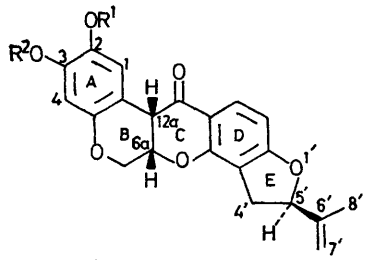
Reaction of Rotenone with Boron Tribromide. Stereospecific ^{2}H-Labelling of (−)-Rotenonic Acid in the 4′(*E*)-Methyl Group

By DAVID CARSON, LESLIE CROMBIE,* and DONALD A. WHITING

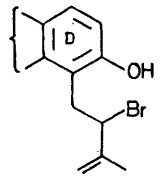
(*Department of Chemistry, The University of Nottingham, Nottingham* NG7 2RD)

Summary Structural revisions are made to products formed when (−)-rotenone is treated with boron tribromide; stereospecific labelling of the 4′ (*E*) methyl of (−)-rotenonic acid, a biosynthetic precursor of rotenone, can be achieved by treating product (**4**) with cyanoborodeuteride in hexamethylphosphorotriamide.

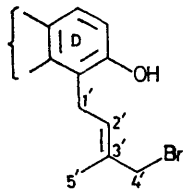
IT has recently been reported that reaction of natural (6a*S*,12a*S*,5′*R*)-(−)-rotenone (**1**) with 1 mol. equiv. of BBr_3 gives the 1′,5′-*seco*-bromide (**2**), whilst with 2 mol. equiv. of BBr_3 gives (**3**).[1,2] Treatment of (**2**) with HCO_3^- provides the only method available for making (5′*S*)-rotenone, which is formed along with the (5′*R*)-diastereoisomer. However, structures (**2**) and (**3**) appeared at



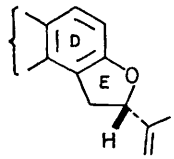
(I) $R^1 = R^2 = Me$
(II) $R^1 = Me$, $R^2 = H$
(12) $R^1 = H$, $R^2 = Me$



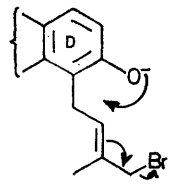
(2) $R^1 = R^2 = Me$
(3) $R^1 = Me$, $R^2 = H$



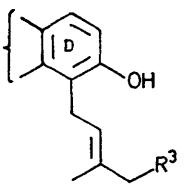
(4) $R^1 = R^2 = Me$
(5) $R^1 = H$, $R^2 = Me$



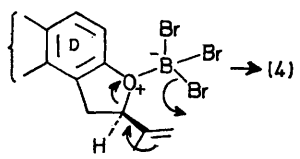
(6) $R^1 = R^2 = Me$



(7)



(8) $R^1 = R^2 = Me$, $R^3 = H$
(9) $R^1 = R^2 = Me$, $R^3 = D$



(10)

variance with the n.m.r. data given[1] and the problem was re-examined. Treatment of rotenone with 1 mol. equiv. of BBr_3 in CH_2Cl_2 for 2 min at −5 to −10 °C gave the 1′,5′-*seco*-bromide, m.p. 152—154 °C, which showed, along with other expected resonances, δ 3·35 (2H, d, 1′-H), 5·58 (1H, t, 2′-vinyl), and 3·87 (2H, s, 4′-CH_2) in the ^1H n.m.r. spectrum. In the ^{13}C n.m.r. spectrum there were resonances at δ 41·8 (t, C-4′), 22·3 (t, C-1′), and 14·7 (q, C-5′); the olefinic carbons resonated at 127·2(2′) and 132·4(3′) p.p.m. The compound is thus (**4**) and the cyclisation is an S_N2' type (**7**); similar cases are known.[4]

Compound (**4**) has provided a means by which (−)-rotenonic acid (**8**) can be stereospecifically labelled in one of the pair of 4′- and 5′-methyls; since (**8**) is a precursor of rotenone,[5] this affords a tool for studying the stereochemistry of formation of the isopropenylated ring E. The 4′- and 5′-methyls of (−)-rotenonic acid are readily distinguished by ^{13}C n.m.r. spectroscopy, the 4′ (*E*)- group resonating at δ 25·8, and the 5′ (*Z*)- group at 17·8 p.p.m.[6] Treatment of (**4**) with sodium cyanoborohydride in hexamethylphosphorotriamide (HMPT) effected displacement of the 4′-halogen without reduction of the 12-carbonyl giving rotenonic acid, m.p. and mixed m.p. 206 °C. Using cyanoborodeuteride, a single deuterium was introduced giving (**9**), M^+ 397, m.p. 206—207 °C. That the replacement involves the 4′ (*E*) carbon, is shown by collapse of the carbon resonance at 25·7 towards a triplet form in the off-resonance spectrum, the resonance at 17·83 p.p.m. being unaffected. The geometry of the bromo-compound is thus (**4**) and the deuterio-compound is (**9**), making the 4′-(*E*) tritiated compound potentially available. The BBr_3 reaction involving ring E may be represented as in (**10**).

The product formed when (−)-rotenone is treated with 2 mol. equiv. of BBr_3 requires further revision. It is reported, on slender n.m.r. spectroscopic evidence, that the second mol equiv. of reagent demethylates the 3-methoxy-group giving (**3**), and then (**11**) on cyclisation.[2,3] The 1-proton in rotenone (**1**) resonates at δ 6·68 and the 4-proton at 6·41. Acetylation of monodemethylated 5′-(*R*)-rotenone formed on HCO_3^- treatment of the bromo-compound shifts the 1-proton from 6·78 to 6·89 leaving the 4-proton little changed in position (6·40 → 6·43). Similarly, when the acetate is 6a,12a-dehydrogenated, the 1-proton resonates at δ 8·52 and the 4-proton at 6·51 (corresponding values for 6a,12a-dehydrorotenone are 8·41 and 6·49). Structural revision of (**11**) to (**12**) and (**3**) to (**5**) is thus indicated. It also appears that monodemethylated rotenone formed as a metabolite,[2] or photochemically,[3] requires similar structural revision as regards ring A.

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[6] L. Crombie, G. Kilbee, and D. A. Whiting, *J.C.S. Perkin I*, 1975, 1497.