148. *Proton Magnetic Studies of Rotenone and Related Compounds.*

By L. Crombie and J. W. Lown.

The proton magnetic resonance spectra of natural rotenoids and their relatives have been explored. Much structural information is quickly accessible by this means and the asymmetric shielding of the 1-proton by the 12-carbonyl group can be used to decide the *cis*- or *trans*-fusion of the B/C rings. Comment is made on the structure of neotenone, a new isoflavanoid.

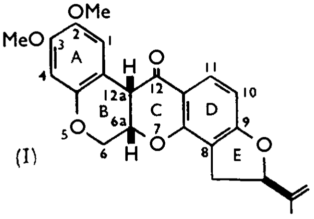
Owing to the difficulties in the isolation of rotenone-like compounds from natural sources, small quantities only are sometimes available and considerable use must be made of physical methods for structural analysis. In this paper, the application of high-resolution proton magnetic resonance spectroscopy to the problem is examined and it is shown that immediate insight into many details of structure is gained. Our main quantitative results are in the annexed Table.

Nuclear magnetic resonance spectra of rotenoids and derivatives. (*J* in c./sec.)

	Ring A OMe	Ring A protons [b]	Ring D protons	Ring E protons	Ring E *C*-Me	Misc.
(−)-Rotenone [a] (I)	6·24 6·24	(1) 3·32 (4) 3·59	(10) 3·53 (11) 2·26 } *J* 11	—	8·25	—
(−)-Isorotenone (IIc; R = R′ = H)	6·26 6·26	(1) 3·21 (4) 3·55	(10) 2·92 (11) 2·20 } *J* 9·5	(4′) 3·45	8·66 8·81	—
(−)-6′,7′-Dihydrorotenone (IIb; R = R′ = H)	6·39 6·39	(1) 3·26 (4) 3·61	(10) 3·62 (11) 2·25 } *J* 8·5	—	9·08	—
(±)-Deguelin (IIe; R = R′ = H)	6·16 6·16	(1) 3·22 (4) 3·59	(10) 3·58 (11) 2·29 } *J* 9	(4′) 3·39 (5′) 4·47 } *J* 10·5	8·54 8·60	—
(−)-Elliptone (IId; R = R′ = H)	6·17 6·10	(1) 3·21 (4) 3·57	(10) 2·85 (11) 2·10 } *J* 8·5	(4′) 3·10 (5′) 2·40 } *J* 3	—	—
(−)-Sumatrol (IIa; R = H, R′ = OH)	6·28 6·28	(1) 3·23 (4) 3·63	(10) 4·10	—	8·22	—
(−)-Sumatrol 11-acetate (IIa; R = H, R′ = OAc)	6·24 6·24	(1) 3·43 (4) 3·62	(10) 3·84	—	8·27	OAc 7·65
(−)-α-Toxicarol (IIe; R = H, R′ = OH)	6·22 6·22	(1) 3·16 (4) 3·55	(10) 4·10	(4′) 3·44 (5′) 4·52 } *J* 10·8	8·51 8·60	OH −2·49
(±)-β-Toxicarol (X)	6·37 6·37	(1) 3·16 (4) 3·55	(8) 4·12	(4′) 2·97 (5′) 4·55 } *J* 10	8·65 8·65	OH −2·22
12-Deoxy-6′,7′-dihydrorotenone (IVb; R = H)	6·24 6·24	(1) 3·34 (4) 3·58	(10) 3·69 (11) 3·24 } *J* 7	—	9·1	—
6a,12a-Dehydrodeguelin (Ve)	6·16 6·04	(1) 1·60 (4) 3·50	(10) 3·12 (11) 2·04 } *J* 10	(4′) 3·25 (5′) 4·35 } *J* 10·5	8·49	—
6a,12a-Dehydroisorotenone (Vc)	6·12 6·23	(1) 1·67 (4) 3·51	(10) 2·73 (11) 2·07 } *J* 8·9	(4′) 3·62	8·61 8·74 } *J* 7·4	—
