

Notes

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Shojiro Uyeo, Hiroshi Irie, Uichiro Kitayama, Tokuyasu Hirose,
and Akira Yoshitake : Tazettine Chemistry. IX.*¹ Isomeric
Lactones Derived from 1-(2-Hydroxymethyl-4,5-methyl-
enedioxyphenyl)-4-hydroxycyclohexanecarboxylic Acid.

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We have reported previously¹⁾ the synthesis of 4'-hydroxy-6,7-methylenedioxy-isochroman-4-spiro-1'-cyclohexane which provided synthetic evidence for the spiro structure of tazettine. In the course of this investigation, we noted that chloromethylation of 4-hydroxy-1-(3,4-methylenedioxyphenyl)cyclohexanecarboxylic acid (I) or the corresponding lactone (II) afforded 1-(2-chloromethyl-4,5-methylenedioxyphenyl)-4-hydroxycyclohexanecarboxylic lactone (III) and a substance, m.p. 215~216°, which was not investigated further.

Hydrolysis of this chloromethyl compound (III) with aqueous sodium hydroxide followed by relactonization with acid gave a hydroxylactone, C₁₅H₁₆O₅, m.p. 156~157°, which was previously assigned the structure (IV) based on the assumption that by such treatment the compound (III) would have been transformed predominantly into IV rather than V. However we noticed later that the hydroxylactone, m.p. 156~157°, upon oxidation with chromic acid-pyridine complex gave a carbonyl compound, C₁₅H₁₄O₅, whose ultraviolet absorption spectrum, λ_{\max} 232 (ϵ 17400), 260 (ϵ 10000) and 341 m μ (ϵ 3570), and the infrared bands at 1727 and 1681 cm⁻¹ indicated that it must be an aromatic aldehyde possessing a six-membered lactone in the molecule and was therefore VI. The aldehyde-lactone reverted to the hydroxy-lactone, m.p. 156~157°, now formulated as V, on treatment with sodium borohydride.

In this connection, we found that the above mentioned substance m.p. 215~216°, now raised to 220~222°, was correctly represented by the formula (IV). It analyzed for C₁₅H₁₆O₅, and exhibited in the infrared spectrum a six-membered lactone band at 1723 cm⁻¹ and a hydroxy absorption at 3558 cm⁻¹, and was also characterized as its acetate (VII). Confirmative evidence was provided by its oxidation with chromic acid-pyridine complex, which gave the ketone (VIII), with the expected ultraviolet spectrum, maximum at 293 m μ (ϵ 4571) characteristic of an isolated methylenedioxybenzene ring, and infrared spectrum, $\nu_{C=O}$ 1704 cm⁻¹ (ketone) and 1730 cm⁻¹ (lactone). Further, the hydroxy-lactone, m.p. 220~222° gave on lithium aluminum hydride reduction the triol (IX) which was converted by acid catalyzed cyclization into the isochroman (X) identical with a sample previously prepared from the hydroxy-lactone, m.p. 156~157° (V) in a similar manner.

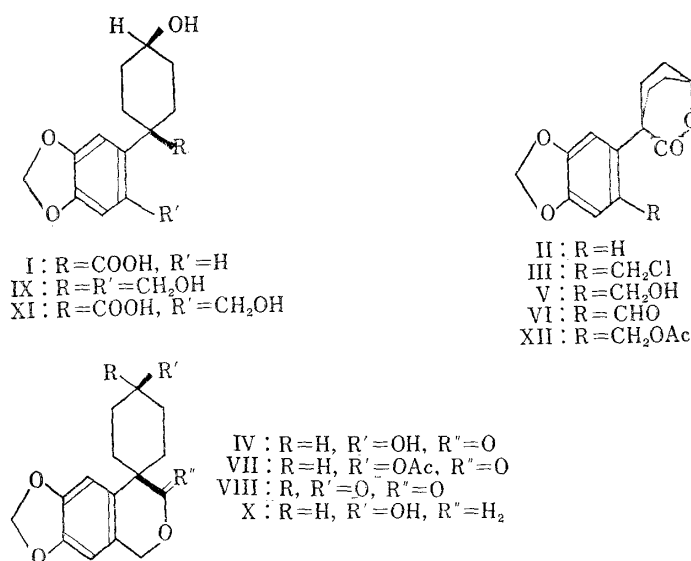
Since the structures of these isomeric hydroxy-lactones (IV and V) were thus esta-

*¹ The following papers are regarded as earlier parts of this series.

