285. *The Relative Stereochemistry of the Rotenoids.**

By Carl Djerassi, W. D. Ollis, and R. C. Russell.

Optical rotatory dispersion studies have shown that six natural rotenoids all have the same absolute configuration at two of their asymmetric centres.

The rotenoids are a family of natural products whose structures show considerable variety and it is therefore of interest to determine the stereochemical relationship between corresponding asymmetric centres. Eight rotenoids (I—VIII) are known and they have all been isolated in an optically active condition. Deguelin (III), however, has not been isolated in a pure state and the figures given for its specific rotation refer to a concentrate.[1] It is unlikely that tephrosin (12a-hydroxydeguelin) is a true natural product as it is probably produced from deguelin (III) by aerial oxidation.[2]

The structural study of rotenone, sumatrol, deguelin, toxicarol, elliptone, and malaccol has been reviewed,[3,4] and the structures of pachyrrhizone [5] and munduserone [6] have been determined more recently. The structures given for sumatrol (III) and malaccol (VI) are probably correct although the alternative linear C/D/E ring fusion is not excluded. The numbering system which we have adopted for the rotenoids is indicated in the formulæ (I—VI) and we should like to thank Dr. R. S. Cahn and Dr. L. Crombie for this proposal and for their advice.

The absolute and relative stereochemistry of the rotenoids has not been defined although it has been subjected to experimental scrutiny.[7,8] The rotenoids (IV—VIII) are racemised

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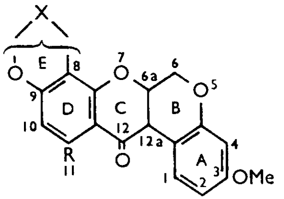
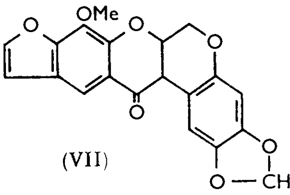
* This paper represents Part XXXVIII in the series by one author (C. D.) and his collaborators on "Optical Rotatory Dispersion Studies" (for Part XXXVII, see R. Villotti, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 5693).

[1] Haller and La Forge, *J. Amer. Chem. Soc.*, 1934, **56**, 2415.
[2] Miyano and Matsui, *Chem. Ber.*, 1959, **92**, 1438.
[3] La Forge, Haller, and Smith, *Chem. Rev.*, 1933, **12**, 182.
[4] Haller, Goodhue, and Jones, *Chem. Rev.*, 1942, **30**, 33.
[5] Bickel and Schmid, *Helv. Chim. Acta*, 1953, **36**, 664.
[6] Finch and Ollis, *Proc. Chem. Soc.*, 1960, 176.
[7] (*a*) Cahn, Phipers, and Boam, *J.*, 1938, 513; (*b*) Jennen, *Bull. Soc. Chim. belges*, 1952, **61**, 536.
[8] Harper, *J.*, 1939, 812.

under the mild conditions of heating with sodium acetate in ethanol and in the case of munduserone (VIII) it has been established that (±)-munduserone is stereochemically similar to (+)-munduserone.[6] Rotenone under similar conditions gives mutarotenone which is an equilibrium mixture of rotenone and a diastereoisomer; these substances have the same stereochemistry at $C_{(5')}$ but are epimeric at $C_{(6a)}$ and $C_{(12a)}$. These base-catalysed equilibrations involve the anions (IX) and (X),[7b] and Miyano and Matsui[9] have interpreted these results as showing that the B/C ring fusion is *trans*. In our view it is not

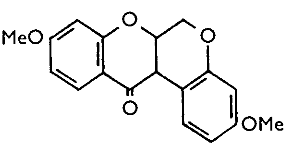


(I - VI)



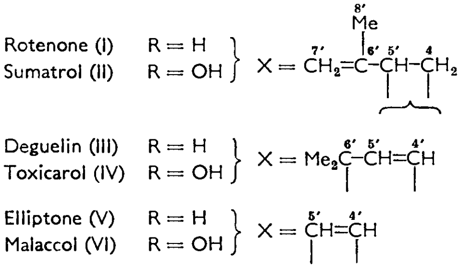
(VII)

