15. *Colouring Matters of the Aphididæ. Part XXII.*[1] *Nuclear Magnetic Resonance Evidence for the Structures and Conformations of the Naphthaquinone Dimethyl Ethers Derived from the Protoaphins, and of the Erythroaphins.*

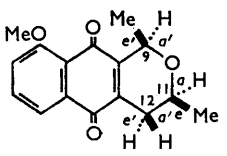
By D. W. Cameron, D. G. I. Kingston, N. Sheppard, and Lord Todd.

Analysis of the nuclear magnetic resonance spectra of eleutherin and isoeleutherin yields the following values for the long-range coupling constants between protons of pseudo-axial (a') and pseudo-equatorial (e') CH bonds in the CH–C=C–CH group of a 4-oxacyclohexene ring: $J^{a'a'} = 3{\cdot}5$, $J^{a'e'} \approx J^{e'a'} \approx 2$—3, $J^{e'e'} < 1$ c./sec.

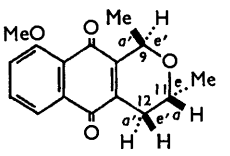
These long-range coupling constants, together with vicinal CH–CH couplings, are used to deduce information about the configurations and conformations of the partially saturated rings in the naphthaquinone dimethyl ethers derived from protoaphin-*fb* and -*sl*, and in the erythroaphins.

In this paper we discuss in some detail the nuclear magnetic resonance spectra from the hydrogen nuclei in the dimethyl ethers of the naphthaquinone derivatives obtained by reduction of protoaphin-*fb* and *sl* with sodium dithionite,[2] and in the natural products eleutherin and isoeleutherin which are of related structure.[3,4] The spectra of eleutherin and isoeleutherin are discussed first. They are readily interpreted in terms of the known structures proved by synthesis[4] and yield values for a type of long-range coupling constant that is of relevance in the interpretation of the spectra of the protoaphin derivatives. The naphthaquinone dimethyl ether, A, derived from protoaphin-*fb*, has a closely similar spectrum to that of isoeleutherin, and this confirms chemical evidence that the two molecules are stereochemically closely related.[2] The spectrum of the naphthaquinone dimethyl ether, A′, from protoaphin-*sl*, together with a comparison of the spectra of the two naphthaquinone dimethyl ethers and the related erythroaphins-*fb* and -*sl*, throw considerable light on the conformational and stereochemical aspects of the structures of all these molecules.

Spectra of Eleutherin and Isoeleutherin.—These two compounds have been shown to have the stereochemical structures (I) and (II) by Schmid and his co-workers.[3,4] Professor Schmid kindly provided us with samples for spectroscopic study.



(I)



(II)

In these structural formulæ the symbols a' and e' denote pseudo-axial and pseudo-equatorial configurations of the bonds in question in the chair-like conformation of the partially unsaturated ring.[5] Structure (II) is epimeric with (I) at C-11. In (I), ring-inversion with respect to (II) has also occurred so as to relieve steric strain that would otherwise result from two axial C–CH_3 groups in positions 9 and 11.

The spectra of the two compounds are shown in Fig. 1 and are particularly notable for the large amount of fine structure associated with the resonances from the chemically non-equivalent hydrogen atoms in the CH_2 group at position 12. Part of this fine structure is caused by spin–spin interaction with the immediately adjacent CH proton at position

[1] Part XXI, Cameron, Cromartie, Hamied, Scott, Sheppard, and Todd, preceding paper.
[2] Part XVII, Cameron, Cromartie, Kingston, and Todd, *J.*, 1964, 51.
[3] Schmid and Ebnöther, *Helv. Chim. Acta*, 1951, **34**, 561, 1041.
[4] Eisenhuth and Schmid, *Helv. Chim. Acta*, 1958, **41**, 2021.
[5] Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 239; Dauben and Pitzer in " Steric Effects in Organic Chemistry," ed. Newman, Wiley, New York, 1956, p. 38.

11, but it is seen that additional structure must be caused by longer-range coupling with the proton of the CH group at position 9. The CH_2 spectrum is therefore to be interpreted as the AB part of an ABXY system [6] with X the proton at 11, and Y the proton at 9.

