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# STRUCTURE AND SYNTHESIS OF ARCHANGELIN. SPECTRAL METHODS FOR DISTINGUISHING BERGAPTYL FROM ISOBERGAPTYL ETHERS

R. B. Bates, D. J. Eckert, S. K. Paknikar, and V. P. Thalacker

Department of Chemistry, University of Arizona, Tucson, Arizona 85721, U.S.A.

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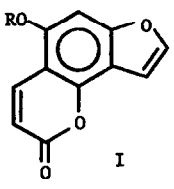
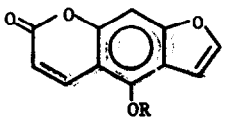
Structure Ic has been proposed for archangelin, a furocoumarin isolated from the root of the Indian medicinal plant *Angelica archangelica* L.[1] Close examination of its spectral properties, however, indicates that this structure is incorrect, and we wish to report evidence that the true structure is IId.



I



II

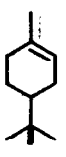
ROH III

RBr IV

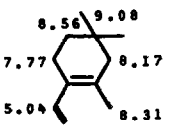
R=

*a*

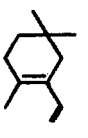
*b*



*c*

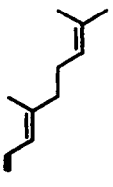



*d*



*e*

*f*



*g*

The NMR spectrum of archangelin (Fig. 1) shows no vinyl hydrogen absorption, ruling out partial structure *c*. The chemical shift assignments (τ) are shown on partial structure *d*; *e* is the only other part structure compatible with the NMR evidence. Structure *d* was favored over *e* on biogenetic grounds, as cyclolavandulol(IIId) is readily derivable from lavandulol (IIIf) *via* acid-catalyzed cyclization[2] (arrows around structure *f*), and the corresponding aldehyde[3] and acid[4] have been found in nature. Partial structure *d* was then verified by synthesis (see below).

A careful comparison of the spectral properties of archangelin with those of bergaptyl (II) and isobergaptyl(I) ethers[5] showed archangelin to be of the former type. In particular: (1) The proton attached to the benzene ring in archangelin absorbs in the NMR at τ 2.87; (2)

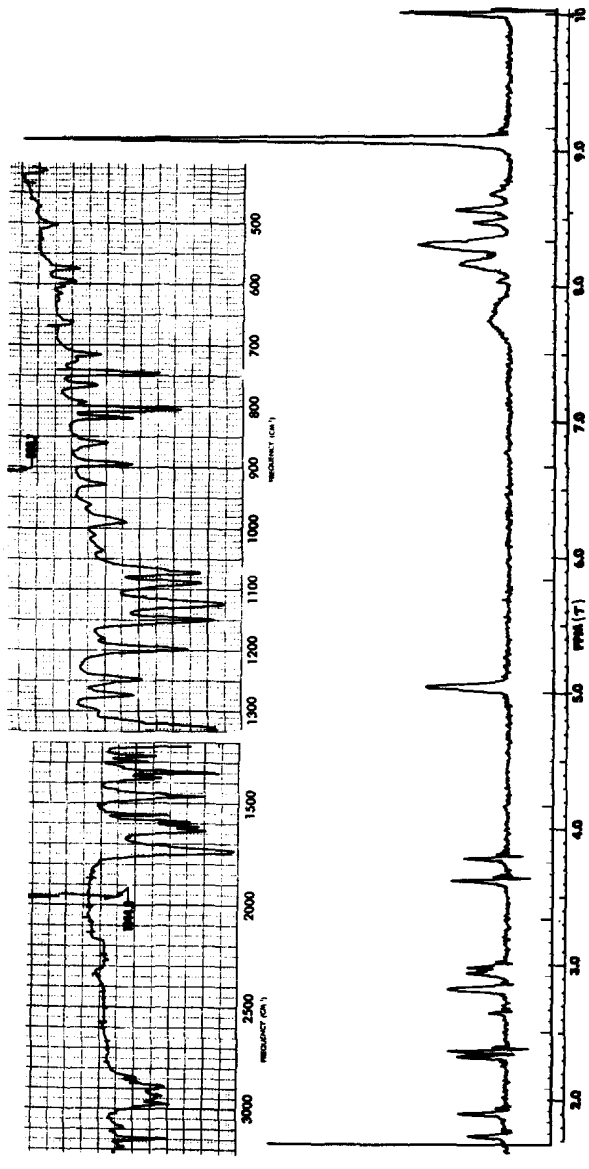



Fig. 1. 60 MHz NMR spectrum ($DCCl_3$, internal TMS standard) and IR spectrum (KBr) of archangelin (IId).

