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121. Yoshisuke Tsuda,[*1] Yoshio Sasaki,[*1] and Shojiro Uyeo[*2]: Tazettine Chemistry. X.[*3] The Structure of Products obtained from O-Methyltazettine Methine Methosalts under the Hofmann Elimination Conditions.[*4]

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In continuation of our previous paper,1) the structures of compounds C, D, and E, obtained in minute yields during the Hofmann degradation of O-methyltazettine methine methohydroxide or in better yields by treatment of the methiodide with *tert*-butoxide under the analogous conditions, were shown to be represented by formulas (VI), (XIV), and (XV), respectively.

(Received September 28, 1966)

In a previous paper1) we have reported that treatment of O-methyltazettine methine methiodide (I) with potassium *t*-butoxide gave a complex mixture of products from which, along with 2-*p*-methoxyphenyl-4,5-methylenedioxybenzyl alcohol (II) and its acetate (III), five α,β-unsaturated ketones (compounds A~E) were isolated. Compounds D and E had been obtained earlier by the Hofmann degradation of O-methyltazettine methine methiodide,2) while the compound C, $C_{18}H_{19}O_4N$, was new. In contrast to compounds A and B, compounds C, D, and E did not contain any methoxyl group in the respective molecules and were racemic. Those facts indicated that they might be products resulting from further transformation of compounds A and B. The structure of compounds A (IV) and B (V) have already been reported,1) and we now wish to present the chemical and spectroscopic evidence which leads to structures (VI), (XIV), and (XV) for compounds C, D, and E, respectively.

Compound C is unstable not only to alumina but also to acids and alkalis and is best isolated by crystallization from a concentrated basic fraction of the reaction mixture. Even prolonged heating in methanol caused decomposition and attempted hydrogenation in ethanol in the presence of palladium-carbon was unsuccessful because of decomposition. Compound C exhibited infrared bands at 1678 and 1412 cm^{-1} characteristic for a cyclohexenone and -CH_2-CO-, respectively. In the nuclear magnetic resonance (NMR) spectrum,[*5] it showed signals at -1.05, 0.00, and $+2.02$ p.p.m. corresponding to methylenedioxy, $ArCH_2O$, and NMe_2 groupings, along with a singlet at -0.41 p.p.m. indicative of a non-coupled olefinic proton. The N-dimethyl signal of this compound is at a lower field by about 0.4~0.5 p.p.m. than that of compound A suggesting that the nitrogen of compound C is negatively substituted. Based on these findings, it seems likely that it has structure (VI) containing an enamino-ether moiety. This inference was supported by its strong UV absorption at 232 mμ (log ε 4.41), the extinction coefficient of which was almost equal to the sum of those of the absorptions

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[*3] Part IX: This Bulletin, **12**, 489 (1964).

[*4] This paper was presented at the 4th Symposium on the Chemistry of Natural Products, Kyoto, Oct. 15, 1960; Abstracts, p. 20.

[*5] The NMR spectrum was taken for a 0.5 mol. chloroform solution on a Varian V 4300, 40 mc. machine. Chemical shifts were measured relative to water (external standard).

1) Y. Tsuda, S. Uyeo: J. Chem. Soc., **1961**, 2485.

2) H. Kondo, T. Ikeda, N. Okuda: Ann. Report Itsuu Lab., **1**, 61 (1950).

of N,N-dimethylvinylamine (log ε 4.00 at 228 mμ)[3] and of compound A (log ε 4.03 at 230 mμ).[1]

Confirmation of the structure (VI) for compound C has now been provided by the following degradative reactions. Hydrolysis of compound C with cold acetic acid gave the keto-aldehyde (VIII) which exhibited, as expected, an NMR doublet for an aldehyde hydrogen at -5.05 p.p.m. (1H, $J=2$ c.p.s.). Along with this doublet the appearance of a new doublet at $+0.63$ p.p.m. (1H, $J=2$ c.p.s.) of the same coupling constant established that the product has a partial structure $O-\overset{|}{C}H-CHO$. Careful oxidation of compound C with sodium dichromate-acetic acid-benzene mixture effected removal of the enamino group, giving the keto-lactone (IX), which on hydrogenation afforded the dihydro-keto-lactone (X). Further treatment of the latter compound (X) with sodium borohydride yielded the dihydro-hydroxy-lactone (XI). The structures of both dihydro-keto-lactone (X) and dihydro-hydroxy-lactone (XI) were confirmed by direct comparison with the respective synthetic specimens.[4]

Compound D, $C_{18}H_{19}O_4N$, is isomeric with compound C and readily distinguishable from the latter by its stability to chromatography on alumina. The UV spectra of compound D and its oxime were very similar to those of deoxytazettinone (XII), and its oxime, respectively (Fig. 1), indicating that no other chromophores than an α,β-unsaturated ketonic group and a methylenedioxybenzene moiety were present in the molecule. In the IR spectrum it exhibited a band at 1672 cm^{-1} for a cyclohexenone, but no absorption characteristic of an active methylene adjacent to a carbonyl group was observed. Hydrogenation of compound D gave the cyclohexanone derivative (XIII) which exhibited a carbonyl band at 1706 cm^{-1} and an active methylene band at 1420 cm^{-1} and afforded a monopiperonylidene derivative on treatment with piperonaldehyde in the presence of potassium *tert*-butoxide. In contrast, compound D was recovered unchanged on attempted treatment with the same reagent. The NMR spectrum of compound D exhibited singlets at $+2.43$, -0.1 and -1.20 p.p.m. for NMe_2, $ArC\underline{H}_2O$, and $-OC\underline{H}_2O-$, respectively, and an additional doublet at $+0.87$ p.p.m. ($J=2$ c.p.s.) which corresponded to one hydrogen coupled with only one adjacent hydrogen attributed to $>C\underline{H}-O-$. The evidence thus accumulated was consistent with structure (XIV) for compound D. This was proven by converting compound C (VI) into compound D by the action of potassium *tert*-butoxide at 130°.

