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ON THE QUESTION OF DISTINGUISHING BETWEEN 2,6- and 2,4-DIARYL-3,7-DIOXABICYCLO[3,3,0] OCTANES

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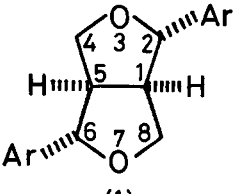
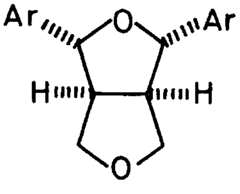
Some lignans of the 2,6-diaryl-3,7-dioxabicyclo[3,3,0]octane series (1) such as pinoresinol (1b) and eudesmin (1c) have been thoroughly characterised.[1] It is however very difficult, without extensive degradation studies, to determine whether in any particular compound the aryl groups are attached at the 2,6- positions, or at the 2,4- positions, as in (2). Indeed the latter were the structures first suggested for these lignans and are biogenetically acceptable. Many compounds have been assigned to the 2,6- diaryl series by analogy, without direct proof, and latterly some natural products with interesting physiological properties have been assigned to the 2,4- series.[2,3] One of these claims has recently been withdrawn[4] following our criticism of the evidence presented.[5] We are not certain that any known natural products can be represented as derivatives of (2). The problem, as with lignans and flavanolignans bearing a benzo-1,4-dioxan ring,[6,7] is that the two oxygen atoms of the central bicyclic nucleus insulate the two sides of the molecule from each other, and spectroscopic data such as ^{1}H, ^{13}C n.m.r. spectra and mass spectra can as readily be interpreted on the basis of (1) as (2).



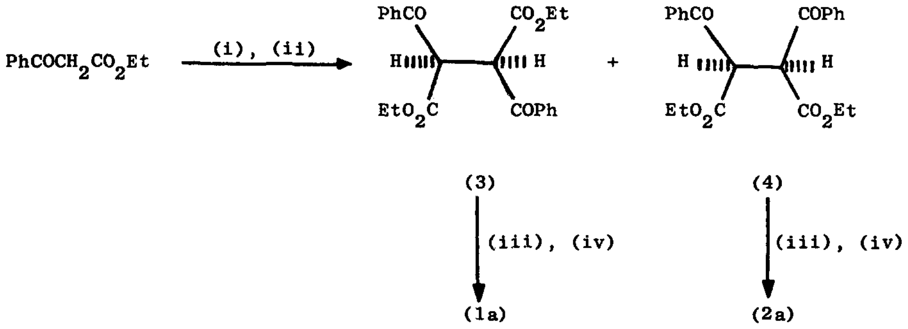
(1)

(a) Ar = phenyl
(b) Ar = 4-hydroxy-3-methoxyphenyl
(c) Ar = 3,4-dimethoxyphenyl
(d) Ar = 4-benzyloxy-3-methoxyphenyl
(e) Ar = 3,4-methylenedioxyphenyl



(2)

Russian workers[8] have previously synthesised the parent compounds (1a) and (2a) as shown in the scheme, and assigned structures to their products on the basis of hydrogenation experiments. We have repeated this sequence in a modified form (details will be given in a full paper) and obtain from the coupling reaction two crystalline solids m.p.125-7° and 74-8°C shown in the event to be (3) and (4). From these, two isomeric compounds (1a) and (2a) were produced by LAH reduction followed by acid treatment and these compounds had mass spectra containing many similar peaks, though of different intensities, and were clearly diaryl-3,7-dioxabicyclo[3,3,0] octanes. The lignan derived from the keto-ester m.p.125-7° had ^{1}H and ^{13}C n.m.r. spectra extremely similar to those of 2,6-diaryl lignans of proven structure and was accordingly assigned structure (1a), in agreement with the previous assignments.[8]



(i) NaH; (ii) I_2; (iii) LAH; (iv) H_3O^+

SCHEME

The product derived from the keto-ester m.p. 74-8° was recrystallised from toluene and subjected to X-ray examination.

Crystal data $C_{18}H_{18}O_2$ M_r = 266.25. Monoclinic, $P2_1$. a = 5.32 (2), b = 8.62 (2), c = 15.79 (3) Å, β = 92.80 (5)° from diffractometer measurements (Mo K$\bar{\alpha}$ radiation). V = 723.8 Å^3, Z = 2, D_c = 1.22 g cm^{-3}, F(000) = 284, μ = 0.43 cm^{-1}.

