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Total Synthesis of the Lycopodium Alkaloid *dl*-Serratinine[1)]

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Total synthesis of *dl*-serratinine (**1**:*dl*-form) has been completed as follows. The Wittig reaction of the aldehyde (**6**) with diethylcyanomethylphosphonate gave the conjugated nitrile (**7**) which was subjected to hydrogenation, followed by $NaBH_4$–$CoCl_2$ reduction to provide the primary amine (**10**). Treatment of (**10**) with NCS and Cu_2Cl_2 gave the aziridine A (**11**) and the aziridine B (**12**). The aziridine A was derived to the aziridinium salt (**14**) *via* the primary alcohol (**13**) and its tosylate, and the reaction of **14** with AcOK afforded the triacetate (**15**). Hydrolysis of **15**, followed by oxidation with Jones' reagent gave the triketone (**18**). Finally, reduction of **18** with $NaBH_4$ afforded *dl*-serratinine (**1**:*dl*-form) and *dl*-8-episerratinine (**19**:*dl*-form).

Serratinine is the major alkaloid of *Lycopodium serratum* Thunb. var. *serratum* f. *serratum* and its absolute structure has been shown to possess the structure (**1**).[3)] This alkaloid is a good target for synthesis because of its unique ring system. However, the complication of the stereochemistry (serial six chiral centers including two adjacent quaternary carbon atoms) had prevented a total synthesis of this alkaloid. We reported a complete synthesis of *dl*-serratinine in a preliminary communication[1)] and this paper concerns with a full detail of the synthesis of this alkaloid.

In previous papers,[4,5)] we have reported the Diels-Alder reaction of **2** with butadiene, followed by Zn–AcOH reduction, $NaBH_4$ reduction, acetylation, OsO_4–$NaClO_3$ oxidation, and catalytic hydrogenation provided the diol (**3**) which gave the dialdehyde (**4**) by periodic acid oxidation. Treatment of **4** with basic alumina or piperidine and AcOH in dry benzene[6)] gave only the aldehyde (**5**), whereas treatment with excess pyrrolidine and AcOH in dry MeOH[5)] afforded selectively the aldehyde (**6**). A complete synthesis of serratinine starting from this aldehyde is described in this paper.

The Wittig reaction of the aldehydes [a mixture of **6** and **5** in an 8/1 ratio] with diethyl cyanomethylphosphonate and sodium hydride, followed by silica gel chromatography gave the conjugated nitrile (**7** and **8**) in 66 and 8% yields, respectively. From their nuclear magnetic resonance (NMR) spectra, it was found that the compound (**7**) is a 1/1 mixture of two geometrical isomers and that the compound (**8**) is a single *trans* isomer. The structures of **7** and **8** were deduced from the component ratio (8/1) of the starting material and from the similar signal patterns of allylic protons in **7** and **8**, respectively, with those of the α,β-unsaturated aldehydes (**6** and **5**)[5)] in their NMR spectra. Catalytic hydrogenation of **7** over $(Ph_3P)_3RhCl$

1) A preliminary communication of this work appeared in *J. Chem. Soc., Chemical Commun.*, **1974**, 827.
2) Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*
3) Y. Inubushi, H. Ishii, B. Yasui, M. Hashimoto, and T. Harayama, *Chem. Pharm. Bull.* (Tokyo), **16**, 82 (1968); *idem*, *ibid.*, **16**, 92 (1968); Y. Inubushi, H. Ishii, B. Yasui, and T. Harayama, *ibid.*, **16**, 101 (1968); K. Nishio, T. Fujiwara, K. Tomita, H. Ishii, Y. Inubushi, and T. Harayama, *Tetrahedron Letters*, **1969**, 861.
4) T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Pharm. Bull.* (Tokyo), **21**, 25 (1973).
5) T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Pharm. Bull.* (Tokyo), **21**, 1061 (1973).
6) R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W.M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952).

in benzene gave solely the nitrile (**9**) in 75% yield, the NMR spectrum of which revealed one olefinic proton signal at 5.65 δ.