Pachyrrhizone (VII)



(VIII)

Munduserone (VIII



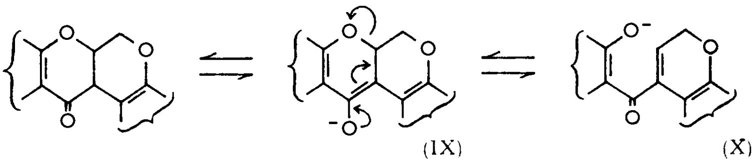
Rotenone (I) R = H
Sumatrol (II) R = OH } $X = \overset{7'}{C}H_2{=}\overset{\overset{8'}{Me}}{\overset{|}{\underset{6'}{C}}}{-}\overset{5'}{C}H{-}\overset{4}{C}H_2$

Deguelin (III) R = H
Toxicarol (IV) R = OH } $X = Me_2\overset{6'}{C}{-}\overset{5'}{C}H{=}\overset{4'}{C}H$

Elliptone (V) R = H
Malaccol (VI) R = OH } $X = \overset{5'}{C}H{=}\overset{4'}{C}H$

possible from an examination of models to decide with certainty which is the more stable of the B/C *cis*- and B/C *trans*-arrangements.

At the beginning of our studies the only stereochemical feature which had been established was that the asymmetry at $C_{(6a)}$ and $C_{(12a)}$ in the natural rotenoids was the one which would be associated with greater stability. The stereochemical relation of $C_{(5')}$



(IX) (X)

to $C_{(6a)}$ and $C_{(12a)}$ in rotenone (I) and in sumatrol (II) was not known and it was not established whether the rotenoids all had the same absolute stereochemistry at $C_{(6a)}$ and $C_{(12a)}$.

Compound	I	II	III	IV	V	VI	VII	VIII
$[\alpha]_D$ (Benzene)	−225° [a]	−184° [b]	−101° [a]	−66° [a]	−18° [a]	+67° [a]	0° [c]	—
$[\alpha]_D$ ($CHCl_3$)	−114° [d]	—	—	—	(+55° [e])	+190° [a]	+96° [c]	+103°

[a] Ref. 10. [b] Ref. 1. [c] Ref. 5. [d] Ref. 11. [e] Ref. 12, in acetone. Ref. 6.

A comparison of the specific rotations (tabulated) did not indicate a stereochemical similarity among the rotenoids so an attempt was made to apply the method of molecular-rotation differences to the problem by determining the optical shifts for three reactions characteristic of rotenoids. The molecular-rotation differences were calculated for reactions

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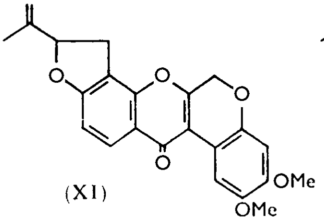
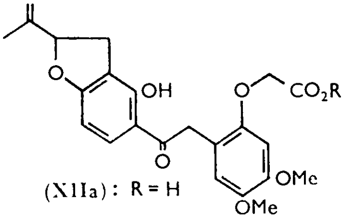
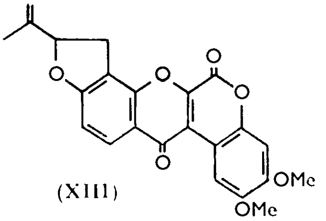
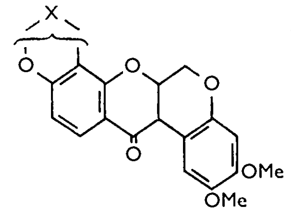
[9] Miyano and Matsui, *Chem. Ber.*, 1958, **91**, 2044.
[10] Harper, *J.*, 1940, 309.
[11] Jones and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 2554.
[12] Harper, *J.*, 1939, 1099.

analogous to the following transformations of rotenone: (*a*) rotenone (I) ⟶ dehydrorotenone (XI); (*b*) rotenone (I) ⟶ derrisic acid (XIIa); (*c*) rotenone (I) ⟶ rotenonone (XIII).