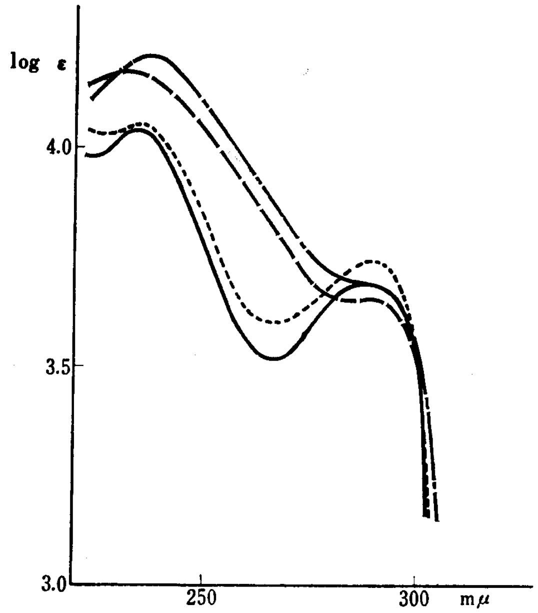

Fig. 1. UV Spectra

———— Compound D (XIV)
------ deoxytazettinone (XII)
— · — · XIV-oxime
– – – – XII-oxime

Compound E was considered to have structure (XV) which differed from compound D in containing a hydroxyl group in place of the NMe_2, since the former exhibited infrared bands at 3390 (OH) and 1664 cm^{-1} (cyclohexenone) and had the very similar UV spectrum as that of compound D. This inference was proven as follows. Acetylation

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[3] A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," p. 51 (1957), Edward Arnold (Publishers), Ltd., London.

[4] S. Uyeo, H. Irie, U. Kitayama, T. Hirose, A. Yoshitake: This Bulletin, **12**, 489 (1964).

of compound E gave the monoacetate (XVI) which showed no hydroxyl band in the IR spectrum, and oxidation with chromium trioxide-pyridine complex afforded the diketone (XVIII) exhibiting an additional absorption for a cyclopentanone at 1757 cm^{-1}, while