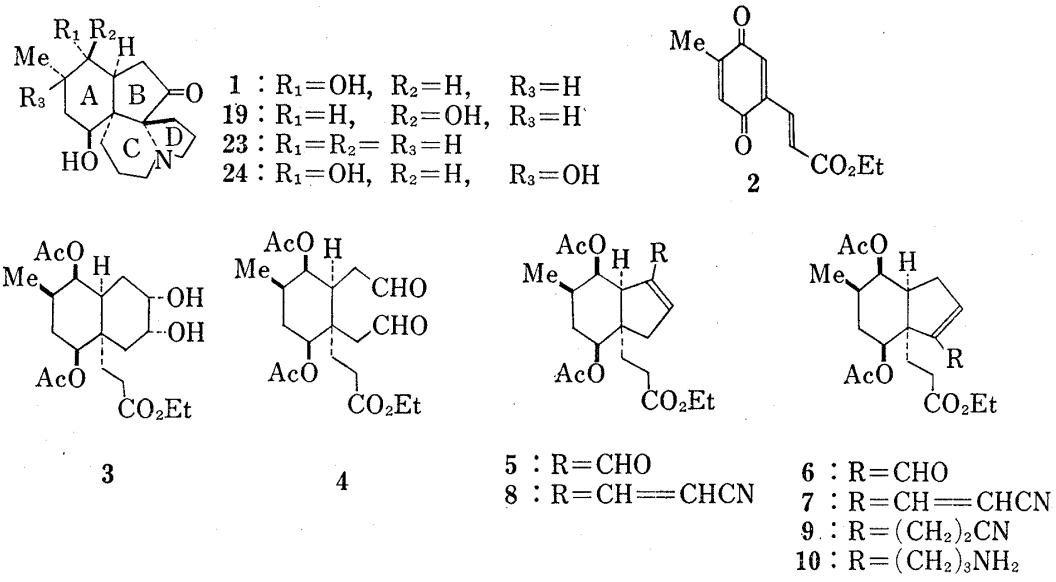


Chart 1

Selective reduction of a cyano group of **9** with $NaBH_4$–$CoCl_2$[7] afforded the primary amine (**10**) which without purification was allowed to react successively with NCS and Cu_2Cl_2 in CH_2Cl_2 to give the aziridine A (**11**: mp 127—129°) and the aziridine B (**12**: mp 82—84°) in 20 and 3% yields, respectively. The NMR spectra of the aziridine A and B showed the presence of two secondary acetoxyl groups and no olefinic proton singal. These aziridines were basic and revealed the correct analytical values, and the fragmentation patterns in their mass spectra were very similar to each other. All these findings suggest that the aziridine A and B are stereoisomeric with respect to the configuration of the aziridine ring. Since the double bond in **10** seems to be attacked preferentially from the convex face, the structure of the main product will be shown by the formula (**11**). The more reliable support for this deduction will be obtained from the chemical reaction described later.

Next, the cleavage reactions of the aziridine ring of **11** with various kinds of nucleophiles, AcONa, AcSK, and NaI were investigated in anticipation of the formation of the D ring of serratinine but no desirable cleavage product was obtained.

For this purpose, an attempt was then made to employ the aziridinium salt which seems to be more reactive species to these nucleophiles. Thus, selective reduction of the ethoxycarbonyl group of **11** with $LiBH_4$ gave the primary alcohol (**13**) in 74% yield. The NMR spectrum of **13** revealed signals due to carbinol methylene protons at 3.61 δ (2H, m.), a signal due to a hydroxyl proton at 2.65—3.05 δ (1H, m., exchangeable with D_2O), and signals due to the ethoxycarbonyl group observed in **11** disappeared. Treatment of **13** with TsCl-pyridine gave the water soluble aziridinium salt (**14**) which without purification was allowed to react with AcOK in dry ethanol to give the triacetate (**15**) possessing the serratinine ring system and an oxygen function on the B ring, in 33% yield from the compound (**13**). The NMR spectrum of **15** showed signals due to three secondary acetoxyl groups at 5.23—4.68 δ (3H, m.), 2.10 δ (6H, s.), and 2.02 δ (3H, s.). The fact that the intramolecular quaternarization of the compound (**13**) thus occurred readily, suggests the *cis* relationship of the aziridine ring with the angular side chain, and inspection of the Dreiding model showed that this type quaternarization may not take place if the aziridine ring and the angular side chain are in the

7) T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, and Z. Imai, *Tetrahedron Letters*, **1969**, 4555.

trans relationship to each other. Thus, the relative configuration of the aziridine ring was ascertained. The same skeletal structure of the triacetate (**15**) as that of serratinine was suggested from the similar mass spectrum fragmentation pattern of **15** to that of the triacetate (**16**) of β-dihydroserratinine.[3]

