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THE $C_{10}H_{17}$ SIDE CHAIN IN MYCELIANAMIDE. THE STEREOCHEMISTRY OF BERGAMOTTIN AND UMBELLIPRENIN

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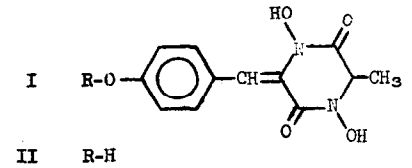
BIRCH and coworkers[1] have suggested structure Ia and/or b for mycelianamide, an antibiotic substance from Penicillium griseofulvum, and have recently investigated its biogenesis using tracer techniques.[2] The structure of the $C_{10}H_{17}$ side chain was based on sodium/NH_3/methanol reduction to 2,6-dimethyl-2,6-octadiene (IIa and/or b), the isolation of acetaldehyde on ozonolysis, and the non-identity of the infrared spectrum of a degradation product, p-myceloxybenzamide, postulated to be IIIa and/or b, with that of IIIc and/or d synthesized from geraniol (IVc) via geranyl bromide (Vc and/or d).[1] The discrepancy between the side chain structure a or b suggested for mycelianamide and the usual side chain structures formed from its demonstrated metabolic precursor--mevalonic acid--brought us to re-examine the structure of the mycelianamide side chain.

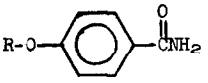
[1] A. J. Birch, R. A. Massy-Westropp, and R. W. Rickards, J. Chem. Soc., 3717 (1956).

[2] A. J. Birch, M. Kocor, N. Sheppard, and J. Winter, ibid., 1502 (1962).



I R-O

II R-H

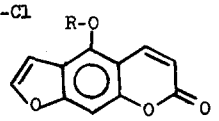


III R-O

IV R-OH

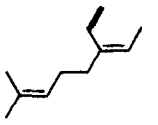
V R-Br

VI R-Cl

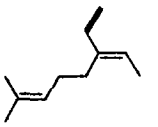


VII

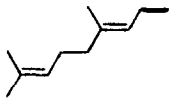
R is:



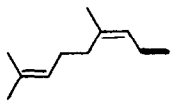
a



b



c



d

e $HOOCCH_2$—

The n.m.r. spectra of mycelianamide and p-myceloxybenzamide are not compatible with structures containing side chains of type a or b, and strongly suggest that the side chains are of type c or d. In particular, the absorptions for the methylenes next to oxygen appear as doublets (7 c/s) at 5.4 τ and there are three essentially unsplit methyl groups, at 8.27, 8.33, and 8.40 τ, as would be expected with groupings c or d.[3]

Further degradative experiments also favor a structure containing a grouping of type c or d. Ozonization of p-myceloxybenzamide (IIIc) with an oxidative workup yielded a mixture of acids, one of which had the formula

[3] R. B. Bates, R. H. Carnighan, R. O. Rakutis, and J. H. Schauble, Chem. and Ind., 1021 (1962).

$C_8H_9NO_4$ and was identified as 4-carbamoylphenoxyacetic acid (IIIe) by mixed m.p. (253-5°), paper chromatography, and infrared spectral comparison with a sample synthesized from p-hydroxybenzoic acid and sodium chloroacetate. Treatment of the mother liquors from the ozonization with DNP reagent gave levulinic acid DNP, identified by mixed m.p. and paper chromatography with a known sample.

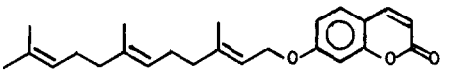
To further test the correctness of structure IIIc or d for p-myceloxybenzamide and to distinguish between these two structures, IIIc was stereospecifically synthesized from geraniol (IVc) via geranyl chloride (VIc), and IIId from nerol (IVd) via neryl chloride (VId).[4] There was some doubt that the chlorides would react stereospecifically with the sodium salt of p-hydroxybenzamide, but only one amide was detected in each case: IIIc, m.p. 118-122°, in 9% yield from IVc, and IIId, m.p. 117-119° (readily distinguishable from IIIc by mixed m.p. (96-103°) and n.m.r.), in 5% yield from IVd. It was later learned that much higher yields can be obtained in such reactions without loss of stereospecificity via the allylic bromides Vc and d: e.g., to 5 mmoles of nerol (IVd) in 25 ml. of ether at -78° was added 5 mmoles of PBr_3; after 6 hrs. at 30° the solution was washed with 5% aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and 50 ml. of DMF and 3.2 mmoles of the sodium salt of p-hydroxybenzamide were added; after removing the bulk of the ether (1 mm., 25°) and stirring for 15 hrs. at 25°, 2.1 mmoles (42%) of IIId, m.p. 117-119°, was isolated. p-Myceloxybenzamide (m.p. 117-119°, mixed m.p. with IIIc, undepressed, and with IIId, 96-103°; n.m.r. identical to that

[4] R. B. Bates, D. M. Gale, B. J. Gruner, and P. P. Nicholas, ibid., 1907 (1961).

of IIIc) was clearly shown to be p-geranoxybenzamide (IIIc) by comparison with these synthetic samples.

Thus, if the previously proposed[1] structure for the heterocyclic ring in mycelianamide is correct, this antibiotic is Ic.

In another application of the above stereospecific synthesis of allyl aryl ethers, umbelliprenin[5,6] was shown to be VIII, the trans-trans-farnesyl ether of umbelliferone, since trans-trans-farnesol gave umbelliprenin in 9% yield (chloride method) whereas none was obtained from cis-trans-farnesol.



VII

No bergamottin[6,7] (VIIc or d) was isolated by the reaction of geranyl chloride or bromide with the sodium salt of bergaptol; a degradative method for determining the stereochemistry of allyl aryl ethers of this type was then developed. In a model reaction, IIId was reduced with Na/NH_3/methanol to IId in 58% yield (no IIc was detected by V.P.C.), and when bergamottin gave IIc in 38% yield with no IId observed (V.P.C.) in the product, it was clear that these reductions go stereospecifically,[8] and that bergamottin is VIIc, the geranyl ether of bergaptol.[9]

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[5] E. Späth and F. Vierhapper, Ber., 71B, 1667 (1938).

[6] Low-yield syntheses of umbelliprenin[5] and bergamottin (A. Chatterjee and B. Chaudhury, J. Chem. Soc., 2246 (1961)) have been reported previously, but neither served to show the configuration of the side chain double bond nearest to the aromatic ring.

[7] E. Späth and P. Kainrath, Ber., 70B, 2272 (1937).

[8] K. W. Greenlee and V. G. Wiley (J. Org. Chem., 27, 2304 (1962)) have shown that alcohols like geraniol are cleaved stereospecifically under these reduction conditions, but this had not been demonstrated previously for aryl ethers of alcohols like geraniol.

[9] This research was supported in part by a grant (GM-07689) from the U.S. Public Health Service.