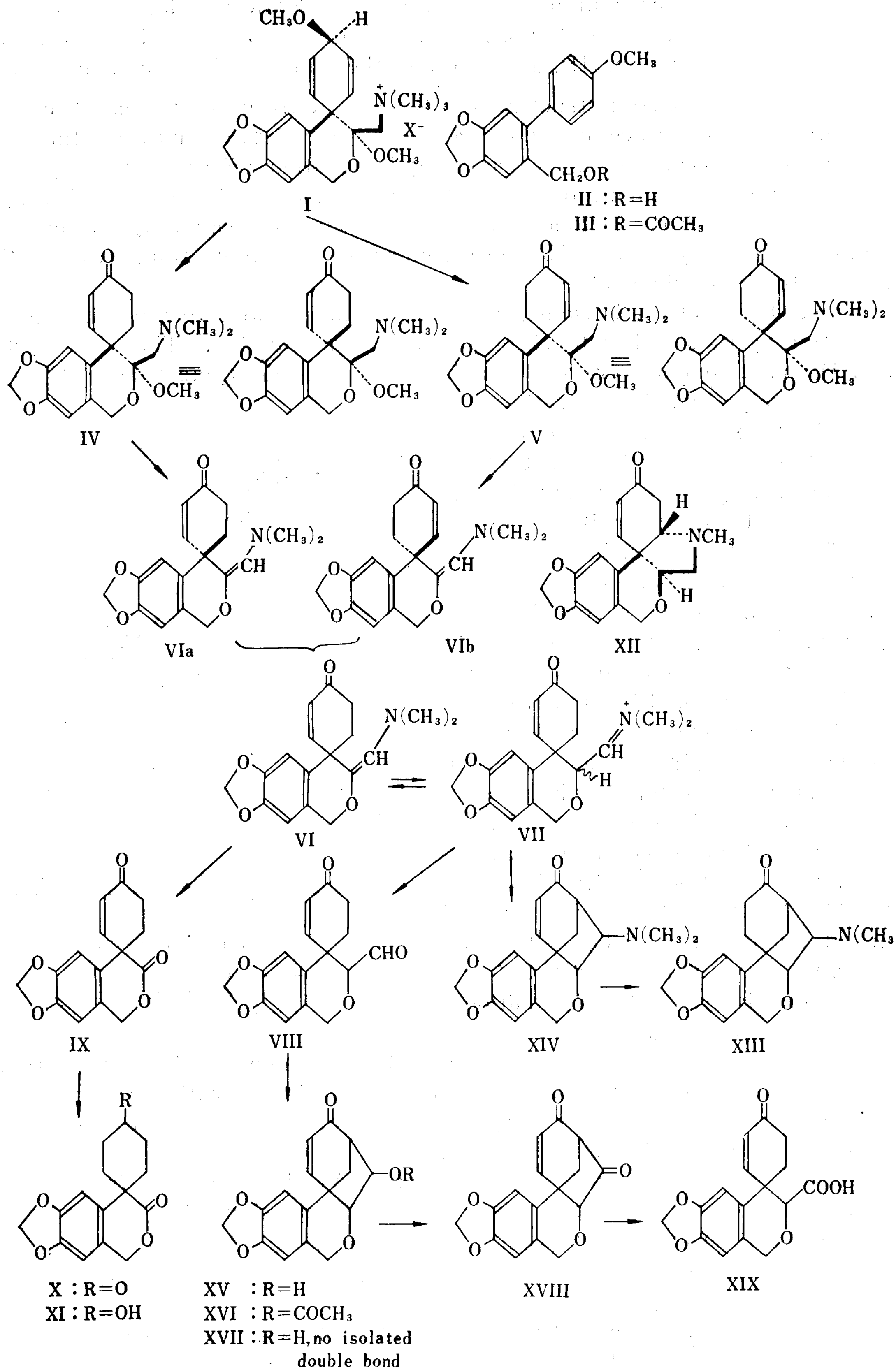

Chart 1.

hydrogenation of compound E led to the dihydro derivative (XVII) which showed in the IR spectrum a hydroxyl band at 3623 cm^{-1} and an unconjugated ketonic absorption at 1724 cm^{-1}. On heating the diketone (XVIII) in a 3% sodium hydroxide solution it was rapidly hydrolysed to the keto-acid (XIX) as a result of retro-Claisen condensation. This would indicate that XVIII is a β-diketone. The higher acid-carbonyl frequency (1745 cm^{-1}) of the keto-acid, in comparison with those of usual aliphatic acids (1725~1700 cm^{-1}),⁵⁾ accounts for the proposed structure (XIX) of an α-oxygenated carboxylic acid.

Partial synthesis of compound E confirmed our view. Though the attempted cyclization of the keto-aldehyde (VIII) with *p*-toluenesulfonic acid in methanol failed, the product being the methoxy-ketoaldehyde (XX), VIII gave compound E in almost quantitative yield when treated it with potassium *t*-butoxide in benzene at room temperature. Furthermore compound E (10% yield) is one of the products formed from compound C during chromatography over alumina. Treatment of compound C with strong alkali in methanol gave likewise a mixture from which compound E (XV) and the methoxy-keto-aldehyde (XX) were isolated in 14 and 4% yield, respectively.

With the structures of compounds C, D, and E established, there still remains the configurations of the dimethylamino grouping in compound D and the hydroxyl group in compound E to be elucidated. The configurations of the other parts of the molecules are fixed, as can be seen from atom models.

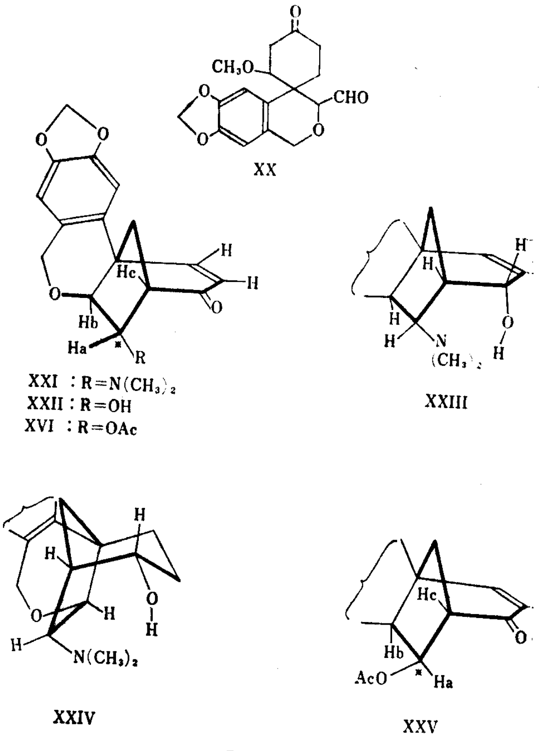

Chart 2.

Since compound D and E are the products formed under thermodynamically equilibrated conditions as demonstrated by their partial syntheses, they must have the most stable stereochemistry as represented by the formulas XXI and XXII. This assignment was supported by the following evidence. Reduction of compound D with sodium borohydride furnished the alcohol (XXIII) and dihydro-alcohol (XXIV) in nearly equal amounts. Dissociation constants of XXIII and XXIV showed that they are stronger bases than compound D by 1.4~2.0 pKa units, indicating that the proton of conjugated acids derived from those derivatives is hydrogen bonded to the hydroxyl group. This requirement is met only if the dimethylamino grouping is α-oriented and the ketonic group has been reduced to the alcohol with α-orientation (written in one of two active forms). In agreement with this assumption, neither of the alcohols showed in the IR spectra any indication of the presence of a non-bonded hydroxyl group in the molecule even in a dilute carbon tetrachloride solution (2.5×10^{-4} mol.). Indeed they exhibited a broad bonded hydroxyl absorption at 3260 cm^{-1} for XXIII and at 3340 cm^{-1} for XXIV.

As for the configuration of the hydroxyl group in compound E, the NMR spectrum of the acetate (XVI) of compound E was used to define its stereochemistry. It exhibited a doublet (J=2 c.p.s.) at +0.67 for $-\text{O}-\overset{|}{\text{C}}\underline{\text{H}}-$ and a quartet (J_1=2 c.p.s., J_2=7 c.p.s.) at

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5) L.J. Bellamy: "The Infra-red Spectra of Complex Molecules," p. 139 (1954).