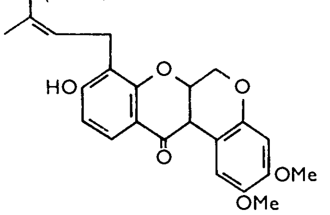

(XI)

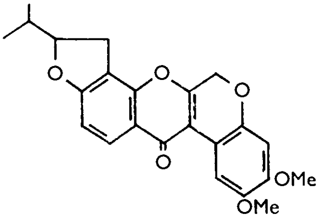

(XIIa): R = H
(XIIb): R = Me


(XIII)


(XIV): X = Me$_2$CH–CH–CH$_2$

(XV): X = Me$_2$CH–C=CH


(XVI)


(XVII)

These reactions are associated with the disappearance of asymmetry at $C_{(6a)}$ and $C_{(12a)}$, and comparison of the molecular-rotation differences for reactions *a* (+229°), *b* (+202°), and *c* (+247°) for rotenone, with the figures for the corresponding reactions of malaccol (VI) (−699°), pachyrrhizone (VII) (−351°) and munduserone (VIII) (−352°) led us to suspect that the configurations of $C_{(6a)}$ and $C_{(12a)}$ in rotenone were opposite to the configurations of these two centres in malaccol, pachyrrhizone, and munduserone. A similar examination of the specific rotations of the rotenoids has been made by Harper[10] and it was shown by comparison of the pairs of compounds (I and II, III and IV, V and VI) that the introduction of the 11-hydroxyl group gave a positive increment in specific rotation. It was concluded that the rotenoids probably belonged to the same stereochemical series. It is probable that the method of molecular-rotation differences cannot be successfully applied in these cases because the systems are far too conjugated and polarised,* but a clear indication of the relative stereochemistry of the rotenoids was provided by rotatory-dispersion studies.

Rotatory dispersion curves recorded in Figs. 1, 2, and 3 were determined for the compounds listed below.

Rotenone (I) and sumatrol (II) are two naturally occurring rotenoids with an asymmetric centre at $C_{(5')}$ and, as shown in Fig. 1, rotenone and sumatrol acetate exhibit positive Cotton effect curves. Whether the quantitative differences in these two curves can be attributed to the presence of the acetoxy-function *peri* to the carbonyl group in sumatrol acetate or to differences in the configuration at $C_{(5')}$, cannot be decided with the information at present available. Both curves show a negative rotation in the visible range of the spectrum and this feature, of course, explains why their sodium-D line rotations are negative.

In Fig. 2 are collected the rotatory dispersion curves of dehydrorotenone (XI), dehydrodihydrorotenone (XVII), and derrisic acid (XIIa) and its methyl ester (XIIb). These four substances contain only the one asymmetric centre, $C_{(5')}$, and the virtually identical plain negative dispersion curves of these compounds can therefore be ascribed to this

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* We thank a Referee for emphasising this point.

sole centre. It is now obvious that the dispersion curves (Fig. 1) of rotenone (I) and sumatrol acetate (cf. II) represent positive Cotton effect curves superimposed upon this negative plain curve and this also applies to the curve of dihydrorotenone (XIV). It is interesting that the amplitude of the Cotton effect of dihydrorotenone (XIV) is considerably smaller than that of rotenone (I) (see Fig. 1). The reason for this is not clear but it is unlikely that this is associated with reduction of the 6′,7′-double bond since this effect is not shown by comparing the dispersion curves of dehydrorotenone (XI) and its 6′,7′-dihydro-derivative (XVII) (see Fig. 2).

FIG. 1.

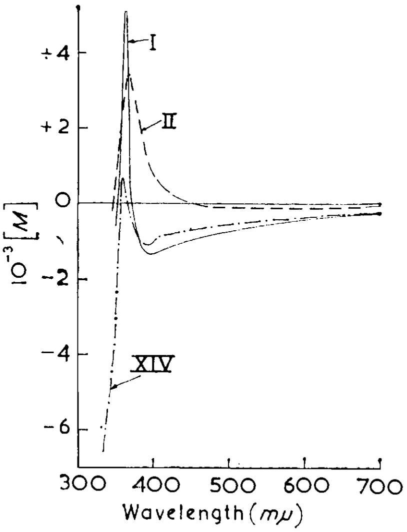

FIG. 2.

