was added to PPA[9] (10 ml) and the mixture was heated at 150—160° with vigorous stirring for 2 hr, then diluted with H_2O (25 ml) and extracted with $CHCl_3$ (15 ml × 3). The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to dryness to a colorless solid which was crystallized from $CHCl_3$ to give VI (400 mg, 51% yield), mp 160°. *Anal.* Calcd. for $C_9H_8O_3N_2S$ (224.17): C, 48.22, H, 3.60, N, 12.50, Found: C, 48.16, H, 3.48, N, 12.37. Mass spectrum *m/e*: 224 (M^+). UV λ_{max}^{EtOH} nm (log ε): 218 (4.34), 294 (4.15). NMR ($CDCl_3$) δ ppm, 3.50 (3H, singlet, CH_3), 3.62 (3H, singlet, CH_3), 6.32 (1H, doublet, J=12.5 Hz, cis –CH=CH–S–), 8.20 (1H, doublet, J=12.5 Hz, cis –CH=CH–S–).

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The Synthesis of 3-Spirooxindole Derivatives. IX.[1] The Reactions of 2-Hydroxytryptamine with Hemiacetals

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The condensation of 2-hydroxytryptamine hydrochloride (IX) with the hemiacetals such as tetrahydropyran-2-ol (X) and morroniside (III), a member of the iridoids, was investigated.

A condensation of IX with X was carried out by standing a solution of IX, X, and sodium acetate in the molar ratio of 1: 1: 2 in an aqueous ethanol at room temperature or at reflux for 42 hr to give the amino-alcohol (XI) in 85% yield, which was further characterized as two isomeric diacetyl derivatives (XIIa, XIIb).

A condensation of IX with morroniside (III) was conducted under a similar condition only by heating a solution of the components at reflux for 42 hr to give the lactams (XIVa, b), which seemed to have been generated through the processes of the Mannich type of condensation like the preliminary work, followed by elimination of methanol.

Attempts to prevent the lactam formation and to isolate the Mannich base were unsuccessful in the latter case, but the condensations of 2-hydroxytryptamine with hemiacetals were proved to have smoothly proceeded to afford the Mannich bases in high yields.

The iridoid glucoside, loganin (I) occupies an important position in the biosynthesis of the indole alkaloids, *i.e.*, the *Corynanthe*, *Aspidosperma* and *Iboga* families.[3] The evidence made to date indicates that loganin becomes the C_9–C_{10} nontryptamine moiety incorporated into the skeleton of these alkaloids. Tracer experiments also show that loganin is a biogenetic precursor of a growing number of iridoid[4] and alkaloid glucosides.[5] Loganin is cleaved *in*

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3) *a*) A.R. Battersby, *Pure and Appl. Chem.*, **14**, 117 (1967); *b*) A.I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970); *c*) H. Inouye, S. Ueda, and Y. Takeda, *Chem. Pharm. Bull.* (Tokyo), **19**, 587 (1971); *d*) H. Goeggel and D. Arigoni, *Chem. Comm.*, **1965**, 538; *e*) J.P. Kutney, "Lectures in Heterocyclic Chemistry," edited by R.N. Castle and E.F. Elslager, S-1 (1972). (A Supplementary Issue of the Journal of Heterocyclic Chemistry, Volume 9). (The lecture was presented at 3rd International Congress of Heterocyclic Chemistry, at Sendai, Japan, August 23–27, 1971).

4) H. Inouye, S. Ueda, and Y. Takeda, *Tetrahedron Letters*, **1970**, 3351; **1971**, 4069, 4073.

5) A.R. Battersby, A.R. Burnett, and P.G. Parsons, *J. Chem. Soc. C*, **1969**, 1187, 1193.

