

7. **Katsumi Tanabe**: Studies on Vitamin A and Its Related Compounds. II.¹⁾ Reformatsky Reaction of β -Cyclocitral with Methyl γ -Bromosenecioate.

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As a new route to the synthesis of vitamin A, a Reformatsky reaction of β -cyclocitral (I) with methyl γ -bromosenecioate (II) was investigated in this laboratory. In the course of this work, the same reaction was reported by Harper, *et al.*,²⁾ who isolated a hydroxy ester (III), which gave by subsequent dehydration methyl β -ionylideneacetate (IV). The author found some interesting observations different from their's.

The product, obtained by the reaction of β -cyclocitral with methyl γ -bromosenecioate in the presence of zinc in benzene solution, was fractionated under a reduced pressure. After a substantial amount of unchanged β -cyclocitral was recovered as a low boiling fraction, a very viscous, pale yellow oily substance, b.p. 177~189°, was obtained as the main product. When the latter was kept in an ice box for a long time or chilled in light petroleum solution with dry ice, about two-thirds of it crystallized, which was separated, and recrystallized from hydrous ethanol or light petroleum, forming colorless needles of m.p. 65~66°.

This substance proved to be a lactone, i.e., 5-hydroxy-3-methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentenoic acid δ -lactone (V, C₁₅-lactone), which is considered to be formed by the elimination of methanol from the intermediate, hydroxy ester (III), during reaction or distillation, and the evidences are as follows. This compound was (i) reduced by lithium aluminum hydride to 3-methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentene-1,5-diol (XV), (ii) saponified to 5-hydroxy-3-methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentenoic acid (XIV) by shaking in aqueous sodium hydroxide at room temperature, and (XIV) reproduced the parent compound by distillation in vacuum and it was reduced to (XV) by lithium aluminum hydride, and (iii) obtained also by the Reformatsky reaction of β -cyclocitral with ethyl γ -bromosenecioate.

Though the ultraviolet spectrum of C₁₅-lactone (Fig. 1) shows only an end-absorption, the molecular extinction coefficient at 220 m μ amounts to ca. 11,000. This fact indicates α,β -unsaturated structure³⁾ for the lactone.

The bands at 5.86 and 6.05 μ in the infrared spectrum of this compound (Fig. 3, I) respectively correspond to the carbonyl and α,β -olefinic double bond-stretching frequen-

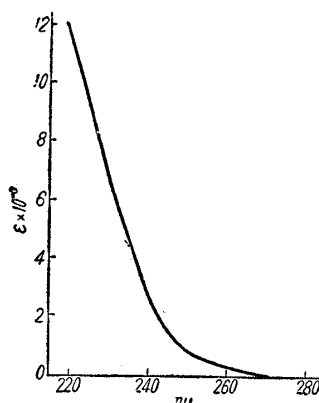


Fig. 1.

Ultraviolet Spectrum of C₁₅-Lactone

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1) Part I: K. Tanabe, Y. Kishida: Ann. Repts. Takamine Lab., 5, 1(1953).

2) S. H. Harper, J. F. Oughton: Chemistry & Industry, 574(1950).

3) W. G. Dauben, *et al.*: J. Am. Chem. Soc., 75, 3352(1953).

When C_{15} -lactone was treated with alcoholic potassium hydroxide or boiled in aqueous potassium hydroxide, it was readily isomerized into an acid of m.p. $99\sim 100^\circ$. The acid obtained here showed absorption maxima at 304 and $258\text{ m}\mu$ (Fig. 2) and absorbed 3 moles of hydrogen by catalytic hydrogenation, yielding a perhydro acid (XVI).

It has been fully investigated by Eisner, *et al.*⁷⁾ that α,β -unsaturated lactone sometimes isomerizes to α,β -*cis*-polyene acid by means of alkaline reagent.

The author assumed the new acid to be an unknown α,β -*cis*- β -ionylideneacetic acid (VI) and proved it to be true by the following experiments.

