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63. Tsutomu Momose, Takuichi Miki,* and Kei Sawada : Studies on Quinols. III.¹⁾ Rearrangements of 2-Oxo-8,10-dihydroxy- $\Delta^{1,9}; 3,4$ -hexahydronaphthyl-7-acetic Acid Lactone.

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A few studies have been presented on the rearrangement of tetralin-quinol derivatives. In an earlier work of this series,²⁾ tetralin-quinol was rearranged to tetrahydronaphthohydroquinone diacetate and hyposantonyl-quinol to catechol derivative by acetic anhydride and sulfuric acid. Later, α -tetralol-quinol was found to undergo rearrangement to dihydronaphthohydroquinone with loss of water by dilute sulfuric acid.¹⁾ Miki³⁾ showed that 1,3-dibromotetralin-quinol was converted to 1,3-dibromo-2,8-diacetoxy-tetrahydronaphthalene by boiling with acetic anhydride and sodium acetate, and finally, Abe⁴⁾ obtained 1,3-dibromo-2-acetoxy-6-aceto-7,8-dihydronaphthalene by heating the same quinol with acetic anhydride and sulfuric acid. The mechanisms of these rearrangements were discussed by one of the authors.⁵⁾

The present paper describes the rearrangements of 2-oxo-8,10-dihydroxy- $\Delta^{1,9}; 3,4$ -hexahydronaphthyl-7-acetic acid lactone (I). When (I) was treated with dilute sulfuric acid, there were obtained two phenols of m.p. 191° and 220°, corresponding to $C_{12}H_{12}O_4$, in poor yields. The compound of m.p. 220° gave a diacetate of m.p. 187°, and was identified as 1,4,8-trihydroxytetrahydronaphthyl-7-acetic acid lactone (IV), which was synthesized by the method mentioned below. The compound of m.p. 191° was also a dihydric phenol, which was oxidized by air in alkaline solution and gave a diacetate of m.p. 127° by acetic anhydride and sulfuric acid.

When (I) was treated with acetic anhydride and one drop of sulfuric acid, there was obtained only a dihydric phenol diacetate of m.p. 127~128°, which was identical with the diacetate of the phenol, m.p. 191°. It was expected from earlier experiences that catechol rearrangement might occur, but the phenol gave only a pale yellow coloration with ferric chloride, and conversely gave a fluorescence reaction with phthalic anhydride and sulfuric acid, which was specific to *m*-dihydroxy derivatives. Therefore, it was concluded that the resorcinol rearrangement might have occurred instead of the catechol one, and the phenol might be 2,4,8-trihydroxytetrahydronaphthyl-7-acetic acid lactone (II), which was not synthesized successfully.

The ultraviolet absorption curve of the phenol acetate (III) was very similar to that of (V) in its shape and intensity (Fig. 1), but the free phenol showed only one maximum absorption at 235 $m\mu$, whereas (IV) had two maxima at 212 and 300 $m\mu$ (Fig. 2).

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1) Part II. Y. Asahina, T. Momose : J. Pharm. Soc. Japan, **64**, 153(1944).

2) Y. Asahina, T. Momose : Ber., **71**, 1421(1938).

3) K. Miki : J. Pharm. Soc. Japan, **61**, 272(1941).

4) Y. Abe : "Rearrangements of quinols," unpublished.

5) T. Miki : J. Japan. Chem., **7**, 468(1953).

Fig. 1. Ultraviolet Spectra of (III) and (V) in Ethanol

Fig. 2. Ultraviolet Spectra of (II) and (IV) in Ethanol

The above conclusion should be supported by the fact that toluquinol acetate underwent rearrangement to diacetylresorcinol by acetic anhydride and sulfuric acid, which was shown recently by Witkop and Goodwin.⁶⁾ They explained that acetate anion added to one of the double bonds by the Thiele reaction, and lost the acetoxyl group which existed from the beginning, forming resorcinol rearrangement.

Hydroquinone rearrangement of tetralin-quinol took place more easily by acetic anhydride and sulfuric acid, but in the case of the quinol (I), whose rearrangement was hindered by the steric factors or by the tension of the lactone ring, acetylation seems to have occurred first, resulting in a resorcinol rearrangement. Hydroquinone rearrangement of (I) by dilute sulfuric acid was also hindered and the resorcinol rearrangement took place simultaneously. The latter mechanism might be explained as an addition of water to the 3—4 double bond, resulting in aromatisation with a loss of water.

6) B. Witkop, S. Goodwin: *Experientia*, 8, 377(1952).