- a) T. Ikeda, W.I. Taylor, S. Uyeo : Chem. & Ind.(London), 1955, 1088.
- b) W.I. Taylor, S. Uyeo, H. Yajima : J. Chem. Soc., 1955, 2962.
- c) T. Ikeda, W.I. Taylor, Y. Tsuda, S. Uyeo : Chem. & Ind.(London), 1956, 411.
- d) T. Ikeda, W.I. Taylor, Y. Tsuda, S. Uyeo, H. Yajima : J. Chem. Soc., 1956, 4749.
- e) H. Irie, Y. Tsuda, S. Uyeo : *Ibid.*, 1959, 1446.
- f) Y. Tsuda, S. Uyeo : *Ibid.*, 1961, 1055.
- g) *Idem* : *Ibid.*, 1961, 2485.
- h) S. Uyeo, T. Hayazaki, H. Yajima : This Bulletin, 11, 1065 (1963).

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- 1) H. Irie, Y. Tsuda, S. Uyeo : J. Chem. Soc., 1959, 1446.



blished, we now attempted to transform one isomer into the other *via* a common intermediate, the dihydroxyacid (XI). We found, however, that for some reason not completely clarified the hydroxylactone (V) did not give on alkaline hydrolysis followed by relactonization any appreciable amount of the isomeric lactone (IV), and the starting material was recovered unchanged in a yield of more than 80%. From the combined mother liquors of crystallizations of the recovered starting lactone (V) a very small amount of the isomeric lactone (IV) was isolated after chromatography. The hydroxy-lactone (V), m.p. 220~222°, was recovered unchanged after the similar treatment.

Thus we found that against our expectation the isomeric hydroxylactones are not easily convertible into the each other *via* alkaline hydrolysis. The possibility that the lactones in these compounds are sterically hindered and were not hydrolyzed under the experimental conditions was eliminated by showing that nothing could be extracted from the alkaline solution. When the alkaline solution was nearly neutralized with hydrobromic acid, concentrated to dryness and a disk of the resulting crystalline mass of the salts in potassium bromide was submitted to the infrared spectrum analysis, no carbonyl band corresponding to the original lactone group was observed, but only a band at the expected position for a carboxylate ion.

On the other hand, treatment with hydrochloric acid in acetic acid transformed the compound (V) to the compound (IV), though the formation of the chloromethyl-lactone (III) as a by-product could not be avoided.

Experimental^{*3}

Chloromethylation of the Lactone (II)—a) The lactone (II) (0.5 g.) and paraformaldehyde (0.5 g.) in AcOH (10 ml.) and conc. HCl (10 ml.) were heated with stirring at 60~65° for 6 hr. After cooling, the mixture was diluted with H₂O (25 ml.), extracted with Et₂O, which was washed with aq. Na₂CO₃ and H₂O, dried and evaporated to dryness to give a brown oil (0.32 g.). This oil was chromatographed in benzene over acid-washed Al₂O₃, and the first benzene eluate gave an oil (50 mg.) which was not investigated further. The second eluate gave the chloromethyl-derivative (III) (150 mg.) m.p. and mixed m.p. 143~145°. Later fractions eluted with benzene-CHCl₃ (2:1) gave the hydroxy-lactone (IV) (12 mg.) which crystallized from Me₂CO-EtOH as needles m.p. 220~222°. IR ν_{\max} cm⁻¹: 3558 (OH), 1723 (six-membered ketone). *Anal.* Calcd. for C₁₅H₁₆O₅: C, 65.21; H, 5.84. Found: C, 65.28; H, 5.72.

b) A mixture of the lactone (II) (0.5 g.), paraformaldehyde (0.5 g.), ZnCl₂ (0.02 g.) and AcOH (20 ml.) was saturated with dry HCl, and heated at 60~63° for 10 hr. The mixture was concentrated to dryness

^{*3} UV spectra were determined for 95% EtOH solutions, and IR spectra were taken on Nujol mulls.

under reduced pressure and the residue taken up in Et₂O which was washed with aq. Na₂CO₃ and H₂O, dried and evaporated to dryness. The resulting yellow oil (0.6 g.) was chromatographed in CHCl₃ on silica gel. The first eluate in CHCl₃ gave the starting lactone (II) (56 mg.) m.p. and mixed m.p. 219~220°. The second eluate gave the chloromethyl-derivative (III) (0.16 g.) m.p. and mixed m.p. 143~145°. The third eluate gave the acetoxylactone (VII) (0.1 g.) which crystallized from EtOH as leaflets, m.p. 219~220°. IR: ν_{\max} 1728 cm⁻¹ (acetyl and six-membered lactone). *Anal.* Calcd. for C₁₇H₁₈O₆: C, 64.14; H, 5.70. Found: C, 64.11; H, 5.96. Further elution with CHCl₃-EtOH (10:1) gave the hydroxylactone (IV) (18 mg.) m.p. and mixed m.p. 220~222°. Acetylation of this hydroxy-lactone by refluxing in Ac₂O or by keeping at room temperature with Ac₂O and pyridine overnight gave an acetate, m.p. 219~220°, identical in all respects with the foregoing acetoxy-lactone, m.p. 219~220°.