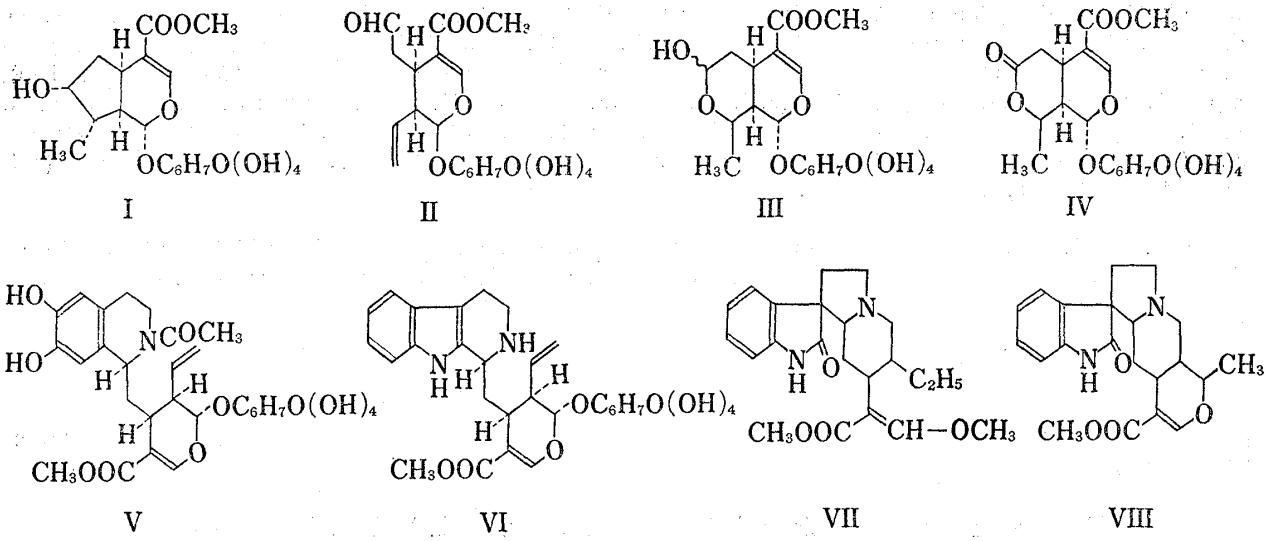


Chart 1

vivo by an oxidation process to yield secologanin (II), which can be considered to condense with tryptamine to give the indole alkaloids through the subsequent biological conversions.[3]

The biogenetic type of synthesis of ipecoside (V) and vincoside (VI) by the condensation of secologanin with 3,4-dihydroxyphenethyl amine and tryptamine, respectively, has been reported by A.R. Battersby.[5]

We wish to report the condensation of 2-hydroxytryptamine hydrochloride with the iridoid glucoside, morroniside (III), and some experiments designed to convert the condensation products to oxindole alkaloids, *i.e.*, rhynchophylline (VII) and uncarine (VIII) *etc.* Morroniside (III) used in the present studies is an iridoid glucoside which was first isolated together with kingiside (IV) from *Lonicera morrowii*[6] by Souzu and Mitsuhashi. The structure and stereochemistry of both iridoids have been established by the same workers[6] and by Inouye.[7] It is noteworthy that morroniside (III) contains an aldehyde group in a masked hemiacetal form, and it is generated from loganin (I) and secologanin (II) in the biosynthesis in plants.[4] Although the condensations of 2-hydroxytryptamine hydrochloride (IX) with various aldehydes in basic media were reported mostly from this laboratory to give the Mannich bases,[1,8] any reaction of IX with hemiacetals had never been attempted.

Therefore, a condensation of IX with tetrahydropyran-2-ol (X) involving a hemiacetal group like morroniside (III) was carried out as a preliminary work. It is well known that the hemiacetals readily generate the corresponding aldehydes by mild acidic hydrolysis, but they are relatively stable in a basic medium. On account of this character of hemiacetals, a basic condition necessary for the condensation was modified to an almost neutral medium.

