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PROTON MAGNETIC RESONANCE STUDIES RELATING TO THE STEREOCHEMISTRY OF SESAMIN, ASARININ AND EPIASARININ

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A LONG series of papers on the structure of sesamin (Ia) and its diastereoisomer, asarinin (Ia), have appeared[1] culminating in the elucidation of their structure by von Bruchhausen and Gerhard[2] in 1939, and in their synthesis by Beroza and Schechter[3] in 1955 and by Freudenberg and Fischer[4] in 1956.

Many natural products have the general structure of formula I but differ in substitutions on the aryl groups or in the configuration of these groups as represented by the forms IIa, IIb, IIc. In 1948, Gripenberg[5] showed that epi-pinoresinol (Ic), which has the same configuration as asarinin, is the unsymmetrical isomer IIa because it forms a different compound depending on which of its two phenyl groups is substituted.

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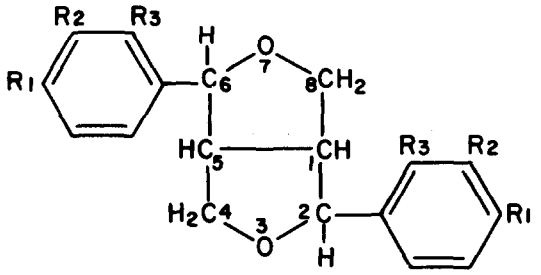
[1] W.M. Hearon and W.S. MacGregor, Chem. Rev. 55, 996 (1955).

[2] F. von Bruchhausen and H. Gerhard, Ber. Dtsch. Chem. Ges. 72, 830 (1939).

[3] M. Beroza and M.S. Schechter, Abstracts, 128th Meeting of A.C.S. Minneapolis, Minnesota, Sept. 15, 1955, pp. 51-60; J. Amer. Chem. Soc. 78, 1242 (1956).

[4] K. Freudenberg and E. Fischer, Naturwissenschaften 1, 16 (1956); Chem. Ber. 89, 1230 (1956).

[5] J. Gripenberg, Acta Chem. Scand. 2, 82 (1948).



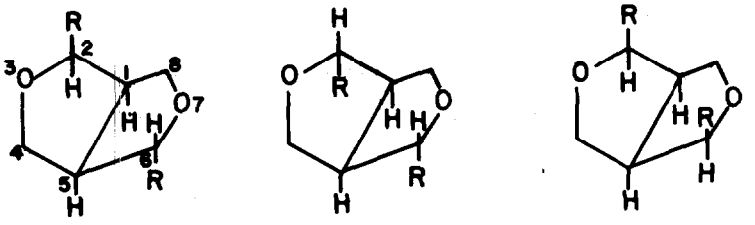
Ia, R_1 and R_2 = $-OCH_2O-$, R_3 = H (sesamin, asarinin, epiasarinin)

Ib, R_1 and R_2 = $-OCH_2O-$, R_3 = Br (dibromosesamin)

Ic, R_1 = $-OH_1R_2$ = $-OCH_3$, R_3 = H (pinoresinol, epipinoresinol)

Id, R_1 = $-O\overset{O}{\overset{\|}{C}}CH_3$, R_2 = $-OCH_3$, R_3 = H (pinoresinol diacetate)

Ie, R_1 = R_2 = $-OCH_3$, R_3 = H (pinoresinol dimethyl ether, eudesmin)



IIa IIb IIc

Similar treatment of sesamin gives only one derivative no matter which phenyl group is substituted;[6] sesamin is therefore a symmetrical compound (either IIb or IIc).

In 1956, Beroza succeeded in preparing by a Walden inversion the previously unknown third isomer and named it epiasarinin.[7] Based on steric considerations and the low yield obtained he assigned structure IIc to it

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[6] B. Carnmalm, H. Erdtman and Z. Pelchowicz, Acta Chem. Scand. 9, 1111 (1955).

[7] M. Beroza, J. Amer. Chem. Soc. 78, 5082 (1956).

and concluded that sesamin and the related pinoresinol (Ic) have structure IIb. Lund[8] confirmed this assignment of structure by an X-ray crystallographic study of the bromo and iodo derivatives of pinoresinol dimethyl ether. Freudenberg and Sidhu[9], who came to the same conclusion on the basis of optical rotatory properties of IIa, IIb and IIc, advanced additional evidence to support the assignment, and established the absolute configuration of the compounds. The stereochemistry of this group of compounds and the host of lignans having the same central nucleus seemed to have been settled.

