juana smoke compared to tobacco, in addition to some qualitative and quantitative changes within the profiles.

Many heavier mixture constitutents that are not directly seen in Figure 1 were selectively enriched by liquid chromatography[8] and spectrally identified. While the detailed analytical data on all mixture constituents are reported elsewhere[9], the Table lists some selected potentially important polycyclics. It should be noted that the well-known carcinogen benzo [a] pyrene is enhanced in marijuana smoke by 70% over that present in tobacco smoke. In addition, indeno [1,2,3-cd] pyrene has been known as a carcinogen[10] and, also, dibenzopyrene has been reported[11] as effective in producing respiratory cancer in hamsters. Carcinogenicity of many other polycyclics found in this work[9] is not presently known, because most of them have never been synthesized or isolated in a pure state for biological experiments.

Further work was directed toward a possible explanation for higher amounts of polynuclears in marijuana smoke, their origin and pyrosynthesis. It has been previously suggested that phytosterols[12] and terpenes[13] may function as specific precursors for polynuclear aromatic hydrocarbons. However, determination of the total sterol fraction by a modified procedure of KELLER et al.[14] yielded lower figures for marijuana as compared to dry tobacco leaf.

Due to their cyclic structures and high content in cannabis plants (in some cases up to 5–10% of total weight[15]), cannabinoids could be a major source of polynuclear aromatic hydrocarbons. To test this hypothesis, we have carried out a model pyrolysis experiment, in which 0.27 g of Δ^9-tetrahydrocannabinol was pyrolyzed in a quartz tube at 850 °C in a stream of helium, the pyrolytic products were collected (yield 0.20 g) and carried through the fractionation procedure used previously for condensates. There is a resemblance of the chromatogram obtained from the polynuclear fraction of the pyrolyzate (Figure 2) with the total smoke profile (Figure 1, B). Naturally, many other constituents of marijuana may contribute of the formation of polynuclear aromatic hydrocarbons. In addition to other cannabinoids, to a lesser degree, nonpolar higher terpenes that are present in marijuana extracts in greater abundance than in tobacco (M. L. LEE and M. NOVOTNY, unpublished experiments), are the most likely candidates.

Although higher mutagenicity of marijuana smoke[4–6] as compared to tobacco smoke may not necessarily mean higher carcinogenicity (evidence from animal studies is needed), the correlation between these biological phenomena and the information on major chemical carcinogens presented in this work is highly suggestive. Furthermore, the presence of co-carcinogens, other tumor promoters, irritants, etc. in marijuana smoke must be considered in future studies.

[9] M. L. LEE, M. NOVOTNY and K. D. BARTLE, Analyt. Chem., in press (1975).
[10] D. HOFFMANN and E. L. WYNDER, Z. Krebsforsch. *68*, 137 (1966).
[11] A. SELLAKUMAR and P. SHUBIK, J. natn. Cancer Inst. *53*, 1713 (1974).
[12] G. M. BADGER, J. D. DONNELLY and T. M. SPOTSWOOD, Austr. J. Chem. *18*, 1249 (1965).
[13] D. HOFFMANN, G. RATHKAMP, K. D. BRUNNEMANN and E. L. WYNDER, Sci. Tot. Envir. *2*, 157 (1973).
[14] C. J. KELLER, L. P. BUSH and C. GRUNWALD, J. agric. Food Chem. *17*, 331 (1969).
[15] J. W. FAIRBAIRN and J. A. LIEBMANN, J. Pharm. Pharmac. *26*, 413 (1974).
[16] M. NOVOTNY and R. FARLOW, J. Chromatogr. *103*, 1 (1975).

Some Aspects of the NMR-Spectra of Aporphine and Phenanthrene Alkaloids[1]

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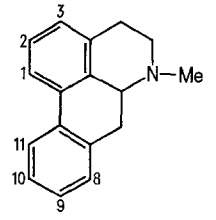
Summary. The C-11 proton of an aporphine possessing a C-1,2 methylenedioxy group falls relatively upfield between δ 7.47 and 7.86. Additionally, the i.c.s. for the two protons of the methylenedioxy group is large (4–12 Hz). The presence of a methylenedioxy at C-3,4 in a phenanthrene alkaloid also results in an upfield shift (δ 8.95–9.00) of the C-5 proton.

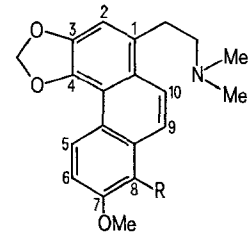
Although useful NMR correlations have been drawn to assist in locating aromatic hydrogens as well as methoxyl substituents on the aporphine skeleton[2], no generalizations have so far been made in the assignment of methylenedioxy groups. However, careful examination of published data has now allowed some firm correlations concerning this dioxygenated substituent.

