[Chem. Pharm. Bull. 24(4) 661—666 (1976)]

UDC 547.94.02 : 581.192

A Revised Structure of Tomatillidine

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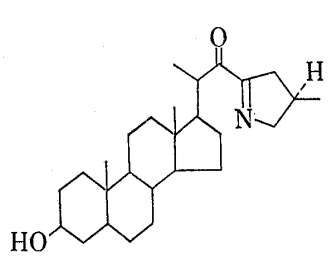
(Received June 28, 1975)

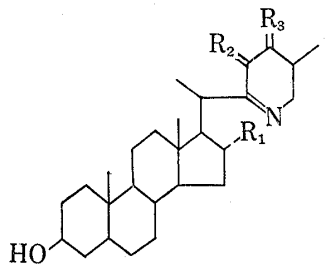
Chemical studies have shown that tomatillidine and dihydrotomatillidine, steroidal alkaloids obtained from *Solanum tomatillo*, are described in revised structures **1a** and **2a** instead of the old structures **1b** and **2b**. An isomerization of $\Delta^{22(N)}$-22,26-imino-23-one moiety to $\Delta^{23(N)}$-23,26-imino-22-one is a major topic.

Introduction

Tomatillidine and dihydrotomatillidine were isolated from *Solanum tomatillo* and the structures **1b** and **2b** were proposed.[2] On the other hand, 24-oxosolacongestidine, for which the structure **2b** was proposed, was obtained as well as solafloridine (**3**), solacongestidine (**4**) and 23-oxosolacongestidine (**5**) as aglycones of glycosides of *S. congestiflorum*.[3] Although the same structure **2b** was proposed for dihydrotomatillidine and 24-oxosolacongestidine, they are different in some properties, especially in the optical rotatory dispersion (ORD) curves and nuclear magnetic resonance (NMR) spectra. In the course of studies to clarify the structural relationship between dihydrotomatillidine and 24-oxosolacongestidine, it happened to find out that the preparation of 23-oxosolacongestidine (**5**) changed on thin-layer chromatography (TLC) plates to other compounds, which were confirmed as mixtures of dihydrotomatillidine and 24-oxosolacongestidine after the separation and comparison of the spectroscopic properties with the authentic specimens. Therefore, the structures of tomatillidine, dihydrotomatillidine and 24-oxosolacongestidine seemed to be somewhat in doubt, because the change of 23-oxosolacongestidine to 24-oxosolacongestidine and dihydrotomatillidine on TLC plates is a kind of an isomerization, but not a combination of reduction of a carbonyl group and oxidation of a methylene group.



1a : Δ^5
2a : 5α-H



1b : Δ^5, R_1=H, R_2=H_2, R_3=O
2b : 5α-H, R_1=H, R_2=H_2, R_3=O
3 : 5α-H, R_1=OH, R_2=R_3=H_2
4 : 5α-H, R_1=H, R_2=R_3=H_2
5 : 5α-H, R_1=H, R_2=O, R_3=H_2

Chart 1

1 *a*) Location: *Aobayama, Sendai, Japan*; *b*) *Bethesda, Maryland 20014, U. S. A.*
2) E. Bianchi, C.D. Djerassi, H. Budzikiewicz, and Y. Sato, *J. Org. Chem.*, **30**, 754 (1965).
3) Y. Sato, Y. Sato, H. Kaneko, E. Bianchi, and H. Kataoka, *J. Org. Chem.*, **34**, 1577 (1969).

We would like to report our data to support the revised structures **1a** and **2a** of tomatillidine and dihydrotomatillidine.

Isomerization

Now 23-oxosolacongestidine was converted into 24-oxosolacongestidine and dihydrotomatillidine, we tried to make sure of this isomerization. A pseudo compound, 3,16-di-O-acetylpseudosolasodine (**7**), which is prepared from solasodine (**6**) under a treatment with acetic acid-acetic anhydride-Zinc chloride,[4] was oxidized with Selenium oxide in dioxane. Although this reaction seemed to afford one major product (**8**) with traces of another product (**9**) on a TLC plate at first, actually two products were obtained in 1:1 ratio through separation using preparative TLC plates, that suggested us a possibility of an isomerization from the major product to the other. Then, the starting compound (**7**) was oxidized with active Manganese dioxide in $CHCl_3$, in which 23-oxocompound (**8**) is expected,[3] the product was purified through recrystallization. The product (**8**), mp 181—185°, $C_{31}H_{45}O_5N$, provided the isomeric compound (**9**), mp 184°, $C_{31}H_{45}O_5N$, in 60% yield after 2 days leaving on TLC plates.