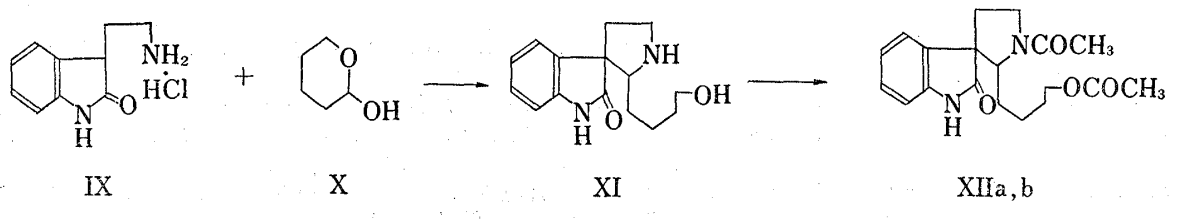
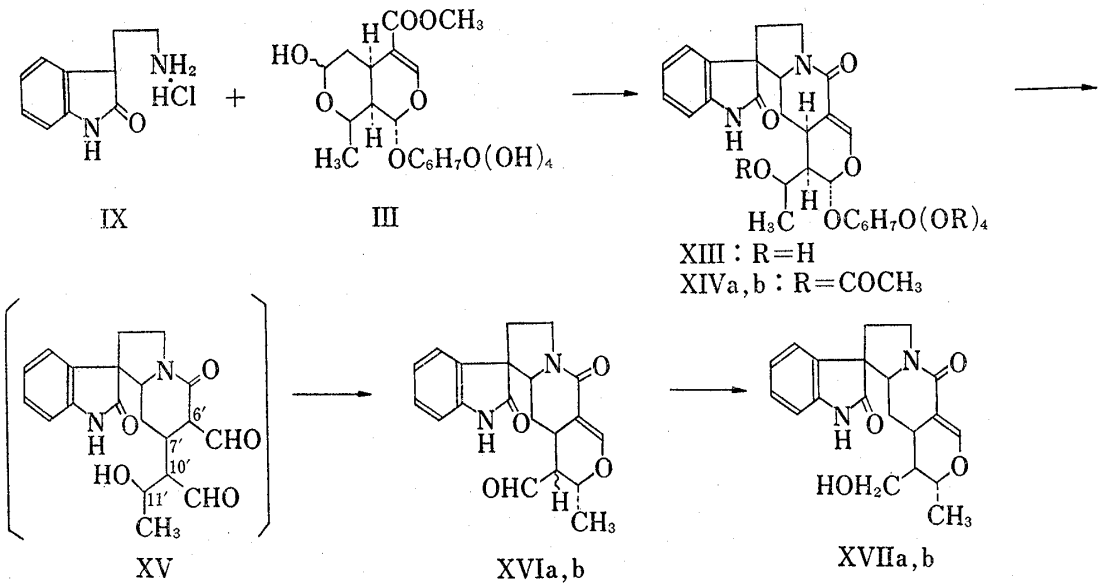


Chart 2

6) I. Souzu and H. Mitsuhashi, *Tetrahedron Letters*, **1969**, 2725.
7) H. Inouye, T. Yoshida, S. Tobita, and T. Nishioka, *Tetrahedron Letters*, **1970**, 2459.
8) *a*) J. Harley-Mason and T. Ingleby, *J. Chem. Soc.*, **1958**, 3639; *b*) Y. Ban and T. Oishi, *Chem. Pharm Bull.* (Tokyo), **11**, 441, 446, 451 (1963); *c*) Y. Ban, M. Seto, and T. Oishi, *ibid.*, **23**, 2605 (1975).

After many experiments, an optimum result for the condensation of the amine (IX) with the above hemiacetal (X) was obtained when a mixture of IX, X, and sodium acetate trihydrate in the molar ratio of 1: 1: 2 in an aqueous ethanol was kept at room temperature for 5 days or heated under reflux for 42 hr to afford the aminoalcohol (XI) as colorless plates, mp 139—141°, [M^+=260, IR ν_{max}^{Nujol}: 1700 cm^{-1} (CO); UV λ_{max}^{EtOH} 253 nm] in a high yield. Acetylation of XI with acetic anhydride and pyridine gave the two isomeric diacetyl derivatives [XIIa and XIIb; both of them indicate m/e=344 (M^+)], which were separated by chromatography on silica gel. The generation of the two isomeric diacetyl derivatives (XIIa, b) from a single amino-alcohol (XI) might be due to the result that the isomerization at the spiroposition occurred during acetylation process.