12-Methyl ether of isorotenolol (IVc; R = OMe)	—	(1) 3·34 (4) 3·67	(10) 3·08 (11) 3·76 } *J* 8·4	(4′) 3·67	8·80	—
Rotenolone A [c, e] (IIa; R = OH, R′ = H)	—	(1) 3·36 (4) 3·56	(10) 3·41 (11) 2·14 } *J* 9·7	—	8·37	—
Rotenolone B [c, f] (IIIa; R = OH, R′ = H)	—	(1) 2·18 (4) 3·62	(10) 3·44 (11) 2·23 } *J* 9·5	—	8·27	—
(±)-Isorotenolone A (IIc; R = OH, R′ = H)	6·36 6·25	(1) 3·37 [d] (4) 3·51	(10) 2·92 (11) 2·21 } *J* 8	(4′) 3·51	8·69 8·79 } *J* 5·8	—
(±)-Isorotenolone B (IIIc; R = OH, R′ = H)	—	(1) 2·13 (4) 3·57	(10) 2·80 (11) 2·14 } *J* 10	(4′) 3·39	8·67 8·77	—
(±)-Tephrosin (IIe; R = OH, R′ = H)	—	(1) 3·34 (4) 3·54	(10) 3·43 (11) 2·34 } *J* 9	(4′) 3·56 (5′) 4·40 } *J* ·10	8·68	—
Rotenolone A Me ether [e] (IIa; R = OMe, R′ = H)	6·24 6·46	(1) 3·51 (4) 3·61	(10) 3·53 (11) 2·16 } *J* 8·5	—	8·31	12a-OMe 6·46
Rotenolone B Me ether [f] (IIIa; R = OMe, R′ = H)	6·16 6·24	(1) 1·96 (2) 3·57	(10) 3·40 (11) 2·16 } *J* 9·1	—	8·16	12a-OMe 6·86
(±)-Isorotenolone A Me ether (IIc; R = OMe, R′ = H)	6·26 6·30	(1) 3·23 (4) 3·50	(10) 2·90 (11) 2·16 } *J* 9·3	(4′) 3·48	8·63 8·74	12a-OMe 6·49
(±)-Isorotenolone B Me ether (IIIc; R = OMe, R′ = H)	6·00 6·03	(1) 1·99 (4) 3·50	(10) 2·88 (11) 2·20 } *J* 10	(4′) 3·57	8·63 8·74	12a-OMe 6·76
(±)-Isorotenolone A acetate (IIc; R = OAc, R′ = H)	—	(1) 3·23 (4) 3·53	(10) 2·87 (11) 2·17 } *J* 8·7	(4′) 3·45	8·66 8·80	OAc 7·91
Rotenone enol acetate (XVIa)	6·14 6·14	(1) 2·65 (4) 3·62	(10) 3·63 (11) 3·24 } *J* 8·6	—	8·24	OAc 7·59
Spiro-compound (XIIa; R = H)	6·46 6·28	(1) 3·72 (4) 3·55	(10) 3·33 (11) 2·38 } *J* 8·5	—	8·24	—
(±)-Isorotenolone C acetate (XIIc; R = OAc)	6·40 6·17	(1) 3·32 (4) 3·61	(10) 2·72 (11) 2·42 } *J* 8·2	(4′) 3·30	8·62 8·74	OAc 8·09
(−)-Rotenonic acid (IIf; R = R′ = H)	6·23 6·25	(1) 3·20 (4) 3·53	(10) 3·29 (11) 2·25 } *J* 10	—	8·4 8·3	5′-H 3·53
Rotenol (XVIIa)	6·18 6·30	(1) 3·54 (4) 3·61	(10) 3·59 (11) 2·19 } *J* 9·1	—	8·26	OH −2·86
Derritol (XVIIIa)	6·23 6·23	(1) 3·33 (4) 3·44	(10) 3·51 (11) 2·11 } *J* 9·1	—	8·32	OH −2·40
Anhydroderritol [g] (XIXa)	6·14 6·14	(1) 3·03 (4) 3·14	(10) 3·54 (11) 2·65 } *J* 8·6	—	8·26	12a-H 3·32
Derritol isoflavone (XXa)	6·50 6·50	(1) 2·09 (4) 3·41	(10) 3·15 (11) 1·90 } *J* 7·9	—	8·27	6a-H 3·41
Pachyrrhizin (XXI)	6·24	(1) 2·23 (4) 3·11	(8) 2·53 (11) 2·35	(5′) 2·35 (4′) 3·15 } $J \ngtr 3$	—	12-H 3·37 CH_2O_2 4·03
Neotenone (XIV)	6·28	(1) 3·40 (4) 3·46	(8) 2·96 (11) 1·76	(5′) 2·45 (4′) 3·30 } *J* 3·25	—	CH_2O_2 4·14