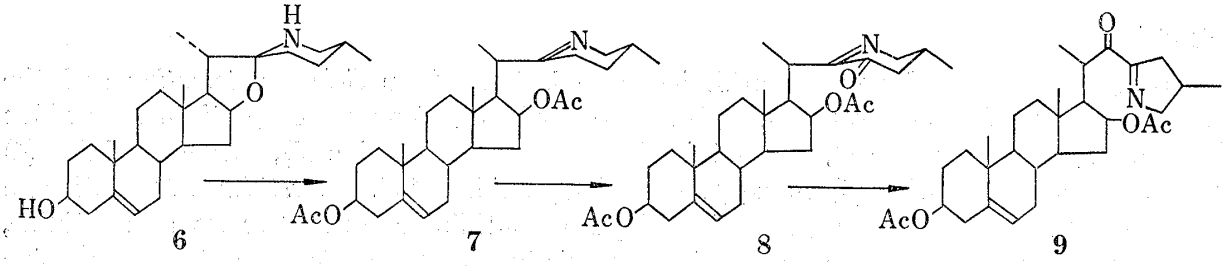


Chart 2

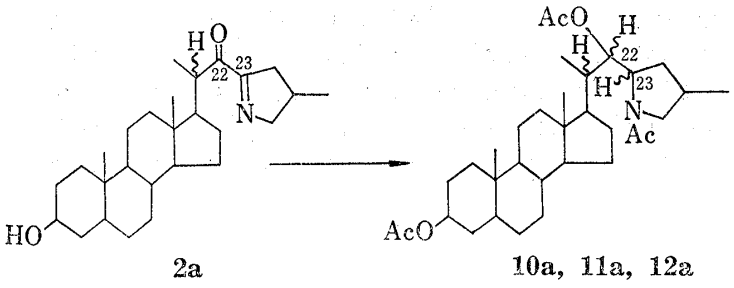
Evidences of the New Structures 1a and 2a for Tomatillidine and Dihydrotomatillidine

In order to certify the structure **2a** of dihydrotomatillidine (**2**), which is rather suitable for the following experiment, because of the absence of a vinyl proton's signal in the NMR spectrum and has been prepared from tomatillidine by catalytic hydrogenation, a sodium boron hydride reduction of dihydrotomatillidine was carried out, followed by acetylation to produce three kinds of triacetyl derivatives (**10**, **11**, **12**). The signals assigned to the proton on C_{22} of the new structures **10a**, **11a** and **12a** in their NMR spectra appear at 5.24 ppm as a quartet (J=8, 1 Hz) in **10**, mp 129—133°, $C_{33}H_{53}O_5N$, at 5.36 ppm as a doublet (J=4 Hz) in **11**, mp 122—125°, $C_{33}H_{53}O_5N$ and at 5.46 ppm as a quartet (J=4, 2 Hz) in **12**, mp 157—159°, $C_{33}H_{53}O_5N$. More complicated signals with bigger coupling constants should have been expected for the proton on C_{24} of the structures **10b**, **11b** and **12b** derived from the old structure **2b** of dihydrotomatillidine.

The experiment of decoupling using the compound (**12**) provided another strong support for the new structure (Fig. 1). On the irradiation at the center (5.46 ppm) of the quartet, which are assigned to C_{22}-H, sharpened signals, which are assigned to C_{23}-H, are recognized. Reversely, on the irradiation at C_{23}-H signals, the change of the quartet to a doublet is realized. This result cancels the structure **2b** definitely.

Solasodine (**6**) was chosen as starting compound to make sure of the new structure **1a** of tomatillidine. 3-O-Acetylsolasodine (**13**), which was prepared with acetic acid-*p*-toluenesulfonic acid,[5] was reduced with sodium boron hydride to a dihydro derivative (**14**). The benzyloxy derivative (**15**) was oxidized to 16-oxo compound (**16**), the thioketal (**17**) of which was treated with Raney-Ni to the alkamine (**18**). The chlorination of this compound and dehydrochlorination of N-chloride (**19**) afforded $\Delta^{22(N)}$-22,26-imino compound (**20**), which was oxidized with

4) Y. Sato, H.G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, **22**, 1496 (1957).
5) G. Kusano, N. Aimi, and Y. Sato, *J. Org. Chem.*, **35**, 2624 (1970).



