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TRACER STUDIES ON THE MECHANISM OF THE DIENONE-PHENOL REARRANGEMENT

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After confirming the structure of the rearranged product of $\Delta^{1,4}$-cholestadien-3-one on treatment with acetic anhydride containing a few drops of sulphuric acid to be the 1-hydroxy-4-methyl compound [1,2], Woodward and Singh[3] suggested two plausible mechanisms for the rearrangement. In both of these mechanisms the initial positions of the methyl group and oxygen atom on ring A were maintained and rearrangement was envisaged as occurring via a direct 1,3 shift of C-9 to C-4(path A), or via a succession of 1,2 shifts through a possible spiran intermediate centered at C-5(path B). Later, evidence was presented by Woodward[4] to support path B from the fact that the optically active dienone(I) rearranged to give the racemic phenol(III) through a symmetrical spiran intermediate(II). Bloom presented further evidence to support path B; first[5], 6,10-dimethyl-$\Delta^{1,4}$-hexadien-3-one(IV) rearranged to give mainly 1,6-dimethyl-4-hydroxytetralin(V), the formation of which could be possibly interpreted by a spiran intermediate formation centered at C-5, followed by a subsequent shift of "more substituted" C-6 to C-4; second[6], the cyclohexadienone fused to a five-membered ring(VI) rearranged to give only m-phenol(VII) because of the difficulty of forming a spiran intermediate of a four-membered ring.

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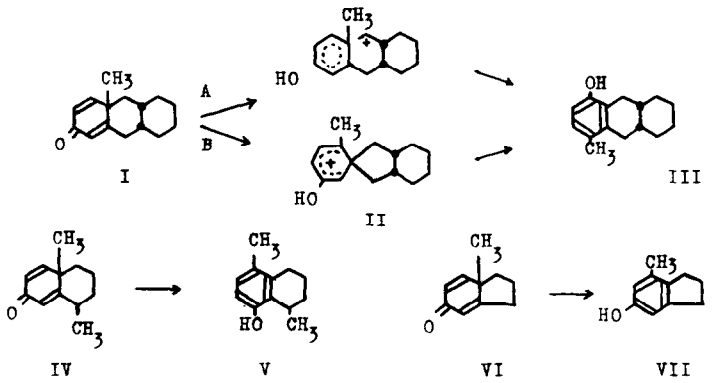
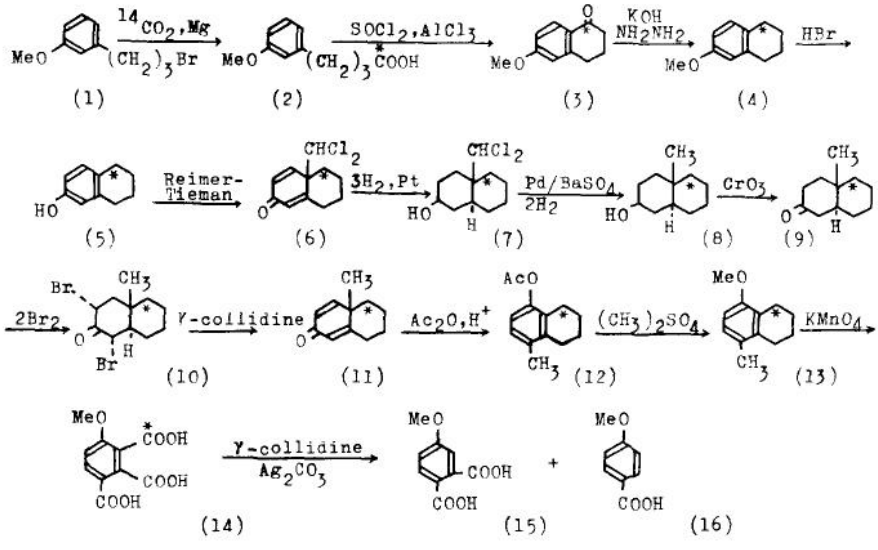


However, the above evidence appears to lack the necessary complementing experiments. Thus for Woodward's case, if the optically active trans-fused dienone(I) were used in contrast to the cis, the rearranged phenol should be active; for Bloom's case, 1-hydroxy-4,6-dimethyltetralin should also be isolated as a minor product to prove the existence of the spiran intermediate. Moreover, if a cyclohexadienone fused to a seven-membered ring were used, it might give rise to a p-phenol.

Actually there are many cases reported to give m-phenol or "abnormal" p-phenol under the above anhydrous acidic conditions.[7,---15] It is obvious from these facts that the dienone systems rearrange to various types of phenol via different pathways determined by subtle structural features. Moreover, it is well known that both of $\Delta^{1,4}$-cholestadien-3-one and 10-methyl-$\Delta^{1,4}$-hexadien-3-one rearrange to afford mainly m-phenol, accompanied by a small amount of p-phenol.[16]

Now the author confines his study of the mechanism of the dienone-phenol rearrangement in the case of the most simple 10-methyl-$\Delta^{1,4}$-hexadien-3-one on treatment with acetic anhydride-sulphuric acid. The above dienone[9-^{14}C] was synthesised by the reactions outlined below.

