Synthesis of Novel Labile Rotenoids with Unnatural *trans*-B/C Ring Systems

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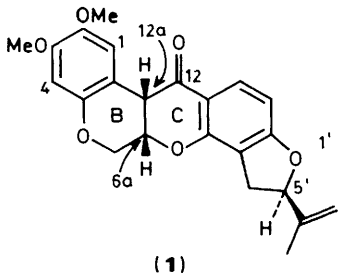
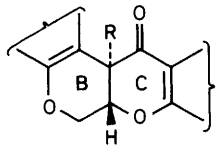
6a,12a-Dehydrorotenoids are cleanly reduced in 1,4-fashion by DIBAL to give rotenoids having the unstable, unnatural, *trans*-B/C fusion, readily epimerised by acid to the *cis*-forms: an *X*-ray structure for (±)-*trans*-isorotenone confirms the nature of the ring fusion.

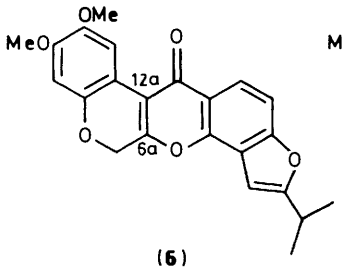
Rotenone (**1**) inhibits the electron transport chain, and its use as an insecticide and fish-poison is well established. It, and all other known natural rotenoids, have been isolated in the thermodynamically stable *cis*-B/C fusion.[1] Except for 12a-hydroxy derivatives (rotenolones) (**2**)[2] and 12a-methyl-isorotenone (**3**)[3] in which enolisation is blocked, the unstable *trans*-forms of the natural or synthetic enolisable rotenoids have remained unknown for more than 50 years.[4] We now report a general method for making 12a-enolisable rotenoids having the *trans*-B/C fusion, which arose from work designed to improve existing synthetic methodology.



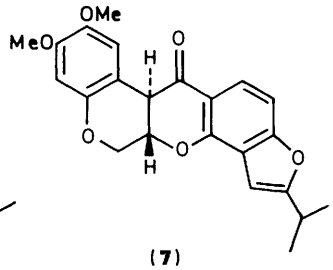
(**1**)



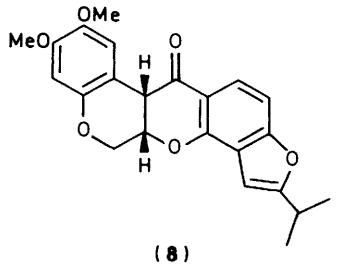
(**2**) R = OH
(**3**) R = Me
(**4**) R = OMe
(**5**) R = H



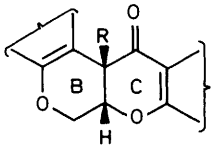
(**6**)



(**7**)



(**8**)

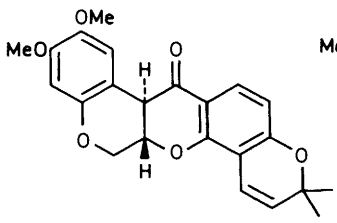


(**9**) R = OH
(**10**) R = OMe
(**11**) R = H

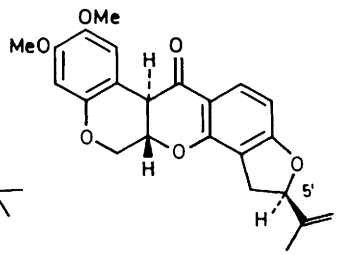
A number of synthetic procedures for rotenoids converge on a 6a,12a-dehydro precursor [*cf.* (**6**)]. A standard procedure[5] is then reduction with sodium borohydride which not only effects 1,4-reduction but further 1,2-reduction of the resulting carbonyl giving a 12-hydroxy derivative. This must then be carefully re-oxidised (Oppenauer oxidation[5] or oxidants such as manganese dioxide or chromium trioxide with avoidance of the ready over-oxidation to the 6a,12a-dehydro level). In attempting to achieve a clean 1,4-reduction we studied a number of reagents for the direct conversion of 6a,12a-dehydroisorotenone (**6**) into (±)-isorotenone and found that di-isobutylaluminium hydride (DIBAL) in toluene—THF (−78—20 °C)[6] was extremely successful in this respect. The product, m.p. 160—163 °C, was however not the same as (±)-*cis*-isorotenone (**8**), m.p. 162—163 °C, since there was a marked depression on mixed m.p. and the substances were chromatographically distinct [silica, eluting with hexane–ethyl acetate (7:3)].