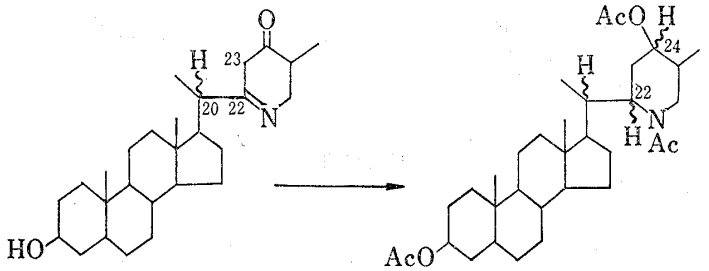


Chart 3

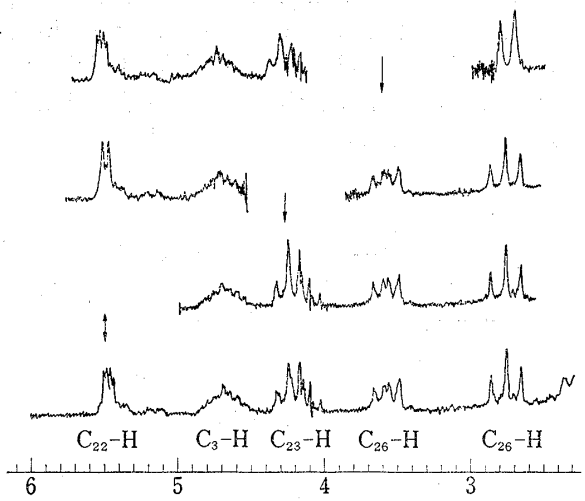


Fig. 1

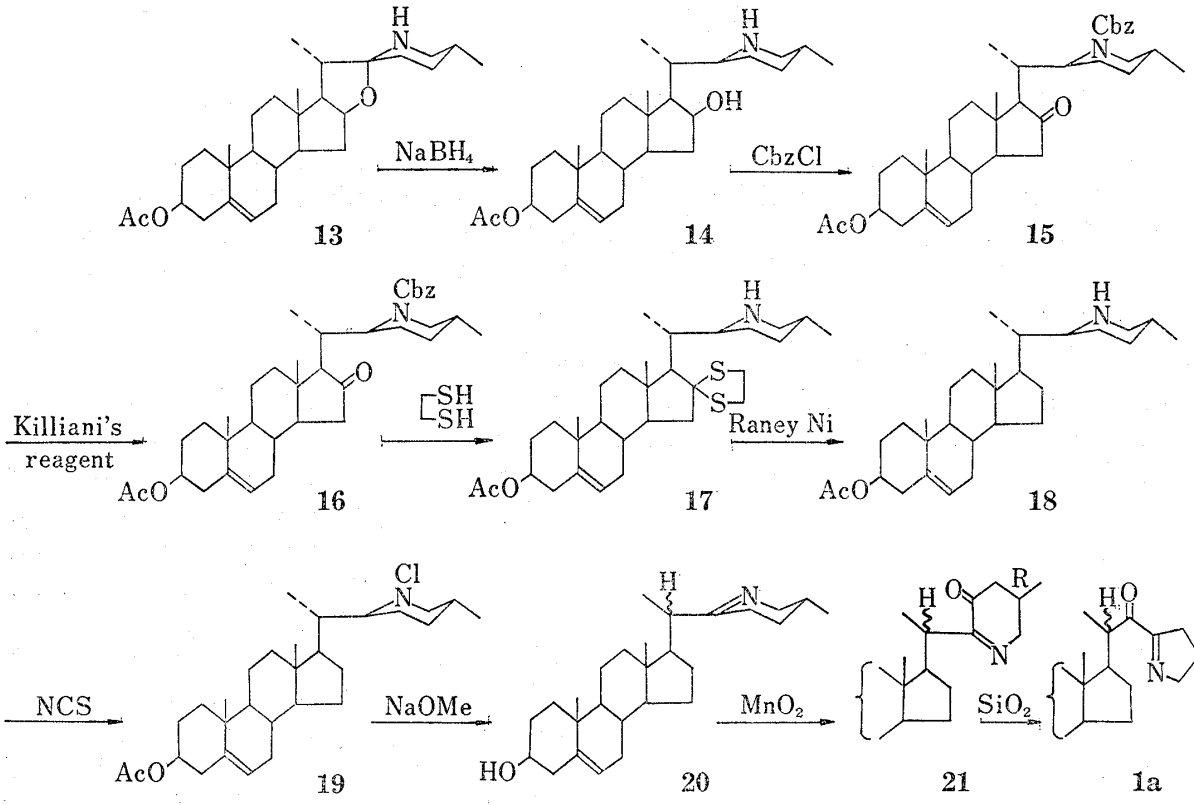


Chart 4

active Manganese dioxide in chloroform to 23-oxo-compound (**21**). The last compound was converted to the isomeric compound, which was identified to tomatillidine, on TLC plates.

The old structure **1b** of tomatillidine was proposed on the basis of the spectroscopic data of tomatillidine and its derivatives, and the results of chemical reactions with deoxotomatillidine, which was obtained by Wolf-Kishner reduction of tomatillidine. The spectroscopic data of tomatillidine and its derivatives support the new structures **1a** and **2a**, too. The main fragment ion at *m/e* 140 in the mass spectra of tomatillidine, dihydrotomatillidine and O-acetyltomatillidine is supposed to be produced through the process depicted as indicated in

