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THE STRUCTURE OF THE MARINE BENZOFURAN, FUROVENTALENE, A NON-FARNESYL SESQUITERPENE[1]

CHEMISTRY OF COELENTERATES. XIV.[2]

Alfred J. Weinheimer and Paul H. Washecheck

Department of Chemistry, The University of Oklahoma, Norman, Oklahoma 73069

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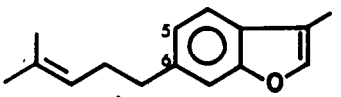
A new liquid C_{15} benzofuran, furvoventalene, Ia, possessing an isoprenoid but nonfarnesyl skeleton has been isolated from the steam volatile material of the sea fan, Gorgonia ventalina, collected at Bermuda. Although the steam distillation step was essential to the successful isolation of this compound, it is not now known whether this is due to its formation (possibly by thermal or solvolytic elimination from a larger molecule) during the prolonged exposure to hot water, or simply to its very low concentration in the gorgonian (0.012%, dry weight). Unlike other gorgonians which contain significant quantities of sesquiterpene hydrocarbons (3), the sea fan is almost devoid of this group.

The nature of the substituents of the benzofuran (M^+ 214; λ_{max} 249, 282, 287 nm, ε 16,000, 4200, 6200; $[\alpha]_D$ 0°) (4) could be deduced from its nmr spectrum. The three benzenoid protons appearing at δ6.98, 7.25 and 7.29 displayed coupling constants (8.0 and 1.2, 1.2 and 0.6, 8.0 and 0.6 Hz) indicative of a 1,2,4 relationship. The downfield chemical shift of a well-defined one proton quartet at δ7.13 (J=1.1 Hz) uniquely characterized the proton at position 2 which was coupled (nmdr) with the doublet methyl, δ1.97 (J=1.1 Hz), at position 3. The side chain containing the remaining six carbon atoms, and situated at either position 5 or 6, was assigned the 4-methylpent-3-enyl structure on the basis of the coupling (nmdr) of the lone vinyl proton, δ5.19 (triplet with fine splitting), with the two vinyl methyl doublets at δ1.50 (J=0.7 Hz) and δ1.64 (J=1.0 Hz), and with the allylic methylene at δ2.30. The allylic methylene comprised the B_2 portion of an A_2B_2 X system involving the benzylic methylene absorbing at δ2.51.

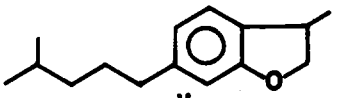
These assignments were corroborated by the presence of the exceptionally intense ion $ArCH_2^+$

(m/e 145) in the mass spectrum of Ia arising from fragmentation at the doubly activated (benzylic, allylic) position, and by the nmr spectrum of tetrahydrofuroventalene, II, which contained signals due to only three protons in the aromatic region and a simple triplet at δ2.51 (J=7 Hz) for the benzylic methylene. Further, the three methyl signals appeared as doublets due to vicinal coupling (J=6 and 6.5 Hz), and the two protons at position 2 absorbed as double doublets at δ4.61 (J=7.5, 8.5 Hz) and 4.00 (J=7.0, 7.5 Hz), their multiplicity attributable to geminal coupling as well as vicinal coupling with the proton at C_3 which appeared at δ3.44 as a broad multiplet.

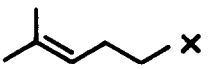
Since Black and Hefferman (5) had demonstrated a solvent dependence of both chemical shift and coupling constant for the benzenoid protons of benzofuran itself, a similar study of furoventalene was undertaken in an attempt to decide between positions 5 and 6 for the side chain. However, the conclusions based on the variation of these properties were in direct conflict, the chemical shift data suggesting 6-substitution, and the J data, 5-substitution. Thus resort was made to synthesis of both possibilities.