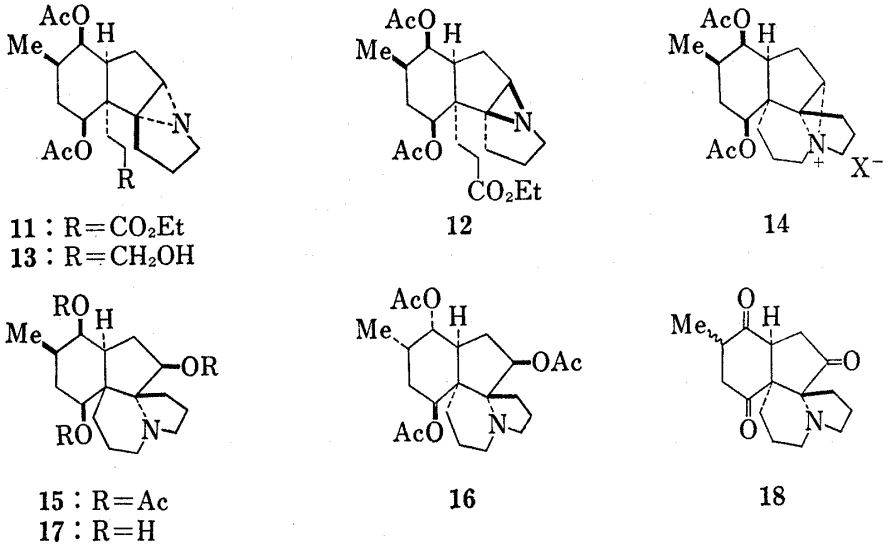
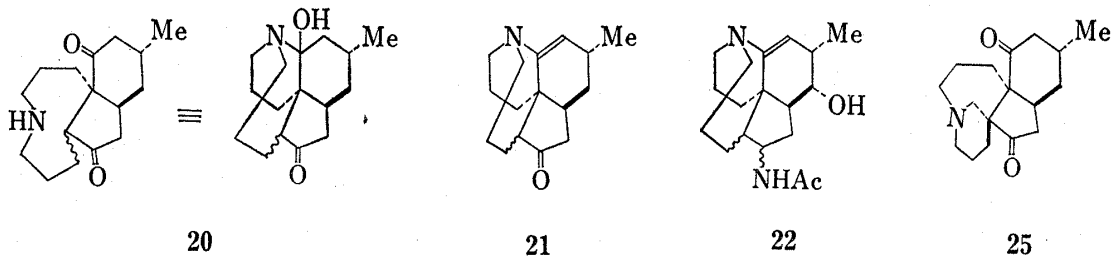


Chart 2

Trials of partial hydrolysis of the triacetate (**15**) were unfruitful. Hydrolysis of **15** with 5% KOH–MeOH provided the triol (**17**) in 87% yield which was oxidized with Jones' reagent to give the triketone (**18**) in 40% yield. The infrared (IR) spectrum of **18** revealed a band due to a five-membered ring ketone at 1735 cm^{-1} and a band due to six-membered ring ketones at 1710 cm^{-1}. The NMR spectrum of **18** suggested that the triketone is a mixture of two kinds of compounds. Since it has been known that the ring junction of A and B ring of serratinine derivative is not epimerized under these reaction conditions,[3] the product (**18**) is assumed to be an epimeric mixture arising from the configuration of a secondary methyl group.

Finally, reduction of the triketone (**18**) with $NaBH_4$ yielded *dl*-serratinine (**1**: *dl*-form), mp 202—203° and *dl*-8-episerratinine (**19**: *dl*-form), mp 205—207°, in 18 and 25% yields, respectively. These two compounds were identical in all respects except the melting points and specific rotations, with authentic specimens of serratinine and 8-episerratinine, respectively.

Since structure elucidation of fawcettimine (**20**),[8] fawcettidine (**21**),[8] serratinidine (**22**),[8] 8-deoxyserratinine (**23**),[8] and serratanidine (**24**)[9] were accomplished by chemical conversion



20 21 22 25

Chart 3

8) H. Ishii, B. Yasui, R. Nishino, T. Harayama, and Y. Inubushi, *Chem. Pharm. Bull.* (Tokyo), **18**, 1880 (1970).
9) Y. Inubushi, T. Harayama, M. Akatsu, H. Ishii, and Y. Nakahara, *Chem. Pharm. Bull.* (Tokyo), **16**, 2463 (1968).

of serratinine to these alkaloids, and most recently, Ayer *et al.* succeeded in the chemical conversion of fawcettimine (**20**) to lycoflexine (**25**),[10] the present synthesis amounts to formal syntheses of these alkaloids.

