alkylation of orcinol (Ia) or olivetol (Ib) was performed in 5% citric acid solution at room temperature for 1-3 days. The products were separated by column or TLC chromatography on silica gel and, when necessary, by preparative gas chromatography.

The alkylation of Ia with piperitol (II), prepared by $NaBH_4$ reduction of commercially available piperitone, gave a mixture of trans-2-(p-menth-1-enyl-3)-orcinol (III), of the cyclized products V and VI, and of dialkylated orcinols, in total yield of 25%. The structure of the products was established by mass and NMR spectra (particularly the 3,4 trans configuration of IIIa by the pattern of the C_3-H NMR signal, compared with that in trans

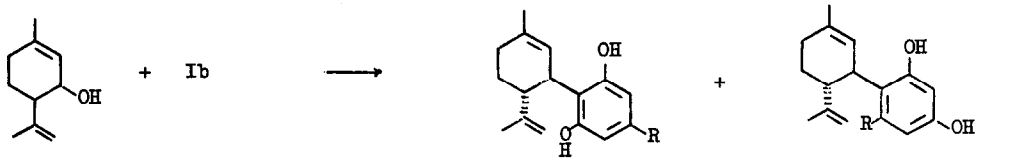
[+] Centro del C.N.R. per lo Studio delle Sostanze Organiche Naturali



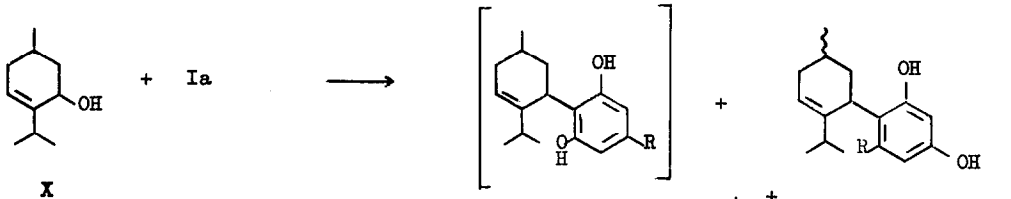
II Ia R = CH_3 Ib R = n-C_5H_{11} III IV



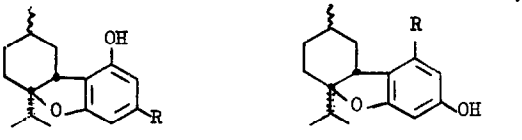
V VI



VII VIIIb IXb



X XIa XIa' XIIa 1,3 cis XIIa' 1,3 trans



XIIIa 1,3 cis XIIIa' 1,3 trans XIVa 1,3 cis XIVa' 1,3 trans

XVI XVa

cannabidiol). Conversion of III into V was also obtained by treatment with p-toluenesulfonic or BF_3 in benzene. This last reagent provoked also rearrangements, with formation of VI and of a dialkylated orcinol. Similar compounds[7] were obtained from olivetol (Ib).

From olivetol (Ib) and isopiperitenol (VII), prepared by $NaBH_4$ reduction of isopiperitenone[8], the hashish constituent cannabidiol (VIIIb)[5] and its isomer IXb[9] were obtained in 10% yield. Cyclization of VIIIb with diluted acid[5,9] gave Δ^6-tetrahydrocannabinol. These results will open a new way of synthesis of tetrahydrocannabinols, if a high-yield synthesis is found of isopiperitenol or of any of its derivatives which can behave like isopiperitenol in acid medium. No attempt has been made so far to improve the yields by change of the solvent or of other reaction conditions.

The reaction of menth-3-en-5-ol (X)[10] with orcinol following the general procedure gave a mixture (20-25% yield) of the new Δ^4 derivatives XIIa, XIIa' and of the cyclized products XIIIa,a' and XIV a,a'. Again XIIa and XIIa' could be converted into XIVa and XIVa' by acid ring closure with citric acid solution or with p-toluenesulfonic acid in benzene. Failure of isolation of XI could be due to the easier cyclization of these symmetric derivatives to XIII. The compounds XIIIa,a' and XIVa,a' could be isolated pure only in minute amounts by preparative gas chromatography. The structure and stereochemistry of XII-XIV a-a' were established from mass and NMR spectra. Comparison with synthetic XIIIa and XIIIa', obtained by acid ring-closure of XVa, prepared according to Razdan[11], established unequivocally the substitution of the orcinol nucleus. The stereochemistry of XIII-XIV a-a' is assigned as it is shown on the basis of NMR data (analysis of the benzylic proton signal)[12], comparison of NMR spectra with those of suitable models with certain cis junction, and conformational analysis (the trans isomers, with the axial isopropyl, are the less-stable isomers)[13]. The same products XIII a and a' and XIV a and a' were obtained by reacting pulegol (XVI) with orcinol in benzene in the presence of p-toluenesulfonic acid. When the reaction was conducted in aqueous medium, no product was obtained, most probably due to the sensitivity of pulegol to the medium.

Although the yields are low (at least in the experimental conditions that we used) and the separation of the products difficult, this approach can lead to the synthesis of new cannabinoid derivatives with "unnatural" double bond position[5] in the monoterpenoid moiety, other than XII. Experiments along this direction are in advanced progress.

REFERENCES

[1] W.D. Ollis, Recent Developments in the Chemistry of Natural Phenolic Compounds, Pergamon Press, London 1961; W.D. Ollis, Experientia 22, 777 (1966); W.D. Ollis and O.R. Gottlieb, Chem. Comm. 1396 (1968)

[2] J. Larkin, D.C. Nonhebel and H.C.S. Wood, Chem. Comm. 455 (1970)

[3] L. Jurd, Experientia 24, 858 (1968); Tetrahedron 25, 1407 (1969); L. Jurd, K. Stevens and G. Manners, Tetrahedron Letters 2275 (1971); S. Mageswaran, W.D.Ollis, R.J. Roberts and I.O. Sutherland, Tetrahedron Letters 2897 (1969)

[4] G. Casnati, A. Guareschi and A. Pochini, Tetrahedron Letters 3737 (1971)

[5] R. Mechoulam and Y. Gaoni, Fortschr. Chem. Org. Naturstoffe 25, 175 (1967); CIBA Foundation Symposium, The Chemistry and Botany of Cannabis, Churchill, London 1970

[6] Abstracts of the Symposium on the Chemistry and Biological Activity of Cannabis, Apotheker Societaten, Stockholm 1971

[7] Y. Gaoni and R. Mechoulam, Israel J. Chem. 6, 679 (1968)

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

[9] T. Petrzilka, W. Haefliger and C. Sikemeier, Helv. Chim. Acta 52, 1102 (1969)

[10] W. Treibs and H. Albrecht, J. Prakt. Chem. 13, 291 (1961)

[11] R.K. Razdan, W.R. Thompson, F.E. Granchelli and H.G. Pars, Abstracts 7th International Symposium on the Chemistry of Natural Products, Riga 1970, p. E113

[12] Compare the results of Y. Ban, H. Kinoshita, S. Murakami and T. Oishi, Tetrahedron Letters 3687 (1971) on the similar hexahydrocarbazole derivatives.

[13] See M. Hanack, Conformation Theory, Academic Press, New York 1965, p. 176 for the corresponding hydrindanes.