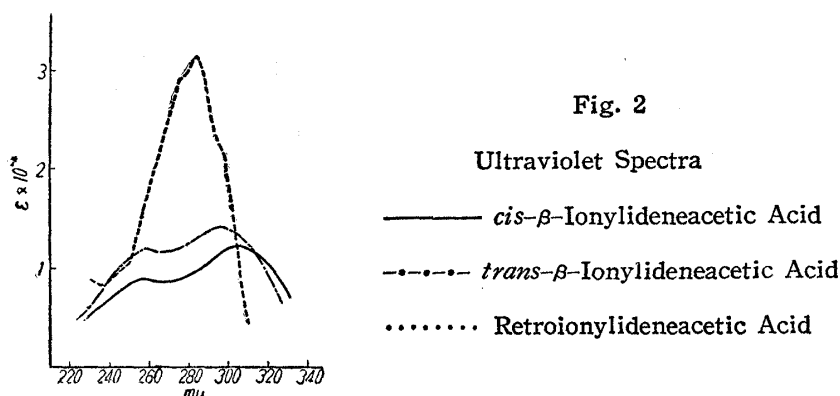


Fig. 2

Ultraviolet Spectra

— *cis*- β -Ionylideneacetic Acid
 - - - *trans*- β -Ionylideneacetic Acid
 Retroionylideneacetic Acid

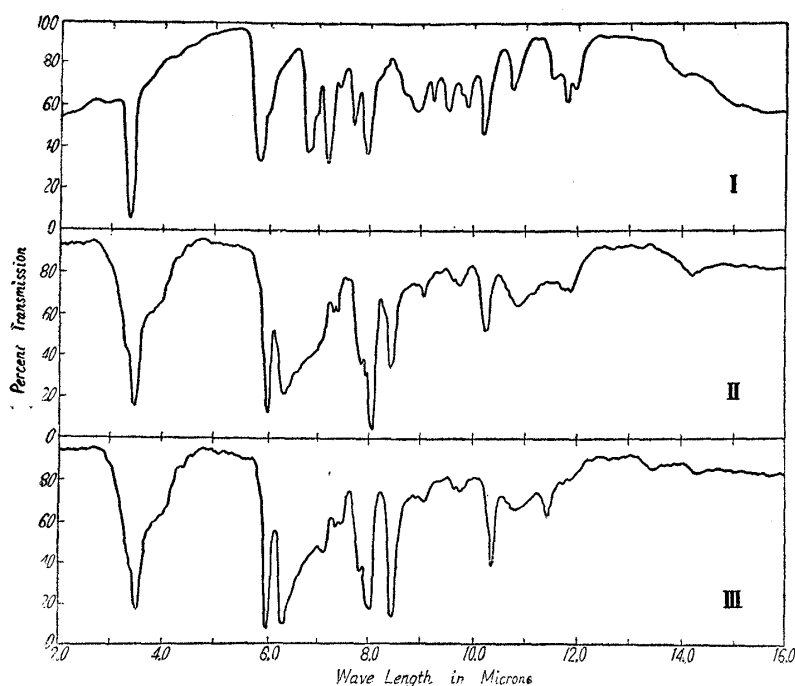


Fig. 3

Infrared Spectra

I. C_{15} -Lactone (in Nujol)
 II. *cis*- β -Ionylideneacetic Acid (in CS_2)
 III. *trans*- β -Ionylideneacetic Acid (in CS_2)

The known β -ionylideneacetic acid (XII) has m.p. $125\sim 126^\circ$, absorption maxima at 296 and $258\text{ m}\mu$ (Fig. 2), and is reduced catalytically to the above-mentioned perhydro acid (XVI) by absorbing 3 moles of hydrogen. This high melting acid is mainly obtained by the saponification of the Reformatsky reaction product from β -ionone (IX) and ethyl bromoacetate.⁸⁾

7) U. Eisner, *et al.*: J. Chem. Soc., **1953**, 1372, 1793, and earlier papers.