It has been known for some time that measurable long-range CH–C=C–CH proton–proton couplings occur by the operation of a mechanism involving hyperconjugation and σ-π-configuration interaction. The present molecules provide a particularly interesting example of this because of the different conformations assumed by the CH bonds with respect to the plane of the C=C group. Karplus [7] has shown that long-range couplings of this type will be greatest between CH bonds which are perpendicular to the plane defined by the double bond, and a minimum (essentially zero) between CH bonds in the plane of the double bond. Eleutherin has pairs of CH bonds at positions 9 and 12 which are pseudo-axial-axial and axial-equatorial, and isoeleutherin has analogous pairs which are equatorial-axial and equatorial-equatorial. A pseudo-axial configuration (*a'*) will be associated with a notably greater angle between the direction of the CH bond and the plane

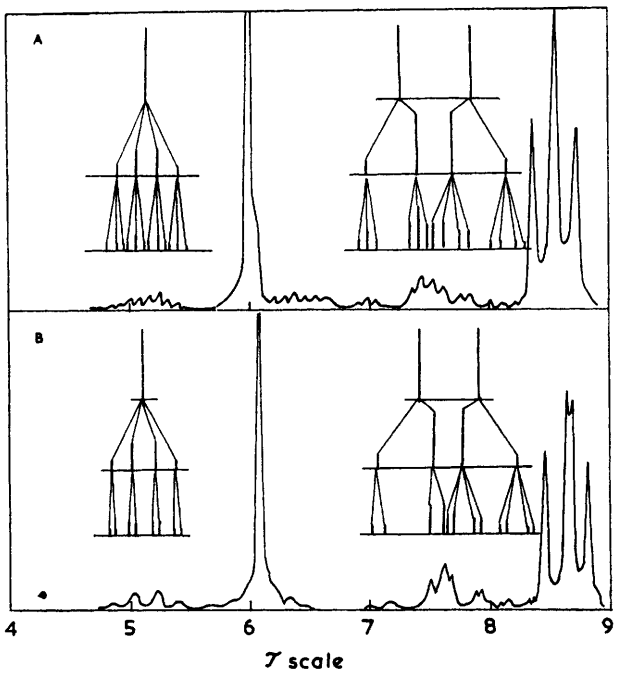


FIG. 1. Nuclear magnetic resonance spectra at 40 Mc./sec. from the hydrogen nuclei of (A) eleutherin and (B) isoeleutherin between 4 and 9 on the τ scale. Line diagrams indicate the interpretation of the fine structure of some of the resonances.

defined by the double bond than a pseudo-equatorial (*e'*) configuration. Hence we might expect the relative magnitudes for $J_{9,12}$ to be $J^{a'a'} > J^{a'e'} \approx J^{e'a'} > J^{e'e'}$. With regard to coupling between CH protons at positions 12 and 11, it is seen that for each molecule there should be large $J^{a'a}$ and smaller $J^{e'a}$ vicinal coupling constants.[8,9] As the magnitudes of such vicinal coupling constants are now well characterised,[10] these can be used to

[6] Pople, Schneider, and Bernstein, " High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, Chapter 6; Jackman, " Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 89.

[7] Karplus, *J. Chem. Phys.*, 1960, **33**, 1842.

[8] Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

[9] Conroy, in " Advances in Organic Chemistry," Interscience Publ., Inc., New York, 1960, Vol. II, p. 311.

[10] Banwell and Sheppard, *Discuss. Faraday Soc.*, 1962, **34**, 115.

determine which of the two resonances from the CH_2 group is associated with the pseudo-axial CH bond and which with the pseudo-equatorial one. This assignment in turn enables the long-range couplings to be separately identified.

The chemical shifts and coupling constants derived from analysis of the spectra of eleutherin and isoeleutherin are listed in Table 1. The chemical shifts of the CH bonds at 11 and 9 were assigned by analogy with the spectra of the erythroaphins discussed in the previous paper,[1] and for eleutherin (where the CH_3–CH coupling constants do not allow a definite assignment) it has been assumed that the high-field methyl resonance is associated with the CH_3 group at position 11. This is the case for isoeleutherin and also for the erythroaphins.

TABLE 1.

Chemical shifts (τ units) and approximate coupling constants (c./sec.) in the spectra of eleutherin and isoeleutherin (see Fig. 1).

Except for the AB part of the CH_2 spectrum, the analysis is a first-order one; the quoted J values are observed spacings.