The synthesis of 1,4,8-trihydroxytetrahydronaphthyl-7-acetic acid lactone was carried out as follows. 1,4-Dimethoxytetralone-(8) was converted to sodium enolate by sodium amide, and condensed with ethyl bromoacetate. Saponification of the resulting substance gave crystals of m.p. 182~183° besides the desired 1,4-dimethoxy-8-oxotetrahydronaphthyl-7-acetic acid (VI), m.p. 139~140°. The compound of m.p. 182~183° was a dicarboxylic acid and gave an anhydride, m.p. 202°, on heating to about 200°, and a dihydric phenol, m.p. 238°, by demethylation. It was proved that two molecules of acetic acid combined to 7-position (VII) by the analytical data. (VI) was demethylated to a dihydric phenol (VIII), m.p. 179°, and reduced by sodium amalgam to a lactone (IV), m.p. 220~221°. This gave an acetate (V), m.p. 187°.

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Experimental

Rearrangement by Dilute Sulfuric Acid—0.5 g. of 2-oxo-8,10-dihydroxy-4^{1,9};3,4-hexahydronaphthyl-7-acetic acid lactone (I)¹⁾ was dissolved in 200 cc. of 5% H₂SO₄ and allowed to stand 10 days at room temperature. The solution was repeatedly extracted with ether, the combined ether extract was dried over anhyd. Na₂SO₄, and concentrated. The residue was dissolved in a small amount of EtOH, and the separated crystals (0.1 g.) were recrystallized from EtOH to plates, m.p. 191°. This phenol gave pale yellow color reaction with FeCl₃. When the phenol was heated to 130° for about 5 mins. with phthalic anhydride and H₂SO₄ and alkylized with NaOH, a yellow fluorescence appeared. *Anal.* Calcd. for C₁₂H₁₂O₄: C, 65.44; H, 5.49. Found: C, 65.20; H, 5.30.

The acetate was obtained from the phenol by Ac₂O and one drop of H₂SO₄. Recrystallization from EtOH gave prisms, m.p. 127°. *Anal.* Calcd. for C₁₆H₁₆O₆: C, 63.15; H, 5.30. Found: C, 63.27; H, 5.72.

From the mother liquor of the above phenol, other crystals (0.05 g.) appeared after several days. Recrystallization from water gave prisms, m.p. 220°, which showed no depression on admixture with 1,4,8-trihydroxytetrahydronaphthyl-7-acetic acid lactone.

The acetate, prepared from the phenol by Ac₂O and H₂SO₄, was recrystallized from EtOH to needles, m.p. 187°, and showed no depression of m.p. by admixture with 1,4-diacetoxy-8-hydroxytetrahydronaphthyl-7-acetic acid lactone.

Rearrangement by Acetic Anhydride and Sulfuric Acid—0.3 g. of the quinol (I) was dissolved in 3 cc. of Ac₂O and one drop of H₂SO₄ was added. Slightly exothermic reaction occurred. The reaction mixture was allowed to stand at room temperature over night, then shaken with 50 cc. of water until all of Ac₂O had been hydrolyzed, and extracted repeatedly with ether. The combined ether extract was washed with dilute NaHCO₃ solution and then dried over anhyd. Na₂SO₄. The residue after concentration of the ether solution was dissolved in EtOH, and the separated crystals (0.1 g.) were recrystallized from EtOH to prisms, m.p. 127~128°, which showed no depression of m.p. by admixture with the acetate prepared from the phenol of m.p. 191°.

1,4-Dimethoxy-8-oxotetrahydronaphthyl-7-acetic Acid (VI)—To a solution of 10 g. of 1,4-dimethoxytetralone-(8)⁷⁾ in 200 cc. of dehydrated benzene 2.3 g. of NaNH₂ was added, and refluxed 6 hrs. in H₂ atmosphere. The resulting suspension of sodium enolate of tetralone was cooled in an ice bath, and a solution of 10 g. of ethyl bromoacetate in 20 cc. of anhyd. benzene was added gradually. The mixture was refluxed for additional 3 hrs. and decomposed with dil. HCl. The separated benzene layer was distilled and the resinous residue was refluxed for 2 hrs. with 200 cc. of 10% aq. solution of NaOH. The alkaline solution was washed with benzene, acidified with HCl, and extracted with benzene. After removal of the solvent a small amount of MeOH was added, and the crystals (4 g.) that separated were recrystallized from MeOH to prisms, m.p. 139~140°. *Anal.* Calcd. for C₁₄H₁₆O₅: C, 63.62; H, 6.10. Found: C, 63.31; H, 5.96.