The five possible locations for a methylenedioxy in an aporphine are 1,2, 2,3, 8,9, 9,10 and 10,11. The presence of a C-1,2 methylenedioxy group in an aporphine (**1**) or a noraporphine free base is evidenced by an upfield shift of the C-11 proton which appears in the range δ 7.47 to 7.86 (Table). But when a hydroxyl or a methoxyl group is at C-1, the C-11 proton signal is further downfield, between δ 7.80 and 8.21.

Additionally, the internal chemical shift for the two protons of the methylenedioxy group is large (4–12 Hz) when the group is located at C-1,2 (Table), and small (2–4 Hz) when at C-2,3. Two aporphines with a methylenedioxy group at C-2,3 are known, namely ocokryptine (1,10-dimethoxy-2,3-methylenedioxy-11-hydroxyaporphine) and *O*-methylocokryptine (1,10,11-trimethoxy-2,3-methylenedioxyaporphine), with internal chemical shift values of 4 and 2 Hz, respectively[3].



1



2, R = H
3, R = OMe

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.

[2] For lead references see M. SHAMMA and S. S. SALGAR, in Specialist Periodical Reports, *The Alkaloids* (Ed. J. E. SAXTON; The Chemical Society, London 1974), vol. 4, p. 264.

[3] M. P. CAVA, Y. WATANABE, K. BESSHO and M. J. MITCHELL, Tetrahedron Lett. *1968*, 2437.

[4] E. GELLERT and R. DUDZATS, Aust. J. Chem. *25*, 2477 (1972).

[5] S. R. JOHNS and J. A. LAMBERTON, Aust. J. Chem. *20*, 1277 (1967).

[6] S. J. WANG and S. H. CHENG, J. pharm. Soc. Japan *88*, 1148 (1968).

[7] S. TEWARI, D. S. BHAKUNI and M. M. DHAR, Phytochemistry *11*, 1149 (1972).

[8] J. KUNITOMO, Y. OKAMOTO, E. YUGE and Y. NAGAI, J. pharm. Soc. Japan *89*, 1691 (1969).

[9] S.-T. LU, S.-J. WANG, P.-H. LAI, C.-M. LING and L.-C. LIN, J. pharm. Soc. Japan *92*, 910 (1972).

[10] I. R. C. BICK, N. W. PRESTON and P. POTIER, Bull. Soc. chim. Fr. *1972*, 4596.

[11] S. R. JOHNS and J. A. LAMBERTON, Aust. J. Chem. *19*, 297 (1966).

[12] M. P. CAVA, K. BESSHO, B. DOUGLAS, S. MARKEY, R. F. RAFFAUF and J. A. WEISBACH, Tetrahedron Lett. *1966*, 1577.

[13] H. FURUKAWA, F. UEDA, M. ITO, K. ITO, H. ISHII and J. HAGINAWA, J. pharm. Soc. Japan *92*, 150 (1972).

[14] M. TOMITA, T. SAWADA, M. KOZUMA, D. HAMANO and K. YOSHIMURA, J. pharm. Soc. Japan *89*, 737 (1969).

[15] M. SHAMMA, J. L. MONIOT, S. Y. YAO and J. A. STANKO, Chem. Commun. *1972*, 408. – M. SHAMMA and J. L. MONIOT, Heterocycles *2*, 427 (1974).

[16] M. LEBOEUF and A. CAVÉ, Plant. Méd. Phytother. *6*, 87 (1972).

[17] For a listing of most of the phenanthrene alkaloids see M. SHAMMA, *The Isoquinoline Alkaloids* (Academic Press, New York 1972), p. 260.

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.

[2] For leading references, see R. MECHOULAM, in *Marihuana* (Ed. R. MECHOULAM; Academic Press, New York, N.Y. 1973), p. 1. – T. B. VREE, D. D. BREIMER, C. A. M. VAN GINNEKEN and J. M. VAN ROSSUM, J. Pharm. Pharmac. *24*, 7 (1972). – J. W. FAIRBAIRN and J. A. LIEBMANN, J. Pharm. Pharmac. *26*, 413 (1974). – H. L. LOTTER, D. J. ABRAHAM, C. E. TURNER, J. E. KNAPP, P. L. SCHIFF, JR., and D. J. SLATKIN, Tetrahedron Lett. *1975*, 2815.

[3] Y. OBATA and Y. ISHIKAWA, Agric. biol. Chem., Japan *30*, 619 (1966).