IX III XIII : R=H XIVa,b : R=$COCH_3$ XV XVIa,b XVIIa,b

Chart 3

Based upon this successful experiment, condensation of IX with morroniside (III) was investigated. As the amine hydrochloride (IX) did not react with morroniside (III) at room temperature under the foregoing condition, the reaction had to be carried out under reflux for 42 hr. The crude condensation product (XIII) was easily soluble in water, and accordingly, it was acetylated with acetic anhydride and pyridine for isolation of the product. The resultant lactam-penta-O-acetates (XIVa and XIVb) were separated as two isomeric forms by chromatography on silica gel. The first fraction furnished an isomer (XIVa) as an oil in 35.9% yield and the subsequent fraction provided the other isomer (XIVb) as fine crystals, mp 251—254°, in 22.3% yield. Spectroscopic evidence [IR ν_{max}^{Nujol} 1660 cm^{-1} (six membered lactam CO)] and elemental analyses of both isomers were compatible with the structures of XIVa and XIVb, which therefore, should be the spiro isomers. Generation of the six-membered lactam (XIVa and XIVb) may be due to the result of the processes of the Mannich type of condensation like the preliminary work, followed by elimination of methanol. But, attempts to prevent the lactam formation and to isolate the Mannich base were unsuccessful.

Thus, upon hydrolysis with 10% hydrochloric acid in an aqueous ethanol, XIVa afforded the lactam-aldehyde (XVIa) in 83.1% yield as needles, mp 255—257°, [M^+=352, IR ν_{max}^{Nujol} 1720 cm^{-1} (CO); NMR (DMSO-d_6) τ: 0.40 (1H, d, J=4 Hz, C<u>H</u>O)]. Similarly, XIVb gave the lactam-aldehyde (XVIb) in 83.4% yield as needles, mp 248.5—249.5° [M^+=352, IR ν_{max}^{Nujol} 1720, 1710 cm^{-1} (both CO), NMR (DMSO-d_6) τ: 0.37 (1H, d, J=4 Hz, C<u>H</u>O)]. These results suggest that XIVa and XIVb were first hydrolyzed to give the lactam-dialdehyde (XV), which underwent an intramolecular cyclization between C-6′ aldehyde and C-11′ hydroxyl groups to give XVIa and XVIb, respectively. The products (XVIa and XVIb) were reduced with sodium

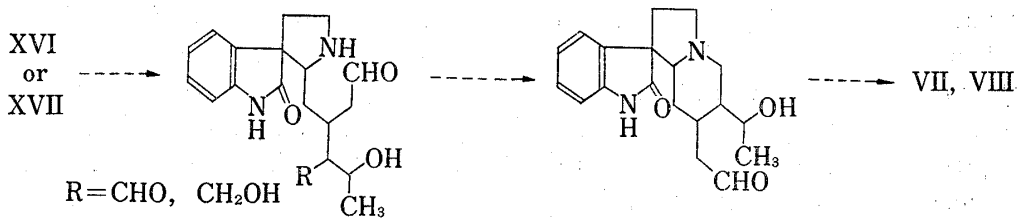


Chart 4

borohydride in isopropanol to afford the lactam–alcohols, (XVIIa, mp 253.5—256°, M^+=354) and (XVIIb, mp 295°, M^+=354), respectively.

A selective hydrolysis of the six-membered lactam moiety of XVI or XVII would be expected to lead to the amino-alcohol (XVIII), a key intermediate for the synthesis of oxindole alkaloids, rhynchophylline (VII) and uncarine (VIII). As a matter of fact, however, the attempted experiments for the hydrolysis of XVI or XVII, resulted in failure. Although the present approaches to the synthesis of oxindole alkaloids were not accomplished in this way, the condensations of 2-hydroxytryptamine with hemiacetals were proved to have smoothly proceeded to afford the Mannich bases.

The other approaches were tried with success to accomplish the total syntheses of the oxindole alkaloids.[8c]

Experimental[9,10]

2′-(4″-Hydroxybutyl)-*spiro*-[indoline-3,3′-pyrrolidine]-2-one (XI)——To a solution of 2-hydroxytryptamine hydrochloride [IX, 1.06 g (5 mmole)] and sodium acetate trihydrate [1.63 g (12 mmole)] in aqueous ethanol [45 ml (water: ethanol=1: 2)] was added tetrahydropyran-2-ol [X, 0.51 g (5 mmole)]. The mixture was allowed to stand at room temperature for 5 days. Ethanol was evaporated *in vacuo* to give the clear aqueous solution, which was made alkaline with aqueous ammonia and extracted with ethyl acetate. The extracts were washed with water, dried over sodium sulfate and the solvent was evaporated to afford the pale yellow gum [1.1 g (84.6%)] which was recrystallized from ethanol and ethyl acetate to give XI as colorless plates, mp 139—141°, Mass Spectrum *m/e*: 260 (M^+), UV λ_{max}^{EtOH} 253 nm, IR ν cm^{-1}: 3320 (OH), 1710 (C=O). NMR (DMSO-d_6) τ: 2.55—3.25 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{15}H_{20}O_4N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.32; H, 7.63; N, 10.66.