archangelin has IR peaks (Fig. 1) at 1725 (s), 1365 (m), 1199 (m), 1090 (m), 855 (w), 503 (w), but not at 1744, 1525, 1167, 1137, 628, 522, 480 or 426 $cm^{-1}$; (3) the UV spectrum of archangelin ($\lambda_{max}^{EtOH}$ 223, 250, 259, 268, 308 nm) includes a peak at 259 nm, and the ratio of peak heights at 250 and 268 nm is 1.13, not 1.47; (4) archangelin on a TLC plate sprayed with 30% $H_2SO_4$ and warmed gives a green spot, not a blue one.

Part structure I was originally assigned to archangelin(IId) on the basis of degradation to isobergaptol(Ia);[1] this was risky in view of the facile interconversion of isobergaptol(Ia) and bergaptol(IIa).[6] In distinguishing isobergaptyl(I) from bergaptyl(II) ethers, it seems much safer to use the spectral methods listed above; though none of these spectral differences is by itself convincing, taken collectively they should permit safe assignment of the direction of lactonization.

To help distinguish between part structures *d* and *e* and to make archangelin available, we synthesized IId. 2,6-Dimethyl-5-hepten-2-ol was prepared from methylheptenone in essentially quantitative yield by the method of Callen, Dornfeld and Coleman;[7] acidification with ammonium chloride solution avoided emulsion and dehydration. This alcohol was smoothly converted to a 60-40 mixture of 1,5,5- and 1,3,3-trimethylcyclohexenes[8] by fractional distillation from an equimolar amount of oxalic acid at atmospheric pressure using a spinning band column; the oxalic acid, which catalyzes the conversion of isomeric hydrocarbons to these two low-boiling olefins, sublimed up the column but did not reach the receiver. This mixture was converted to a 60-40 mixture of 1-acetyl-2,4,4- and 6-acetyl-1,3,3-trimethylcyclohexenes,[9] which on refluxing for 4 hr with N,N-dimethylaniline gave the equilibrium mixture (85-15) of these ketones. Hypobromite oxidation and crystallization gave 1-carboxy-2,4,4-trimethylcyclohexene,[9] which on esterification with diazomethane followed by $LiAlH_4$ reduction gave IIId in nearly quantitative yield. The alcohol IIId (0.1 mmol) in ether (5 ml) was converted to the corresponding bromide IVd (89% yield) by adding $PBr_3$ (10 mmol) at -75°, stirring at 25° for 5 hr, diluting with ether, washing with 2% KOH, drying over $MgSO_4$, and evaporating.[10]

Bergaptene(IIb) and bergamottin(IIg), both from bergamot oil,[11] were cleaved to bergaptol(IIa) with $MgI_2$[12] and acetic acid,[11] resp. Bergaptol(IIa, 0.53 mmol) was converted to its sodium salt by adding NaOMe (1.1 mmol) in MeOH (4.5 ml) at 70° under argon. The MeOH evaporated over 3 hr, and after DMF (22 ml) and the bromide IVd (0.53 mmol) were added at -78°, the mixture was heated for 16 hr at 90°. Ether and aqueous acid were added, and archangelin(IId, 51% from IIa) was obtained from the ether solution by evaporation and recrystallization from

MeOH. The only characterized (MS, NMR, IR, UV) by-product, obtained by TLC on the mother liquors, is apparently IId with an extra *d* grouping replacing the benzenoid hydrogen (6% from IIa); it may be formed by a *p*-Claisen rearrangement of IId followed by O-alkylation.

After showing the identity of the major product of this synthesis with archangelin by comparison of X-ray powder photographs, IR, UV, and NMR spectra, $R_f$ values on TLC, and by mixed mp, we conclude that archangelin is IId.

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## Footnotes and References

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