Experimental

All melting points were determined with a microscopic hot-stage apparatus and uncorrected. Unless otherwise stated, IR spectra were measured for solution in chloroform with a Hitachi EPI spectrometer and NMR spectra were recorded on a Varian A-60 instrument with $CDCl_3$ as a solvent and tetramethylsilane as a reference and chemical shifts are given in δ ppm. Mass spectra were taken with a Hitachi RMU-6C spectrometer with a heated direct inlet system. Thin-layer chromatography (TLC) was carried out on Kieselgel G (nach Stahl) and plates were developed with $Ce(SO_4)_2$. Column chromatography was performed on silica gel (Mallinckrodt, 100 mesh) (A), silica gel (Merck, 70—230 mesh) (B), and alumina (Brockmann Activity II-III) (C).

The Conjugated Nitrile (7) and the Conjugated Nitrile (8)——To a suspension of 1.6 g of sodium hydride (containing a mineral oil in 50% extent) in 200 ml of dry benzene was added portionwise a solution of 6 g of diethyl cycanomethylphosphonate in 50 ml of dry benzene under ice-cooling and a nitrogen atmosphere and the mixture was stirred for 30 min. To this mixture was added dropwise a solution of 7 g of α,β-unsaturated aldehydes [a mixture of **6** and **5** in an 8/1 ratio] in 50 ml of dry benzene. The reaction mixture was stirred for 1 hr, poured into water and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated. The residue in chloroform was chromatographed on silica gel (A:150 g) and the column was eluted with the same solvent. The earlier eluate gave 4.9 g of the α,β-unsaturated nitrile (**7**: colorless oil; a mixture of two geometrical isomers) in 66% yield. IR ν_{max} cm^{-1}: 2230 (CN), 1730 (ester), and 1620 (C=C). NMR δ: 7.14 (0.5H, d., J=17 Hz, olefinic proton), 6.85 (0.5H, d., J=12 Hz, olefinic proton), 6.74 (0.5H, m., olefinic proton), 6.28 (0.5H, m., olefinic proton), 5.52 (0.5H, d., J=17 Hz, olefinic proton), 5.27 (0.5H, d., J=12 Hz, olefinic proton), 4.80—5.25 (2H, m., CH–OAc), 4.12 (2H, q., J=7 Hz, $COOCH_2CH_3$), 2.11, 2.07, and 2.05 (total 6H, $OCOCH_3$), 1.25 (3H, t., J=7 Hz, $COOCH_2CH_3$), and 0.93 (3H, d., J=7 Hz, $CH–CH_3$). Mass Spectrum m/e: 403 (M^+). Further elution of the column with chloroform afforded 550 mg of the conjugated nitrile (**8**: colorless oil), in 8% yield. IR ν_{max} cm^{-1}: 2230 (CN), 1725 (ester), and 1620 (C=C) cm^{-1}. NMR δ: 7.04 (1H, d., J=17 Hz, olefinic proton), 6.29 (1H, m., olefinic proton), 5.27 (1H, d., J=17 Hz, olefinic proton), 4.80—5.27 (2H, m., CH–OAc), 4.10 (2H, q., J=7 Hz, $COOCH_2CH_3$), 1.92 and 2.05 (each 3H, s., $OCOCH_3$), 1.23 (3H, t., J=7 Hz, $COOCH_2CH_3$) and 0.90 (3H, d., J=6 Hz, $CH–CH_3$). Mass Spectrum m/e: 403 (M^+).

The Nitrile (9)——To a solution of 4.8 g of the conjugated nitrile (**7**) in 250 ml of dry benzene was added 2.2 g of tris(triphenylphosphine)chlororhodium, and the mixture was hydrogenated for 4 days at room temperature and atmospheric pressure. The solvent was removed under reduced pressure and the residue in chloroform was chromatographed on silica gel (A:130 g). Elution of the column with the same solvent gave 3.6 g of the nitrile (**9**: colorless oil) in 75% yield. IR ν_{max} cm^{-1}: 2250 (CN) and 1730 (ester). NMR δ: 5.65 (1H, m., olefinic proton), 4.70—5.25 (2H, m., CH–OAc), 4.11 (2H, q., J=7 Hz, $COOCH_2CH_3$), 2.05 (6H, s., $OCOCH_3$), 1.22 (3H, t., J=7 Hz, $COOCH_2CH_3$) and 0.91 (3H, d., J=7 Hz, $CH–CH_3$). Mass Spectrum m/e: 405 (M^+).