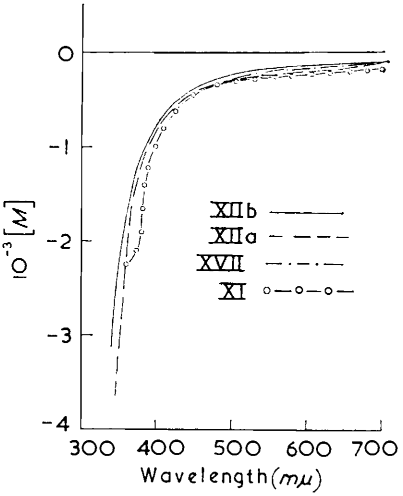

FIG. 3.

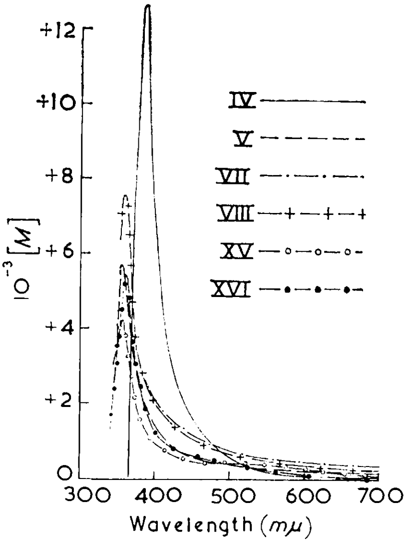

Fig. no.	Substance	Asymmetric centres		
1	Rotenone (I)	$C_{(6a)}$	$C_{(12a)}$	$C_{(5')}$
	Sumatrol acetate (cf. II) [7]	,,	,,	,,
	Dihydrorotenone (XIV) [3]	,,	,,	,,
2	Dehydrorotenone (XI) [3]	$C_{(5')}$		
	Dehydrodihydrorotenone (XVII) [13]	,,		
	Derrisic acid (XIIa) [3]	,,		
	Methyl derrisate (XIIb) *	,,		
3	Toxicarol (IV) [8]	$C_{(6a)}$	$C_{(12a)}$	
	Elliptone (V) [12]	,,	,,	
	Pachyrrhizone (VII) [5]	,,	,,	
	Munduserone (VIII) [6]	,,	,,	
	Rotenonic acid (XVI) [3]	,,	,,	
	Isorotenone (XV) [3]	,,	,,	

* See p. 1453.

Toxicarol (IV), elliptone (V), pachyrrhizone (VII), and munduserone (VIII) all exhibit positive Cotton effect curves (Fig. 3) which are positive throughout the spectral range under examination. These rotenoids lack the asymmetric centre at $C_{(5')}$ and hence are

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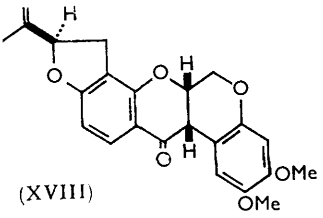
[13] La Forge and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 1094.

not subject to the initial negative rotational drift in the visible range, as is the case with rotenone (I), where the effect of the positive Cotton effect becomes only noticeable in the ultraviolet region. Since the sign and magnitude of the Cotton effect is associated with the stereochemical environment[14] of the carbonyl chromophore, the positive Cotton effect curves (Figs. 1 and 3) of the naturally occurring rotenoids (I, II, IV, VI, VII, and VIII) can be taken as virtually conclusive evidence of identical absolute configuration at positions 6a and 12a in these substances. The only possible source of ambiguity could arise if two ketones with antipodal absolute configuration at $C_{(6a)}$ or $C_{(12a)}$ *as well as* different ring fusion (*cis* in one case, *trans* in the other) could still exhibit Cotton effect curves of identical sign. At this stage it is not possible to evaluate the significance of quantitative variations in these positive Cotton effect curves as these are partly or completely due to the different substitution patterns in the aromatic ring.