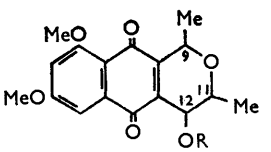
Grouping		Eleutherin	Isoeleutherin
C–CH_3 (11)	τ	~8·64 (D)	8·74 (D) •
	J	(~6·7)	(~6)
(9)	τ	~8·47 (D)	8·55 (D)
	J	(~6·7)	(~7)
CH_2 (12)	τ	7·85 (D × D × D)	7·92 (D × D × D)
	J	(17·8, 3·5, 9·2)	(18·8, 8·8, 2·0)
	τ	7·28 (D × T)	7·41 (D × D, bd)
	J	(17·8, 2 × 2·9)	(18·8, 4·5, <1)
CH–O (11)	τ	~6·38 (complex)	~6·1 (overlapped)
	J	(spacings ~3)	
(9)	τ	~5·15 (complex)	5·13 (Q, bd)
	J	(spacings ~3·3)	(7, ~2)
MeO	τ	6·00	6·08
Arom. CH	τ	~2·8 (D?),* 2·43,* 2·3	2·44,* 2·37

Assignments of coupling constants: Eleutherin, $J^{gem}_{12.12}$ 17·8, $J^{a'a}_{12,11}$ 9·2, $J^{e'a}_{12.11}$ 2·9, $J^{a'a'}_{9.12}$ 3·5, $J^{a'e'}_{9.12}$ 2·9 c./sec.; isoeleutherin, $J^{gem}_{12.12}$ 18·8, $J^{a'a}_{12,11}$ 8·8, $J^{e'a}_{12.11}$ 4·5, $J^{e'a'}_{9,12}$ 2·0, $J^{e'e'}_{9.12}$ <1 c./sec.

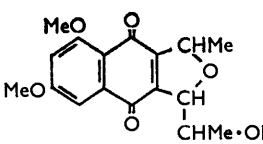
(D) = Doublet; (T) = triplet; (Q) = quartet; (D × D) = doublet of doublets, etc. * Resonances overlapped by solvent band.

The previous assignment of the CH at position 11 to an axial configuration for both molecules [4] is confirmed by the fact that one of the $J_{12,11}$ vicinal coupling constants has the large value typical of axial-axial CH configurations (an equatorial CH at 11 would have caused both the $J_{12,11}$ coupling constants to be small). Finally the pseudo-axial CH bond at 9 for eleutherin should lead to readily measurable $J_{9,12}$ couplings and a complex resonance is found at τ 5·15, in agreement with expectation.

It is seen that the qualitative features of the nuclear magnetic resonance spectra are interpretable in detail in terms of the stereochemical and conformational aspects of formulæ (I) and (II). The values found for the long-range $J_{9,12}$ couplings are in the order expected, *viz.*, $J^{a'a'} = 3{\cdot}5$ and $J^{a'e'} = 2{\cdot}9$ (from eleutherin), and $J^{e'a'} = 2{\cdot}0$ and $J^{e'e'} <$ 1 c./sec. (from isoeleutherin).



(III)



(IV)

Spectra of the Substituted Naphthaquinone Dimethyl Ethers Derived from Protoaphins-fb *and* -sl.—The spectra of the naphthaquinone dimethyl ethers A (from protoaphin-*fb*) and A′ (from protoaphin-*sl*) (III; R = H) [2] are shown in Fig. 2. The spectra of the dimethyl

TABLE 2.

Chemical shifts (τ units) and coupling constants (c./sec.) in the spectra of naphthaquinone dimethyl ethers A and A′ (from protoaphin-*fb* and -*sl*) (see Fig. 2) (derived by first-order analysis).

Grouping		Naphthaquinone A(*fb*)	Acetylated naphthaquinone A	Naphthaquinone A′(*sl*)
C–CH_3 (11)	τ	8·63 (D)	8·75 (D)	8·61 (D)
	J	(~6·3)	(6·5)	(6·3)
(9)	τ	8·44 (D)	8·42 (D)	8·49 (D)
	J	(~6·8)	(6·8)	(6·7)
CH–O (11)	τ	~6·15	~5·95	~6·0 (Q × D?)
	J	(overlapped)	(overlapped)	(~6, ~2)
(12)	τ	5·57 (D × D)	4·26 (D × D)	5·52 (D)
	J	(8·0, ~1·5)	(5·5, ~1·5)	(2·0)
(9)	τ	5·08 (Q × D)	5·08 (Q × D)	5·00 (Q)
	J	(6·5, ~1·5)	(6·3, ~1·7)	(6·8)
MeO	τ	6·05	6·03	6·03
AcO	τ	—	7·89	—
OH	τ	6·99	—	7·55
Arom. CH	τ	3·27 (D)	3·27 (D)	3·27 (D)
	J	(2·7)	(2·5)	(2·5)
	τ	2·74 (D)	2·78 (D)	2·74 (D)
	J	(~2·5)	(2·5)	(2·5)