−0.79 p.p.m. for $-\underset{|}{\mathrm{C}}\underline{\mathrm{H}}-\mathrm{OAc}$. The magnitudes of these coupling constants are in excellent agreement with those predicted from the assigned configuration. Thus, the dihedral angles between H_a and H_b, and H_a and H_c in structure (XVI) are, as measured from atom models, roughly 120° and 20°, respectively. The coupling constants of these pairs of hydrogens are 2.1 and 7.2 c.p.s., respectively as calculated by use of the Karplus equation, in good agreement with the observed values. If, on the other hand, compound E had had the alternate structure (XXV) epimeric about C*, the dihedral angles between the corresponding protons would have been 0° and 90° and accordingly the coupling constant should have been 8.2 and 0 c.p.s. which are far different from the experimental results.

A likely mechanistic route for the formation of compounds C, D, and E appeared, as mentioned above, to be that through diastereoisomeric compounds A and B, which would lead to enantiomeric enamines Ⅵa and Ⅵb, respectively, by loss of the elements of methanol under strong alkaline conditions. Since we can expect the formation of these enantiomers in equal amounts, complete racemization of the enantiomers is expected to occur, giving rise to compound C. Starting with compound C, compounds D and E would be formed under the strong alkaline conditions in the presence or absence of water. When a small amount of water is present in the reaction mixture, hydrolytic cleavage of the enamine would readily take place to give dimethylamine and the aldehyde (Ⅷ), the latter of which cyclizes with strong alkali to compound E by the intramolecular aldol condensation.

In the absence of water, on the other hand, the enamine will cyclize *via* the protonated form (Ⅶ) to compound D by a Mannich type reaction. This reaction was found to take place only at an elevated temperature (at least 130°), since in a boiling benzene solution the enamine did not cyclize to compound D even in the presence of *tert*-butoxide.

Experimental

Ultraviolet absorption spectra were determined for 95% EtOH solutions, and infrared spectra were taken in Nujol mulls unless otherwise stated. Nuclear magnetic resonance spectra were determined in 0.5∼1 mol. $CHCl_3$ solutions on a Varian V 4300 instrument operating at 40 Mc/sec. pKa's were measured for 50% aqueous MeOH solutions. Identities were confirmed by infrared comparisons.

O-Methyltazettine Methine——This was prepared by the method reported by Kondo, Ikeda, and Okuda.[2] The oily methine had $[\alpha]_D$ −180°(c=0.9, EtOH). UV λ_{max} mμ (log ε): 243 (3.78), 292 (3.64). NMR $\delta_{p.p.m.}$: −1.23 (OCH_2O), 0.00 ($ArCH_2O$), +1.25 ($2OCH_3$ and O-CH<), +2.16 ($-N-CH_2-$), +2.40 (NMe_2).

The methine was recovered unchanged after chromatography in benzene over alumina, and refluxing in 3% ethanolic KOH for 5 hr.

O-Methyltazettine Methine Methiodide (I)——O-Methyltazettine methine was quantitatively converted into its methiodide by keeping it in MeOH with CH_3I at room temperature for 2 hr. Crystallization from MeOH gave prisms, m.p. 214∼215°(lit.[2] m.p. 214∼215°), $[\alpha]_D$ −121°(c=0.9, EtOH). UV λ_{max} mμ (log ε): 243 (3.64, inflexion), 291 (3.67).

The methiodide was recovered unchanged after chromatography in Me_2CO over alumina and on heating in MeOH-H_2O in a sealed tube at 100° for 8 hr.

Treatment of O-Methyltazettine Methine Methiodide (I) with Sodium Hydroxide——A solution of the methiodide (I) (0.2 g.) in 30% NaOH (10 ml.) was heated on a water-bath for 2 hr. After cooling, the mixture was extracted with $CHCl_3$ and the $CHCl_3$ extract washed with H_2O, dried, and evaporated to dryness to give a residue which was chromatographed in benzene over alumina. The benzene and $CHCl_3$ eluates were combined and rechromatographed in benzene over alumina to give a small amount of Ⅱ (8 mg.), m.p. and mixed m.p. 147∼149°.

Hofmann Degradation of O-Methyltazettine Methine Methosalt (I)

1) **Pyrolysis of the Methohydroxide (I; X=OH)**——The methiodide (I) (1.4 g.) in H_2O (20 ml.) and MeOH (20 ml.) was stirred with freshly prepared and well washed Ag_2O (from 3 g. of $AgNO_3$ and excess of NaOH). The filtrate was evaporated to dryness under reduced pressure and the residue heated at 5 mm. and 100° for 20 min. The product was taken up in ether which was washed with 2% HCl and concentrated to dryness. The residue (0.55 g.) was chromatographed in benzene over acid-washed alumina. The benzene

eluate gave III (0.3 g.), m.p. and mixed m.p. 87～89°. Elution with ether afforded II (0.15 g.), m.p. and mixed m.p. 148°. The $CHCl_3$ eluate gave an amorphous substance which was discarded. Further elution with Me_2CO gave compound E (XV) (4 mg.), m.p. 239～240°. The above acidic washing was basified with NH_3 and extracted with ether which was concentrated and the residue (0.13 g.) crystallized from MeOH to give compound C (VI) (80 mg.), m.p. 163～165°.