Two additional transformation products of rotenone, namely, isorotenone (XV) and rotenonic acid (XVI), have also been examined. In these two substances, the negative rotatory contribution attributable to $C_{(5')}$ has been removed by the absence of asymmetry at that centre and in accordance with expectation, the two ketones now show positive Cotton effect curves (Fig. 3) which do not start on the negative side in the visible region.

It should be noted that conclusions, based upon molecular-rotation differences for sodium-D light, which might have been drawn regarding the relative stereochemistry of the rotenoids would not necessarily have agreed with these results of optical rotatory dispersion study. The present investigation thus represents a particularly good example of the disadvantage of monochromatic rotation measurements.[15]

Since it has been shown[16] that dihydrodeguelin is identical with β-dihydrorotenone it follows that deguelin (III) has the same configuration at $C_{(6a)}$ and $C_{(12a)}$ as has rotenone. These dispersion measurements demonstrate that all the naturally occurring rotenoids which have been examined possess identical absolute configurations at $C_{(6a)}$ and $C_{(12a)}$, but it is not possible to use the octant rule[17] at the present time to predict what the actual configuration is, owing to the uncertainty about the B/C ring fusion and conformations of rings B and C. It is, however, of considerable interest that seven natural rotenoids all have the same absolute configuration at $C_{(6a)}$ and $C_{(12a)}$, which illustrates the stereoselectivity of their biosynthesis.[18] A similar stereoselectivity also apparently operates in the biosynthesis of flavanoids since those naturally occurring flavans which have been examined and are asymmetric at $C_{(2)}$, all have the same absolute (*R*)-configuration at this centre.[19]



(XVIII)

Note added on 1*st October,* 1960: After this paper was submitted for publication the absolute configuration of the three asymmetric centres of rotenone were determined[20] as (6a*S*, 12a*S*, 5'*R*), giving the full structure (XVIII) for rotenone. This work is complementary to our study and it is now possible to define the absolute stereochemistry of all the rotenoids which we have examined as (6a*S*, 12a*S*). The configuration of $C_{(5')}$ in sumatrol remains to be determined.

Experimental.—All the rotatory dispersion measurements were carried out using dioxan solutions.

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[14] Djerassi, " Optical Rotatory Dispersion," McGraw-Hill, New York, 1960.

[15] Ref. 14, pp. 236—237.

[16] Haller and La Forge, *J. Amer. Chem. Soc.*, 1934, **56**, 2417.

[17] Ref. 14, Chapter 13.

[18] Grisebach and Ollis, *Experientia*, 1961, **17**, 4.

[19] Clark-Lewis, " Stereochemistry of Catechins and Related Flavan Derivatives " in " Current Trends in Heterocyclic Chemistry," Ed. A. Albert, G. M. Badger, and C. W. Shoppee, Butterworths, 1958, p. 6.

[20] Büchi, Kaltenbronn, Crombie, Godin, and Whiting, *Proc. Chem. Soc.*, 1960, 274.

Methyl derrisate (XIIb). Derrisic acid (290 mg.), methanol (10 ml.), and concentrated sulphuric acid (0·2 ml.) were heated under reflux for 5 hr., cooled, and diluted with water. The chloroform extract was washed with aqueous potassium hydrogen carbonate and dried ($MgSO_4$); it yielded *methyl derrisate* (297 mg.) as needles, m. p. 96—97° from methanol [Found: C, 65·25; H, 6·20; OMe, 20·74. $C_{21}H_{17}O_5(OMe)_3$ requires C, 65·15; H, 5·92; OMe, 21·06%].

The botanical sources of the rotenoids are as indicated in the references. We thank Professor H. Schmid, Professor S. H. Harper, and Dr. N. C. Brown for gifts of specimens, Dr. B. F. Burrows and Mr. D. R. George for their assistance with the preparation of some of the compounds studied, and Mrs. T. Nakano for the optical rotatory dispersion measurements.

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