Assignment of coupling constants: Naphthaquinone dimethyl ether A, $J_{12.11}$ 8·0, $J_{9.12}$ ~1·5 c/sec. Naphthaquinone dimethyl ether A′, $J_{12.11}$ 2·0, $J_{9,12}$ ~0 c./sec.

(D) = doublet; (Q) = quartet; (D × Q) = doublet of quartets, etc.

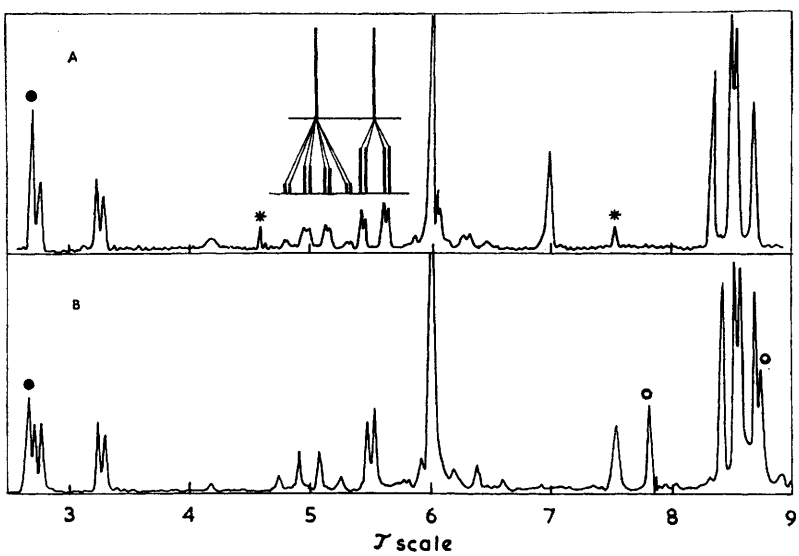


FIG. 2. Nuclear magnetic resonance spectra at 40 Mc./sec. of the naphthaquinone dimethyl ethers derived (A) from protoaphin-*fb*, (B) from protoaphin-*sl*, between 2·5 and 9 on the τ scale. ○ resonances believed to be caused by impurity; * spinning side-band; ● resonance of residual $CHCl_3$ in $CDCl_3$.

ethers rather than the dihydroxynaphthaquinone derivatives [2] were studied because of their greater solubility in chloroform. The derived chemical shifts and coupling constants are listed in Table 2.

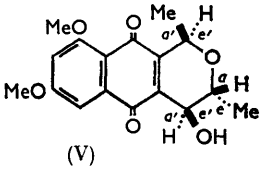
In each case the two aromatic CH resonances near τ 2·75 and 3·27 show the expected mutual coupling constant of 2·5 c./sec. characteristic of CH groups in the *meta*-position

to each other. The higher-field resonance is probably associated with the aromatic CH bond flanked by two methoxyl groups.

The large value of 8 c./sec for the $J_{12,11}$ coupling constant in the spectrum of compound A indicates essentially axial configurations for each of the two vicinal CH bonds, implying that both the hydroxyl substituent at position 12 and the methyl group at 11 have pseudo-equatorial configurations. The long-range coupling constant $J_{9,12}$ of *ca.* 1·5 c./sec. suggests that it is of the $J^{e'a'}$ type (see above) and hence that the CH at position 9 has the pseudo-equatorial configuration. This implies that the partially saturated ring of compound A is the same as that of isoeleutherin, both in configuration and conformation, except for the replacement of the equatorial CH of isoeleutherin at position 12 by the hydroxyl group. The fact that all the chemical shifts of the partially saturated ring in compound A are closely similar to those of isoeleutherin except for the CH group at position 12 (Tables 1 and 2) adds further spectroscopic support to the stereochemical assignment which already had strong chemical backing.[2]

The spectrum of the *O*-acetyl derivative of compound A shows the expected strong low-field shift of the resonance of CH at position 12, and the acetyl substituent also causes appreciable changes in the chemical shifts of the adjacent CH–CH_3 group at position 11. This spectrum was originally obtained to provide a distinction between structural formula (III) for the naphthaquinone A and a, at that stage, possible alternative (IV). Had (IV) been correct the resonance of the CH group labelled 11 in Table 2 would have been the one shifted most to low field on acetylation.