Data were collected for 0-5 kl with θ_{max} = 25° on a Stoe STADI-2 2-circle diffractometer (graphite monochromated Mo K$\bar{\alpha}$ radiation). This gave 1218 data of which 681 unique reflexions with I> 3σ(I) were used in subsequent calculations. Lorentz and polarization corrections (but none for extinction or absorption) were applied, and the data scaled by a Wilson plot. The structure was solved by direct phasing methods with the SHELX-76 system of crystallographic programs,[9] which was used for all calculations. Complex neutral atomic scattering factors were taken from International Tables for X-ray Crystallography (1974).[10] Weighted full-matrix least squares refinement (including isotropic hydrogen atoms) converged at R = 0.042 for 681 observed reflexions ($R = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$); R_w = 0.035 ($R_w = \Sigma(||F_o| - |F_c||.w^{\frac{1}{2}}) / \Sigma(|F_o|.w^{\frac{1}{2}})$, $w = 2.19/(\sigma^2(F_o) + .00012\,F_o^2)$. In the final cycle all shifts in parameters were less than their standard deviations.*

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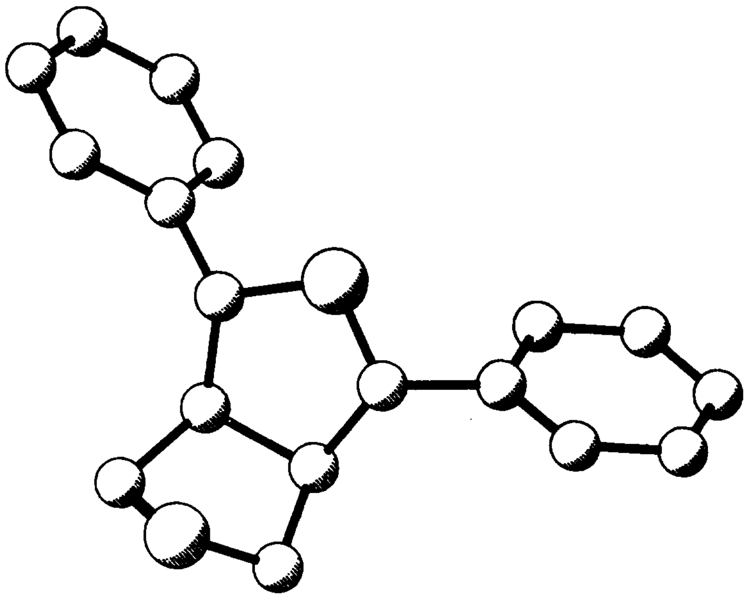
* The atomic coordinates are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this paper.



FIGURE

The structure found is shown in the figure and establishes (4) as the precursor of 2,4-di(eq)phenyl-3,7-dioxabicyclo[3,3,0]octane(2a). The differences in the spectral properties of (1a) and (2a) can then be used as the basis for differentiation of the two series.

We have also carried through a similar sequence to that shown in the Scheme to give (2d). A comparison of the ^{1}H n.m.r. spectra is shown in Table 1.

TABLE 1

Comparison of the ^{1}H n.m.r. spectra[*] of (1) and (2)

	(2a)	(2d)		(1a)	(1c)	(1d)	(1e)
H1/5	7.13m	7.07m	H1/5	6.96m	6.85m	6.88m	6.85-7.05m
H2/4	5.46d(8)	5.48d(7)	H2/6	5.22d(4)	5.25d(4)	5.24d(4)	5.29d(4)
H6e/8e	6.02d(8)	6.00d(9)	H4e/8e	5.77dd(9,7)	5.6-5.8m	5.76dd(9,7)	5.77dd(9,7)
H6a/8a	6.50dd(8,5)	6.43dd(9,5)	H4a/8a	6.11dd(9,3)	6.0-6.2m	6.1-6.3m	6.14dd(9,4)

[*] All spectra run in $CDCl_3$, TMS as internal standard, values given in τ

The appearance of the ^{1}H n.m.r. spectra of the two series (1) and (2) are self-consistent and are visually quite different. The signals due to the benzylic and methylene protons of (1) are all shifted upfield relative to (2) whilst those of the methine protons are shifted downfield. The coupling constants of the benzylic protons also vary in a reproducible fashion.

TABLE 2

Comparison of the ^{13}C n.m.r. spectra* of (1) and (2)

	(2a)	(2d)		(1a)	(1c)	(1d)†	(1e)
C1/5	55.44	55.06	C1/5	54.38	54.31	54.46	54.24
C2/4	87.15	86.95	C2/6	85.79	85.77	87.64ø	85.61
C6/8	71.53	71.57	C4/8	71.92	71.72	71.10	71.55

* All spectra run in CDCl$_3$, values given in p.p.m. from TMS

† Figures taken from the spectrum of the epi-isomer

ø Characteristic of *eq*-aryl group in *epi*-isomer[11]

The ^{13}C n.m.r. spectra (Table 2) also have clearly distinguishing features, these being most marked for the carbon atoms to which the aryl groups are attached. These carbon atoms are shifted upfield in (1) by *ca*. 1.2-1.3 p.p.m. whilst C-1/5 are also shifted upfield by 0.7-0.9 p.p.m.

We suggest that any lactols or lactones of this series whose structures are in dispute should be converted to the parent compounds (1) or (2) by reduction and cyclisation. Comparison of their ^{1}H and ^{13}C n.m.r. spectra with Tables 1 or 2 will then allow clear structure assignment.

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