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Synthetic Studies on Lycoricidine and Related Compounds. I.[1] Synthesis of 4a*H*-*r*,2*H*-*cis*,2-Hydroxy-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6(5*H*)-phenanthridone

Shunsaku Ohta and Shoshichiro Kimoto

Kyoto College of Pharmacy[2]

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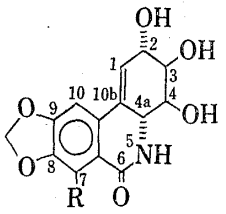
4a*H*-*r*,2*H*-*cis*,2-Hydroxy-2,3,4,4a-tetrahydro-8,9-methylenedioxy-6(5*H*)-phenanthridone, which was an important compound lacking two hydroxyl groups at 3- and 4-position in the structure of lycoricidine, was synthesized and configuration of the hydroxyl group was comfirmed to be α-quassi-axial on the basis of NMR data. A new lactam cyclization technique using borontrifluoride etherate on the course from phenethyl isocyanates to the corresponding lactams was examined.

Lycoricidine[3] (margetine[4,5]) and lycoricidinol[3] (narciclasine[6,7], **1**), non-basic constituents of Amaryllidaceae plants, are of biological interest because of their antimitotic activity. Although the plane formula of lycoricidine was reported as **2**, configuration of the hydroxyl groups is not fully established. However, the stereostructure **2** is presumed to be correct since the reported nuclear magnetic resonance (NMR) spectrum of lycoricidine triacetate is very close to that of lycoricidinol tetraacetate,[3] whose structure has already been established by X-ray annalysis.[7]



1: R=OH
2: R=H

Fig. 1

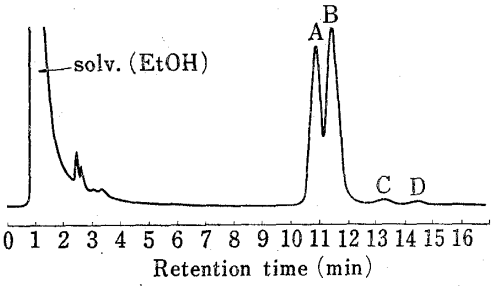


Fig. 2. GLC of Diels-Alder Adduct obtained from **4** and Ethyl Acrylate

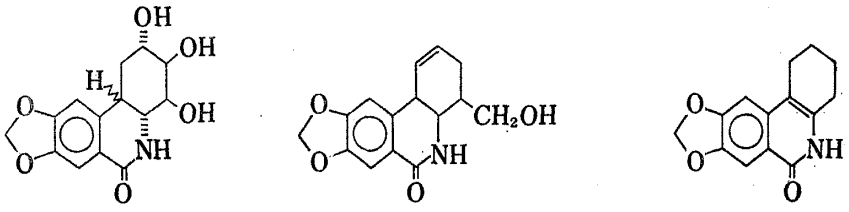
Column: SE-30 (100 cm × 0.3 cm), temp.: 260°, carrier gas: N_2, ditecter: FID

The authors wish to clarify relations between biological activity and structure of lycoricidine related compounds. This paper deals with synthesis of 4a*H*-*r*,2*H*-*cis*,2-hydroxy-2,3,4,4a-tetrahydro-8,9-methylenedioxy-6(5*H*)-phenanthridone[8] (**3**), which is an important compound, lacking two hydroxyl groups at 3- and 4-position in the structure of lycoricidine (**2**).

1) Communication: S. Ohta and S. Kimoto, *Tetrahedron Letters*, **1975**, 2279.
2) Location: *Misasagi-Nakauchi-cho, Yamashina-ku, Kyoto, 607, Japan.*
3) T. Okamoto, Y. Torii, and Y. Isogai, *Chem. Pharm. Bull.* (Tokyo), **16**, 1860 (1968).
4) C. Fuganti, A. Selva, and F. Piozzi, *chim. et Ind.* (Milano), **49**, 1196 (1967).
5) A. Mondon and K. Krohn, *Chem. Ber.*, **103**, 2727 (1970).
6) G. Ceriotti, *Nature*, **213**, 595 (1967); F. Piozzi, C. Fuganti, R. Mondelli, and G. Ceriotti, *Tetrahedron*, **24**, 1119 (1968).
7) A. Immirzi and C. Fuganti, *Chem. Commun.*, **1972**, 240.
8) *r*: reference The steric expression of compounds in this paper is described according to IUPAC Tentative Rules for the Nomenclature of Organic chemistry, Section E: Fundamental Stereochemistry.

Reaction of 3,4-methylenedioxyphenyl allyl carbinol (**4**)[9] with ethyl acrylate at 180° in the presence of a small amount of *p*-toluenesulfonic acid gave a mixture of Diels-Alder adducts in 55.5% yield. Gas-liquid layer chromatogram (GLC) of the product showed presence of four compounds, which should have been stereoisomeric but were not characterized, in a ratio of A: B: C: D=30: 33.5: 1: 1[10] (Fig. 2). The mixture was treated with sodium ethoxide (GLC; A: B=12.4: 1) and followed by hydrolysis to give only a carboxylic acid (**7**) (mp 103°) in 74.2% yield, whose steric arrangement was presumed to be *trans* according to the ordinary stereochemical concept. NMR spectrum of the carboxylic acid (**7**) showed two vinylic protons and two methine protons, but these signals could not elucidate steric relationship between the two methine protons, because of complexity of their signals.