Chart 5 while the possible explanation was proposed as described in Chart 6.[2] The most abundant ion at *m/e* 114 in the mass spectrum of hexahydrotomatillidine is thought to be formed by cleavage of 20,22-bond as in Chart 7, which the expected manner was proposed as in Chart 8.[2] The doublet (J=3 Hz) at 6.05 ppm in the NMR spectrum of O,N-diacetyl-Δ^{22}-tomatillidine is ascribed to the C_{23}-olefinic proton more reasonably in the new structure than in the old structure (Chart 9).[2]

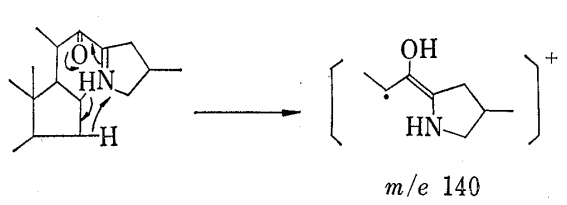


Chart 5

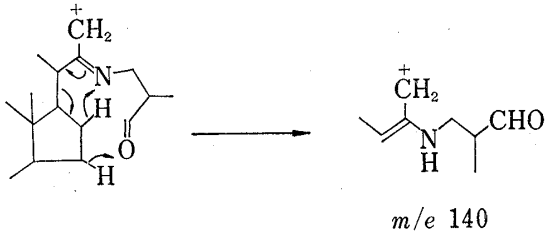


Chart 6

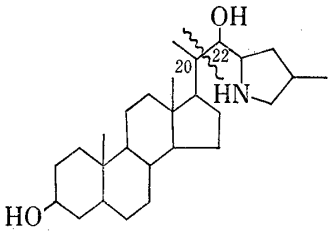


Chart 7

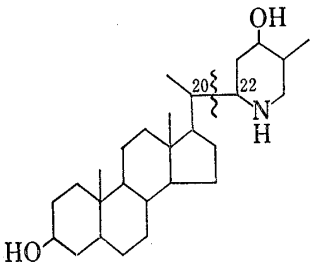


Chart 8

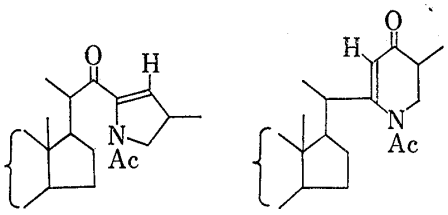


Chart 9

On the other hand, the results of chemical reactions with deoxotomatillidine is not rationalized until a reversion of tomatillidine to 23-oxo-$\Delta^{22(N)}$-22,26-iminocholestanol before the reduction of a carbonyl group during a treatment of Wolf-Kishner reduction is elucidated, but it should be kept in mind that special experiments would be necessary to establish this suspected transformation.

