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23. Seigo Fukushima: Studies on Benzochromones. III.[1] The Mechanism of Novel Cyclization of 1-Methoxy-2-acetyl-3,4-diacetoxynaphthalene to 2-Methyl-5,6-dihydroxy-7,8-benzochromone.

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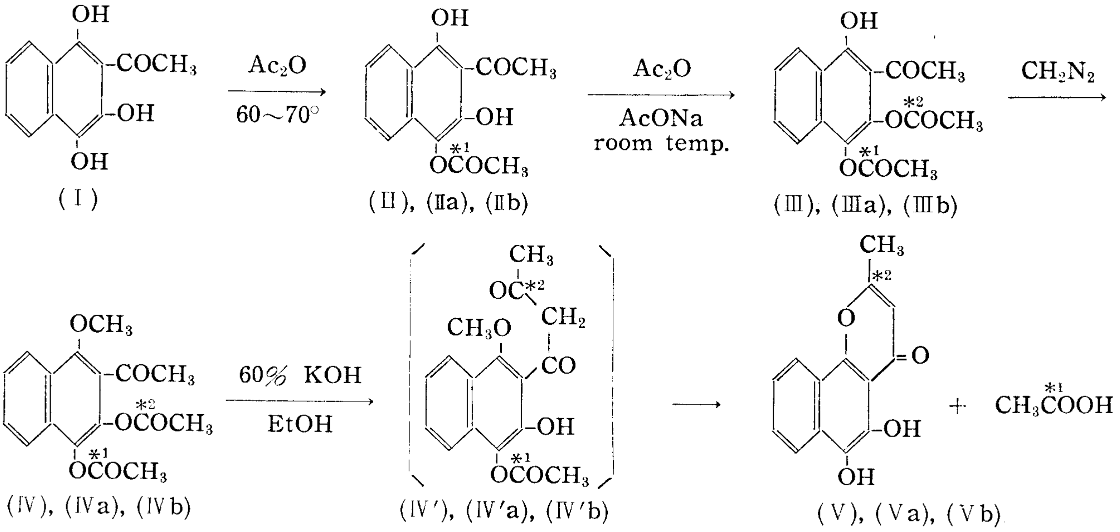
In the preceding paper,[2] it was reported that treatment of 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene (IV) with alcoholic potassium hydroxide gave 2-methyl-5,6-dihydroxy-7,8-benzochromone (V) and the mechanism of this novel cyclization was assumed as the rearrangement of acetyl from acetoxyl group in 3-position to the ω-carbon atom of methylketone group in 2-position, forming an intermediate (IV') followed by cyclization to form (V).

The present paper describes the result of the ^{14}C-tracer experiments which were carried out in order to confirm the above assumption.



In (II), (III), (IV), (IV') and (V) : *1=*2=inactive C
In (IIa), (IIIa), (IVa), (IV'a) and (Va) : *1=^{14}C; *2=inactive C
In (IIb), (IIIb), (IVb), (IV'b) and (Vb) : *1=inactive C; *2=^{14}C

1-Methoxy-2-acetyl-3-acetoxy-4-acetoxy[*carbonyl*-^{14}C]-naphthalene (IVa) and 1-methoxy-2-acetyl-3-acetoxy[*carbonyl*-^{14}C]-4-acetoxynaphthalene (IVb) were prepared through two steps of preferential acetylation followed by methylation, and each of them was respectively converted to 2-methyl-5,6-dihydroxy-7,8-benzochromone, (Va) and (Vb), in the same way as previously reported.[2]

The radioactivity of completely purified samples of (IVa), (IVb), (Va), and (Vb) was measured with Windowless-type, low-background 2π-Q-Gas Flow Counter and their specific activity (c.p.m./mM) is shown in Table I.

Table I.

Compd. No.	c.p.m./mM×10^{-3}	%	Compd. No.	c.p.m./mM×10^{-3}	%
(IVa)	12.5	100	(Ib)	14.1	100
(Va)	1.26	10	(IIb)	12.8	91

[*1] Tamagawa-Yoga-machi, Setagaya-ku, Tokyo (福島清吾).
1) Part II : This Bulletin, 8, 1036 (1960).
2) Part I : *Ibid.*, 8, 1028 (1960).

If the reaction in question exclusively followed the route of (IV)→(IV′)→(V), the radioactivity of (Va) would be nil and the specific activity of (Vb) would be equal to that of (IVb). However, actual values of specific activity of (Va) and (Vb) were 10% and 91% of (IVa) and (IVb), respectively.