The carboxylic acid (**7**) was converted to the corresponding acid azide by the modified Curtius reaction[11] and the azide was heated in toluene to give an isocyanate (**8**) (IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250). Lactam cyclizations of phenethyl isocyanate derivatives and biphenyl-2-isocyanate derivatives are known,[12] but in general they are reported to be in poor yield. Application of above-mentioned methods failed to convert the isocyanate (**8**) to the lactam (**9**). However, by use of excess of borontrifluoride etherate (BF_3·ether) as catalyst, the lactam (**9**) (mp above 285° (decomp.)) was successfully obtained in 70—88.5% yield. NMR spectrum of the lactam (**9**) showed two singlets of two aromatic protons at δ 7.33 and 7.13, and two vinylic protons at 6.4—5.6, and absorption bands of infrared (IR) spectrum at 3370 (NH) and 1660 cm^{-1} (lactam carbonyl) showed formation of lactam ring, furthermore, ultraviolet (UV) spectrum was very similar to those of dihydrolycoricidine (**10**)[3] and a known compound (**11**).[13] Experiments on application of the new lactam cyclization technique will be described later in this paper.



10 **11** **24**

Fig. 3

A dibromide (**12**) (mp 186° (decomp.)) was formed from the lactam (**9**) with pyridinium hydrobromide perbromide in acetic acid, and the dibromide was converted by dehydrobromination with 1,8-diaza-bicyclo (5,4,0) undecene-7 (DBU) in dimethyl sulfoxide (DMSO) and followed by air oxidation to the known 8,9-methylenedioxy-6(5*H*)-phenanthridone (**13**), which had been prepared photochemically from piperonylic acid anilide (**19**).[14] It is considered that the result is an additional evidence for the structure of the lactam (**9**) and the position of the carboxylic acid (**7**). In order to approach to synthesis of lycoricidine (**2**), it was throught advisable that NH group in **9** was protected with an easily-removable group at first and C-ring of **2** was successively constructed by appropriate reactions. So **9** was treated with

9) R. Quelet and R. Dran, *Compt. Rend.*, **258**, 1826 (1964).
10) On the other hand Diels-Alder reaction of 1-phenylbutadiene and methyl acrylate was known to afford a mixture of methyl 2-phenyl-3-cyclohexene-1-carboxylate and 3-phenyl-4-cyclohexene-1-carboxylate in 60% yield in the ratio of 39: 1, respectively, but the ratio among their diastereoisomers was not reported. [V.J. Sauer, *Angew. Chem.*, **79**, 76 (1972)].
11) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).
12) F. Eloy and A. Deryckere, *Helv. Chim. Acta.*, **52**, 1775 (1960) and the references therein; H.W. Gschwend, *ibid.*, **56**, 1763 (1973); J.S. Swenton, T.J. Ikeler, and G.L. Smyser, *J. Org. Chem.*, **38**, 1175 (1973); J.B. Hendrickson, C. Foote, and N. Yoshimura, *Chem. Commun.*, **1965**, 165.
13) H. Irie, Y. Nishitani, M. Sugita, and S. Uyeo, *Chem. Commun.*, **1970**, 1313.
14) A. Mondon and K. Krohn, *Chem. Ber.*, **105**, 3726 (1972).

acetic anhydride in pyridine under reflux to convert to an acetylimide (**14**), which was brominated with N-bromosuccinimide (NBS) in the presence of a small amount of benzoylperoxide for the purpose to obtain the corresponding allylic-position-brominated compound. However, the resulting product was found to be the phenanthridone (**13**)[14] in 84% yield. In the case of benzylation of **9** using benzyl chloride and sodium hydride in dimethylformamide (DMF), an N-benzyl lactam (mp 152°) was obtained in 28.8% yield. Since NMR spectrum of the N-benzyl lactam showedonly one vinylic proton and the UV spectrum was very similar to that of lycoricidine (**2**),[3] it is rational that the structure of this compound was considered to be **15**, in which the original double bond shifted from 1,2-position to more stable 1,10b-position in a very strong basic medium. The N-benzyl lactam (**15**) also gave the aromatic compound (**16**) (mp 161°) by bromination in the same manner as mentioned above. However, the carboxylic acid (**7**) was smoothly brominated by the same bromination to give **17** (mp 147°) in 67.8% yield, NMR spectrum of which showed three methine protons. The bromocarboxylic acid (**17**) could not be converted to a lactam (**18**) by application of above-mentioned lactam cyclization procedure because of formation of a resinous product.