[a] Signs of rotation in benzene. [b] Number in parentheses denotes position of the proton. [c] All values in $CDCl_3$ except these, which are in dioxan. [d] In dioxan, τ 3·43. [e] Unseparated 6aβ,12aβ,5′β- and 6aα,12aα,5′β-diastereoisomers. The methyl ether, m. p. 174° (lit.,[15] m. p. 174—175°), was formed from this mixture. Unseparated 6aβ,12aα,5′β- and 6aα,12aβ,5′β-diastereoisomers. The methyl ether, m. p. 153° (lit.,[15] m. p. 148—149°), was formed from these. A preparation of the literature m. p. contained rotenolone A methyl ether; the material used was free from this (infrared spectrum). [g] This and other compounds are numbered as degraded rotenoids to make comparisons easier.

Methoxyl Groups.—The 2,3-methoxyl groups of rotenone (I),[1] which occur in all but one of the known natural rotenoids, are generally coincident in the region τ 6·10—6·50 p.p.m., but sometimes when asymmetric shielding is operative the lines are separated by up to 0·23 p.p.m. Separation occurs particularly when the structure involves an unnatural 12a-spiro-B/C system. In view of the possibility of obtaining detailed information about the stereochemistry of the B/C ring junction in natural rotenoids from spin–spin coupling data, it is unfortunate that the methoxy-signals overlap the appropriate multiplets.



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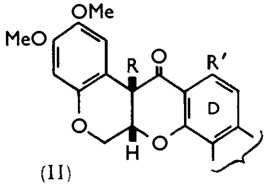

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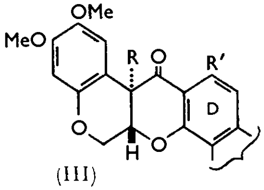

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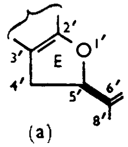

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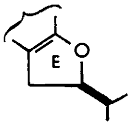

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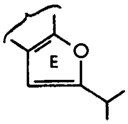

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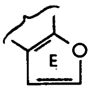

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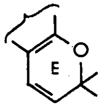

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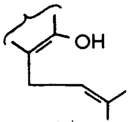

(f)

Carbon-methyl Groups Attached to Ring E.—The only *C*-methyl groups in known rotenoids are attached to ring E and the possible variants (*gem*-dimethyl, isopropyl, and isopropenyl) are readily distinguished as there is no interfering absorption in appropriate regions of the spectrum. The *gem*-dimethyl groups in the deguelin and toxicarol series, being attached to a carbon atom itself linked to oxygen, give sharp bands near 8·5—8·6 having the expected shift from the usual position (~9·1) for saturated methyl:[2] in certain cases the two methyl groups show non-equivalence.