Stereochemistry of Tomatillidine and Dihydrotomatillidine

During the transformation from solasodine (**6**) to tomatillidine (**1**), any change of the configuration is not suspected, except the orientation of the C_{20}-methyl group, suggesting C_{25R} configuration in **1a** and **2a**. Because the same circular dichroism (CD) curves are observed in **1**, **2** and synthesized tomatillidine (**2**), the same stereochemistry in the side chain moeity is concluded for them (Fig. 2). When dihydrotomatillidine (**2**) was treated with 90% aqueous MeOH–conc.HCl (20:1) mixture, with which the glycosides of *Solanum congestiflorum* were hydrolysed,[3] 24-oxosolacongestidine was found with others, the structures of which have not been concluded. After all, the stereochemistry of tomatillidine and dihydrotomatillidine is illustrated in **1a** and **2a**, in which orientation of the methyl group on C_{20} is still obscure. Dihydrotomatillidine and 24-oxosolacongestidine should be stereoisomers at C_{20} and/or C_{25} configuration. An experiment for the confirmation of this point is on working.

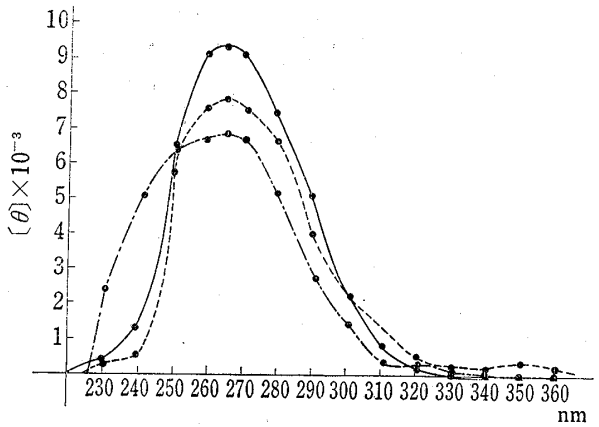


Fig. 2. CD Curves of Tomatillidine, Synthesised Tomatillidine and Dihydrotomatillidine (MeOH)

——: dihydrotomatillidine
--------: synthesised tomatillidine
——: tomatillidine

Experimental[6]

Selenious Acid Oxidation of 3,16-di-O-Acetylpseudosolasodine (7)——A pseudo compound, 3,16-di-O-acetylsolasodine (**7**), 450 mg was dissolved to dioxane 20 ml containing a few drops of water and SeO_2 100 mg was added to the solution, heating on steam bath for 2 hr. Ethyl acetate 100 ml was added and the solution was passed through Al_2O_3 5 g. The eluate was condensed and the residue was separated on a TLC plate (20×20 cm², 2000 μm thick, silica gel GF, solvent: benzene–AcOEt (4: 1)), 4 fractions were separated and the two highest bands were joined to rechromatograph on 8 TLC plates. The highest band gave colorless needles (**9**, 178 mg) after recrystallization from AcOEt, mp 184°. *Anal.* Calcd. for $C_{31}H_{45}O_5N$: C, 72.76; H, 8.86; N, 2.74. Found: C, 72.63; H, 9.15; N, 2.48. Mass Spectrum *m/e*: 511 (M^+), 451 (M^+–AcOH), 391 (M^+-2×AcOH), 140 (base peak). UV λ_{max}^{EtOH} nm (ε): 270 (170), 210 (7700, end absorption). IR $\nu_{max}^{CHCl_3}$ cm⁻¹: 1729 (OAc), 1692 (CO), 1614 (C=N). NMR ($CDCl_3$) ppm: 5.40 (1H, m, C_6–H), 5.01 (1H, m, C_{16}–H), 4.76 (1H, m, C_3–H), *ca.* 4.0 (2H, m, C_{26}–2H), 2.03 (3H, s, OAc), 1.79 (3H, s, OAc), 1.18 (3H, d, J=7 Hz), 1.08 (3H, d, J=7 Hz), 1.03 (3H, s), 0.93 (3H, s). The second highest band provided yellow needles (**8**, 194 mg) after recrystallization from AcOEt, mp 181—185°. *Anal.* Calcd. for $C_{31}H_{45}O_5N$: C, 72.76; H, 8.86; N, 2.74. Found: C, 72.63; H, 9.15; N, 2.48. Mass Spectrum *m/e*: 511 (M^+, base peak), 451 (M^+–AcOH). UV λ_{max}^{EtOH} nm (ε): 277 (260), 230 (2500, end absorption). IR $\nu_{max}^{CHCl_3}$ cm⁻¹: 1725 (OAc), 1703 (CO), 1630 (C=N). NMR ($CDCl_3$) ppm: 5.37 (1H, m, C_6–H), 5.05 (1H, m, C_{16}–H), 4.75 (1H, m, C_3–H), 2.02 (3H, s, OAc), 1.80 (3H, s, OAc), 1.03 (3H, s), 1.04 (3H, d, J=7 Hz), 0.99 (3H, d, J=7 Hz), 0.95 (3H, s).