In our earlier work on rotenolones, isorotenolones and their methyl ethers[7] we showed that 1-H of the dimethoxylated ring-A of the *trans*-B/C series, *e.g.* (**2**) and (**4**), was deshielded [δ($CDCl_3$) 7.6—8.0], being approximately in plane with the 12-carbonyl. On the other hand, in the *cis*-series, *e.g.* (**9**) and (**10**), the 1-H lies near the nodal shielding surface [δ($CDCl_3$) 6.4—6.8]. These large shifts provide a simple diagnostic tool.[7] Whereas in (±)-*cis*-isorotenone (**8**) 1-H resonated at δ([$^2H_6$]acetone) 6.71, in the new isomer from DIBAL reduction it had δ([$^2H_6$]acetone) 7.64 and clearly belonged to the (±)-*trans*-B/C series (**7**). Treatment with a little acid readily epimerised it giving the *cis*-isomer (**8**). (±)-*trans*-Isorotenone (**7**) is stable in the crystalline state and is moderately stable to chromatography on silica from hexane–ethyl acetate, though it is readily epimerised in chloroform (noticeable after a few minutes, depending on its acidity). In a similar way we have also made (±)-*trans*-deguelin (**12**), m.p. 161—164 °C.

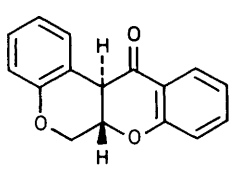
6a,12a-Dehydrorotenone retains a chiral centre at C-5′ [*cf.* (**1**)] and reduction with DIBAL gave a pair of diastereoisomeric *trans*-rotenoids, 6a*R*,12a*S*,5′*R* and 6a*S*,12a*R*,5′*R*. These were



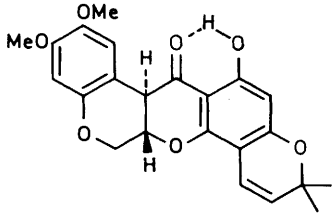
(**12**)



(**13**)



(**14**)



(**15**)

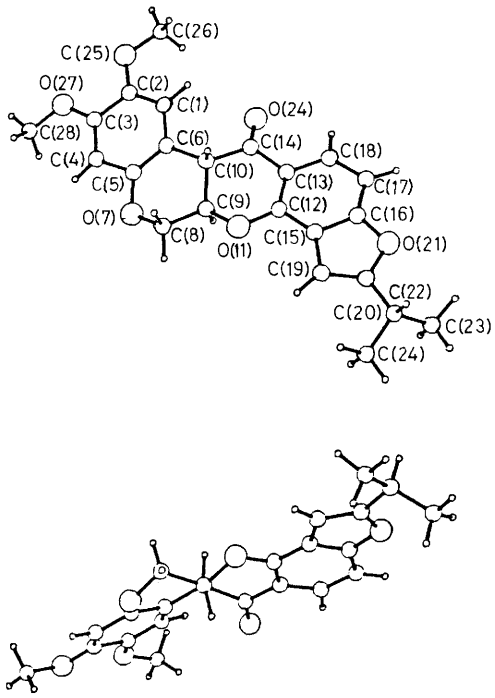


Figure. The *X*-ray structure of (±)-*trans*-isorotenone with crystallographic numbering

partially separated by chromatography on silica eluting with hexane–ethyl acetate (4:1), followed by purification by crystallisation from methanol, monitoring by h.p.l.c. The isomer having the longer column retention time proved to be the 6a*R*,12a*S*,5′*R* (**13**) since epimerisation at 6a (hydrogen chloride *in methanolic* chloroform)* gave rotenone identical with the natural 6a*S*,12a*S*,5′*R*-stereoisomer (**1**).†

By similar reduction methods we have also made the unsubstituted (±)-*trans*-'rotenoid core' (**14**) from the corresponding dehydro compound,[9] though it was much more easily epimerised in chloroform or acetone than the 2,3-dimethoxyl derivatives above. As an example of the natural 11-hydroxy rotenoid group we have converted 6a,12a-dehydrotoxicarol into (±)-*trans*-toxicarol (**15**), m.p. 169—171 °C, by DIBAL reduction. This too was more easily epimerised to the natural *cis*-fusion than its deguelin (**12**) or isorotenone (**7**) counterparts, and the ease of epimerisation may be ascribed to the facilitation of 12a-enolisation through hydrogen bonding to the 12-carbonyl.