The isopropyl groups in compounds with a furanoid ring E give rise to doublets (J ~ 6—8 c./sec.) in the region 8·6—8·8 with the accompanying characteristic septet of the isopropyl hydrogen centred at 7·0—7·1. These line positions are low for saturated methyl groups which are presumably experiencing the effect of a ring current generated by the neighbouring furan ring. Other evidence supports the fact that the furan ring sustains such a current, *e.g.*, in limonin and related structures methyl groups adjacent to a furanoid ring are appreciably shifted as compared with " normal " aliphatic methyl groups.[3]

Aromatic Protons of Ring A.—The *p*-aryl protons of ring A in natural rotenoids give rise to two sharp singlets in the region 3·2—3·7. The 4-proton, which must be less susceptible to structural changes at $C_{(12)}$ and $C_{(12a)}$ than the 1-proton, is assigned a steady position near 3·6. Study of the 1-proton resonances in rotenoids throws valuable light on the geometry of the B/C fusion.

In 6a,12a-dehydroisorotenone (Vc) (τ 1·67) and 6a,12a-dehydrodeguelin (Ve) (τ 1·60) the 1-hydrogen atoms are approximately coplanar with the 12-carbonyl group and show the expected negative shieldings [cf. 12-deoxy-6',7'-dihydrorotenone (IVb; R = H) (τ 3·34)]. Rotenolone B (IIIa; R = OH, R' = H) and isorotenolone B (IIIc; R = OH, R' = H), and their methyl ethers,[4] have τ values of about 2·0 for their 1-hydrogen atoms and this is consistent with the rigid and fairly flat *trans*-B/C fusion (VI; R = OH or OMe),

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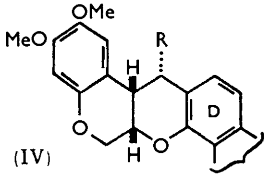
[1] Büchi, Crombie, Godin, Kaltenbronn, Siddalingaiah, and Whiting, *J.*, 1961, 2843.

[2] Jackman, " Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959.

[3] Barton, Pradhan, Sternhell, and Templeton, *J.*, 1961, 255.

[4] Crombie and Godin, *J.*, 1961, 2861.

for in this the 1-hydrogen must be subject to negative carbonyl long-range shielding. On the other hand, the corresponding A compounds (II; R = OH or OMe, R′ = H)[4] have



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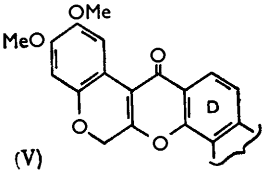
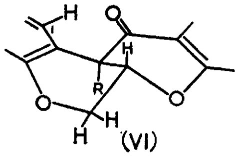


(V)

the 1-hydrogen line near 3·3. This indicates that it lies in a region of low positive or negative shielding and agrees with the *cis*-B/C conformation (VIII; R = OH or OMe) in which the 1-hydrogen atom lies near the presumed nodal surface of carbonyl magnetic shielding (cf. VII).[2,5] Such stereochemical assignments agree with our earlier views on the rotenolones and isorotenolones which are based on quite different evidence.[4] In the *cis*-fused rotenolone A and isorotenolone A, infrared studies in chloroform and carbon tetrachloride show that a strong hydrogen bond is formed between the hydroxyl and the carbonyl group[4] and this, too, supports conformation (VIII; R = OH) rather than (IX; R = OH). The possible shielding of the 1-hydrogen by aryl ring D has been estimated by Johnson and Bovey's method[6] and does not influence the above interpretation as the effect would be only about 0·2 τ for either configuration.



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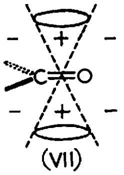

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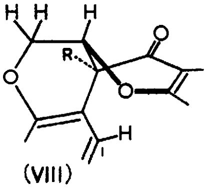

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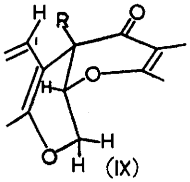

(IX)