In the spectrum of the naphthaquinone dimethyl ether A′, derived from protoaphin-*sl*, the small $J_{9,12}$ coupling constant (<0·5 c./sec.) suggests pseudo-equatorial configurations for the CH groups in both locations. The vicinal coupling constant $J_{12,11}$ (2·0 c./sec.) would be consistent with CH at 11 in either the axial or the equatorial configuration, given CH at 12 in the equatorial position. The chemical evidence for the structures of the erythroaphins [11] requires that the difference between naphthaquinone dimethyl ethers A and A′ should be in the stereochemistry of the 12-hydroxyl substituent. If this is so, it follows from the spectroscopic evidence that the detailed conformations of the rings are as in (V) and (VI). The very similar pattern of chemical shifts from the nuclei in the partially saturated rings of these two compounds further supports structure (VI) for the protoaphin-*sl* derivative.



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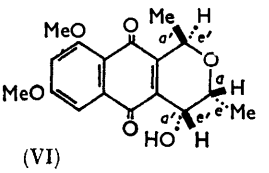

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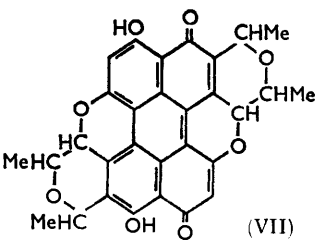


(VII)

*Comparison of the Spectra of the Erythroaphins and the Naphthaquinone Dimethyl Ethers Derived from Protoaphin-*fb *and* -sl.—The stereochemical structures of the naphthaquinone-dimethylethers A and A′ described above (V and VI) should be related to those of the erythroaphins (VII).[1,11] However, the necessity for linking the oxygen atom of the hydroxyl groups in the former compounds with the additional aromatic rings in the latter must lead to strain which might cause changes in the conformations of the partially saturated rings.

For compound A derived from protoaphin-*fb* the hydroxyl group in question already has a pseudo-equatorial configuration. Although Dreiding molecular models show that even so some distortion of the heterocyclic ring is necessary to give the erythroaphin

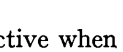
[11] Part XVIII, Cameron, Cromartie, Hamied, Scott, and Todd, *J.*, 1964, 62.

structure, there would not in this case seem to be a necessity for a notable change in ring conformation. In agreement with this, the general pattern of chemical shifts in the incomplete spectrum of erythroaphin-*fb*, and the more detailed one of dihydrotetramethylerythroaphin-*fb* (see preceding paper [1]) is not very different from that of compound A except for a general lowering of τ values by a few tenths of a unit. The ring currents in additional aromatic rings probably account for the latter effect.[12] In addition the $J_{12,11}$ coupling (9·6 c./sec.) remains large in the spectrum of dihydrotetramethylerythroaphin-*fb*,[1] indicating that the CH bonds at positions 12 and 11 both remain essentially axial. The last-mentioned spectrum does show a much smaller value of $J_{9,12}$ (<0·5 c./sec.) than does that of compound A. However, the magnitude of this type of long-range coupling decreases rapidly with the double-bond character of the C=C group,[7] and such a decrease will undoubtedly occur on passing from the erythroaphins themselves to the dihydrotetramethyl derivatives. Unfortunately the weakness of the spectrum of erythroaphin-*fb* does not in this case allow either $J_{12,11}$ or $J_{9,12}$ to be measured.

A more notable change occurs on passing from the spectrum of compound A′ from protoaphin-*sl* to that of erythroaphin-*sl*. This concerns the chemical shifts and coupling constants of the CH group at position 12. In the compound A′ this CH gives τ 5·52, $J_{12,11} = 2{\cdot}0$, $J_{9,12} < 0{\cdot}5$ c./sec., and in the erythroaphin, as discussed in the preceding paper,[1] τ 4·29, $J_{12,11}$ 5·8, and $J_{9,12} = 2{\cdot}8$ c./sec.

