NMR-spectra of aporphine free bases ($CDCl_3$ or DMSO)

Aporphine		C-11 H	i.c.s. $O-CH_2-O$	References
Anolobine	1,2-Methylenedioxy-9-hydroxynoraporphine	δ7.86	–	4
Mecambroline	1,2-Methylenedioxy-10-hydroxyaporphine	7.47	4 Hz	5
Laureline	1,2-Methylenedioxy-10-methoxyaporphine	7.66	9	5
Actinodaphnine	1,2-Methylenedioxy-9-hydroxy-10-methoxynoraporphine	7.66	10	6
N-methylactinodaphnine	1,2-Methylenedioxy-9-hydroxy-10-methoxyaporphine	7.75	11	7
Phanostenine	1,2-Methylenedioxy-9-methoxy-10-hydroxyaporphine	7.70	6	8
Dicentrine	1,2-Methylenedioxy-9,10-dimethoxyaporphine	7.67	9	9
Cryptodorine	1,2,9,10-Dimethylenedioxynoraporphine	7.79	7	10
Neolitsine	1,2,9,10-Dimethylenedioxyaporphine	7.57	8	11
Cassythine	1,2-Methylenedioxy-3,10-dimethoxy-9-hydroxynoraporphine	7.55	10	11
O-Methylcassyfiline	1,2-Methylenedioxy-3,9,10-trimethoxynoraporphine	7.61	9	11
Ocoteine	1,2-Methylenedioxy-3,9,10-trimethoxyaporphine	7.61	9	11
Cassythidine	1,2,9,10-Dimethylenedioxy-3-methoxynoraporphine	7.55	8	11
Nandigerine	1,2-Methylenedioxy-10-hydroxy-11-methoxynoraporphine	–	11	12
N-methylnandigerine	1,2-Methylenedioxy-10-hydroxy-11-methoxyaporphine	–	12	13
Bulbocapnine	1,2-Methylenedioxy-10-methoxy-11-hydroxyaporphine	–	9	14

No splitting of the methylenedioxy protons is observed when the group is at C-9,10. The two known exceptions are thalphenine and bisnorthalphenine which possess an extraneous C-1 to C-11 methylenoxy bridge which further contributes to the asymmetry of the aporphine nucleus[15].

When the methylenedioxy group is located at C-10,11, the NMR-spectrum is characterized by the absence of a C-11 downfield aromatic proton, and by a large internal chemical shift ($\approx$ 8 Hz) of the two methylene protons, as in the spectra for ovigerine (1,2,10,11-dimethylenedioxynoraporphine) and N-methylovigerine[12]. No fully authenticated aporphine with a C-8,9 methylenedioxy substituent is known.

The above generalization concerning the effect of a methylenedioxy at C-1,2 on the chemical shift of the C-11 proton is also valid for the phenanthrene alkaloids. The presence of a methylenedioxy at C-3,4 in this series results in an upfield shift of the C-5 proton as with uvariopsine (**2**) and 8-methoxyuvariopsince (**3**) which show peaks at δ 9.00 and 8.95, respectively[16]. Other phenanthrene bases with methoxyl or hydroxyl groups at C-3,4 exhibit NMR-spectra with C-5 proton peaks downfield between δ 9.3 and 9.9[17].

[1] This project was supported by NIH research grant No. HL-12971, awarded by the National Heart and Lung Institute, PHS/DHEW.

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The Structure of Cannabitriol

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Summary. Cannabitriol, a constituent of *Cannabis sativa* L., has been shown to have the structure (I).

There has been a continuing interest in the constituents of *Cannabis sativa* L.[2]. OBATA and ISHIKAWA[3] reported the isolation of a compound which they called cannabitriol from *Cannabis sativa* (ganja) of Japanese origin. It had

[1] We thank the Ministry of Health, Jamaica and Hoffmann-La Roche Inc. for financial support and Dr. G. E. M. HUSBANDS, Wyeth Laboratories, Philadelphia, for the mass spectrum.

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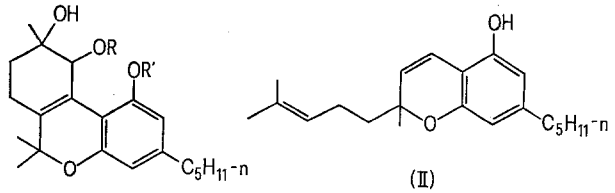
m.p. 170–172° and gave a positive test with Gibbs reagent. We have isolated a compound with similar properties to those of cannabitriol from a sample of Jamaican ganja and propose the structure (I) for this compound.