According to this nuclear magnetic resonance criterion, natural, optically active rotenone (I) (τ 3·32), sumatrol (IIa; R = H, R′ = OH) (τ 3·23), elliptone (IId; R = R′ = H) (τ 3·21), and α-toxicarol (IIe; R = H, R′ = OH) (τ 3·16) all have the *cis*-B/C fusion. This applies also to (±)-β-toxicarol (X) (τ 3·16) and isorotenone (IIc; R = R′ = H), and various other rotenoids with the thermodynamically favoured B/C fusion. The *cis*-B/C fusion of the acetate (IIc; R = OAc, R′ = H) formed from (±)-isorotenolone A or B,[4] is also confirmed. By using the earlier establishment of the *cis*-B/C fusion and complete absolute configuration of rotenone,[1] similar conclusions can be reached for natural rotenoids by comparing optical rotatory dispersion curves.[7] The latter method compares absolute configurations, but the present one is applicable to either optically active or (±)-6a,12a-compounds. Also, the nuclear magnetic resonance method is absolute in type, rather than dependent on correlation with a previously worked-out standard.

Aromatic Protons of Ring D.—Ring D in most rotenoids can have two ring protons which may be oriented either *o* or *p*. In the former case, the spectrum consists of a pair of doublets with $J \sim 7$—10 c./sec. constituting an AB system (terminology of Pople *et al.*[8]), whilst the latter class gives rise to two singlets. The question of angular or linear fusion of the D/E rings is thus easily decided. In the tabular data the centres of gravity

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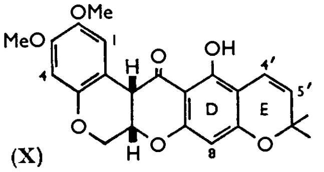
[5] Pople, *Proc. Roy. Soc.*, 1957, **239**, *A*, 550.
[6] Johnson and Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.
[7] Djerassi, Ollis, and Russell, *J.*, 1961, 1448.
[8] Pople, Schneider, and Bernstein, " High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959.

of the AB multiplets have been determined to give accurate chemical shifts. When a carbonyl group in ring C is adjacent to the 11-proton, a considerable paramagnetic shift to 2·1—2·2 is observed and in 6a,12a-dehydro-rotenoids still further shifting to 1·9—2·1 occurs. This may indicate more efficient shielding from a carbonyl group held accurately in plane with ring D, or reflect a ring current in the γ-pyrone ring C. The proton at $C_{(10)}$ appears to be influenced by the 12-carbonyl group to only a small extent. The line position is more sensitive to the nature of the adjoining oxygen group in ring E, being considerably diamagnetically shielded by a dihydrofuran ring, or a dimethyl-2*H*-pyran, but to a smaller extent by a furan ring. This is compatible with the generation of an appreciable ring current in the latter and the shielding of the 10-proton becomes a compromise between the substituent effect of the neighbouring oxygen and the effect of the ring current.

In those rotenoids with an 11-hydroxyl group which is strongly internally bonded with the 12-ketone group, the position of the remaining aromatic proton is surprisingly high (τ 4·1). This is in the region for the protons of a dienone ring. [Dr. J. Elvidge and Dr. L. M. Jackman have kindly informed us [9] that the assignments for the dienone (XI) are: methyl groups 8·75, α-proton 4·09, β- 3·04, γ- and δ- 3·81]. If chelation is prevented by acetylating the 11-hydroxyl group, the proton position is lowered. The mesomeric effect of the 7-oxygen in ring D may be involved, for in other chelated compounds (*e.g.*, rotenol and derritol) the proton resonances in ring D are more normal. The high position of the aromatic proton may signify a reduced ring current and lessened aromatic character in ring D and the situation is being further examined. Nuclear magnetic resonance methods are less easily used for deciding between linear and angular fusions in the D/E ring systems of 11-hydroxy-rotenoids, but the problem can be solved chemically by means of the Gibbs test at the cost of only small amounts of material.[10]



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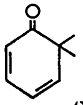
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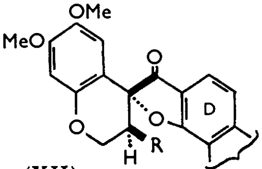

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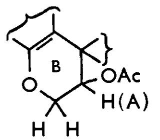

(XIII)

Protons of Rings B *and* C.—Interest attaches to the possibility of obtaining detailed information about the geometry of the B/C fusion of rotenoids by an alternative approach. In principle, it is possible to analyse the appropriate spin–spin multiplet and, using theoretical and empirical correlations between dihedral bond angles and coupling constants, to derive the required angles [11] and hence the geometry of the fusion. At present this approach is spoiled because all known natural rotenoids contain methoxyl and the resonances from these overlap the multiplets to be studied. However, another example of interest to us, (±)-acetylisorotenolone C (XII; R = OAc) [4] is discussed and illustrates the method. The shielding influence of the acetyl group shifts the adjacent proton resonance sufficiently to give a well-defined ABC spectrum.