These spectral differences presumably reflect considerable conformational changes in the ring, and such changes are clearly necessary if the pseudo-axial hydroxyl group in the quinone is to be brought close to the plane of the aromatic system in the erythroaphin in order to form a second heterocyclic ring.

Dreiding models suggest that possible conformational changes are inversion of the original heterocyclic ring to the alternative chair form, or its conversion into the boat form. Ring-inversion would lead to the CH groups at positions 9 and 12 both becoming pseudo-axial in configuration, and to a $C_{11}H$–$C_{12}H$ dihedral angle of ~70° (estimated from the Dreiding model). Expected values of the coupling constants in this case would be $J_{9,12} \sim 3{\cdot}5$ and $J_{12,11} < 3$ c./sec. Conversion into a boat form would make CH at position 12 pseudo-axial and that at 9 pseudo-equatorial (expected $J_{9,12} \sim 2{\cdot}5$), with an estimated dihedral angle of ~40° (expected $J_{12,11} \sim 5$ c./sec.).[8,9] The observed coupling constants of 2·8 and ~5·8 c./sec., respectively, agree fairly well with expectation for the boat form of the ring.

A partial explanation of the low-field shift of 1·24 p.p.m. in the resonance of the proton attached to C-12 can also be given in terms of a boat-like ring conformation, for this leads to a C–O bond at C-12 that is very close to the plane of the aromatic system. In these conditions alternative mesomeric structures, with the oxygen atom achieving a partial positive charge with respect to the aromatic ring, become important; these in turn should lead to a low-field shift of the proton resonance at C-12. This mechanism is probably the cause of a considerable part of the well-known low-field shift found for the CH group when CH·OH is replaced by CH·OAc,[13] as in the acetyl derivative of compound A discussed above. However, this will only be effective when the  skeleton is near-planar so that there can be efficient interaction between the *p*-type lone pair on the oxygen atom and the π-electron system associated with the double bond. A boat-like conformation of the 4-oxacyclohexene ring would readily provide the near-planar skeleton, whereas a chair-like conformation leads (according to molecular models) to a C_{12}–O bond at a considerable angle to the aromatic plane.

A final point in favour of a boat-like ring conformation in erythroaphin-*sl* is that the 11-methyl group is then brought into a position where its resonance might move to higher-fields as a result of ring currents in the aromatic system. A characteristic of both the *sl*

[12] Pople, Schneider, and Bernstein, *op. cit.*, p. 181; Jackman, *op. cit.*, p. 19.
[13] Jackman, *op. cit.*, p. 55.

and the *tt* spectrum is such a high-field methyl resonance, as mentioned in the previous paper. A point of argument against a boat-like ring conformation is that it brings the CH bond and the C–CH_3 groups at positions 12 and 9 close to each other. However, some distortion from the boat conformation in the vicinity of position 9 might occur without making a comparable change in the stereochemistry in the vicinity of position 12.

Although the evidence given above for the conformation of the partially saturated ring in erythroaphin-*sl* is of only an indicative nature, it allows a very satisfactorily consistent overall explanation to be given of the nuclear magnetic resonance spectra. In any case, it is clear that the combination of vicinal $J_{12,11}$ and long-range $J_{9,12}$ coupling constants has enabled valuable conclusions to be drawn about ring stereochemistry in the naphthaquinone dimethyl ethers, and in erythroaphin-*fb*, where the rings have very probably the less-strained pseudo-chair conformations.

Experimental.—The eleutherin and isoeleutherin spectra were measured for chloroform solutions with a Varian 4300B spectrometer. Other spectra were obtained by using the Perkin-Elmer spectrometer and near-saturated solutions in $CDCl_3$. Tetramethylsilane was used as the internal standard (τ 10·00) [14] throughout. All spectra were obtained at 40 Mc./sec. according to the procedure described in more detail in the preceding paper.[1]

We are very grateful to Professor H. Schmid for supplying samples of eleutherin and isoeleutherin. The Varian Associates spectrometer was bought with a grant from the Wellcome Foundation. One of us (D. G. I. K.) acknowledges financial assistance from a D.S.I.R. Studentship.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 2nd,* 1963.]

[14] Jackman, *op. cit.*, p. 47.