Conformation and Absolute Configuration of Rotenone: Examination of 8′-Bromorotenone by *X*-Ray Methods

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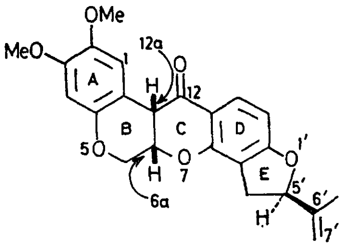
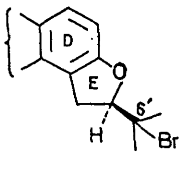
Summary The *X*-ray structure of (−)-rotenone (as its 8′-bromoderivative) shows its bent geometry and confirms its stereochemistry: reference is made to possible biochemical consequences.

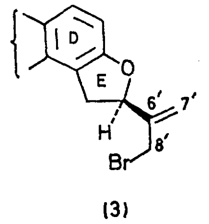
(−)-ROTENONE [(**1**), (6a*S*,12a*S*,5′*R*)] is the best-known of the growing class of natural rotenoids; its absolute configuration and conformation have been based previously on chemical[1,2] and n.m.r. spectroscopic[3] investigations. Configurations of all other rotenoids have been correlated with that of rotenone by o.r.d. or c.d.,[4] and the structure has become a stereochemical reference point. Thus, its degradation product (*R*)-(−)-dihydrotubaic acid (**4**) is configurationally linked with compounds such as (*R*)-(−)-tremetone and 2(*S*),3(*S*)-(−)-toxol, as well as (*S*)-(+)-dihydro-orselol, (*S*)-(+)-marmesin, (*S*)-(+)-visamminol *etc.* in the enantiomeric series.[5] In view of its importance, we have undertaken an *X*-ray analysis of a suitable derivative of rotenone.



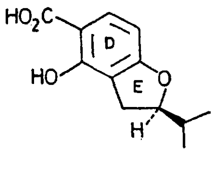
(1)



(2)



(3)



(4)

Initially rotenone hydrobromide (**2**), $C_{23}H_{23}O_6Br$, was employed; the orthorhombic crystals ($P2_12_12_1$) had a = 9·48, b = 12·34, c = 21·25 Å, Z = 4, and intensities for 1430 independent reflections were observed (Mo-K_α). The bromine was located by Patterson synthesis and the remaining 29 non-hydrogen atoms found by Fourier methods. Refinement by block-diagonal least-squares to an R-index of 12·0% was carried out using anisotropic temperature factors, but at this stage a difference Fourier map revealed that the structure was disordered about the C(5′)–C(6′) bond, with the bromine atoms partially occupying the positions of the 7′- and 8′-methyl groups. Although the overall structure of rotenone was confirmed, the disorder meant that determination of absolute configuration by anomalous dispersion would be unreliable, and the project was begun again with another derivative.

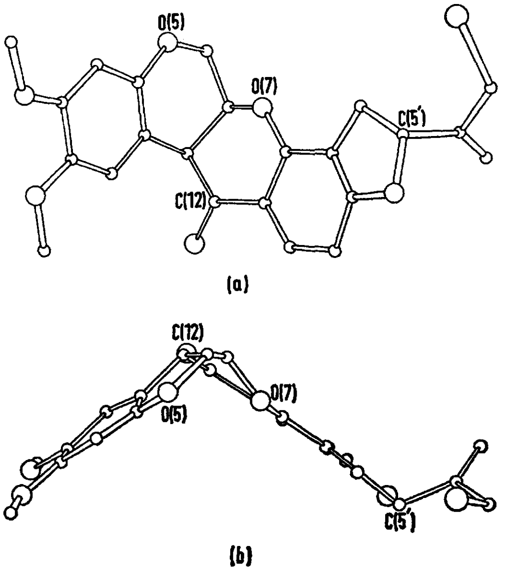


FIGURE. Two projections of the molecular structure of 8′-bromorotenone.

8′-Bromorotenone (**3**)† was selected as having lower symmetry around C(6′); the crystal was orthorhombic ($P2_12_12_1$), $a = 4{\cdot}60$, $b = 15{\cdot}72$, $c = 28{\cdot}72$ Å, $Z = 4$. Intensity data were collected as before (727 reflections) but interpretation of the Patterson synthesis proved inconclusive, so the structure was partially solved by direct methods using the Multan programme,[6] completed by Fourier methods, and refined by block-diagonal least-squares to an R-index of 9·7% (isotropic temperature factors, except for bromine). The absolute configuration was determined by anomalous dispersion (difference between enantiomers significant beyond the 0·005 level)[7] and confirmed by independent measurement of Bijvoet pairs of reflections. Of 16 pairs compared (for which F_c differed by >10%, and observed intensities were significantly different), 15 supported the assigned absolute configuration. The resulting structure is shown in the Figure and the second projection (b) emphasises the bent nature of the molecule consequent upon *cis*-B/C-fusion. The lone-pair orbitals on O(5) and O(7) point towards each other and provide a complexing site in which the 12-carbonyl group or a 12α-hydroxyl group may also play a part. The availability of such a site may prove of interest in connection with the inhibition of respiration in mitochondria and inhibition of NADH dehydrogenase by rotenone or its 12β-dihydro-derivative.[8] The solid-state conformation arrived at approximates closely to that proposed from spectral study of rotenone and the rotenolones in solution;[2,3,4d] the absolute configurations at 6a, 12a, and 5′ are confirmed.[1]

We thank the S.R.C. for support.

(*Received*, 18*th August* 1975; *Com.* 948.)

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† We thank Mr. G. Kilbee for preparation of 8′-bromorotenone (from amorphigenin).

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[4] *Inter alia*, (a) C. Djerassi, W. D. Ollis, and R. S. Russell, *J. Chem. Soc.*, 1961, 1448; (b) L. Crombie and R. Peace, *ibid.*, p. 5445; (c) L. Crombie and D. A. Whiting, *ibid.*, 1963, 1569; (d) W. D. Ollis, C. A. Rhodes, and I. O. Sutherland, *Tetrahedron*, 1967, **23**, 4741; (e) D. Adinarayana, R. V. M. Campbell, L. Crombie, M. Radhakrishniah, and J. Rajasekhara Rao, *J. Chem. Soc.* (*C*), 1971, 29.

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