Manganese Dioxide Oxidation of 3,16-di-O-Acetylsolasodine (7)——3,16-di-O-Acetylpseudosolasodine (473 mg) was dissolved to $CHCl_3$ 50 ml and active MnO_2 5 g was added, stirring for 4 hr at room temperature. The inorganic material was filtered and washed with $CHCl_3$. The combined solution was passed through an Al_2O_3 coloumn (10 g), the eluate was condensed and the residue was recrystallized from MeOH to give yellow needles 352 mg. TLC, mp, IR, NMR-spectrum showed the same results to **8** at the above experiment.

Isomerization of 23-Oxo-3,16-di-O-acetylpseudosolasodine (8) on TLC Plates——23-Oxo-compound (**8**, 210 mg) was dissolved to $CHCl_3$ 20 ml and the solution was dropped on a whole TLC to stand on for 2 days. Silica gel was collected and extracted with AcOEt. The solvent was evaporated and the residue was separated on 4 TLC plates (solvent: benzene–AcOEt (4: 1)). The highest moved fraction was recrystallized from MeOH to give pale yellow flakes 130 mg, identifed to **9**.

Reduction and Acetylation of Dihydrotomatillidine (2)——Dihydrotomatillidine 111 mg was dissolved to MeOH 20 ml and $NaBH_4$ 200 mg was added, stirring at room temperature over night. Water was added, then the precipitate was filtered, washed and dried. The dried precipitate was acetylated with pyridine–acetic anhydride at room temperature over night. TLC showed three kinds of the products with traces of others. They were separated on 2 preparative TLC plates (solvent: benzene–AcOEt (4: 1), twice developed). The highest moved fraction afforded needles (**10a**, 26 mg) after recrystallization from hexane, mp 129—133°. *Anal.* Calcd. for $C_{33}H_{53}O_5N$: C, 72.89; H, 9.82, N, 2.58. Found: C, 72.76; H, 9.72; N, 2.44. IR $\nu_{max}^{CHCl_3}$ cm⁻¹: 1730 (OAc), 1660 (NAc). NMR ($CDCl_3$) ppm: 0.71 (3H, s), 0.81 (3H, s), 0.85 (3H, d, J=6.5 Hz), 1.03 (3H, d, J=6.5 Hz), 2.04 (6H, s, 2 OAc), 2.08 (3H, s, NAc), 2.74 (1H, t, J_1=J_2=10 Hz, C_{26}–H), 3.56 (1H, q, J_1=10, J_2=8 Hz, C_{26}–H), 4.22 (1H, octet, J_1=12, J_2=8, J_3=1 Hz, C_{23}–H), 4.67 (1H, m, C_3–H), 5.24 (1H, q, J_1=8, J_2=1 Hz, C_{22}–H). The second highest fraction gave needles (**11a**, 30 mg) after recrystallization from AcOEt, mp 122—125°. *Anal.* Calcd. for $C_{33}H_{53}O_5N$: C, 72.89; H, 9.82; N, 2.58. Found: C, 72.71; H, 9.62; N, 2.24. IR $\nu_{max}^{CHCl_3}$ cm⁻¹: 1730 (OAc), 1662 (NAc). NMR ($CDCl_3$) ppm: 0.60 (3H, s), 0.85 (3H, s), 0.90 (3H, d, J=6.5 Hz), 1.22 (3H, d, J=6.5 Hz), 2.96 (1H, t, J_1=J_2=10 Hz), 3.24 (1H, q, J_1=10, J_2=5 Hz, C_{26}–H), 4.28 (1H, m, C_{23}–H), 4.67 (1H, m, C_3–H), 5.36 (1H, d, J=4 Hz, C_{22}–H). The third fraction gave needles (**12a**, 45 mg) after recrystallization from AcOEt, mp 157—159°. *Anal.* Calcd. for $C_{33}H_{53}O_5N$: C, 72.89; H, 9.82; N, 2.58. Found: C, 72.80; H, 9.81; N, 2.47. IR $\nu_{max}^{CHCl_3}$ cm⁻¹: 1728 (OAc), 1665 (NAc). NMR ($CDCl_3$) ppm: 0.71 (3H, s), 0.80 (3H, s), 0.85 (3H, d, J=7 Hz), 1.03 (3H, d, J=6.5 Hz), 2.04 (3H, s, OAc), 2.07 (3H, s, OAc), 2.74 (1H, t, J_1=J_2=10 Hz, C_{26}–H), 3.66 (1H, q, J_1=10, J_2=8 Hz, C_{26}–H), 4.20 (1H, o, J_1=2, J_2=8, J_3=14 Hz, C_{23}–H), 4.7 (1H, m, C_3–H), 5.46 (1H, q, J_1=2, J_2=4 Hz, C_{22}–H).