The following explanations would be possible for such discrepancies : 1) Interchange of acetyl group takes place during the preferential acetylation process from 1,3-dihydroxy-2-acetyl-4-acetoxynaphthalene (II) to 2-acetyl-3,4-diacetoxy-1-naphthol (III). 2) Base-catalyzed interchange of acetyl groups between acetoxyl groups at 3- and 4-positions takes place prior to the rearrangement of acetyl group to form (IV′). 3) Intra- and/or intermolecular rearrangement of acetyl in acetoxyl group at 4-position to the ω-carbon atom of acetyl group at 2-position takes part in this reaction.

In reference to the second possibility, Schmid3) also assumed such a base-catalyzed interchange of benzoyl groups in Baker-Venkataraman transformation and actually proved the interchange by means of ^{14}C-tracer method.

In order to confirm such a possibility, the following experiments were carried out. A mixture of inactive 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene (IV) and radioactive acetic-[*carbonyl*-^{14}C] anhydride, and the same mixture with sodium acetate or pyridine, were placed under several different conditions, and the radioactivity of separated and purified samples of 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene was determined. The results of these experiments are shown in Table II.

TABLE II.

Expt. No.	1	2	3	4
Inactive (IV)	0.30 g.	0.20 g.	0.10 g.	0.10 g.
Acetic[*carbonyl*-^{14}C] anhydride (1.13×10^6 c.p.m./g.)	18.0 g.	8.0 g.	4.0 g.	4.0 g.
Addition	AcONa 18 mg.	——	Pyridine 1.0 g.	Pyridine 10 drops
Condition	Shaken for 6 hr. at room temp.	Boiled for 4 min.	Stood for 1.5 hr. at room temp.	Boiled for 4 min.
Total activity of Ac_2O used (c.p.m.)	2.04×10^7	9.04×10^6	4.52×10^6	4.52×10^6
Calcd. total activity of (IV) when 100% interchange of acetyl groups takes place (c.p.m.)	1.09×10^5	7.24×10^4	3.62×10^4	3.62×10^4
Found total activity of (IV) (c.p.m.)	Nil	Nil	225	1.72×10^3
Migration ratio of radioactivity (%)	0	0	0.6	4.8

As is evident from Table II, no migration of radioactivity is observed under the conditions of Expt. Nos. 1 and 2, which are equal to those in preferential acetylation of 1,3-dihydroxy-2-acetyl-4-acetoxynaphthalene (II) to 2-acetyl-1,4-diacetoxy-1-naphthol (III). This fact suggests that no interchange of acetyl groups takes place during preferential acetylation. The presence of pyridine, which is a kind of a base, provoked appreciable migration of radioactivity, especially when heated, as seen in Expt. Nos. 4 and 5. This seems to suggest indirectly the second possibility cited above.

In short, about nine-tenths of this reaction follows the route of (IV)→(IV′)→(V), but complicated intra- and/or inter-molecular rearrangement and mutual interchange of acetyl groups might take part partly in this reaction.

Experimental[*2]

1,3-Dihydroxy-2-acetyl-4-acetoxy[*carbonyl*-^{14}C]-naphthalene (IIa)—A mixture of 6 g. of 1,3,4-trihydroxy-2-acetylnaphthalene (I) and 45 g. of $(CH_3{}^{14}CO)_2O$ was warmed to 60~70° for several min.,

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[*2] All m.p.s of radioactive samples were not depressed by admixture with authentic samples of inactive compounds.

3) H. Schmid, *et al.* : Helv. Chim. Acta, **37**, 1706 (1954).

separated yellow needles were collected, and washed three times with a small amount of cold EtOH. It was recrystallized four times from EtOH to give 1.2 g. of 1,3-dihydroxy-2-acetyl-4-acetoxy[*carbonyl*-^{14}C]-naphthalene (IIa), m.p. 192∼193°.

2-Acetyl-3-acetoxy-4-acetoxy[*carbonyl*-^{14}C]-1-naphthol (IIIa)—A mixture of 0.4 g. of 1,3-dihydroxy-2-acetyl-4-acetoxy[*carbonyl*-^{14}C]-naphthalene, 16 g. of Ac$_2$O, and 12 mg. of AcONa was shaken mechanically for 2.5 hr. to result in clear solution. After the decomposition of excess Ac$_2$O, separated crystals were collected and recrystallized four times from EtOH to 0.13 g. of 2-acetyl-3-acetoxy-4-acetoxy[*carbonyl*-^{14}C]-1-naphthol (IIIa), m.p. 184°.