8) a) P. Karrer, *et al.*: Helv. Chim. Acta, **15**, 883(1932). b) H. Sobotka, *et al.*: J. Am. Chem. Soc., **65**, 1961(1943). c) W.G. Young, *et al.*: *Ibid.*, **66**, 520(1944). d) N.L. Wendler, *et al.*: *Ibid.*, **73**, 719(1951).

α, β -Double bond of this acid is formed (i) by dehydration of the intermediate compound, hydroxy ester (X), at α, β -position, or (ii) by the shifting of the conjugated double bond system in retroionylideneacetic acid (XI).^{9,10} Therefore, it should possess a *trans*-configuration. γ, δ -Double bond is considered also to have a *trans*-configuration, because it is the so-called "sterically ineffective."¹¹

Allowing that the double bond in the cyclohexene ring and that of γ, δ -position are placed in *s-trans*-configuration,¹² it may be possible that the known β -ionylideneacetic acid is Δ^{α} -*trans*- Δ^{γ} -*trans*-acid and the new low melting one, Δ^{α} -*cis*- Δ^{γ} -*trans*-acid, as shown in (a) and (b), respectively.



Generally speaking, among the carotenoides, *cis*-isomers have been found to absorb at shorter wave lengths than the corresponding *trans*-compounds.¹³ In this case, however, *cis*-isomer has absorption maxima at the longer wave length than that of the *trans*-isomer. Such anomalies were observed, e.g., between vitamin A and neovitamin A,¹⁴ between *cis*- and *trans*- β -ionylideneacetaldehyde.^{8a)}

The infrared transmission spectrum of *cis*- β -ionylideneacetic acid is compared with that of its *trans*-isomer in Fig. 3, II and III. The curves are almost identical, with slight difference occurring in the position of the bands at 10.26 and 11.85 μ .

Methyl *cis*- and *trans*- β -ionylideneacetate were converted by lithium aluminum hydride to the corresponding *cis*-(VII) and *trans*- β -ionylideneethanol (XIII), respectively.

On oxidation of (VII) and (XIII) by manganese dioxide in light petroleum, the same *trans*- β -ionylideneacetaldehyde was obtained.

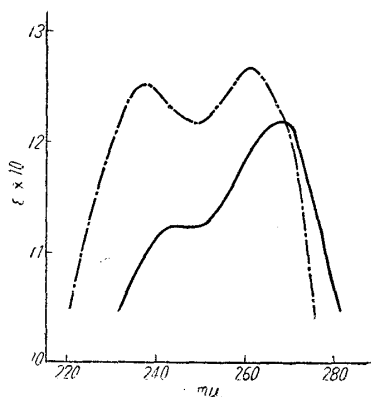


Fig. 4. Ultraviolet Spectra of *cis*- β -Ionylideneethanol (—) and *trans*- β -Ionylideneethanol (---)

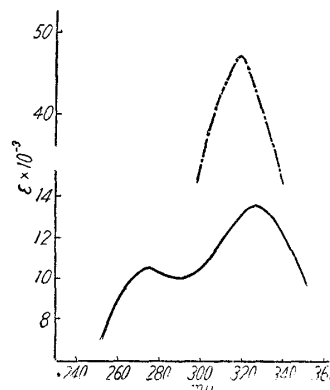


Fig. 5. Ultraviolet Spectra of *trans*- β -Ionylideneacetaldehyde (—) and Its Semicarbazone (---)

Ultraviolet spectra of (VII) and (XIII) (Fig. 4), and m.p.s of their anthraquinone- β -carboxylate show the fact that the reduction by lithium aluminum hydride is indifferent