Ia
(Ib = 5-isomer)



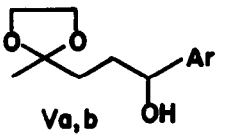
II



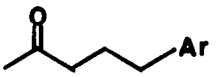
III

Ar Br

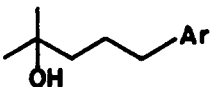
IVa,b



Va,b

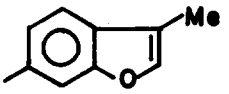


VIa,b

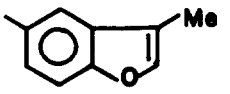


VII a,b

Series a: Ar =



Series b: Ar =

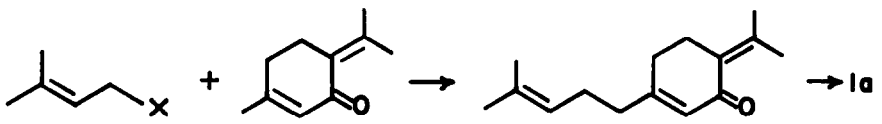


Direct coupling of the homallylic bromide or tosylate, III, with organometallic derivatives of 5-bromo-3-methylbenzofuran, IVb, prepared by PPA cyclodehydration of p-bromophenoxyacetone, failed to form detectable quantities of Ib due to preferential elimination to form the conjugated methyl pentadiene. In an alternative approach, the Grignard reagent from IVb was condensed with levulinaldehyde ethylene ketal, followed by Pd/C hydrogenolysis of the resulting benzyl alcohol, Vb, which occurred with concurrent ketal hydrolysis, forming the ketone VIb. Condensation of this ketone with methyl magnesium iodide and subsequent dehydration of the tertiary alcohol, VIIb, with $POCl_3$/pyr led to a mixture consisting of tricyclic alkylation product, the terminal olefin and the desired internal olefin, Ib, which was readily isolated by chromatography on $AgNO_3$-impregnated silica gel. Although the nmr spectrum of Ib contained all the features of that of furoventalene, chemical shifts were slightly different, and its non-identity with Ia was clearly evident from the ir spectrum.

Synthesis of the alternate isomer was modeled after the preceding method, and employed IVa as the starting material. This was formed as the minor product of PPA ring closure of m-bromophenoxyacetone and was readily distinguished from the major product, 4-bromo-3-methylbenzofuran, by the substitution pattern evident from the aromatic region of the nmr spectrum (H_7:δ7.38, J_m= 1.6, J_p=0.5 Hz; H_5:δ7.10, J_o=8.2, J_m=1.6 Hz; H_4:δ6.84, J_o=8.2, J_p=o.5 Hz), and the deshielding of the 3-methyl signal of the 4-isomer, δ2.14, relative to that of IVa, δ1.86. Grignard condensation led to Va which underwent hydrogenation of the furan ring at a rate comparable with hydrogenolysis of the benzyl alcohol, leading ultimately to 2,3-dihydro-VIa which was dehydrogenated over Pd/C at 170° to VIa. Analogous formation of the tertiary alcohol VIIa and dehydration led again to a mixture from which the desired 3-methyl-6-(4'-methylpent-3'-enyl) benzofuran, Ia, was readily isolated. Its nmr and ir spectra were identical in all respects to those of furoventalene.

Neither a possible skeletal rearrangement during isolation nor biogenetic methyl migrations appear readily to accommodate the structure of furoventalene to a farnesyl precursor. Indeed, its carbon skeleton is nicely isoprenoid and can be regarded as arising from the union of the tails of two isoprene units with the head of a third. A chemically reasonable biosynthetic scheme might involve dimethylallylation of a suitable monoterpenoid intermediate, e.g., piperitenone, at the gamma position, followed by furan development and aromatization, Similar alkylations have been postulated to account for two other abnormal isoprenoid sesquiterpene skeletons

(6). Furan ring closure from the unsaturated ketone precursor, initially postulated by Reitsema (7), has been demonstrated by Battaile and Loomis (8) in the piperitenone-pulegone-menthofuran sequence in peppermint species.



piperitenone

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