In the analysis of an ABC spectrum, the possibility of alternative assignments must be considered. Banwell and Sheppard [12] have, however, pointed out that when combination lines are weak a best fit of frequencies, followed by an exploration of changes in the relative signs of the coupling constant, suffices for the analysis. The spectrum was analysed by a linear algebraic programme developed for a Deuce computor by Mr. A. L. Hardisson de la Rosa and based on the iterative procedure of Reilley and Swalen.[13] An accurate fit of the

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[9] Elvidge and Jackman, personal communication.

[10] Crombie and Peace, *J.*, 1961, 5445.

[11] Clark-Lewis and Jackman, *Proc. Chem. Soc.*, 1961, 165.

[12] Banwell and Sheppard, *Mol. Phys.*, 1960, **3**, 351.

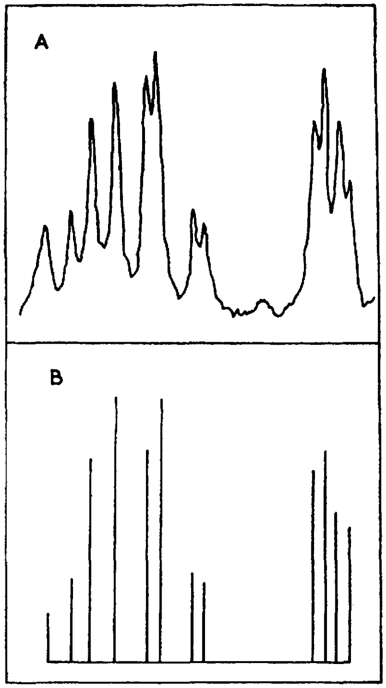
[13] Reilley and Swalen, *J. Chem. Phys.*, 1960, **32**, 1378.

spectrum with respect to both energies and intensity was obtained with the following parameters (in c./sec.; cf. XIII): J_{AB} 2·51, J_{AC} 11·45, J_{BC} 6·83; ν_A 176·31, ν_B 135·35, ν_C 114·35.

The calculated and observed line frequencies are listed below, and are shown in Fig. 1. By employing Conroy's relation[14] between the extent of coupling and dihedral bond angle,

Calc. (c./sec.)	72·94	103·81	110·28	115·27	121·74	129·53	132·41	141·00
Obs. (c./sec.)	—	103·93	110·12	115·15	121·93	129·72	132·28	141·12
Calc. (c./sec.)	143·87	152·61	171·87	174·74	178·34	181·21	200·47	
Obs. (c./sec.)	144·03	—	171·97	174·80	178·53	181·01	—	

an angle A–B ≈ 55° and A–C ≈ 180° is predicted. If ring B assumes predominantly a half-chair form with the acetate grouping equatorial, the A–B and A–C angles are approximately those predicted from the coupling constants. The proton A shows a considerable paramagnetic shift relative to B and C because of the acetate group attached to the same carbon atom: this alone rules out the types of structure assigned to isorotenolone A or B (IIc or IIIc; R = OAc, R′ = H), which were at one time thought possibilities for isorotenolone C.[15]



A, Observed nuclear magnetic resonance spectrum of isorotenolone C acetate (56·445 Mc.). B, Calculated ABC spectrum.