2) **Pyrolysis of the Methocarbonate (I; X=1/2 CO_3)**——Carbon dioxide was passed through a solution of the methohydroxide (I : X=OH) (prepared from 1 g. of the methiodide) and the solution was evaporated to dryness to give the methocarbonate which was heated at 5 mm. and 150° for 30 min. The product was worked up as mentioned in **1** and the neutral fraction (0.3 g.) gave, on chromatography over acid-washed alumina, II (0.1 g.) and III (0.15 g.). The basic fraction (0.145 g.) was filtered in benzene through a short column of alumina and the filtrate extracted with 2% HCl. The acidic extract was basified with NH_3 and re-extracted with ether. Evaporation of the solvent from the dried ethereal extract gave compound A (IV) (0.1 g.), m.p. and mixed m.p. 98～100°, as colorless prisms (from MeOH). $[\alpha]_D$ +46° (c=3.5, $CHCl_3$). pKa′=6.67.

3) **Reaction of the Methiodide (I; X=I) with Potassium *tert*-Butoxide**——a) O-Methyltazettine methine methiodide (I : X=I) (2 g.) and *tert*-BuOK (1 g.) in *tert*-BuOH (40 ml.) were heated under reflux for 10 hr. The solvent was evaporated under reduced pressure and the residue heated at 5 mm. and 120～130° for 30 min. Water was added to the cooled mixture, the whole was saturated with NH_4Cl and extracted with benzene. The benzene layer was washed with 5% HCl and chromatographed over acid-washed alumina to yield III (50 mg.), and II (70 mg.) from benzene and ether eluates, respectively. Further elution with $CHCl_3$ and acetone gave compound E (XV) (50 mg.), m.p. 239～240°. The acidic aqueous phase was basified with Na_2CO_3 and repeatedly extracted with ether Concentration of the dried ether yielded compound C (VI) (0.27 g.), m.p. 163～165°, which was removed by filtration. The mother-liquor was evaporated and triturated with MeOH, to give compound D (XIV) (40 mg.), m.p. 204～205°. Chromatography of the mother-liquor from compounds C and D in benzene over alumina gave compound A (IV), (0.2 g.), m.p. 101～102°. The aqueous solution from which the basic substances had been removed by extraction with ether was heated, after addition of NaOH, on a water-bath for 5 min. and then extracted again with benzene. The benzene extract gave, on evaporation and vacuum-distillation, compound B (V) (0.1 g.), as a viscous oil, $[\alpha]_D$ −238° (c=3.6, $CHCl_3$).

b) When the temperature of pyrolysis of the mixture of the methiodide and potassium *t*-butoxide was raised to 150～170°, compound D (0.2 g.) crystallized directly on concentration of the ethereal extract of the basic fraction and very poor yield of compound C (0.02 g.) was obtained from the mother-liquor of compound D. In case of the yields of both compounds C and D were very poor (trace and 0.08 g., respectively), considerable amount of compound E (0.22 g.) was obtained from the neutral fraction.

Compound C (VI)——Compound C crystallized from MeOH or ether as pale yellow needles, m.p. 163～165°. It is dimorphous and, when crystallized from Me_2CO, it sometimes formed yellow prisms, m.p. 180～182°. Either form can be obtained by cross seeding. $[\alpha]_D$ ±0° (c=0.5, $CHCl_3$). pKa′=6.11. UV λ_{max} mμ (log ε) : 232 (4.41), 292 (3.84). IR cm^{-1} : 1670 (cyclohexenone), 1412 ($COCH_2$), 1038, 930 (OCH_2O), 823 and 814 (trisubstituted olefin) in Nujol mull, 1653 (cyclohexenone) in KBr disc, and 1678 (cyclohexenone), 1412 ($COCH_2$) in $CHCl_3$. NMR $\delta_{p.p.m.}$: −1.05 (OCH_2O), −0.41 (-CH=N-), 0.00 ($ArCH_2O$), +2.02 (NMe_2). *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found : C, 68.91; H, 5.93; N, 4.21; OMe, 0.

a) Compound C could be sublimed with slight decomposition at 0.05 mm. and 200～220° (bath temperature). b) Compound C (36 mg.) was chromatographed in benzene over alumina (1 x 10 cm.). The residue from the combined benzene, $CHCl_3$, and MeOH eluates, was separated with 5% HCl into a neutral and basic fractions. The neutral fraction (20 mg.) was chromatographed in benzene over acid-washed alumina. Elution with benzene and $CHCl_3$ gave an amorphous substance which showed IR absorptions, at 3390, 1709, and 1675 cm^{-1}. Second eluate with acetone gave on crystallizations from benzene, compound E (XV) (4 mg.), m.p. and mixed m.p. 226～229°. c) Compound C (0.5 g.) and *tert*-BuOK (0.5 g.) in MeOH (20 ml.) were heated on a water-bath for 6 hr. The neutral fraction (0.3 g.) was chromatographed in benzene over acid-washed alumina. Benzene eluate gave the methoxy-keto-aldehyde (XX) (20 mg.), m.p. 240～242°, and $CHCl_3$-acetone eluate afforded compound E (XV) (70 mp.), m.p. and mixed m.p. 228～231°. d) Compound C (65 mg.) in MeOH (5 ml.) containing conc. HCl (0.5 ml.) was heated on a water bath for 2 hr. The neutral fraction (30 mg.) was chromatographed in benzene over acid-washed alumina to give XX (8 mg.), m.p. and mixed m.p. 240～241°. The basic fraction (10 mg.) afforded colorless prisms, m.p. 160～161°. IR cm^{-1} : 1709 (CO) in KBr disc. This showed depression (135～140°) on admixture with compound C. e) Compound C (30 mg.) and 15% Pd-C (100 mg.) in EtOH (20 ml.) were shaken for 3 hr. in an atmosphere of H_2. The resulting mixture had an odor of an amine (dimethylamine !). Removal of the catalyst and the solvent left a neutral gum (30 mg.), which was chromatographed in benzene over acid-washed alumina. The benzene eluate gave an oil which was discarded. Second elution with benzene-MeOH gave crystals (10 mg.), m.p. 225～229°. IR cm^{-1} : 3333 (OH), 1692 (CO) in KBr disc. This substance is probably identical with dihydro-compound E (XVII).