2-Acetyl-3-acetoxy[*carbonyl*-^{14}C]-4-acetoxy-1-naphthol (IIIb)—Starting with 1.0 g. of 1,3-dihydroxy-2-acetyl-4-acetoxynaphthalene (II), 40 g. of (CH$_3{}^{14}$CO)$_2$O, and 30 mg. of AcONa, 0.35 g. of 2-acetyl-3-acetoxy[*carbonyl*-^{14}C]-4-acetoxy-1-naphthol (IIIb), m.p. 184°, was obtained by the same method as above.

1-Methoxy-2-acetyl-3-acetoxy-4-acetoxy[*carbonyl*-^{14}C]-naphthalene (IVa)—To a suspension of 110 mg. of 2-acetyl-3-acetoxy-4-acetoxy[*carbonyl*-^{14}C]-1-naphthol (IIIa) in 10 cc. of dehyd. benzene and 0.2 cc. of MeOH, an Et$_2$O solution of CH$_2$N$_2$ prepared from 0.5 g. of N-methyl-N-nitrosourea was added. The reaction mixture, after standing for 3 hr., was evaporated in vacuum to an oil, which solidified on cooling and scratching. To this, 0.2 g. of inactive 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene (IV) was added and was recrystallized three times from EtOH to yield 188 mg. of 1-methoxy-2-acetyl-3-acetoxy-4-acetoxy[*carbonyl*-^{14}C]-naphthalene (IVa), m.p. 105∼106°.

1-Methoxy-2-acetyl-3-acetoxy[*carbonyl*-^{14}C]-4-acetoxynaphthalene (IVb)—To a suspension of 122 mg. of 2-acetyl-3-acetoxy[*carbonyl*-^{14}C]-4-acetoxy-1-naphthol (IIIb) in 10 cc. of dehyd. benzene and 0.2 cc. of MeOH, Et$_2$O solution of CH$_2$N$_2$ prepared from 0.5 g. of N-methyl-N-nitrosourea was added, the mixture was treated by the same procedures as above, and 210 mg. of 1-methoxy-2-acetyl-3-acetoxy-[*carbonyl*-^{14}C]-4-acetoxynaphthalene (IVb), m.p. 105∼106°, was obtained.

2-Methyl-5,6-dihydroxy-7,8-benzochromone (Va)—To a solution of 136 mg. of 1-methoxy-2-acetyl-3-acetoxy-4-acetoxy[*carbonyl*-^{14}C]-naphthalene (IVa) in 2 cc. of EtOH, 0.2 cc. of 60% KOH was added in N$_2$ flush, the reaction mixture was allowed to stand for 4 min. in N$_2$ atmosphere, and acidified with AcOH. Separated yellow needles were collected, washed with a small amount of cold EtOH, and recrystallized three times from EtOH to 30 mg. of (Va), m.p. 224∼225°.

2-Methyl-5,6-dihydroxy-7,8-benzochromone (Vb)—To a solution of 162 mg. of 1-methoxy-2-acetyl-3-acetoxy[*carbonyl*-^{14}C]-4-acetoxynaphthalene (IVb) in 2.4 cc. of EtOH, 0.24 cc. of 60% KOH was added in N$_2$ atmosphere, the mixture was treated by the same procedures as above, and 35 mg. of (Vb), m.p. 224∼225°, was obtained.

Migration Test for Radioactivity—All the mixture of (CH$_3{}^{14}$CO)$_2$O and (IV) listed in Table II were treated with H$_2$O to decompose excess Ac$_2$O, separated crystals were collected, washed thoroughly with H$_2$O, and recrystallized three times from EtOH.

Analysis of Radioactivity—The derivative to be examined was ground in an agate mortar to a fine powder and weighed into a stainless counting dish, 25 mm. in diameter. A small amount of petr. benzine was added to disperse the sample as uniformly as possible and it was dried. Radioactivity was measured with ALOKA LBC-1 type low-background 2π-Q-Gas Flow Counter.
Correction of self absorption[4] was carried out as follows : In each case, the activity of a series of samples of varying weight was measured and the data were plotted on semi-logarithmic graph (ordinate, c.p.m./mg; abscissa, weight of sample). The approximately straight line obtained was extrapolated to the axis of ordinate. The extrapolated value was regarded as the count per minute per milligram (c.p.m./mg.) without self-absorption.

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Summary

The mechanism of novel cyclization of 1-methoxy-2-acetyl-1,3-diacetoxynaphthalene (IV) to 2-methyl-5,6-dihydroxy-7,8-benzochromone (V) was investigated with ^{14}C-tracer method and it was found that about 90% of the reaction followed the route of (IV)→(IV′)→(V).

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[4] Committee of Kagaku no Ryōiki : "Experimental Techniques of Isotopes," Vol. 1, Tracer Technique, 245 (1955). Nankōdō, Tokyo.