- 9) a) W. Orosnik, *et al.*: J. Am. Chem. Soc., **74**, 295(1952). b) P. Karrer, *et al.*: Helv. Chim. Acta, **35**, 2570(1952).
- 10) E. M. Shanz, *et al.*: U. S. Pat. 2,576,104 (Nov. 27, 1951).
- 11) L. Pauling: Fortschr. Chem. Org. Naturstoffe, **3**, 203(1939).
- 12) E. A. Braude, *et al.*: J. Chem. Soc., **1949**, 1890.
- 13) L. Zechmeister: Chem. Revs., **34**, 267(1944).
- 14) C. D. Robeson, *et al.*: J. Am. Chem. Soc., **69**, 136(1947).

to *cis*-configuration. Oxidation by manganese dioxide* inverts, at least partly, *cis*-into *trans*-configuration.

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Experimental

Light absorption measurements were carried out in 95% EtOH. Active hydrogen was determined by Zerewitinoff's method.

β -Cyclocitral (I)—Citral fraction, b.p.₄ 90~94° (n_D^{25} 1.4868~1.4873), of the lemongrass oil was cyclized to a mixture of α - and β -cyclocitral according to the method of Henbest, *et al.*¹⁵⁾ Treatment of this isomeric mixture with methanolic KOH¹⁶⁾ gave β -cyclocitral, b.p.₁₂ 92~94°.

β -Cyclocitral used, b.p.₇ 84°, was regenerated from its semicarbazone (m.p. 165~166°) by the method reported by Young, *et al.*¹⁷⁾

Methyl and Ethyl γ -Bromosenecioate (II)—Bromination of methyl and ethyl senecioate by N-bromosuccinimide according to the method of Ziegler, *et al.*¹⁸⁾ gave methyl- and ethyl γ -bromosenecioate, b.p.₁₂ 90~92° and b.p.₁₄ 102~103°, respectively.

5-Hydroxy-3-methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentenoic acid δ -lactone (V: C₁₅-Lactone)—i) A mixture of β -cyclocitral (30 g.), methyl γ -bromosenecioate (38.4 g.), activated Zn¹⁹⁾ (12.8 g.), and thiophene-free benzene (200 cc.) was warmed on a sand bath until benzene commenced to boil. A vigorous reaction set in when a few crystals of iodide was added. Heating was regulated to maintain gentle boiling and the vigorous reaction ceased in about 15 mins. Refluxing was continued for an additional 15 mins. The mixture was then cooled to the room temperature and hydrolyzed with ice-cold 10% H₂SO₄. The benzene layer was separated and washed successively with dil. (NH₄)₂SO₄, Na₂S₂O₃, and NaHCO₃, and dried (Na₂SO₄). The solvent was removed by distillation at a slightly reduced pressure and the residue was fractionated in vacuum.

Fraction 1. b.p.₁₂ 88~99°, 12 g. Fraction 2. b.p.₅ 100~176°, 3 g. Fraction 3. b.p.₅ 177~189°, 18 g.

Unchanged β -cyclocitral was contained mainly in fraction 1.

By chilling the solution of fraction 3 in light petroleum (b.p. 60~80°; 40 cc.) with dry ice, crude crystals (12 g.) of C₁₅-lactone were obtained, which were recrystallized from 50% EtOH, forming colorless needles, m.p. 65~66°. *Anal.* Calcd. for C₁₅H₂₂O₂: C, 76.89; H, 9.44. Found: C, 77.27; H, 9.30.

This showed only a negligible amount of active hydrogen.

ii) A mixture of β -cyclocitral (13 g.), ethyl γ -bromosenecioate (17 g.), activated Zn (5.6 g.), and thiophene-free benzene (80 cc.) was treated in the same manner as above. The product obtained (4.3 g.) was crystallized from 50% EtOH to colorless needles, m.p. 65~66°, which was found to be identical with C₁₅-lactone by a mixed melting point determination.