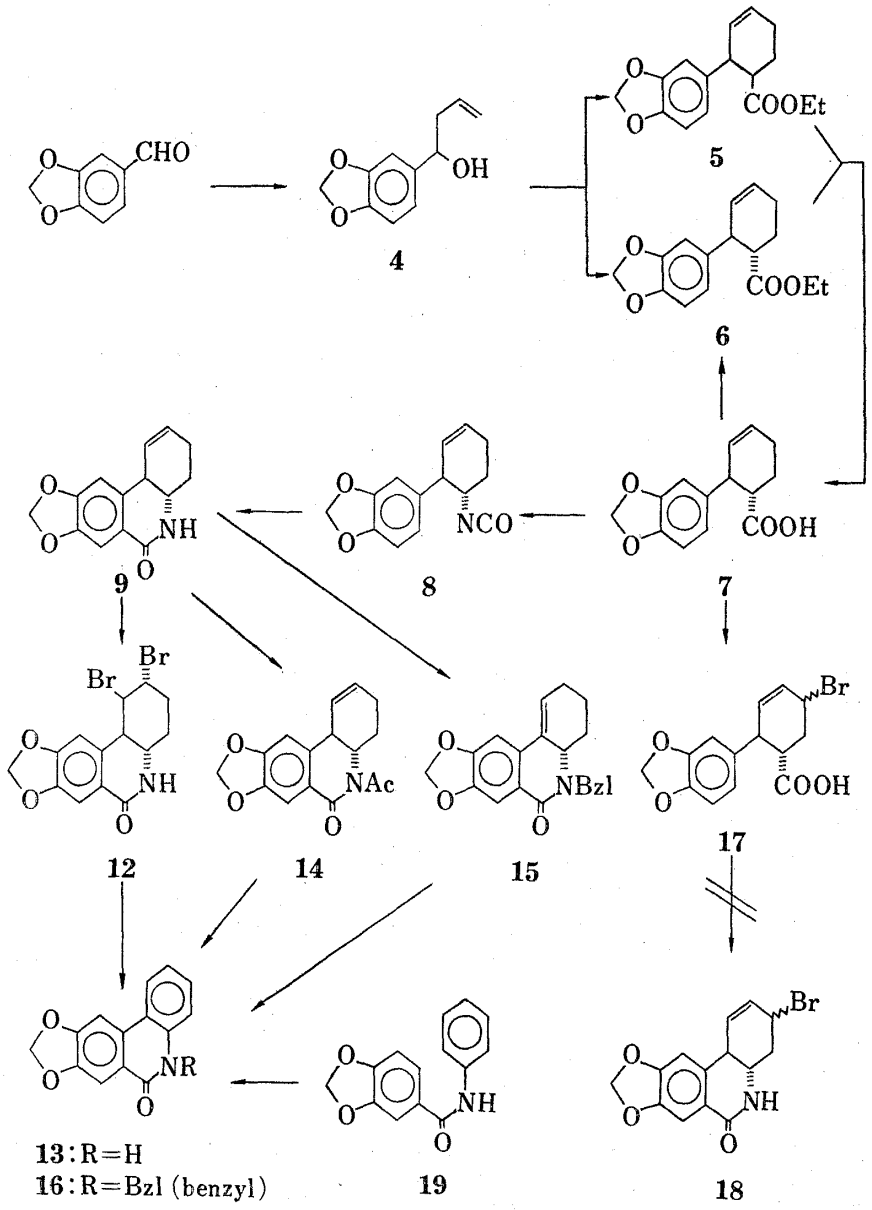


Chart 1

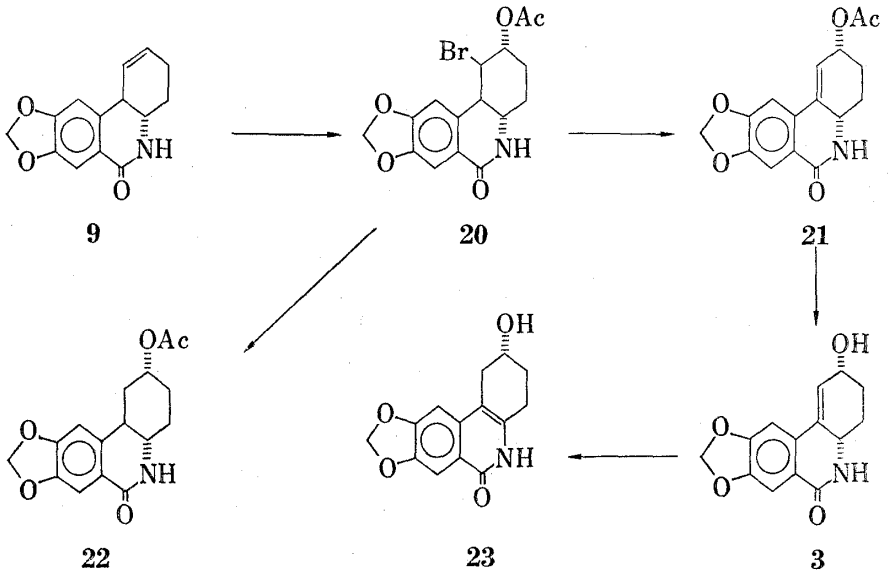


Chart 2

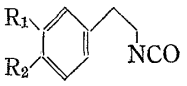
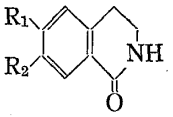
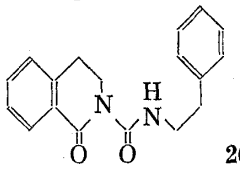
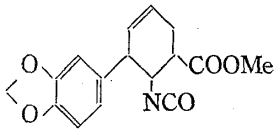
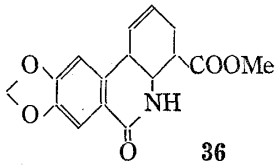
Into a solution of the lactam (**9**) in acetic acid was added NBS and the resulting solution was kept standing overnight. Work-up of the reaction mixture gave the bromohydrine acetate (**20**) (mp 213° (decomp.)) in 81.4% yield. Dehydrobromination of **20** with DBU afforded the allylic alcohol acetate (**21**) (mp 290° (decomp.)), NMR spectrum of which showed one vinylic proton and the UV spectrum corresponded on that of lycoricidine.[3] Ammonolysis of the acetate (**21**) gave the allylic alcohol (**3**) (mp 280° (decomp.)) in quantitative yield. In order to clarify configuration of the hydroxyl group of **3** by applying a rule of half band width[15] of the adjacent proton to the acetoxyl group (>CHOAc) of a hexahydrolactam such as **22**, catalytic hydrogenation of the allylic alcohol (**3**) over PtO_2 was examined, but uptake of hydrogen was not only obserbed but also **3** was not recovered, leading to a double bond-shifted product (**23**) (mp 290° (decomp.)) in 75% yield. The structure of the product was confirmed by disappearance of vinylic proton signal in its NMR spectrum and by agreement of its UV spectrum with that of the known 1,2,3,4-tetrahydro-8,9-methylenedioxy-6(5*H*)-phenanthridone (**24**). Such double bond shifting have already been reported in narciclasine derivative[16] and the fact seems to support π-allyl complex mechanism in catalytic hydrogenation of olefins.[17] So the authors tried debromination of the bromohydrine acetate (**20**) with Raney-nickel catalyst. The debromination proceeded successfully to give the acetate (**22**) (mp above 290° (decomp.)), NMR spectrum of which showed an adjacent proton to the acetoxyl group (>CHOAc) at δ 5.12 in half band width=8 Hz. Hence, the configuration of the C_2-substituent should be α-axial in the compounds (**22** and **20**), and α-quassi-axial in the compound (**21** and **3**).