1′-Acetyl-2′-(4″-acetoxybutyl)-*spiro*-[indoline-3,3′-pyrrolidine]-2-one (XIIa and XIIb)——A solution of the amino-alcohol (XI, 200 mg) in pyridine (2 ml) was cooled in an ice bath, to which was added acetic anhydride (2 ml). The mixture was left at room temperature for one night and the solution was concentrated on water bath *in vacuo*. After cooling, water was added and the whole mixture was extracted with ethyl acetate. The extract was washed with water, sodium bicarbonate solution, and dried over sodium sulfate. The ethyl acetate was removed by evaporation to leave 245 mg of the crude oil, which was purified by chromatography on silica gel. Elution with ethyl acetate–ether (1: 9—5: 5) gave XIIa as an oil [100 mg (38.6%)] and XIIb as colorless needles, mp 121—122°, [122 mg (47.2%)]. Isomer XIIa: Mass Spectrum *m/e*: 344 (M^+). IR νcm^{-1}: 1725 (ester C=O), 1610 (amide C=O). NMR ($CDCl_3$) τ: 0.95 (1H, b. s, NH) 7.80 (3H, s, OCO-CH_3) 8.05 (3H, s, NCOCH_3). Isomer XIIb: Mass Spectrum *m/e*: 344 (M^+). IR νcm^{-1}: 1730 (ester C=O), 1610 (amide C=O). NMR ($CDCl_3$) τ: 0.81 (1H, b,s, NH), 7.82 (3H, s, OCOCH_3) 8.05 (3H, s, NCOCH_3). *Anal.* Calcd. for $C_{19}H_{24}O_4N_2$: C, 66.26; H, 7.02; N, 8.12. Found: C, 66.13; H, 6.92; N, 8.10.

Lactam-penta-O-acetate (XIVa and XIVb)——A solution of 2-hydroxytryptamine hydrochloride (IX, 423 mg (2.0 mmole)], morroniside (III, 550 mg (1.36 mmole) and sodium acetate trihydrate [544 mg (4.0 mmole)] in aqueous ethanol [12 ml (H_2O: EtOH=1: 2)] was heated under reflux for 42 hr. The solvent

9) Melting points were measured with a hot stage microscope, (Yanaco MP-J2) and uncorrected. Spectra reported herein were measured on a Hitachi EPS-3T spectrophotometer, JASCO DS-701G and 215 Hitachi grating infrared spectrophotometer, a Hitachi R-20B (NMR, 60 MHz), and a Hitachi RMU-7M double forcussing mass spectrometer. The authors are indebted to Misses H. Kakizaki, M. Satoh, A. Maeda, and C. Ohara for microanalyses, to Mmes. M. Ohnuma and K. Tsuta, and Miss S. Okayama for obtaining NMR spectra and to Miss Masako Takahashi for Mass spectral measurements.

10) The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet, DMSO=dimethyl sulfoxide.

was removed by concentration *in vacuo*, and the residue was treated with acetic anhydride (3 ml) and pyridine (6 ml). After being kept at room temperature for 1 day, the solution was evaporated and water (5 ml) was added to the residue. The mixture was extracted with ethyl acetate. The extracts were combined, washed with water, and with 15% sodium carbonate solution, and dried over sodium sulfate. The ethyl acetate was removed by evaporation to leave 1.1 g of the residue. Chromatography of the residue on silica gel in a mixture of ethyl acetate–ether (3: 7) gave the lactam-penta-O-acetate (XIVa) as an oil [360 mg (35.9%)] and the other isomer (XIVb) as powders [230 mg (22.3%)], mp 251—254° (from ethyl acetate–ether). Isomer XIVa: IR ν cm^{-1}: 1750 (ester C=O), 1720 (ester C=O), 1660 (lactam C=O). NMR ($CDCl_3$) τ: 1.28 (1H, b,s, NH) 8.95 (3H, d, $J=6$ Hz, CH–CH$_3$). Isomer XIVb: IR ν cm^{-1}: 1755 (ester C=O), 1735 (ester C=O), 1660 (lactam C=O)]. NMR ($CDCl_3$) τ: 1.65 (1H, b,s, NH) 8.80 (3H, d, $J=6$ Hz, CH–CH$_3$). *Anal.* Calcd. for $C_{36}H_{42}O_{15}N_2$: C, 58.21; H, 5.70; N, 3.77. Found: C, 58.19; H, 5.66; N, 3.53.