3-Methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentene-1,5-diol (XV)—C₁₅-Lactone (1 g.) in anhyd. ether (20 cc.) was added to a solution of LiAlH₄ (200 mg.) in anhyd. ether (40 cc.). After the solution was stirred for 2 hrs. at room temperature, the excess of reagent was decomposed with 10% H₂SO₄. The ethereal layer was separated, washed with water, and dried (Na₂SO₄). Evaporation of the solvent gave 3-methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentene-1,5-diol, which was recrystallized from 50% EtOH to colorless needles, m.p. 99~100°. *Anal.* Calcd. for C₁₅H₂₆O₂: C, 75.58; H, 10.99. Found: C, 75.66; H, 10.72. Active hydrogen: 2.09, 1.89.

5-Hydroxy-3-methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentenoic acid (XIV)—A suspension of C₁₅-lactone (500 mg.) in aq. NaOH (10%; 20 cc.) was shaken at room temperature until all crystals had dissolved (ca. 5 hrs.). The solution was then acidified with 10% H₂SO₄ and extracted with ether. Evaporation of the solvent gave 5-hydroxy-3-methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentenoic acid, which was crystallized from 50% EtOH to colorless needles, m.p. 124~125° (decomp.). *Anal.* Calcd. for C₁₅H₂₄O₃: C, 71.39; H, 9.59. Found: C, 71.93; H, 9.18.

Distillation of the hydroxy acid (XIV; 200 mg.) under reduced pressure gave a crystalline mass, which was crystallized from 50% EtOH to form colorless needles of m.p. 65~66°. This showed no

* N. L. Wendler, *et al.*^{8a)} claimed to have obtained *cis*- β -ionylideneacetaldehyde together with its *trans*-isomer by the oxidation of β -ionylideneethanol by this substance.

15) J. Chem. Soc., **1952**, 1154.

16) L. Colombi, *et al.*: *Helv. Chim. Acta*, **34**, 265(1951); V. Prelog, *et al.*: *Ibid.*, **31**, 417(1948).

17) J. Am. Chem. Soc., **69**, 2072(1947).

18) *Ann.*, **551**, 80(1942).

19) L. F. Fieser, *et al.*: J. Am. Chem. Soc., **62**, 575(1940).

depression of melting point with C_{15} -lactone.

A solution of hydroxy acid (XIV; 200 mg.) and $LiAlH_4$ (200 mg.) in anhyd. ether (30 cc.) was refluxed for 10 hrs., and then treated as usual. The reduction product thus obtained was recrystallized from 50% EtOH to colorless needles, m.p. 98~99.5°; yield, 110 mg. This proved to be identical with (XV) by admixture.

cis- β -Ionylideneacetic Acid (VI)—i) To a solution of C_{15} -lactone (5 g.) in MeOH (15 cc.) was added a solution of KOH (2.4 g.) in MeOH (15 cc.). After being kept for 3 hrs. at a room temperature, the solution was diluted with water (100 cc.), acidified with 10% H_2SO_4 , and extracted with ether. The extract was washed well with water, dried (Na_2SO_4), and the solvent was evaporated, giving crude crystals of *cis*- β -ionylideneacetic acid, which were recrystallized from 50% EtOH to colorless needles, m.p. 99~100°. λ_{max} 304~306 m μ ($\epsilon=12,400$) and 258 (8,850). *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.89; H, 9.44. Found: C, 76.83; H, 9.17.

ii) C_{15} -Lactone (200 mg.) in aq. KOH (10%; 15 cc.) was boiled until the mixture became homogeneous (about 10 mins.). After the solution was cooled, the acid liberated by 10% H_2SO_4 was collected and recrystallized from 50% EtOH to colorless needles, m.p. 98.5~99.5°. It was undepressed when mixed with a specimen of *cis*- β -ionylideneacetic acid described above.

cis- β -Ionylideneacetic acid distilled without any change under a reduced pressure and it failed to isomerize into its *trans*-isomer on refluxing with aq. KOH (20%) for 2 hrs. and the original acid was recovered.