The lactam cyclization by using BF_3·ether was applied to several substituted phenethyl isocyanates and their results are listed in Table I. Isocyanate (**25**) was prepared from the corresponding carboxylic acid, 1*H-r*,2*H-cis*,6*H-cis*,2-(3′,4′-methylenedioxyphenyl)-6-methoxycarbonyl-3-cyclohexene-1-carboxylic acid, which had not been isolated in a pure state[13] and was prepared from the corresponding acid anhydride[9] by refluxing it in methanol-acetic acid and keeping the reaction mixture at a room temperature to crystallize. Lactam cyclization proceeded successfully in the case of alkoxy-substituted phenethyl isocyanates. Phenethyl isocyanate (**31**) itself gave a product (mp 100°), NMR spectrum of which showed nine aromatic

15) Y. Kawazoe, Y. Sato, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963).
16) A. Mondon and K. Krohn, *Tetrahedron Letters*, **1972**, 2085.
17) C.J. Timmons (translated into Japanese by M. Mukaiyama), "Modern Reactions in Organic Synthesis", Hirokawa-shoten, Tokyo), 1973, p. 4.

protons and IR spectrum showed two carbonyl absorption bands (1690 and 1642 cm^{-1}), so structure of the product was considered to be **26**. Structures of products obtained from isocyanates (**27** and **28**) could not be elucidated nevertheless by using IR, NMR spectra and elemental analysis data. Recently, Irie reported that $SnCl_4$ was a favorable reagent for the lactam cyclization of isocyanate (**25**) containing some amount of an isomer,[18] and Tsuda also reported that $POCl_3$ was a favorable reagent for the lactam cyclization of N-phenethyl urethanes.[19]

TABLE I. Lactam Cyclization of Isocyanate with BF_3·Ether

Isocyanate		Product		Yield (%)
	**29** R_1, R_2= $-OCH_2O-$		**32**[a] R_1, R_2= $-OCH_2O-$	53.5
	30 R_1=OMe, R_2=H		**33**[a] R_1=OMe, R_2=H	49.4
	27 R_1=Cl, R_2=H		**34** unidentified colorless needles, mp 218°	—
	28 R_1=NO_2, R_2=H		**35** unidentified colorless prisms, mp 254°	—
	31 R_1, R_2=H	 **26**		25.0
 **25**		 **36**		89.5

a) These are known compounds[20]

Experimental[21]

Diels-Alder Reaction of 3,4-Methylenedioxyphenyl Allyl Carbinol (4) with Ethyl Acrylate——A mixture of ethyl acrylate (30 g), **4**(48 g) and *p*-toluenesulfonic acid (90 mg) was heated at 180—190° in a sealed tube for 6 hr. Ethereal solution of the product was shaken with 10% $NaHCO_3$ and with water then dried. After removal of the solvent, the resulting oily material was distilled at 5 mmHg to give a fraction below 150° (8 g, the starting material) and a fraction of 150—170° (Diels-Alder adducts). GLC of the later fraction is shown in Fig. 2. Yield, 40.5 g (55.5%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1723 (COOEt).

***trans*-2-(3′,4′-Methylenedioxyphenyl)-3-cyclohexene-1-carboxylic Acid (7)**——To a solution of the Diels-Alder adduct (33 g) in anhyd. EtOH (100 ml) was added an alcoholic NaOEt solution prepared with Na (3 g) and EtOH (100 ml). The solution was refluxed for 2 hr. To the resulting solution was added 20 ml of water and refluxed again for 3.5 hr. The solution was concentrated *in vacuo* and the residue was dissolved in a mixture of ether and water. The aqueous layer was acidified with conc. HCl and followed by extraction with ether. The ethereal layer was dried and evaporated, the resulting oily material was solidified by cooling, collected by filtration and washed with ether-pet. ether. The material was recrystallized from ether-pet. ether to give colorless prisms, mp 102—103°. Yield, 23.8 g (74.2%). *Anal.* Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.08; H, 5.48. IR ν_{max}^{KBr} cm^{-1}: 2650—2400, 1700 (COOH). NMR (in $CDCl_3$) δ: 9.1 (1H, broad, COO<u>H</u>), 6.68 (3H, m, arom. protons), 5.90 (2H, s, $-OC\underline{H}_2O-$), 6.0—5.45 (2H, m, $-C\underline{H}=C\underline{H}-$), 3.85—3.5 (1H, m, $>C\underline{H}COOH$), 2.75—2.3 (1H, m, 2-position), 2.3—1.6 (4H, m, $-C\underline{H}_2C\underline{H}_2-$).