N-Benzyloxy Derivative (15) from O-Acetyldihydrosolasodine (14)[5]——O-Acetyldihydrosolasodine (**14**, 34.8 g) was suspended to benzene 1000 ml and 5% $NaHCO_3$ 500 ml was added while stirring at room temperature. CbzCl 35 ml was added dropwise with drastic stirring for 30 min. After the addition of the rea-

6) Melting points were determined on Kofler and Yanagimoto hot stages and are uncorrected. Microanalyses were performed by the Microanalysis Services Unit of NIADD of NIH and the Analysis center of Pharmaceutical Institute of Tohoku University. Infrared (IR) spectra were obtained with Perkin-Elmer Model 421 and Shimazu IR-27G photometers. NMR spectra were determined on the Model A-60 and HA-100 Varian Associates spectrometers and Hitachi Perkin-Elmer R-20 and JEOL PS-100 spectrometers using tetramethylsilane as internal standard. Mass spectra were measured with AEI MS-9 and Hitachi RUM-7 spectrometers. CD curves were measured with a JASCO DIP-SL polarimeter. TLC plates were precoated with silica gel GF and purchased from Andltech. Inc., Wilmington, Del., U. S. A. Precoated 20×20 cm², 250 mμ thick TLC plates were used for preparative TLC unless otherwise specified.

gent, the mixture was stirred for 10 hr. The precipitate was removed and the benzene layer from the filtered solution was separated, washed and dried over Na_2SO_4. Benzene was evaporated and the residue was chromatographed on Al_2O_3 200 g. Hexane–benzene (1: 1) eluate gave needles (**15**, 35.5 g) after recrystallization from hexane–benzene (1: 1), mp 124—127°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (OAc), 1670 (NC=O). *Anal.* Calcd. for $C_{37}H_{53}O_5N$: C, 75.09; H, 9.03; N, 2.37. Found: C, 75.01; H, 9.00; N, 2.21.

Oxidation of N-Benzyloxy-carbonyl Compound (15)——O-Acetyl-N-benzyloxydihydrosolasodine (30.0 g) was dissolved to acetone 500 ml and Killiani's reagent 50 ml was added to the solution while stirring at room temperature. After standing over night, MeOH 10 ml and then water were added and the mixture was extracted with $CHCl_3$, where the $CHCl_3$ layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on SiO_2 150 g. Benzene–AcOEt (19: 1) eluate gave needles (**16**, 28.1 g) after recrystallization from hexane–benzene (1: 1), mp 162—164°. IR $\nu_{max}^{CHCl_3}cm^{-1}$; 1734 (OAc, C=O), 1687 (NC=O). *Anal.* Calcd. for $C_{37}H_{51}O_5N$: C, 75.34; H, 8.72; N, 2.38. Found: C, 75.11; H, 8.71; N, 2.29.