The appearance of an article by Govil et al.[10], describing the proton magnetic resonance spectra of sesamin and asarinin reactivated the problem. These authors stated that sesamin and epiasarinin have structures opposite to the ones assigned by the aforementioned workers. Their conclusions are based on their measurements of the coupling constants of the bridgehead hydrogens (1 and 5) with the hydrogens on the adjacent carbon atoms (2 and 6) that hold the aryl groups. Theorizing that the coupling constants for sesamin and asarinin would be of the same order of magnitude as in a substituted chair-type cyclohexane ring, that is, 3 cps for an equatorial or cis-position coupling and 7 cps for an axial- or trans-position coupling,[11] they concluded that sesamin's bridgehead and adjacent hydrogens are in the cis-position because their coupling constants are 3.9 cps. The authors were unaware of the preparation of epiasarinin by Beroza and presumed the coupling constant of its pertinent hydrogens would be about 7 cps.

Prior to the appearance of the paper by Govil et al., we had under-

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[8] E.W. Lund, Acta Chem. Scand. 14, 496 (1960).

[9] K. Freudenberg and G.S. Sidhu, Tetrahedron Letters No. 20, 3 (1960); Chem. Ber. 94, 851 (1961).

[10] G. Govil, C.R. Kanekar and C.L. Khetrapal, Curr. Sci. 30, 253 (1961).

[11] J.A. Pople, W.G. Schneider and H.J. Bernstein, High Resolution Nuclear Magnetic Resonance p. 193. McGraw-Hill, New York (1959).

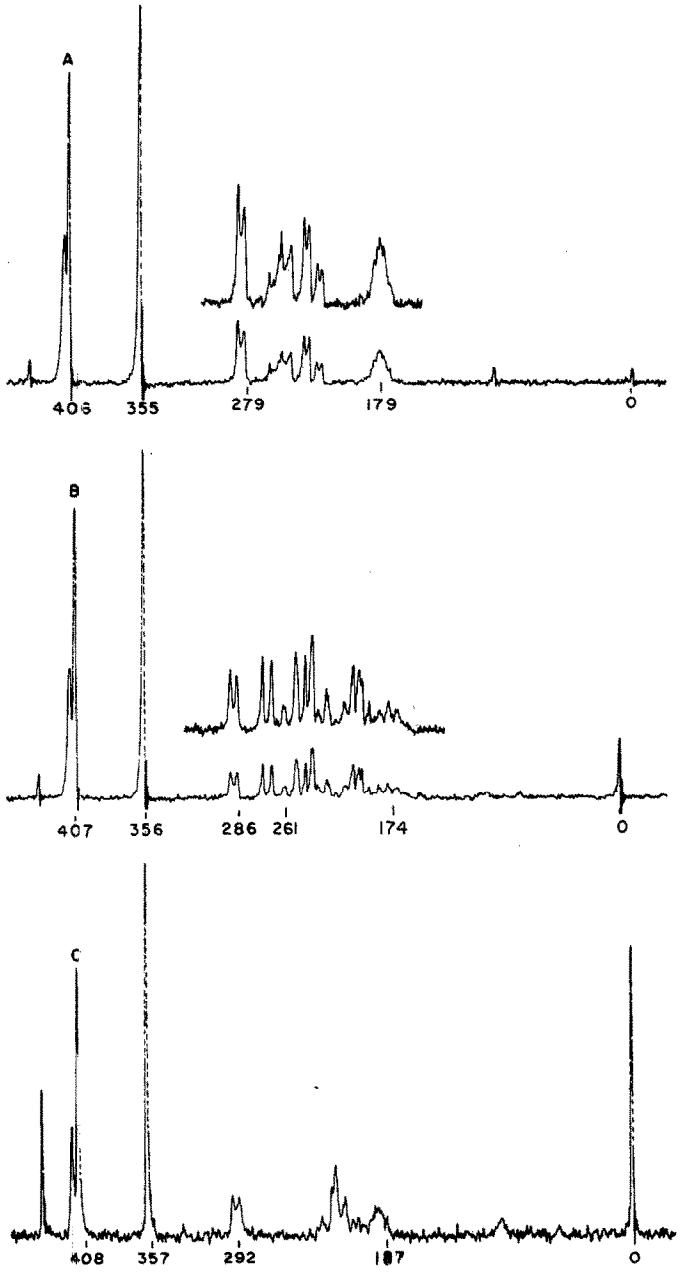

FIG. 1. NMR spectra of (A) sesamin, (B) asarinin and (C) epiasarinin, at 60 mc in $CDCl_3$. Frequencies given in cps from internal tetramethylsilane.