18) H. Irie, "Papers of the 95th annual meeting of this Society," Vol. I, April. 1975, p. 128.
19) K. Isobe, J. Taga, and Y. Tsuda, "Paper of the 2nd Symposium on Progresses of Reaction and Synthesis", November, 1975, p. 89.
20) A. Brossi, J. Wuersch, and O. Schneider, *Chimia* (Switz.), **12**, 114 (1958).
21) All melting points were uncorrected. NMR spectra were determined with Varian A-60A Analytical Spectrometer using TMS as an internal reference.

Into a solution of **7** (500 mg) in ether was added excess of ethereal diazoethane solution. After removal of the solvent, the residual oil was distilled at 169—174° (5 mmHg). Yield of **6**, 490 mg (87.5%). GLC retention time of this product agreed with A-peak in Fig. 2. *Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.03; H, 6.50. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (COOEt). NMR (in $CDCl_3$) δ: 6.68 (3H, s, arom. protons), 5.90 (2H, s, $-OCH_2O-$), 5.85—5.4 (2H m, $-CH=CH-$), 4.03 (2H, quartet, $J=7$ Hz, $-OCH_2CH_3$), 3.83—3.45 (1H, broad, $>CHCOOEt$), 2.75—1.7 (5H, m, 2-position and $-CH_2CH_2-$), 1.13 (3H, t, $J=7$ Hz, $-OCH_2CH_3$).

4*H*-*r*,3*H*-*trans*,4-Isocyano-3-(3′,4′-methylenedioxyphenyl)-cyclohex-1-ene (8)——Into a solution of **7** (20 g) in acetone (100 ml) and water (20 ml) was added Et_3N (8 g), then ClCOOEt (8.6 g) in acetone (20 ml) under cooling. One hour later, a solution consisting of NaN_3 (7.8 g) and water (20 ml) was added under stirring. Half an hour later, to the reaction mixture were added toluene (200 ml) and water (150 ml). The toluene layer was washed with water and dried, then heated carefully to boil. After refluxing for 4 hr, removal of toluene *in vacuo* gave slightly brown oil (19.5 g), which was used for the next process without purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (NCO).

4a*H*-*r*,10b*H*-*trans*,8,9-Methylenedioxy-3,4,4a,10b-tetrahydro-6(5*H*)-phenanthridone (9)——To the isocyanate (**8**) (19.5 g) was added BF_3-ether (40 ml) under cooling and then the resulting solution was kept standing for several hours. Precipitated crystals were collected by filtration and washed with ether. As the same crystals were formed gradually on concentration, they were collected by suction and combined. The mother liquor was diluted with ether and washed with water several times and dried. Removal of the solvent gave slightly brown oil which showed still presence of isocyanate in IR, so the same procedure was repeated using BF_3·ether (5 ml) and gave an additional small amount of the same material. Combined material was 18.5 g. The material was rinsed with MeOH containing a small amount of pyridine to give 17.7 g of colorless prisms (88.5%), which were recrystallized from AcOH to afford colorless needles (mp 220° (decomp.)). Sublimation *in vacuo* (200°/5 mmHg) yielded colorless prisms, mp above 285° (decomp.). *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.93; N, 5.76. Found: C, 68.98; H, 5.53; N. 5.83. IR ν_{max}^{KBr} cm^{-1}: 3370 (NH), 1660 (NHCO). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 223.5 (4.64), 263 (3.77), 271 (sh), 306 (3.90). NMR (in DMSO-d_6) δ: 8.06 (1H broad, NH), 7.33 (1H, s, 7-position) 7.13 (1H, s, 10-position) 6.4—5.6 (2H, m, $-CH=CH-$), 6.07 (2H, s, $-OCH_2O-$), 3.5—3.15 (2H, m, $>CH-CH<$), 2.4—1.8 (4H, m, $-CH_2CH_2-$).

4a*H*-*r*,1*H*-*trans*,2*H*-*cis*,10b*H*-*trans*,1,2-Dibromo-8,9-methylenedioxy-3,4,4a,10b-tetrahydro-6(5*H*)-phenanthridone (14)——Into a solution of **9** (220 mg) in AcOH (5 ml) was added $C_5H_5N\cdot HBr\cdot Br_2$ (300 mg) and the resulting solution was stirred for 15 min. Precipitates were collected by filtration and washed with ether. Yield, 365 mg (quantitative). Recrystallization from AcOH gave colorless prisms, mp 186° (decomp.). *Anal.* Calcd. for $C_{14}H_{13}O_3NBr_2$: C, 41.78; H, 3.25; N, 3.47. Found: C, 41.83; H, 3.40; N, 3.75. IR ν_{max}^{KBr} cm^{-1}: 3180, 1672 (NHCO). NMR (in DMSO-d_6) δ: 7.48 (1H, s, 7-position), 6.48 (1H, s, 10-position), 6.06 (2H, s, $-OCH_2O$), 5.20 (1H, broad, 1- or 2-position), 5.0 (1H, broad, 2- or 1-position), 4.15—3.5 (2H, m, 4a- and 10b-position), 3.0—2.0 ($-CH_2CH_2-$, accompanying solvent signals).

4a*H*-*r*,10b*H*-*trans*,5-Acetyl-8,9-methylenedioxy-3,4,4a,10b-tetrahydro-6(5*H*)-phenanthridone (14)—— The lactam (**9**) (10 g) was refluxed in Ac_2O (100 ml) and pyridine (100 ml) for 1 hr. Removal of the reagents *in vacuo* gave crystalline mass, which was rinsed with MeOH (50 ml) and collected by suction. Yield, 9.7 g (82.9%). Recrystallization from EtOH gave colorless needles, mp 157—158°. *Anal.* Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.30; H, 5.30 N, 5.10. IR ν_{max}^{KBr} cm^{-1}: 1723, 1650 ($-CONCO-$). NMR (in $CDCl_3$) δ: 7.50 (1H, s, 7-position), 6.86 (1H, s, 10-position), 6.03 (4H, m, $-OCH_2O-$ and $-CH=CH-$), 3.85—3.60 (2H, m, $>CHCH<$), 2.57 (3H, s, $COCH_3$), 3.0—1.17 (4H, m, $-CH_2CH_2-$).