1,4-Dimethoxy-8-oxotetrahydronaphthyl-7,7-diacetic Acid (VII)—From the mother liquor of the above acid different crystals (2 g.) appeared. It was recrystallized from MeOH to prisms, m.p. 182~183°. *Anal.* Calcd. for C₁₆H₁₈O₇: C, 59.62; H, 5.63; COOH, 27.94. Found: C, 60.12; H, 5.60; COOH, 24.61.

The anhydride was obtained when the dicarboxylic acid was heated at about 200°. Recrystallization from EtOH gave prisms, m.p. 202°. *Anal.* Calcd. for C₁₆H₁₆O₆: C, 63.15; H, 5.30. Found: C,

7) T. Momose, H. Oya, Y. Ohkura, M. Iwasaki: This Bulletin, 2, 119 (1954).

63.11; H, 4.98.

Demethylation of the acid with 50% HI gave the phenol which was recrystallized from EtOH to prisms, m.p. 238°(decomp.). *Anal.* Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 56.67; H, 4.70.

1,4-Dihydroxy-8-oxotetrahydronaphthyl-7-acetic Acid (VIII)—3 g. of (VI) was refluxed with 10 g. of 50% HI for 15 mins. in CO_2 atmosphere, and then 50 cc. of water was added. Separated crystals (1.8 g.) were recrystallized from water to pale yellow prisms, m.p. 179°. *Anal.* Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.64; H, 5.03.

1,4,8-Trihydroxytetrahydronaphthyl-7-acetic Acid Lactone (IV)—To a solution of 1.5 g. of (VIII) in 50 cc. of 2% aq. solution of $NaHCO_3$, 20 g. of 3% sodium amalgam was added, and the mixture was stirred in CO_2 atmosphere for 12 hrs. The aq. layer was acidified with dil. HCl and separated crystals were recrystallized from EtOH to prisms, m.p. 220–221°. The compound gave yellow coloration with $FeCl_3$. *Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.43; H, 5.23.

The acetate (V) was prepared with Ac_2O and H_2SO_4 . Recrystallization from EtOH gave needles, m.p. 187°. *Anal.* Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.46; H, 5.24.

Summary

2-Oxo-8,10-dihydroxy- $\Delta^{1,9}$; 3,4 -hexahydronaphthyl-7-acetic acid lactone underwent rearrangement to 2,4,8- and 1,4,8-trihydroxytetrahydronaphthyl-7-acetic acid lactone by dilute sulfuric acid, and to 2,4-diacetoxy-8-hydroxytetrahydronaphthyl-7-acetic acid lactone by acetic anhydride and sulfuric acid. It was concluded that when hydroquinone rearrangement was hindered a resorcinol rearrangement might take place instead of catechol rearrangement. A synthesis of 1,4,8-trihydroxytetrahydronaphthyl-7-acetic acid lactone was also described.

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64. Izumi Imaseki: Phytochemical Investigation on Cultivation of Medicinal Plants. IX.¹⁾ On the Alkaloid Biogenesis in *Datura*. (2).

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In the previous communications^{1,2)} Shibata and Imaseki have shown by the grafting experiments that the alkaloids in *Datura* are formed principally in the root, though some possibility of alkaloid formation in the leaves cannot entirely be ruled out.^{3,4)} It was shown, moreover, that the ratio of the contents of hyoscyamine and scopolamine (hyoscine) in the root and aerial part of the plant varies during the growth.¹⁾ Almost simultaneously, a similar observation was given by Evans and Partridge.⁵⁾

In the present work ^{15}N -labelled ammonium sulfate was fed to *Datura tatula* L. to trace the rate of alkaloidal formation during a definite growing period, referring to the proportional contents of scopolamine and hyoscyamine in the leaves.

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1) Part VIII: S. Shibata, I. Imaseki: *J. Pharm. Soc. Japan*, **74**, 862(1954).

2) S. Shibata, I. Imaseki: *Ibid.*, **73**, 797(1953).

3) cf. Dawson: "Recent Advances in Enzymology," **8**, 203(1948); W. O. James: "The Alkaloids," Ed. Holmes and Manske, Academic Press, Vol. **1**, p. 15(1950).

4) References to the recent works on the problems of the site of *Datura* alkaloid formation were cited in the footnote to the paper published by B. T. Jackson and J. M. Rowson(*J. Pharm. Pharmacol.*, **5**, 778(1953)); W. C. Evans, M. W. Partridge: *Ibid.*, **6**, 702(1954).

5) W. C. Evans, M. W. Partridge: *Ibid.*, **5**, 772(1953).