taken a comprehensive investigation of the proton magnetic resonance spectra of a number of lignans. We present here some preliminary results which are at variance with those of Govil et al., and which negate their conclusion on the stereochemistry of sesamin.

The NMR spectra of sesamin, asarinin and epiasarinin in $CDCl_3$ solution are shown in Fig. 1. The spectra of sesamin and asarinin show details not evident in those reported by Govil et al.; the poorer quality of the spectrum of epiasarinin is due to the limited amount of material available. In agreement with Govil et al., we assign the strong peaks at low field in all three spectra to the aromatic and methylenedioxy protons and the unresolved multiplets in the region 160-200 cps to the bridgehead protons (1 and 5). Protons at positions 2 and 6 are responsible for the doublets centered at 279 in sesamin and 292 in epiasarinin. In asarinin, these two protons are non-equivalent. The integral of its spectrum shows that the doublet at 286, assigned by Govil et al., to both the 2 and 6 protons, is actually due to only one proton, the other very probably giving rise to the doublet at 261.

The magnitude of splitting in the 2 and 6 doublets is given in Table 1 for these three compounds as well as for other related lignans. The coupling constants vary significantly, from a low of 3.2 cps for dibromosesamin (Ib) to a high of 6.6 cps for one of the couplings in asarinin. The coupling constant in epiasarinin is 5.1 cps, not 7 cps as predicted by Govil et al. The interpretation of Govil et al., based on analogy to couplings in cyclohexane derivatives, is thus seen to be inapplicable to the lignans. This is scarcely surprising in view of the difference in geometry. In fact, Dreiding stereomodels of the lignan skeleton indicate that the dihedral angle between the planes $H_1C_1C_2$ and $H_2C_2C_1$ is either about 0° or 120°, whereas in cyclohexane the corresponding angles are 60° and 180°. Theoreti-

cally, Karplus[12] finds that the coupling for cis protons (0°) should be about 8 cps and that for protons at 120° should be about 2 cps. Exceptions

Table 1

Coupling Constants, J_{12} and J_{56}

Compound[a]	Frequency[b]	Splitting (cps)[c]
Sesamin	279	4.6 ± 0.2
Sesamin (in pyridine)	288	4.3 ± 0.3
Asarinin	286 261	5.0 ± 0.1 6.7 ± 0.1
Asarinin (in pyridine)	290 275	4.9 ± 0.2 6.6 ± 0.1
Epiasarinin	292	5.1 ± 0.3
Dibromosesamin (Ib)	304	3.2 ± 0.2
Pinoresinol diacetate (Id)	288	4.4 ± 0.1
Eudesmin (Ie)	285	4.3 ± 0.1

[a] In $CDCl_3$ except where indicated.

[b] In cps from internal tetramethylsilane (at 60 mc).

[c] In cps; average of four or more measurements; average deviation given.

to Karplus' relation are known to occur in some cyclic systems (e.g. β-propiolactone, and 2,3-dihydrofuran).[13] The differences noted in Table 1 between compounds known to have the same configuration (e.g. sesamin and dibromosesamin) demonstrate that lignans also deviate appreciably from the theoretical prediction.

It is apparent from the foregoing discussion and the data in Table 1 that no valid conclusions on the configuration of sesamin can be drawn solely from the values of the coupling constants J_{12} and J_{56}. Whether other NMR data can be helpful in this respect is not yet clear. Possibly

[12] M. Karplus, J. Chem. Phys. 30, 11 (1959)

[13] See L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry p. 84. Pergamon Press, London, New York (1959).

a complete analysis of the complex region about 220 to 260 cps for the series of compounds will be of value. We have made a preliminary analysis of this region in sesamin and dibromosesamin, but do not yet have final values for the series of lignans.

At present, then, we find no reason from NMR data for altering the conclusions reached previously[7-9] assigning to sesamin the structure IIb.