The Aziridine A (11) and the Aziridine B (12)——To a solution of 4.6 g of the nitrile (**9**) and 8 g of cobaltous chloride in 400 ml of methanol was added portionwise 8 g of sodium borohydride for 30 min under stirring at room temperature, and stirring was continued for further 30 min. The reaction mixture was mixed with ether and extracted with 5% hydrochloric acid. The aqueous acidic solution was made alkaline with ammonia and extracted with chloroform. The chloroform extract was dried over anhydrous K_2CO_3 and evaporated under reduced pressure to leave 4 g of the crude primary amine (**10**). To a solution of this crude primary amine in 400 ml of dry methylene chloride was added 1.6 g of N-chlorosuccinimide under nitrogen atmosphere and the mixture was stirred for 15 min at room temperature. To this mixture was then added 400 mg of cuprous chloride and the mixture was stirred for 1.5 hr at room temperature. The reaction mixture was diluted with water, made alkaline with ammonia, and extracted with chloroform. The extract was dried over anhydrous K_2CO_3 and evaporated under reduced pressure to leave 4.5 g of an oil. This oil in chloroform was chromatographed on silica gel (B:80 g) and the column was eluted with 0.3% methanol in chloroform. The earlier eluate was solidified and recrystallization from ether afforded 930 mg of the aziridine A (**11**) as colorless prisms, mp 127—129°, in 20% yield. *Anal.* Calcd. for $C_{22}H_{33}O_6N$: C, 64.84; H, 8.16. Found: C, 64.81; H, 8.24. IR ν_{max} cm^{-1}: 1730 (ester) and 1250 (C–O). NMR δ: 4.83—5.25 (2H, m., CH–OAc), 4.12 (2H, q., J=7 Hz, $COOCH_2CH_3$), 2.02 and 2.04 (each 3H, s., $OCOCH_3$), 1.23 (3H, t., J=7 Hz, $COOCH_2CH_3$), and 1.11 (3H, d., J=7 Hz, $CH–CH_3$). Further elution of the column with the same solvent mixture left a solid mass and recrystallization from *n*-hexane gave 120 mg of the aziridine B (**12**) as colorless prisms, mp 82—84°, in a 3% yield. IR ν_{max} cm^{-1}: 1730 (ester) and 1250 (C–O). NMR δ: 4.82—5.16 (2H, m., CH–OAc), 4.13 (2H,

10) W.A. Ayer, Y. Fukazawa, P.P. Singer, and B. Altenkirk, *Tetrahedron Letters*, **1973**, 5045.

q., J=7 Hz, $COOCH_2CH_3$), 2.07 and 2.09 (each 3H, s., $OCOCH_3$), 1.25 (3H, t., J=7 Hz, $COOCH_2CH_3$), and 0.91 (3H, d., J=6 Hz, $CH-CH_3$). Mass Spectrum m/e: 407 (M^+).

The Primary Alcohol (13)——To a solution of 900 mg of the aziridine A (**11**) in 100 ml of dry ethanol was added portionwise 2.2 g of lithium borohydride under ice-cooling and stirring was continued for further 1.5 hr at room temperature. The reaction mixture was poured into water and extracted with chloroform. The extract was dried over anhydrous K_2CO_3 and evaporated. The residue in chloroform was chromatographed over silica gel (B: 15 g) and elution of the column with 2% methanol in chloroform gave 600 mg of the primary alcohol (**13**: colorless oil) in 74% yield. IR ν_{max} cm^{-1}: 3000—3500 (OH), 1725 and 1250 (OAc). NMR δ: 4.80—5.24 (2H, m., CH–OAc), 3.61 (2H, m., CH_2OH), 2.65—3.05 (1H, m., OH), 2.01 and 2.03 (each 3H, s., $OCOCH_3$) and 1.10 (3H, d., J=7 Hz, $CH-CH_3$). Mass Spectrum m/e: 365 (M^+).

