Hydrobenzofuranoid–Bicyclo[3.2.1]octanoid Neolignan Rearrangement

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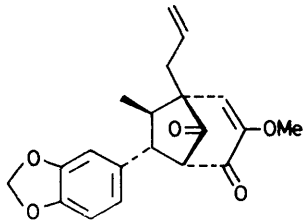
Summary The acid catalysed rearrangement of hydrobenzofuranoid neolignans into bicyclo[3.2.1]octanoid compounds is described; this rearrangement which, according to a literature report, can also take place in the opposite direction, seems to be governed by stereochemical factors.

IN a recent communication on biomimetic syntheses of neolignans, Büchi and Mak[1] attributed the isomerization of the bicyclo[3.2.1]octanoid (**1**) to the hydrobenzofuranoid (**2**) to the more extensive electronic delocalization of the latter. Since we have observed this reaction to occur in the opposite sense in substrates of different stereochemistry, we believe steric interactions to be additional factors in the stability of such systems.



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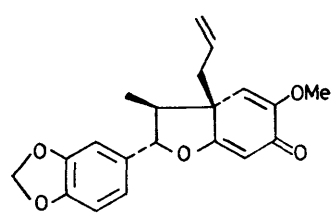

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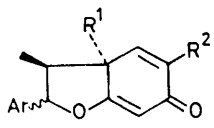
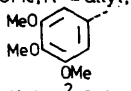
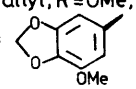
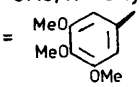
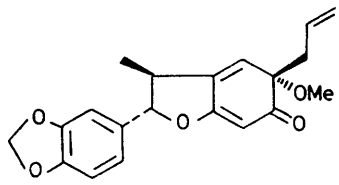


(3) R^1 = OMe, R^2 = allyl, Ar = 

(4) R^1 = allyl, R^2 = OMe, Ar = 

(5) R^1 = OMe, R^2 = allyl, Ar = 



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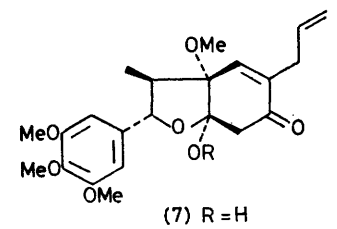

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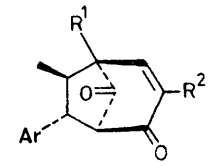
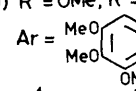
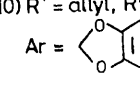
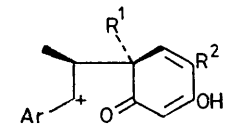
(8) R = Me



(9) R^1 = OMe, R^2 = allyl, Ar = 

(10) R^1 = allyl, R^2 = OMe, Ar = 



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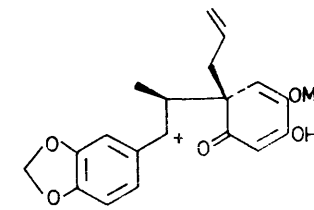

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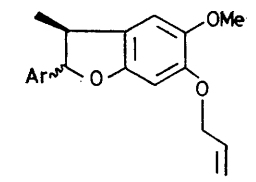
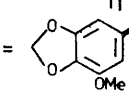
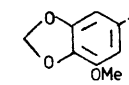


(13) Ar = 

(14) Ar = 

In a small scale experiment, monitored by t.l.c., burchellin (**2**), as was expected, was stable to toluene-*p*-sulphonic acid in acetonitrile at room temperature for at least 1 h, conditions which caused considerable transformation of the other hydrobenzofuranoids (**3**) and (**4**) within 30 min. When treatment with acid, on a preparative scale, was extended to 6 h, (**2**) still did not yield a bicyclo-octanoid and besides starting material only (**6**)[2] was isolated. Mirandin-A (**3**)[3] in methanol containing *p*-$MeC_6H_4SO_3H.H_2O$ at room temperature isomerized to (**5**)[3] (32%), viscous oil, i.r. (film) 1672 and 1629 cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 0·52 (d, 3H, *J* 7 Hz), and added elements of water and methanol leading to the products (**7**) (18%), m.p. 173—175 °C, i.r. (KBr) 3480 and 1665 cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 1·06 (d, 3H, *J* 7 Hz), and (**8**) (31%), m.p. 98—100 °C, i.r. (KBr) 1675 cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 1·02 (d, 3H, *J* 7 Hz). Relevant features of the ^1H n.m.r. data of (**7**) and (**8**) are comparable with those for piperenone[4] and thus they should possess the same relative stereochemistry. At reflux temperature, however, the reaction gave the bicyclo-octanoid (**9**) (76%), m.p. 141—143 °C, i.r. (KBr) 1757 and 1667 cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 1·10 (d, 3H, *J* 7 Hz) and 5·0—5·3 (m, 2H), ^{13}C n.m.r. ($CDCl_3$) δ 202·2 (s), 194·3 (s) 118·0 (t), and 13·8 (q) p.p.m. This compound is stable to toluene-*p*-sulphonic acid in acetonitrile at room temperature for at least 100 h. The analogous transformation of (**4**) (*p*-$MeC_6H_4SO_3H$, MeOH) into (**10**)[5] (40%) proceeded at room temperature.† Compounds (**9**) and (**10**) gave nearly superimposable o.r.d. curves, and (**9**) should

† Consistent analytical and spectral data were obtained for all new compounds.

thus, in spite of the vigorous conditions required for its formation, possess the indicated stereochemistry.

The preferential directions of these rearrangements thus seem to be determined by the relative configuration of the tetrasubstituted sp^3-C atom and 'burchellins' [*e.g.* (**2**), (**3**), and (**4**)] are not generally more stable than 'guianins' [*e.g.* (**1**), (**9**), and (**10**)] as was proposed.[1] Inspection of models of the intermediate benzylic ions shows that in the case of (**11**) cyclization to the hydrobenzofuranoid (**2**) should be favoured, since of the two alternative bicyclo-octanoids, (**1**) carries the aryl group in the sterically crowded *endo* arrangement and the other has three adjacent *cis* substituents on a cyclopentane. However, in the case of (**12**) cyclization may also lead to bicyclo-octanoids, such as (**9**) and (**10**), which have *exo* aryl groups and all-*trans* substitution on the cyclopentane. In the absence of a driving force causing the formation of bicyclo-octanoids, acid catalyses the rearrangement of *cis* into *trans* 2,3-dihydro-benzofuran systems, *e.g.* the rearrangement of (**13**), a thermal rearrangement product of (**4**), into (**14**).[6]

As hydrobenzofuranoid neolignans are relatively abundant natural products of known absolute configuration,[7] these rearrangements provide a semi-synthetic entry into, and a method for stereochemical studies in, the bicyclo-[3.2.1] octanoid neolignan series.

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