Hydrolysis of Compound C (VI)——Compound C (VI) (90 mg.) in benzene (5 ml.) was added dropwise to a stirred solution of AcOH (2 ml.) and benzene (2 ml.) at 0°. The mixture immediately became colorless.

After 1 hr's stirring, H_2O was added and the mixture was repeatedly extracted with benzene. The combined benzene extracts were washed with H_2O, dried (Na_2SO_4), and evaporated. Crystallization of the residue from benzene gave the keto-aldehyde (VIII) (75 mg.), as colorless prisms, m.p. 141~142°. UV $\lambda_{\max}$ mμ (log ε): 236 (3.67), 291 (4.02). IR cm^{-1}: 1700 (CHO), 1668 (conjugated ketone), 1418 shoulder ($COCH_2$), 1142 and 932 (OCH_2O). NMR $\delta_{\text{p.p.m.}}$: −5.05 doublet (CHO), −1.22 (OCH_2O), −0.27 ($ArCH_2O$), +0.63 doublet (O-CH<). *Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.12; H, 4.99.

The Methoxy-keto-aldehyde (XX)——a) The keto-aldehyde (VIII) (30 mg.) and *p*-toluenesulfonic acid (5 mg.) in MeOH (8 ml.) were kept overnight at room temperature, and then evaporated to dryness under reduced pressure. The residue was taken up in $CHCl_3$, washed with a 5% Na_2CO_3 solution, dried, and evaporated to give a gum, which on trituration with MeOH crystallized to give XX,[*6] as leaflets (from $CHCl_3$-MeOH), (10 mg.), m.p. 248°. UV $\lambda_{\max}$ mμ (ε): 240 (3.78), 294 (3.85). IR cm^{-1}: 1724 (CHO), 1712 (CO) in KBr disc. *Anal.* Calcd. for $C_{17}H_{18}O_6 \cdot 1/3 H_2O$: C, 62.92; H, 5.80; OMe, 9.57. Found: C, 62.81; H, 5.30; OMe, 10.4. This compound depressed the m.p. of compound E to 210~220°.

b) To a stirred solution of the keto-aldehyde (VIII) (10 mg.) in MeOH (4 ml.) was added NaOH (20 mg.) in MeOH (2 ml.) at 0°. After 30 min., the mixture was poured into H_2O and extracted with $CHCl_3$. Removal of the solvent from the dried extract afforded XX (10 mg.), m.p. and mixed m.p. 246~248°.

Oxidation of Compound C (VI)——To a stirred solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (0.18 g.) in AcOH (2 ml.) and benzene (2 ml.) was added dropwise compound C (VI) (93 mg.) in benzene (4 ml.) during 20 min. at 0°. After additional 1 hr.'s stirring, MeOH (1 ml.) was added to destroy the excess reagent, and the mixture was diluted with H_2O and extracted with benzene. The combined benzene extracts were washed successively with a 10% Na_2CO_3 solution, 10% HCl, and H_2O, dried (Na_2SO_4), and evaporated to give the keto-lactone (IX) (65 mg.). It crystallized from benzene as needles, m.p. 168~169°. UV $\lambda_{\max}$ mμ (log ε): 292 (3.67), 220~230 (4.05~4.02 end absorption). IR cm^{-1}: 1730 (δ-lactoue), 1675 (cyclohexenone). *Anal.* Calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.23; H, 4.61.

The Dihydro-keto-lactone (X)——The keto-lactone (IX) (50 mg.) in EtOH (10 mg.) was hydrogenated for 3 hr. over 10% Pd-C at room temperature. Removal of the catalyst and solvent left X (40 mg.) which crystallized from benzene as prisms, m.p. 136~138°. UV $\lambda_{\max}$ mμ (log ε): 244 (3.50), 293 (3.66). IR cm^{-1}: 1730 (δ-lactone), 1704 (cyclohexanone). *Anal.* Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.19. Found: C, 65.84; H, 5.32.

The Dihydro-hydroxy-lactone (XI)——a) To a stirred solution of the dihydro-keto-lactone (X) (40 mg.) in MeOH (3 ml.) was added dropwise $NaBH_4$ (10 mg.) in MeOH (3 ml.) at 0.° After 1 hr.'s stirring, the mixture was evaporated to dryness under reduced pressure and the residue taken up in $CHCl_3$ which was washed with H_2O, dried, and evaporated to give XI as leaflets (from EtOH), (25 mg.), m.p. 222~223°. UV $\lambda_{\max}$ mμ (log ε): 244 (3.48), 293 (3.62). IR cm^{-1}: 3500 (OH), 1717 (δ-lactone). *Anal.* Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.96; H, 5.94. This showed no depression of m.p. on admixture with the synthetic specimen[4)] and the infrared spectra of both specimens were superimposible.

b) The keto-lactone (IX) (5 mg.) in EtOH (5 ml.) was hydrogenated over PtO_2 (30 mg.) at room temperature for 3 hr. Chromatography of the product in benzene over acid-washed alumina gave XI (3 mg.), m.p. and mixed m.p. 220~222°.