The Triacetate (15)——To a solution of 400 mg of the primary alcohol (**13**) in 20 ml of pyridine was added 450 mg of *p*-toluenesufonyl chloride under ice-cooling and the mixture was stirred overnight at room temperature. The mixture was poured into water and extracted with ether. The aqueous layer was evaporated to dryness under reduced pressure and the residue was dissolved in 50 ml of dry ethanol. To the ethanol solution was added 3 g of the freshly fused potassium acetate, and the mixture was refluxed for 4 hr. The mixture was diluted with water, made alkaline with ammonia and extracted with benzene. The benzene extract was dried over anhydrous K_2CO_3 and evaporated under reduced pressure. The residue in *n*-hexane was chromatographed on alumina (C: 10 g) and elution of the column with 50% ether–*n*-hexane gave a solid mass. Recrystallization from ether provided 150 mg of the triacetate (**15**) as colorless prisms, mp 161—163°, in 33% yield. IR ν_{max} cm^{-1}: 1720 and 1250 ($OCOCH_3$). NMR δ: 4.68—5.23 (3H, m., CH–OAc), 2.02 (3H, s., $OCOCH_3$), 2.10 (6H, s., $OCOCH_3$), and 1.10 (3H, d., J=7 Hz, $CH-CH_3$). Mass Spectrum m/e: 407 (M^+). *Anal.* Calcd. for $C_{22}H_{33}O_6N$: C, 64.84; H, 8.16. Found: C, 64.90; H, 8.21.

***β*-Dihydroserratinine Triacetate (16)**——To a solution of 340 mg of *β*-dihydroserratinine[3] in 10 ml of acetic anhydride was added a small amount of *p*-toluenesulfonic acid. The reaction mixture was heated on a water bath for 10 hr, concentrated under reduced pressure, poured into ice-water, made alkaline with ammonia, and extracted with ether. The extract was dried over anhydrous K_2CO_3 and evaporated. The residue in *n*-hexane was chromatographed on alumina (C: 10 g) and elution of the column with 50% ether in *n*-hexane gave a solid mass. Recrystallization from *n*-hexane provided 260 mg of *β*-dihydroserratinine triacetate (**16**), colorless prisms, mp 89—91°, in 53% yield. Mass Spectrum m/e: 407 (M^+).

The Triol (17) and the Triketone (18)——A solution of 200 mg of the triacetate (**15**) in a 5% KOH solution in methanol was refluxed on a water bath for 1 hr. The reaction mixture was diluted with water and extracted with ethyl acetate using salting-out technique. The extract was dried over anhydrous K_2CO_3 and evaporated. The residue was solidified and recystallization from benzene left 120 mg of the triol (**17**), colorless needles, mp 223—226°, in 87% yield. Mass Spectrum m/e: 281 (M^+). To a solution of 120 mg of the triol (**17**) in 40 ml of acetone was added 1.2 ml of Jones' reagent under ice-cooling and the mixture was stirred for 15 min at the same temperature. Stirring was continued for further 1.5 hr at room temperature and excess reagent was decomposed by addition of methanol. The reaction mixture was poured into ice-water, made alkaline with ammonia, and extracted with ethyl acetate. The extract was dried over anhydrous K_2CO_3 and evaporated. The residue in benzene was chromatographed on silica gel (B: 2 g) and the column was eluted with benzene. Then, the eluting solvent was replaced by 10% chloroform in benzene. The eluate was solidified and recrystallization from ether gave 47 mg of the triketone (**18**), colorless plates, mp 143—146° in 40% yield. IR ν_{max} cm^{-1}: 1735 and 1710 (CO). Mass Spectrum m/e: 275 (M^+).

***dl*-Serratinine (1: *dl*-form) and *dl*-8-Episerratinine (19: *dl*-form)**——To a solution of 99 mg of the triketone (**18**) in absolute alcohol was added portionwise 300 mg of sodium borohydride under ice-cooling and stirring was continued for further 5 hr room temperature. The reaction mixture was diluted with water and extracted with chloroform. The extract was dried over anhydrous K_2CO_3 and evaporated under reduced pressure. The residue in chloroform was chromatographed on alumina (C: 6 g). Elution of the column with chloroform gave a solid mass and recrystallization from ether provided 18 mg of *dl*-serratinine (**1**: *dl*-form), colorless prisms, mp 202—203°, in 18% yield. A sample was identified with an authentic sample of natural serratinine by comparison of IR, Mass spectra and TLC behaviour. Further elution of the column with ethyl acetate gave a solid mass and recrystallization from acetone gave 25 mg of 8-episerratinine (**19**: *dl*-form), colorless prisms, mp 205—207°, in 25% yield. A sample was identified with an authentic specimen of 8-episerratinine derived from natural serratinine by comparison of IR, mass spectra, and TLC behaviour.