4-Hydroxy-1-(2-formyl-4,5-methylenedioxyphenyl)-cyclohexanecarboxylic Lactone (VI)—The hydroxy-lactone (V) was prepared from the chloromethyl-derivative (III) in the similar way as reported previously¹⁾ and characterized as its acetyl derivative (XII) which formed prisms, m.p. 107~108° (from Et₂O). *Anal.* Calcd. for C₁₇H₁₈O₆: C, 64.14; H, 5.70. Found: C, 64.21; H, 5.83. The hydroxy-lactone (V) (40 mg.) was added to CrO₃ (40 mg.) in pyridine (0.5 ml.). The mixture was kept in a refrigerator overnight, diluted with H₂O and extracted with CHCl₃. The CHCl₃ extract was washed with dil. HCl, aq. Na₂CO₃ and H₂O, dried and evaporated to dryness to give the aldehydo-lactone (VI) (18 mg.) which crystallized from EtOH as prisms, m.p. 161~162°. IR ν_{\max} cm⁻¹: 1727 (six-membered lactone), 1681 (conjugated CO). UV λ_{\max} m μ (ϵ): 232 (17400), 260 (10000), 341 (3570). *Anal.* Calcd. for C₁₅H₁₄O₅: C, 65.69; H, 5.15. Found: C, 65.57; H, 5.19. The 2,4-dinitrophenyl hydrazone crystallized from EtOH as reddish yellow needles, m.p. 280~285°. *Anal.* Calcd. for C₂₁H₁₈N₄O₈: C, 55.51; H, 3.99. Found: C, 54.94; H, 3.93.

6,7-Methylenedioxy-3,4'-dioxoisochroman-4-spiro-1'-cyclohexane (VIII)—A mixture of the hydroxy-lactone (IV) (54 mg.) and CrO₃ (50 mg.) in pyridine (0.5 ml.) was left at room temperature overnight. Working up the mixture in the usual way gave the keto-lactone (VIII) which crystallized from benzene as prisms (23 mg.), m.p. 136~137°. IR ν_{\max} cm⁻¹: 1730 (six-membered lactone), 1704 (six-membered ketone). *Anal.* Calcd. for C₁₅H₁₄O₅: C, 65.69; H, 5.15. Found: C, 65.51; H, 5.31.

4'-Hydroxy-6,7-methylenedioxyisochroman-4-spiro-1'-cyclohexane (X) from the Hydroxy-Lactone (IV)—The hydroxy-lactone (IV) (25 mg.) and LiAlH₄ (0.1 g.) were heated under reflux in tetrahydrofuran (20 ml.) for 5 hr. The mixture was concentrated to a small volume, and after addition of a few drops of H₂O, acidified with 10% H₂SO₄ (30 ml.). The aqueous solution was heated on a water bath for 5 hr. and then extracted with Et₂O. The ethereal extracts were washed with aq. Na₂CO₃ and H₂O, dried and evaporated to dryness to give an oil (20 mg.) which was chromatographed in benzene over acid-washed Al₂O₃. Elution with benzene (10:1) gave the isochroman (X) (12 mg.) which crystallized from benzene as needles, m.p. 146~147°, undepressed on admixture with a sample prepared from the hydroxy-lactone (V) in the manner as reported previously.¹⁾ The infrared spectra of the two samples were also superimposable.

Treatment of the Hydroxy-Lactone (V) with Potassium Hydroxide—The hydroxy-lactone (V) (40 mg.) was heated in an aq. 10% solution (30 ml.) of KOH on a water bath for 5 hr. After cooling, the aqueous layer was washed with CHCl₃, acidified with dil. H₂SO₄, again heated on a water bath for 1 hr. and extracted with CHCl₃. The CHCl₃ extract was washed with aq. Na₂CO₃ and H₂O, dried and evaporated to dryness, to give a residue (34 mg.) which on crystallization from EtOH gave the starting hydroxy-lactone (V) (28 mg.) as prisms, m.p. and mixed m.p. 156~157°. The mother liquors from repeated runs were combined and evaporated to dryness and the resulting residue (24 mg.) was passed through a column of silica gel and the eluate fractionally crystallized from EtOH to give the sparingly soluble compound (IV) (2 mg.) and the more soluble starting lactone (V) (16 mg.).

Treatment of the Hydroxy-Lactone (V) with Hydrochloric Acid in Acetic Acid—The hydroxy-lactone (V) (50 mg.) in a mixture of AcOH (2 ml.) and conc. HCl (2 ml.) was heated on a water bath at 60~65° for 24 hr. The mixture was evaporated to dryness under reduced pressure and the resulting residue taken up in CHCl₃. The CHCl₃ solution was washed with aq. Na₂CO₃ and H₂O, dried and evaporated to dryness to give a solid which was chromatographed in benzene over acid-washed Al₂O₃. The benzene eluate gave the chloromethyl derivative (III) (25 mg.), m.p. and mixed m.p. 143~145°. Elution with CHCl₃-benzene (1:1) gave the hydroxy-lactone (IV) (10 mg.), m.p. and mixed m.p. 220~222°.

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