8,9-Methylenedioxy-6(5*H*)-phenanthridone (13)——i) From the Dibromide (**12**): Into a solution of the dibromide (**12**) (201.5 mg) in hot DMSO (5 ml) was added DBU (160 mg) and the mixture was refluxed for 2 hr and kept standing at a room temperature overnight to give leaflets, which were collected and washed with EtOH. Yield, 87 mg (72.8%). The material was recrystallized from DMF to give colorless leaflets, mp above 300° (decomp.), which were identified with authentic sample[14] by comparison of UV and IR spectra.

ii) From the Imide (**14**): Into a solution of **14** (200 mg) in CCl_4 (30 ml) were added benzoyl peroxide (5mg) and NBS (252 mg). The mixture was refluxed for 0.5 hr. The resulting precipitate was collected and heated in MeOH, then an insoluble portion was recrystallized from DMF to give **13**, which was identified with authentic sample[14] by comparison of IR spectrum. Yield, 145 mg (84%).

5-Benzyl-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6(5*H*)-phenanthridone (15)——The lactam (**9**) (735 mg) was dissolved in anhyd. DMF and into the solution were added NaH (90 mg) and benzoyl chloride (400 mg) and the resulting solution was heated at 85—90° for 1 hr. The solvent was removed *in vacuo* and to the residue were added water and $CHCl_3$ and the mixture was shaken. To the $CHCl_3$-extract was added a small amount of MeOH to give crystals, which were recrystallized from EtOAc to afford 280 mg (28.8%) of colorless prisms, mp 150—152°. *Anal.* Calcd. for $C_{20}H_{19}O_3N$: C, 74.73; H, 5.96. Found: C, 75.08; H, 5.78. NMR (in $CDCl_3$) δ: 7.64 (1H, s, 7-position), 7.24 (5H, $-C_6H_5$), 6.85 (1H, s, 10-position), 6.3—5.93 (3H, m, $>C=CH-$ and $-OCH_2O-$), 4.94 (2H, dd, $-CH_2C_6H_5$), 4.23 (1H, broad, $>CH-NH$) 2.5—1.2 (6H, m, $-CH_2CH_2CH_2-$). UV $\lambda_{max}^{95\%\ EtOH}$ nm (qualitative): 244, 302. IR ν_{max}^{KBr} cm^{-1}: 1635 (NHCO).

5-Benzyl-8,9-methylenedioxy-6(5*H*)-phenanthridone (16)——To a solution of **15** (100 mg) in CCl_4 (10 ml) were added NBS (57 mg) and benzoyl peroxide (2.5 mg) and the mixture was refluxed for 15 min. Precipitate formed was removed by filtration. The solvent of the filtrate was evaporated. Addition of a small amount

of EtOAc to the residue gave colorless needles. Recrystallization of the crystals from EtOAc afforded colorless needles, mp 160—161°. Yield, 70 mg (70.9%). *Anal.* Calcd. for $C_{20}H_{15}O_3N$: C, 75.69; H, 4.76; N, 4.41. Found: C, 75.98; H, 4.98; N, 4.52. NMR (in $CDCl_3$) δ: 8.2—7.8 (3H, m, arom. protons), 7.57 (1H, s, arom. proton), 7.24 (6H, s+m, arom. proton and $-C_6\underline{H}_5$), 6.08 (2H, s, $-OC\underline{H}_2O-$), 5.62 (2H. s, $-C\underline{H}_2C_6H_5$). IR ν_{max}^{KBr} cm^{-1}: 1640 (NHCO).

1*H*-*r*,2*H*-*trans*,2-(3′,4′-Methylenedioxyphenyl)-5-bromo-3-cyclohexene-1-carboxylic Acid (17)——Into a solution of **7** (1.25 g) in CCl_4 (25 ml) were added NBS (900 mg) and benzoyl peroxide (50 mg) and the reaction mixture was refluxed for 15 min. The precipitated succinimide was discarded and removal of the solvent *in vacuo* gave yellow oil, ethereal solution of which was passed through a short column of neutral alumina. Solvent of the eluate was evaporated to crystallized. Recrystallization of the compound from ether-*n*-hexane afforded colorless needles, mp 146—147°. Yield, 1.12 g (67.8%). *Anal.* Calcd. for $C_{14}H_{12}O_4Br$: C, 51.70; H, 4.03. Found: C, 51.77; H, 4.01. IR ν_{max}^{KBr} cm^{-1}: 3300—2400, 1710 (COOH), 1663 (olefin). NMR (in $CDCl_3$) δ: 9.0—8.0 (1H, broad, COO$\underline{H}$), 6.73 (3H, s, arom. protons), 6.25—5.57 (2H, m, $-C\underline{H}=C\underline{H}-$), 5.94 (2H, s, $-OC\underline{H}_2O-$), 4.9 (1H, broad, >C$\underline{H}$Br), 4.0—3.64 (1H, m, >C$\underline{H}$COOH), 3.38—2.9 (1H, m, 2-position), 2.67—2.2 (2H, m, $-C\underline{H}_2-$).