The Structure of Neotenone.—Application of the results obtained has supplemented chemical work on a new isoflavanone, neotenone, isolated from the bark of *Neorautanenia pseudopachyrrhizus*.[16] The spectrum shows an aryl-methoxyl and a singlet at 4·14 corresponding to two protons: this is assigned to a methylenedioxy-grouping[17,18] (cf. piperonaldehyde and pachyrrhizin, τ 3·92 and 4·03, respectively). A closely spaced multiplet

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[14] Conroy in "Advances in Organic Chemistry, Methods and Results," Vol. II, ed. Raphael, Interscience Publ., Inc., New York, 1960, p. 311.

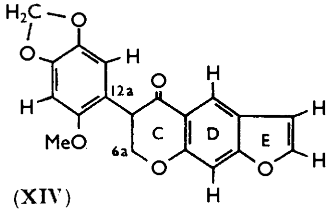
[15] LaForge and Haller, *J. Amer. Chem. Soc.*, 1934, **56**, 1620.

[16] Crombie and Whiting, unpublished work.

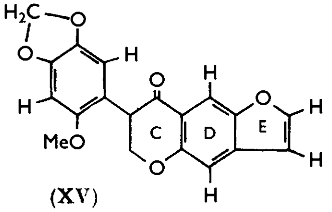
[17] Goodwin, Shoolery, and Johnson, *Proc. Chem. Soc.*, 1958, 306.

[18] Bick, Harley-Mason, Sheppard, and Vernengo, *J.*, 1961, 1896.

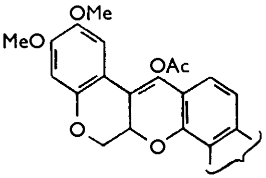
near $\tau = 6$ showed nine lines and corresponded in intensity to three protons. It resembles an AB_2 structure and is assigned to the 6a- and 12a-hydrogen atoms. In the aryl and olefinic region one AB quartet was found with coupling constant 3·25 c./sec. and centres of gravity at 2·45 and 3·30. This is due to the adjacent protons on the furanoid ring. No other AB quartet was discernible, so a linear D/E fusion is favoured leaving two *p*-protons in ring A and two in ring D. The nuclear magnetic resonance data allow ring D to be a resorcinol (XIV) or a quinol (XV) derivative. Biogenetic considerations favour the former and chemical work to decide the issue is in progress.



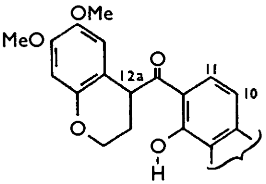
(XIV)



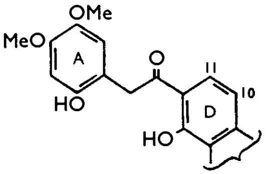
(XV)



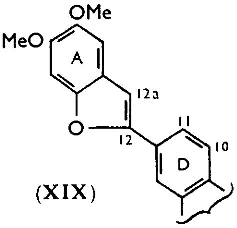
(XVI)



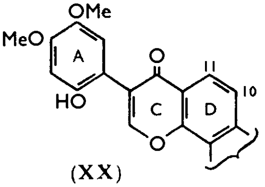
(XVII)



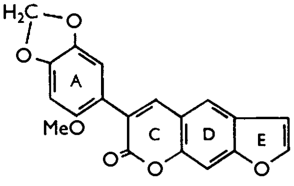
(XVIII)



(XIX)



(XX)



(XXI)

EXPERIMENTAL

The spectra were determined at 56·445 Mc. on a Varian Associates nuclear magnetic resonance spectrometer (model V.4300). All compounds were determined as 5—10% solutions with tetramethylsilane as internal standard, and results are expressed in the notation of Tiers.[19] Line positions were measured by the conventional side-band technique, a Muirhead-Wigan Decade Oscillator D-695-A being used. The credentials of most of the compounds used are to be found in other papers.[1,4,10,20]

We thank Dr. L. M. Jackman for discussions and Mr. A. L. Hardisson de la Rosa for computational assistance in the analysis of the ABC spectrum. Specimens of elliptone and derritol isoflavone were gifts from Professor S. H. Harper.

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[19] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.

[20] Crombie, Godin, Whiting, and Siddalingaiah, *J.*, 1961, 2876.