Compound D (XIV)——Compound D crystallized from MeOH in prisms, m.p. 204~205°. It showed no depression of m.p. on admixture with the original sample,[2)] m.p. 202°, $[\alpha]_D$ ±0° (c=0.8, EtOH). pKa′=5.20. UV $\lambda_{\max}$ mμ (log ε): 235 (4.05), 290 (3.74). IR cm^{-1}: 2778 (NMe_2), 1672 (cyclohexenone), 1036, 928 (OCH_2O), 3030, 712 (*cis*-CH=CH-), 892, 883 (Ar-H) in Nujol mull, 2778 (NMe_2), 1681 (cyclohexenone) in $CHCl_3$. NMR $\delta_{\text{p.p.m.}}$: −1.20 (OCH_2O), −0.10 ($ArCH_2O$), +0.87 doublet (O-CH<), +2.43 (NMe_2). *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.91; H, 6.13; N, 4.79; OMe, 0; CMe, 0. This could be sublimed without decomposition at 0.01 mm. and 170° (bath temperature).

The perchlorate formed prisms from H_2O, m.p. 200~202°. IR cm^{-1}: 2700 ($>N^+$-H), 1664 (cyclohexenone). *Anal.* Calcd. for $C_{18}H_{19}O_4N \cdot HClO_4 \cdot H_2O$: C, 50.06; H, 5.14. Found: C, 50.58; H, 5.25.

The oxime crystallized in prisms from EtOH, m.p. 237~240° (decomp.). UV $\lambda_{\max}$ mμ (log ε): 237 (4.34), 290 (3.72). *Anal.* Calcd. for $C_{18}H_{20}O_4N_2$: N, 8.53. Found: N, 8.26.

The methiodide crystallized as prisms from EtOH, m.p. 258~260° (decomp.). IR cm^{-1}: 1672 (cyclohexenone). *Anal.* Calcd. for $C_{18}H_{19}O_4N \cdot CH_3I \cdot H_2O$: C, 48.21; H, 5.11; N, 2.96. Found: C, 48.15; H, 5.18; N, 2.81.

Hydrogenation of Compound D (XIV)——Compound D (XIV) (100 mg.) and 10% Pd-C (100 mg.) in EtOH (15 ml.) were stirred in H_2 for 2 hr. at room temperature. Removal of the catalyst and solvent left the dihydro-compound D (XIII) (95 mg.). It crystallized as prisms from EtOH, m.p. 197~198°, $[\alpha]_D$ ±0° (c=3.0, $CHCl_3$). UV $\lambda_{\max}$ mμ (log ε): 235 (3.73), 290 (3.73). IR cm^{-1}: 2770 (NMe_2), 1706 (cyclohexanone), 1420 ($COCH_2$). NMR $\delta_{\text{p.p.m.}}$: −1.21 (OCH_2O), +0.08 ($ArCH_2O$), +0.68 doublet (O-CH<), +2.38 (NMe_2). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.01; H, 6.62.

[*6] The presence of both aldehyde and saturated ketonic function in this compound was confirmed by the polarographic analysis for which the authors are indebted to Dr. M. Masui, Osaka University.

Piperonylidene Derivative of Dihydro-compound D (XIII)——Dihydro-compound D (XIII) (20 mg.), piperonaldehyde (20 mg.), and *tert*-BuOK (20 mg.) in MeOH (5 ml.) were kept at room temperature for 2 days. The mixture was evaporated and the residue washed with ether-light petroleum to remove unchanged piperonaldehyde, and then crystallized from EtOH to give the piperonylidene derivative as pale yellow needles, m.p. 228~230°. UV λ_{max} mμ (log ε): 243 (4.20), 298 (4.06), 343 (4.14). IR cm^{-1}: 2778, 1692, 1670, 1603, 1557. *Anal.* Calcd. for $C_{26}H_{25}O_6N$: C, 69.78; H, 5.63; N, 3.13. Found: C, 69.20; H, 5.40; N, 3.13.

Transformation of Compound C (VI) to Compound D (XIV)——Compound C (VI) (20 mg.) was melted at 160~170° (bath-temperature), then *tert*-BuOK (6 mg.) and a drop of *tert*-BuOH were added, and the whole was maintained at 160° for 10 min. Water was added to the cooled mixture, which was saturated with NH_4Cl, and extracted with benzene. The benzene extract was re-extracted with 5% HCl, the aqueous acidic phase basified with Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated and the residue chromatographed in benzene over alumina. The $CHCl_3$ eluate gave compound D (XIV) (5 mg.), m.p. and mixed m.p. 193~196°.