4a*H*-*r*,1*H*-*trans*,2*H*-*cis*,10b*H*-*trans*,1-Bromo-2-acetoxy-8,9-methylenedioxy-1,2,3,4,4a,10b-hexahydro-6(5*H*)-phenanthridone (20)——Into a solution of **9** (500 mg) in AcOH (10 ml) was added NBS (400 mg) and the resulting solution was kept standing overnight at a room temperature. Into the reaction mixture were added water (30 ml) and $CHCl_3$ (50 ml) and the mixture was shaken. The $CHCl_3$-layer was washed with 10% NaOH and with water, then dried Removal of the solvent *in vacuo* gave a crystalline mass, which was recrystallized from AcOH–ether to give colorless prisms, mp 211—213° (decomp.). Yield, 640 mg (81.4%). *Anal.* Calcd. for $C_{16}H_{16}O_5NBr$: C, 50.25; H, 4.22; N, 3.66. Found: C, 50.25; H, 4.32; N, 3.26. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1727 ($OCOCH_3$), 1655 (NHCO). NMR (in $CDCl_3$): 7.65 (1H, s, 7-position) 6.73 (1H, s, 10-position), 6.03 (1H, s, $-OC\underline{H}_2O-$), 5.4 (1H, m, >C$\underline{H}$Br), 4.73 (1H, m, >C$\underline{H}$–OAc)' 3.41—3.1 (1H, m, >C$\underline{H}$–NH), 2.12 (3H, s, $COC\underline{H}_3$), 2.30—1.67 (4H, m, $-C\underline{H}_2C\underline{H}_2-$).

4a*H*-*r*,2H-*cis*,2-Acetoxy-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6(5*H*)-phenanthridone (21)——A solution of **20** (900 mg) and DBU (400 mg) in benzene (100 ml) was refluxed for 1.5 hr. After removal of the solvent, to the residue were added 10% HCl and $CHCl_3$ and the mixture was shaken, then the $CHCl_3$-layer was washed with water and dried. Removal of the solvent gave crystalline mass, which was recrystallized from EtOH to give colorless prisms, mp 290° (decomp.). Yield, 650 mg (88.5%). *Anal.* Calcd. for $C_{16}H_{15}O_5N$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.77; H, 5.45; N, 4.50. IR ν_{max}^{KBr} cm^{-1}: 3180 (NH), 1730 ($OCOCO_3$), 1670 (NHCO). NMR (in DMSO-d_6) δ: 8.03 (1H, broad, N$\underline{H}$), 7.33 (1H, s, 7-position), 7.20 (1H, s, 10-position), 6.30—6.0 (3H, m, $-C\underline{H}=C<$ and $-OC\underline{H}_2O-$), 5.3 (1H, broad, >C$\underline{H}$–OAc), 4.2 (1H, m, >C$\underline{H}$–NH), 2.03 (3H, s, $COC\underline{H}_3$), 2.3—1.5 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 243 (4.46), 280 (sh), 306 (3.87).

4a*H*-*r*,2*H*-*cis*,2-Hydroxy-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6(5*H*)-phenanthridone (3)——A solution of **21** (600 mg) in MeOH (200 ml) was saturated with NH_3 and the mixture was kept standing overnight at a room temperature. Removal of the solvent gave crystalline mass, which was recrystallized from EtOH to give colorless prisms, mp 280° (decomp.). Yield, 520 mg (quantitative). *Anal.* Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.41; H, 5 55; N, 4.93. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3180 (NH), 1663 (NHCO). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 241 (4.50), 280 (sh), 303 (3.80). NMR (in DMSO-d_6) δ: 7.96 (1H, broad, N$\underline{H}$), 7.31 (1H, s, 7-position), 7.20 (1H, s, 10-position), 6.33—6 0 (1H, m, $-C\underline{H}=C<$), 6.10 (2H, s, $-OC\underline{H}_2O-$), 4.90 (1H, d, J=5 Hz, O$\underline{H}$), 4.13 (2H, broad, >C$\underline{H}$–OH and >C$\underline{H}$–NH), 2.5—1.5 (4H, broad, $-C\underline{H}_2C\underline{H}_2-$).

2-Hydroxy-8,9-methylenedioxy-1,2,3,4-tetrahydro-6(5*H*)-phenanthridone (23)——A solution of **3** (100 mg) in AcOH (20 ml) was hydrogenated over PtO_2 (20 mg) under an atmospheric pressure, but uptake of H_2 was not observed. Five hours later, the catalyst was removed by filtration and the filtrate was evaporated to dryness to give crystalline mass, which was recrystallized from AcOH to give colorless prisms, mp above 290° (decomp.). Yield, 75 mg (75%). *Anal.* Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5 05; N, 5.40. Found: C, 65.34; H, 5.33; N, 5.24. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3150 (NH), 1640 (NHCO). UV $\lambda_{max}^{95\%\ EtOH}$ (log ε): 227.5 (4.29), 249 (4.34), 263.5 (4.27), 247 (sh), 280 (3.75), 297 (3.78), 322 (sh), 337 (3.57), 352 (3.39). NMR (in DMSO-d_6) δ: 7.50 (1H, s, 7-position), 7.0 (1H, s, 10-position), 6.13 (2H, s, $-OC\underline{H}_2O-$), 4.80 (1H, d, O$\underline{H}$), 4.23—3.70 (1H, broad, >C$\underline{H}$–OH), 3.0—1.5 (6H, m, $-(C\underline{H}_2)_3-$).