***trans*- β -Ionylideneacetic Acid (XII) and Retroionylideneacetic Acid (XI)**—According to the method of Karrer, *et al.*,^{8a)} β -ionone was treated with ethyl bromoacetate in the presence of Zn in thiophene-free benzene. Saponification of the purified reaction product gave an oily acid, which was dissolved in aq. EtOH and allowed to stand at -10° for several days to give a small amount of crystalline *trans*- β -ionylideneacetic acid, which was recrystallized from 50% EtOH, forming colorless plates, m.p. 125~126°. λ_{max} 296 m μ ($\epsilon=14,200$) and 258 (12,000). (Young, *et al.*^{8c)} gave the maxima as 294 and 260 m μ , and Wendler, *et al.*^{8d)} 300 and 255 m μ). *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.89; H, 9.44. Found: C, 77.04; H, 9.66.

Treatment of the oily acid, separated from β -ionylideneacetic acid as described above, with S-benzylthiuronium chloride in the usual manner gave S-benzylthiuronium salt of retroionylideneacetic acid, which was recrystallized from aq. EtOH to colorless plates, m.p. 138~139°; λ_{max} 285 m μ ($\epsilon=30,700$). *Anal.* Calcd. for $C_{23}H_{32}O_2N_2S$: C, 68.96; H, 8.05; N, 6.99. Found: C, 69.15; H, 8.33; N, 7.13.

By shaking the S-benzylthiuronium salt with 10% HCl, retroionylideneacetic acid was regenerated as an oil, which was extracted with ether. The extract was washed with water, dried, and the solvent was evaporated; the residue was distilled in vacuum (b.p._{0.5} 156~158°) giving a pale yellow oil. Yield, 1.3 g. λ_{max} 284 m μ ($\epsilon=31,500$).

Methyl *cis*- and *trans*- β -Ionylideneacetate—*cis*- and *trans*- β -Ionylideneacetic acid were respectively esterified with CH_3N_2 in anhyd. ether. *cis*-Ester: b.p._{0.5} 110~111°, n_D^{20} 1.5487; λ_{max} 311~312 m μ ($\epsilon=11,700$) and 259 (8,600).

trans-Ester: b.p._{0.5} 123~124°; n_D^{20} 1.5476; λ_{max} 303 m μ ($\epsilon=14,300$) and 259 (11,700).

***cis*- (VII) and *trans*- β -Ionylideneethanol (XIII)**—According to the method of Wendler, *et al.*,^{8d)} methyl *cis*- and *trans*- β -ionylideneacetate were respectively reduced with $LiAlH_4$ in anhyd. ether. *cis*- β -Ionylideneethanol: b.p._{0.5} 116~117°; λ_{max} 268 m μ ($\epsilon=12,200$) and 243~249* (11,200). Anthraquinone- β -carboxylate: Yellow needles (from aq. acetone), m.p. 104~105°. *Anal.* Calcd. for $C_{30}H_{30}O_4$: C, 79.30; H, 6.65. Found: C, 78.85; H, 6.51.

trans- β -Ionylideneethanol: b.p._{0.5} 131~132°; λ_{max} 261 m μ ($\epsilon=12,700$) and 236~239 (12,500). (Oroshnik, *et al.*^{9a)} gave the maxima as 265 m μ ($\epsilon=11,800$), and Baxter, *et al.*,²⁰⁾ 264 and 242 m μ).

Anthraquinone- β -carboxylate: Yellow needles (from acetone), m.p. 133~134°. *Anal.* Calcd. for $C_{30}H_{30}O_4$: C, 79.30; H, 6.65. Found: C, 78.81; H, 6.80

***trans*- β -Ionylideneacetaldehyde (VIII)**—A solution of *cis*- β -ionylideneethanol (4.5 g.) in light petroleum (b.p. 60~80°; 170 cc.) was shaken with active MnO_2 ²¹⁾ (45 g.) in N_2 atmosphere for 3 hrs. at a room temperature. The mixture was filtered and the precipitate was washed well with the fresh solvent. Evaporation of the combined filtrate and washings gave a dark red product. Distillation of the residue gave *trans*- β -ionylideneacetaldehyde as a yellow oil (3.8 g.), b.p._{0.5} 120~121°; n_D^{20} 1.5670; λ_{max} 325 m μ ($\epsilon=13,600$) and 273 (10,600). (Baxter, *et al.*²⁰⁾ gave the maxima as 326 and 272 m μ in EtOH, and Wendler, *et al.*,^{8d)} 315 and 265 m μ in isoöctane).