Thioketal (17) from the 16-Oxo-derivative (16)——After N-benzyloxy-carbonyl-16-oxo compound (**16**, 3.23 g) was dissolved to AcOH 30 ml, 1,2-ethanedithiol (1 ml) and *p*-TsOH (1.41 g) were added while stirring at room temperature. After 3 days' stirring, the reaction solution was poured into water 100 ml and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with $NaHCO_3$ solution, water and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was chromatographed on SiO_2 10 g. The benzene–AcOEt (20: 1) eluate gave needles (**17**, 2.91 g) after recrystallization from EtOH–acetone mp 115—118°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (OAc), 1687 (NC=O). *Anal.* Calcd. for $C_{39}H_{55}O_4NS_2$: C, 70.44; H, 8.29; N, 2.11. Found: C, 70.55; H, 8.34; N, 2.22.

O-Acetyl Deoxosolasodine (18)——The thioketal (**18**, 2.70 g) was dissolved to ab. EtOH 100 ml, and Raney-Ni 20 g was added with help of ab. EtOH 100 ml. After 4.5 hr' refluxing, the reaction solution was left at room temperature over night. Raney-Ni was removed, the solution was condensed, and then the residue was recrystallized from AcOEt, needles (**18**, 1.86 g), mp 256—257°. *Anal.* Calcd. for $C_{29}H_{47}O_2N$: C, 78.86; H, 10.73; N, 3.17. Found: C, 78.98; H, 10.42; N, 2.85.

O-Acetyl-N-Cl-deoxosolasodine (19)——The acetate (**18**, 0.375 g) was dissolved to $CHCl_3$ 30 ml and N-Cl-succinimide 0.217 g was added to stand at room temperature over night. Water was added and the $CHCl_3$ layer was separated, washed with water 5 times and dried over Na_2SO_4. The solvent was evaporated and the residue was recrystallized from MeOH, needles (**19**, 0.253 g), mp 275—279° (decomp). *Anal.* Calcd. for $C_{29}H_{46}O_2NCl$: C, 73.30; H, 9.76; N, 2.95. Found: C, 73.07; H, 9.62; N, 2.94.

$\Delta^{22(N)}$-22,26-Imino Compound (20)——N-Chloride (**19**, 142.6 mg) was refluxed under a flow of nitrogen gas in MeOH 50 ml containing 1 g of sodium metal for 2 hr, MeOH was evaporated and water was added to produce precipitates, which were filtered and dried. A silica gel chromatography was undertaken, and the eluate with benzene–AcOEt (3: 1) gave needles (**20**, 87 mg) after recrystallization from MeOH–aq·NH_3, mp 169—171°. *Anal.* Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90; N, 3.52. Found: C, 81.41; H, 10.77; N, 3.38. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3300, 1650 (C=N). NMR ($CDCl_3$) ppm: 0.70 (3H, s), 0.91 (3H, d, J=6 Hz), 0.99 (3H, s), 1.07 (3H, d, J=6 Hz), 5.32 (1H, m, vinyl proton).

23-Oxo-derivative (21)——The compound (**20**, 200 mg) was dissolved to $CHCl_3$ 30 ml and active MnO_2 1 g was added, stirring at room temperature for 2 hr. The reagent was removed and the solution was passed through an Al_2O_3 (10 g) column with $CHCl_3$–AcOEt (1: 1). The solvent was evaporated, and the residue was recrystallized from MeOH, yellow needles (**21**, 140 mg), mp 215—220°. *Anal.* Calcd. for $C_{27}H_{41}O_2N$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.61; H, 9.89; N, 3.19.

Isomerization to Tomatillidine (1) from 23-Oxo Compound (21)——23-Oxo compound (**21**, 100 mg) was dissolved to $CHCl_3$ 10 ml and the solution was put on a TLC plate to leave for 3 days. The silica gel was collected and extracted with AcOEt. The solution was condensed and the residue was separated on TLC plates. The highest band gave colorless needles (**2**, 33 mg) which were identified to tomatillidine by comparing with the authentic specimen in IR, NMR, and mass spectra, and ORC curves.

Acknowledgement Most parts of chemical research on tomatillidine, dihydrotomatillidine and 24-oxosolacongestidine were undertaken by the previous workers, for whom the present authors appreciate so much.