The important structural feature of this dienone is the symmetry of the spiran intermediate, similar to Woodward's dienone(I). Hence, the dienone [9-^{14}C] would give only 1-hydroxy-4-methyltetralin [9-^{14}C] if it rearranged via path A, whilst it would give an equimolecular mixture of both of the tetralin [9-^{14}C] and [6-^{14}C] if it rearranged via path B.



Synthesis The dibromide(1) was obtained after six steps starting with m-methoxycinnamic acid. The Grignard reaction of the "tracer run" was carried out with 1 mc of barium radiocarbonate. Cyclyzation of the acid(2) by the Friedel-Crafts method gave the cyclic ketone(3)[17], which was reduced to (4) by the Huang-Minlon modification of the Wolf-Kischner method. The methyl ether(4) was hydrolysed to β-tetralol(5) on treatment with boiling HBr-HOAc. It was converted further to trans-10-methyl-3-decalone(9) by the reactions as indicated above (5)----(9), which were presented by Woodward.[18] Dibromination of (9) with bromine in glacial acetic acid gave the dibromide(10), long needles, m.p.121-123°(from petr. ether)(lit[19] 121.5-123°). The dibromide, reported earlier to give the $\Delta^{4,6}$-

dienone on treatment with hot γ-collidine[19], gave mainly the desired $\Delta^{1,4}$-dienone(11) as a faint yellow oil(yields,75%), accompanied by a small amount of the $\Delta^{4,6}$-dienone. The cause of the difference from the earlier results depends solely on the quality of the γ-collidine used. Details of that will be reported elsewhere.

Rearrangement The crude dienone(400mg) was worked up as described by Woodward[3] to afford colourless plates of the phenol acetate(12) (330mg),m.p.78-81°(lit.[3]81°). The acetate was directly methylated with excess dimethyl sulphate in methanolic potassium hydroxide, followed by steam-distillation to give long needles of the methyl ether(13), m.p.43-44; (lit.[20] 43-43.5°).

Degradation The methyl ether(13)(1.02g) was oxidised with potassium permanganate(9.2g) at 74-76°, first in aqueous suspension, then in acidic conditions. The acid obtained by ethyl acetate extraction crystallised from acetone-petr.ether in white cubes of 4-methoxybenzen-1,2,3-tricarboxylic acid(14)(470mg), m.p.215-216;(lit.[21] 215-216°). It(400mg) was heated with γ-collidine(2.2ml) and silver carbonate(230 mg) at 145-150° for an hour, and the reaction mixture was extracted with ether, from which were isolated 4-methoxyphthalic acid(15)(crude, 45mg),longneedles, m.p.168-170°,(from water)(lit.[22] 168-170°), and p-methoxybenzoic acid(16)(crude,23mg), needles, m.p.182-183°(from dilute methanol).

The products, (13), (14) and its trimethyl ester, (15) and its anhydride, and (16) were also identified respectively by independent synthesis.**

Results The distribution of the radioactivity is compiled in Table 1. It is obvious from the data that it is in good agreement with that predicted from path B within the ordinary range of isotope effect. Since,the phenol acetate(12) is equally labeled at C-6 and C-9 after the rearrangement through the spiran intermediate in which C-6 and C-9 are equivalent, the radioactivity of the dicarboxylic acid(15) would be precisely half of that of the tricarboxylic acid(14). The p-methoxybenzoic acid(16) would be inactive, as the carboxyl group is derived from the angular methyl group(not labeled) of the dienone (11). Whereas, via path A,(15) would also be inactive as shown in the sequence of the asterisked formulae,(11)---(16).

Table 1

Distribution of ^{14}C in products derived from 10-methyl-$\Delta^{1,4}$-hexadien-3-one [9-^{14}C] (11)

Compound	c.p.m. of the sample	$\times 10^2$ c.p.m./m mol
(13)	122.4 ± 1.5	46.06
(14)	93.9 ± 1.3	46.31
(15)	66.1 ± 1.1	24.20
(16)	none	none

The specific activities were determined on a low-background 2π gas-flow counter, with background 1.91 ± 0.18 c.p.m.. The radiochemical purities were determined by isotope dilution method. The samples were mounted on stainless-steel dishes(φ 2.5cm) prevented from creeping, with thickness 0.9mg/cm^2.* Also (13) was determined comparing with (14) to estimate the accuracy of the determination.

*cf. Calvin,"Isotopic Carbon", John Wiley & Sons, New York,1960,p.115

Recently, Capsi reported at the IUPAC Symposium(1964) held at Kyoto, Japan, that $\Delta^{1,4}$-androstadien-3,17-dione [4-^{14}C] rearranged to the ordinary 1-hydroxy-4-methyl compound, in which all of ^{14}C were located at C-10. This is a confirmation of the fact that ring migration occures but not methyl and oxygen migration during the rearrangement. However, this does not give a confirmative proof distinguishing between path A and B.

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** All temperatures are not corrected.

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