Lactam-aldehyde (XVIa)——A solution of the lactam-penta-O-acetate (XIVa, 600 mg) in ethanol (30 ml) and 10% hydrochloric acid (30 ml) was heated under reflux for 10 hr. Ethanol was removed by concentration *in vacuo*, and the residue was extracted with chloroform. The extract was washed with water and dried over sodium sulfate. The chloroform was evaporated to leave 280 mg of the residue as a caramel, which was submitted to chromatography on silica gel. The fraction eluted with chloroform–aceton (9: 1—8: 2) afforded the lactam–aldehyde (XVIa) [236 mg (83.1%)] which was recrystallized from chloroform–ethyl acetate to give colorless needles, mp 261—264°. Mass Spectrum *m/e*: 352 (M^+). IR ν cm^{-1}: 1720 (aldehyde C=O), 1655 (lactam C=O). NMR (DMSO-d_6) τ: 0.40 (1H, d, $J=3$ Hz, CHO), 8.77 (3H, d, $J=6$ Hz, CH–CH$_3$). *Anal.* Calcd. for $C_{20}H_{20}O_4N_2$: C. 68.17; H, 5.72; N, 7.95. Found: C, 68.13; H, 5.64; N, 7.89.

Lactam-aldehyde (XVIb)——Hydrolysis of the penta-O-acetate (XIVb, 500 mg) by the method described above for the synthesis of XVIa yielded the lactam–aldehyde [XVIb, 198 mg (83.4%)] as colorless needles, mp 248.5—249.5° (from chloroform–ethyl acetate). Mass Spectrum *m/e*: 352 (M^+). IR ν cm^{-1}: 1720 (aldehyde C=O), 1655 (lactam C=O). NMR (DMSO-d_6) τ: 0.37 (1H, d, $J=3$ Hz, CHO), 8.74 (3H, d, $J=6$ Hz, CH–CH$_3$). *Anal.* Calcd. for $C_{20}H_{20}O_4N_2$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.16; H, 5.71; N, 7.69.

Lactam-alcohol (XVIIa)——A solution of the lactam–aldehyde [XVIa, 63 mg (0.17 mmole)] in isopropanol (6 ml) was kept below 10°, to which was added sodium borohydride [6.4 mg (0.17 mmole)]. The mixture was stirred at room temperature for 15 hr. The solvent was evaporated *in vacuo*, and water (10 ml) was added to the residue. The mixture was extracted with chloroform and dried over sodium sulfate. The solvent was removed by concentration to leave 63 mg of the crude oil, which was purified by chromatography on silica gel in ethyl acetate–acetone (9: 1) to afford the lactam–alcohol (XVIIa) [47 mg (74.2%)] as colorless prisms, mp 253—256° (from methanol–ethyl acetate). Mass Spectrum *m/e*: 354 (M^+). IR ν cm^{-1}: 3600 (OH), 1725 (lactam C=O), 1625 (lactam C=O). NMR ($CDCl_3$) τ: 0.70 (1H, b,s, NH), 8.65 (3H, d, $J=6$ Hz, CH–CH$_3$). *Anal.* Calcd. for $C_{20}H_{22}O_4N_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.53; H, 6.37; N, 8.05.

Lactam-alcohol (XVIIb)——The procedure was the same as for the synthesis of XVIIa. XVIIb was obtained in 74.8% yield as colorless needles, mp 295° (from methanol). Mass Spectrum *m/e*: 354 (M^+). IR ν cm^{-1}: 3600 (OH), 1710 (lactam C=O), 1640 (lactam C=O). NMR (DMSO-d_6) τ: −0.37 (1H, b,s, NH). 8.75 (3H, d, $J=6$ Hz, CH–CH$_3$). *Anal.* Calcd. for $C_{20}H_{22}O_4N_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.54; H, 6.35; N, 7.62.

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