A single crystal *X*-ray structure of (±)-*trans*-isorotenone has been undertaken to ascertain details of the molecular shape, the structure being refined to a final *R*-value of 3.84%.‡ The flattened B/C-structure (see Figure) may be contrasted with the bent, ridge-tile like, structure caused by the *cis*-fusion in our earlier[10] *X*-ray structure of 6′-bromorotenone.

* Acid epimerises 6a- *via* enolisation: base racemises 6a- and 12a-*via* β-elimination.[8]

† The 6a*R*,12a*R*,5′*R*-stereoisomer is separable from (**1**) by h.p.l.c.

‡ Crystal data for compound (**7**). Triclinic, a = 4.651(1), b = 9.325(1), c = 22.721(2) Å, α = 100.72(1), β = 91.73(1), γ = 100.36(1), U = 950.43 Å^3, Z = 2, D_c = 1.38 g cm^{-3}. 1 991 Observed reflections on CAD4 diffractometer. Final R value 3.84%. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See ' Instructions for Authors (1989),' *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

Experimental

(±)-trans-*Isorotenone* (**7**).—DIBAL in toluene (1.0M; 0.67 ml) was added to 6a,12a-dehydroisorotenone (100 mg) in dry THF (5 ml) at −78 °C, and stirred (1 h) under nitrogen. After the mixture had been warmed to room temperature methanol (2 ml) was added to it and the whole stirred (30 min). It was then poured into 1M hydrochloric acid (5 ml) and quickly extracted with dichloromethane, the extracts being washed with an aqueous suspension of calcium carbonate and brine. The extract was dried ($MgSO_4$) and evaporated and the residue was flash chromatographed on silica [elution, hexane–ethyl acetate (4:1)] and recrystallised from chloroform–methanol to give needles (32 mg, 32%), m.p. 160—163 °C (Found: C, 70.05; H, 5.73%; M^+, 394.1407. $C_{23}H_{22}O_6$ requires C, 70.04; H, 5.62%; M^+, 394.1416); $\lambda_{max.}$(EtOH) 202, 241, and 286 nm (ε 13 150, 13 600, and 2 500); $\nu_{max.}$(KBr) 1 691 (C=O) and 1 620 and 1 595 cm^{-1} (Ar); δ([$^2H_6$]acetone) 1.37 (6 H, d, *J* 6.9 Hz, 7′- and 8′-Me), 3.14 (1 H, dsp, *J* 6.9 and 0.7 Hz, 6′-H), 3.79 (3 H, s, OMe), 3.81 (3 H, s, OMe), 4.24 (1 H, d, *J* 12.7 Hz, 12a-H), 4.31 (1 H, dd, *J* 10.1 and 10.1 Hz, 6-H_a) 4.62 (1 H, dd, *J* 9.8 and 4.2 Hz, 6-H_b), 4.88 (1 H, ddd, *J* 12.8, 10.5, 4.1 Hz, 6a-H), 6.48 (1 H, s, 4-H), 6.65 (1 H, s, 4′-H), 7.24 (1 H, d, *J* 8.7 Hz, 10-H), 7.64 (1 H, s, 1-H) and 7.81 (1 H, d, *J* 8.7, 11-H). δ_C([$^2H_6$]acetone) 21.1 (CH_3, C-7, C-8), 28.9 (CH, C-6′), 46.9 (CH, C-12a), 56.0 (CH_3, 3-OMe), 56.9 (CH_3, 2-OMe), 67.4 (CH_2, C-6), 76.0 (CH, C-6a), 98.3, (CH, C-4′), 101.7 (CH, C-4), 106.6 (CH, C-10), 108.0 (C, C-12b), 115.7 (CH, C-1), 117.6 (C, C-8), 119.0 (C, C-11a), 123.7 (CH, C-11), 144.5 (C, C-2), 149.5 (C, C-4a), 150.9 (C, C-3), 155.2 (C, C-7a), 160.2 (C, C-9), 166.5 (C, C-5′), and 190.2 (C, C-12).

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