The semicarbazone, prepared in the usual manner, formed yellow needles (from MeOH), m.p. 195~196°. *Anal.* Calcd. for $C_{16}H_{25}ON_3$: C, 69.82; H, 9.09; N, 15.27. Found: C, 69.56; H, 8.78; N, 15.26; λ_{max} 319 m μ ($\epsilon=47,200$). (Huisman²²⁾ gave the maximum as 320 m μ in EtOH and Wendler,

* Inflection.

20) Fortschr. Chem. Org. Naturstoffe, **9**, 48(1952).

21) J. Attenburrow, *et al.*: J. Chem. Soc., **1952**, 1104.

et al.,^{8d)} at 323 m μ in CHCl₃).

By the procedure described above, the same *trans*- β -ionylideneacetaldehyde was obtained from *trans*- β -ionylideneethanol.

Hydrogenation—i) *cis*- β -Ionylideneacetic acid (126 mg.) in 95% EtOH was shaken in an H₂ atmosphere with PtO₂ catalyst (40 mg.) and 41.2 cc. of H₂ was absorbed at 29°/762.2 mm. Hg, equivalent to 3.1 double bonds per molecule. After removal of the catalyst and evaporation of the solvent, the residual saturated acid was converted into its *p*-nitrophenacyl ester and S-benzylthiuronium salt. *p*-Nitrophenacyl ester: Colorless plates (from 85% EtOH), m.p. 59–60.5°. *Anal.* Calcd. for C₂₃H₃₃O₅N: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.02; H, 7.91; N, 3.66.

S-Benzylthiuronium salt: Colorless needles (from 80% EtOH) m.p. 156°. *Anal.* Calcd. for C₂₃H₃₃O₅N₂S: C, 67.94; H, 9.42; N, 6.89. Found: C, 67.73; H, 9.61; N, 6.72.

ii) *trans*- β -Ionylideneacetic acid (33 mg.) was hydrogenated as above and 10.8 cc. of H₂ was absorbed at 27°/769.2 mm. Hg, equivalent to 3.2 double bonds per molecule. *p*-Nitrophenacyl ester and S-benzylthiuronium salt derived from the product were identical with those described above.

iii) Retroionylideneacetic acid (100 mg.) was hydrogenated in glacial AcOH with PtO₂ and 33.2 cc. of H₂ was absorbed at 32.5°/762 mm. Hg, equivalent to 3.1 double bonds per molecule. The same S-benzylthiuronium salt, m.p. 156°, was obtained.

iv) C₁₅-Lactone (124 mg.) on hydrogenation in glacial AcOH with PtO₂ catalyst absorbed 41.5 cc. H₂ at 33°/761 mm. Hg, equivalent to 3.3 double bonds per molecule. Isolation of the product and treatment with S-benzylthiuronium chloride gave the S-benzylthiuronium salt, m.p. 156°, undepressed by admixture with the specimen described above.

Summary

By the Reformatsky technique of β -cyclocitral with γ -bromosenecioate, 5-hydroxy-3-methyl-5-(2',6',6'-trimethyl-1'-cyclohexen-1'-yl)-2-pentenoic acid δ -lactone was obtained. This lactone readily isomerized into *cis*- β -ionylideneacetic acid, which was led to *cis*- β -ionylideneethanol by the lithium aluminum hydride reduction. Oxidation of *cis*- β -ionylideneethanol with manganese dioxide gave *trans*- β -ionylideneacetaldehyde.

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