4a*H*-*r*,2H-*cis*,10b*H*-*trans*,2-Acetoxy-8,9-methylenedioxy-1,2,3,4,4a,10b-hexahydro-6(5*H*)-phenanthridone (22)——Into a solution of **20** (500 mg) in EtOH (250 ml) was added Raney-nickel catalyst (W-6, prepared from 12.5 g of the alloy) and the resulting mixture was stirred at a room temperature for 10 hr and then filtered. Removal of the solvent of the filtrate gave crystalline mass. The filtered catalyst was extracted with hot $CHCl_3$ several times and the $CHCl_3$ solutions was evaporated to dryness to give a small amount of crystals, which was combined with the crystals previously obtained and recrystallized from EtOH to give colorless needles, mp 254—256°. Yield, 250 mg (49.7%). *Anal.* Calcd. for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.71; H, 5.93; N, 4.96. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1733 ($OCOCH_3$), 1668 (NHCO). NMR (in DMSO-d_6) δ: 7.7 (1H, broad N$\underline{H}$), 7.33 (1H, s, 7-position), 6.85 (1H, broad, 10-position), 6.05 (2H, s, $-OC\underline{H}_2-$O–), 5.12 (1H, broad, >C$\underline{H}$–OAc, $W/2$=8 Hz), 3.5—2.7 (2H, m, 4a- and 10b-position), 2.05 (3H, s, $COC\underline{H}_3$), 2.0—1.0 (6H, m, other protons).

1*H*-*r*,2*H*-*cis*,6*H*-*cis*,2-(3′,4′-Methylenedioxyphenyl)-6-methoxycarbonyl-3-cyclohexene-1-carboxylic Acid——The corresponding acid anhydride[9] was heated in a mixture of MeOH (40 ml) and AcOH (40 ml) to reflux for 1 hr and the resulting mixture was kept standing overnight at a room temperature to give colorless needles, mp 168—170°. Recrystallized. from MeOH. *Anal.* Calcd for $C_{16}H_6O_6$: C, 63.15; H, 5.30. Found: C, 63.23; H, 5.40. IR ν_{max}^{KBr} cm^{-1}: 3040—2550, 1710 (COOH), 1730 (COOMe). NMR (in $CDCl_3$) δ: 8.1—7.5 (1H, broad, COOH), 6.70 (3H. s, arom. protons), 6.15—5.55 (4H, m s, $-OCH_2O-$ and $-CH=CH-$), 3.67 (3H, s, $COOCH_3$), 4.0—2.3 (5H, m, other protons).

Lactam Cyclization with BF_3·Ether——i) General Procedure: Isocyanates were prepared from corresponding carboxylic acid by Weinstock's procedure.[11] An isocyanate (1 g) was dissolved in BF_3·ether (2 ml) under cooling and the resulting solution was kept standing overnight at a room temperature, then precipitated crystals were collected by filtration and washed with ether. To the filtrate were added ether and water, and the mixture was shaken. The ethereal layer was washed with water and dried. Removal of the solvent gave an oily residue, to which was added BF_3·ether (1 ml) to give an additional amount of the same crystals. Yield are summarized in Table I. Additional items for qualification were mentioned below.

ii) **32**: Recrystallized from water. mp 181—182° (literature[20], mp 181°).

iii) **33**: Recrystallized from MeOH–H_2O to give colorless prisms, mp 139—140° (literature[20], mp 139°).

iv) **36**: Recrystallized from MeOH to give colorless prisms, mp 184—185°. *Anal.* Calcd. for $C_{16}H_{15}O_5N$: C, 63.78; H, 5.02; N 4.65. Found: C, 63.80; H, 4.81; N, 4.72. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1740 (COOMe), 1660 (NHCO). NMR (in $CDCl_3$) δ: 7.50 (1H, s, 7-position), 6.67 (1H, s, 10-position), 6.20 (1H, broad, NH), 6.00 (2H, s, $-OCH_2O-$), 5.9—5.1 (2H, m, $-CH=CH-$), 4.35 (1H, d, $J=4$ Hz, $>CH-COOMe$), 3.78 (3H, s, $COOCH_3$), 3.47 (1H, broad, $>CH-NH$), 3.0—2.25 (3H, m, 10b-position and $-CH_2-$).

v) **26**: Recrystallized from MeOH to give colorless leaflets, mp 99—100°. *Anal.* Calcd. for $C_{18}H_{18}O_2N_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.52; H, 6.02; N, 9.52. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1690, 1642 (CON-CONH). NMR (in $CDCl_3$) δ: 9.7 (1H, broad, NH), 8.2—7.1 (9H, m+s, arom. protons), 4.3—2.75 (8H, m, aliph. protons).

vi) **34**: Recrystallized from THF–*n*-hexane to give colorless needles, mp 215—218°. Yield, 683.5 mg, *Anal.* Found: C, 38.84: H, 2.39; N, 10.24. IR ν_{max}^{KBr} cm^{-1}: 3200, 3020. 2900, 1597, 1537, 1483, 1350, 1140—1035. NMR (in DMSO-d_6) δ: 8.23—7.0 (broad m), 3.07 (m), ratio of the area was 4: 3, which was changed by D_2O addition to 3: 3.

vii) **35**: Recrystallized from EtOAc–pet. ether to give colorless leaflets, mp 252—254°. Yield, 168 mg. *Anal.* Found: C, 40.30; H, 2.98; N, 4.32. IR ν_{max}^{KBr} cm^{-1}: 3280, 3020, 2930, 1603, 1480, 1085. NMR (in DMSO-d_6): 7.65 (broad, this signal was disappered by D_2O addition), 7.35 (m), 3.3—2.65 (m), ratio of the area was 1: 4: 3. This crystal was soluble in water, but precipitate was not formed by addition of alkali to the solution.

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