The benzene extract from the dried leaves, twigs and flowering tops was partitioned between light petroleum and 10% aqueous methanol. The neutral portion of the aqueous methanolic extract was chromatographed on alumina, and the material eluted with 20% ethyl acetate in benzene was subjected to further fractionation by PLC on silica. The major UV-active band gave a compound (0.025% from dried weight of plant material) identical by m.p., published IR-spectra (Nujol and KBr) and colour reactions with cannabitriol.

Cannabitriol, $C_{21}H_{30}O_4$ (analysis and mass spectrum), m.p. 171–173°, $[\alpha]_D$ −107° ($CHCl_3$), had absorption maxima in the UV (EtOH) at 231 and 279 nm (ε 25,000 13,800 respectively) indicative of the presence of a styrene type chromophore [cf. cannabichromene (II): λ_{max} 228 and 280 nm (ε 25,100 and 8,900 respectively)[4]]. Addition of base to the ethanolic solution led to the formation of a new maximum at 326 nm (ε 7,200).



(I) R = R' = H
(III) R = H; R' = Me
(IV) R = R' = Ac.

(II)

Treatment of cannabitriol in methanol with a trace of sulphuric acid at reflux for 2 h led to the isolation of cannabinol (69%) which could not be crystallized but was identified by its TLC behaviour and by comparison of its IR- and NMR-spectra with the published data[5]. This conversion establishes the carbon skeleton of cannabitriol. The location in ring A of the double bond and the two remaining oxygen atoms became evident from an examination of the NMR-spectra of the methyl ether (III) and the diacetate (IV).

The methyl ether (III), $C_{22}H_{32}O_4$, m.p. 111–113°, prepared by overnight treatment of cannabitriol with diazomethane in ether/methanol, had λ_{max} 227 and 277 nm (ε 27,600 and 14,800 respectively). The NMR-spectrum ($CDCl_3$) confirmed the presence of a primary methyl (triplet at δ 0.90), 3 tertiary methyls [singlets at 1.30 (3H) and 1.38 (6H)], a methoxy group (3.92) and 2 aromatic protons (6.40 and 6.43). Deuterium exchange revealed a singlet at 4.27 attributable to C*H*OH. The appearance of this signal indicates that there are no protons on the adjacent carbons.

The gummy diacetate (IV), obtained by treatment of cannabitriol with acetic anhydride and pyridine overnight at room temperature, partially regenerated cannabitriol on attempted purification by PLC. It had hydroxy absorption in the IR. The NMR-spectrum ($CDCl_3$) showed the presence of 5 methyl groups: 1 as a triplet at 0.89 (side-chain methyl), 3 as singlets at 1.13, 1.20 and 1.40, and 2 as acetates at 2.03 and 2.25. A proton at the base of an acetate appeared as a broadened singlet at 5.68 and 2 nonequivalent aromatic protons as doublets (J 2Hz) at 6.47 and 6.69. The above evidence can only be interpreted in terms of the structure (I) for cannabitriol. Cannabitriol is recovered unchanged from attempted oxidation with manganese dioxide or on treatment with acetone and anhydrous copper sulphate.

An ester of cannabitriol, linked through the C-1 hydroxy group with cannabidiolic acid, has been reported as a constituent of ganja of Turkish origin[6].

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Detection and Substitution-Pattern Determination of Guanidines[1]

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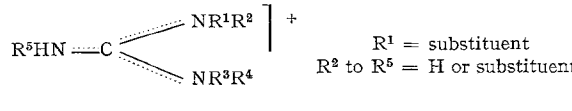
Summary. The guanidine function can be detected and its substitution pattern determined taking into account the ^{1}H-NMR signals of the N–H and N–C–H groups. Satisfactory results were obtained with mono- to penta-substituted guanidines (as picrate salts).

Guanidine and its derivatives bearing up to 5 substituents occur in plants or animals[2]. The guanidine function was usually detected by pKa measurements[3] and colour tests[4], and with more limitations by electrophoretic mobility[5], IR-[6] or mass[7] spectra. Colour tests[4] and IR-absorption[8], and less frequently electronic[9] or fluorescence[10] spectra were used for direct determination of the number and location of substituents; the scope of these methods is limited, e.g. IR-spectra do not distinguish N_1-mono from N_1,N_1-di-substituted guanidines. Besides, colour tests[11,12] may lead to contradictory or erroneous conclusions. Even the non-direct methods based on degradations[2,4] may give ambiguous results[13].

We report here a direct method for both purposes; it is based on the ^{1}H-NMR signals of N–H and N–C–H of the guanidine group (as picrate salt). The method gave good results with numerous synthetic or natural compounds of the types shown in the scheme.



The spectrum and integration curves (60 MHz) of the guanidinium picrate (0.15 mmol) were recorded at 35 °C in acetone (0.5 ml) using tetramethylsilane as internal standard; after addition of methanol (75 µl) the measurements were repeated. The same NMR measurements were then performed dissolving the guanidinium picrate