Sodium Borohydride Reduction of Compound D (XIV)——Compound D (XIV) (0.1 g.) and $NaBH_4$ (0.1 g.) in MeOH (5 ml.) were heated for a few minutes, and kept overnight at room temperature. The solvent was evaporated, the residue taken up in benzene, and chromatographed over alumina. Benzene and benzene-$CHCl_3$ eluates gave the hydroxy-compound (XXIII) (40 mg.). It crystallized in needles from MeOH, m.p. 201~203°. pKa' 6.63. IR cm^{-1}: 3226 (OH). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.99; H, 6.78. This compound depressed the m.p. of compound D to *ca.* 190°.

Further elution with benzene-$CHCl_3$ and with $CHCl_3$ gave the hydroxy-dihydro-compound (XXIV) (42 mg.), m.p. 159~160°, as prisms (from MeOH). pKa' 7.18. IR cm^{-1}: 3378 (OH). *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31. Found: C, 68.20; H, 6.97.

The Hydroxy-dihydro-compound (XXIV)——a) The hydroxy-compound (XXIII) (30 mg.) in EtOH (10 ml.) was hydrogenated in H_2 over PtO_2 (50 mg.) for 2 hr. at room temperature. The product was chromatographed in benzene over alumina afford XXIV (18 mg.), m.p. 167~168°. This is dimorphous with the modification, m.p. 159~160°, obtained above, since the IR spectra of both modifications in $CHCl_3$ were superimposable and they were interchangeable by cross-seeding.

b) The dihydro-compound D (XIII) (20 mg.) in EtOH (10 ml.) was hydrogenated over PtO_2 (50 mg.) and H_2 for 3 hr. Chromatography of the product gave XXIV (15 mg.), m.p. and mixed m.p. 167~168°.

Compound E (XV)——Compound E crystallized from $CHCl_3$ as fine prisms, m.p. 239~240°, which showed no depression on admixture with the original sample,[2] m.p. 230~231°. $[\alpha]_D$ ±0° (c=1.0, acetone). UV λ_{max} mμ (log ε): 235 (4.14), 290 (3.72). IR cm^{-1}: 3390 (OH), 1664 (cyclohexenone). *Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 66.92; H, 4.76.

Acetylation of Compound E (XV)——Compound E (XV) (20 mg.) and Ac_2O (0.5 ml.) in pyridine (1 ml.) were kept at room temperature for 12 hr., poured into H_2O, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried, and evaporated to give the acetate (XVI) (20 mg.). It crystallized in prisms from EtOH, m.p. 204~205°. IR cm^{-1}: 1724 (OAc), 1682 (cyclohexenone) in Nujol mull, 1745 (OAc), 1692 (cyclohexenone) in $CHCl_3$. NMR $\delta_{p.p.m.}$: −1.27 (OCH_2O), −0.79 quartet (>$C\underline{H}$-OAc), +0.10 ($ArCH_2O$), +0.67 doublet (O-CH<), +2.68 ($OCOCH_3$). *Anal.* Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 66.04; H, 5.08.

Dihydro-compound E (XVII)——Hydrogenation of compound E (XV) (20 mg.) in EtOH (20 ml.) over 10% Pd-C for 5 hr. furnished prisms (from benzene), m.p. 236°. IR cm^{-1}: 3390 (OH), 1691 (cyclohexanone) in Nujol mull, 3623 (OH), 1724 (cyclohexanone) in CCl_4 (10^{-4} mol. solution). *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.63; H, 5.78.

Conversion of the Keto-aldehyde (III) to Compound E (XV)——The keto-aldehyde (VIII) (20 mg.) and *tert*-BuOK (10 mg.) in benzene (5 ml.) were stirred for 30 min. at room temperature. The mixture was poured into H_2O which was saturated with NH_4Cl, and extracted with benzene. The benzene extract was washed with H_2O, dried, and evaporated to give compound E (XV), m.p. and mixed m.p. 228~231°.

Oxidation of Compound E (XV)——Compound E (XV) (30 mg.) in pyridine (1 ml.) was added to a suspension of CrO_3 (0.1 g.) in pyridine (1 ml.), and kept at room temperature for 24 hr. The mixture was poured into H_2O and extracted with $CHCl_3$ which was washed with H_2O, dried (Na_2SO_4), and evaporated to leave a solid (25 mg.). Crystallization of this from MeOH and from $CHCl_3$-MeOH furnished the diketone (XVIII) as needles, (10 mg.), m.p. 230~232°. UV λ_{max} mμ (log ε): 234 (4.10), 291 (3.75). IR cm^{-1}: 1757 (cyclopentanone), 1672 (cyclohexenone). *Anal.* Calcd. for $C_{16}H_{12}O_5 \cdot \frac{1}{2}H_2O$: C, 65.52; H, 4.47. Found: C, 65.74; H, 4.09. The diketone (XVIII) decomposed upon chromatography over acid-washed alumina.

Alkaline Treatment of the Diketone (XVIII)——Diketone (XVIII) (20 mg.) in 3% aq. NaOH (3 ml.) and EtOH (1 ml.) was heated on a water-bath for 20 min. The mixture was diluted with H_2O which was saturated with NH_4Cl, and extracted with $CHCl_3$ to remove some neutral substances (2 mg.). The aqueous layer was acidified with HCl, and extracted with EtOAc. The organic layer was washed with a saturated NaCl solution, dried, and evaporated to yield the keto-acid (XIX) which crystallized as needles from EtOH (15 mg.), m.p. 217~218°. UV λ_{max} mμ (log ε): 234 (4.17), 291 (3.79). IR cm^{-1} 1660 (cyclohexenone), 2670~2530 and 1745 (COOH). *Anal.* Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 62.93; H, 4.88.