[Chem. Pharm. Bull. 20(8)1800—1804(1972)]

UDC 547.94.057 : 547.833.04

Studies on the Syntheses of Heterocyclic Compounds. CDLXXXVIII.[1] An Alternative Synthesis of "Isocularine" by an Intramolecular Ullmann Reaction

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(Received February 7, 1972)

5,5a,6,7,8-Pentahydro-1-hydroxy-2,11-dimethoxybenzo[*b*]oxepino[7,6,5-*ij*]isoquinoline (III) was synthesized by an intramolecular Ullmann reaction of 1-(3-benzyloxy-2-bromo-4-methoxybenzyl)-5-bromo-1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-2-methylisoquinoline (X), followed by hydrogenolysis of the product (XI), and also by reduction of N-ethoxycarbonyl analogue (XV) derived from Ullmann reaction product (XIV) of the phenolic bromoisoquinoline (XIII).

In a previous paper,[3] we reported a biogenetic type synthesis of cularine (I) by phenolic oxidation of the diphenolic isoquinoline (II). In this reaction, unexpected compound was obtained as a main product, which was assigned tentatively the structure (III) by the spectroscopic method and its methylation product (IV) was named as "isocularine".

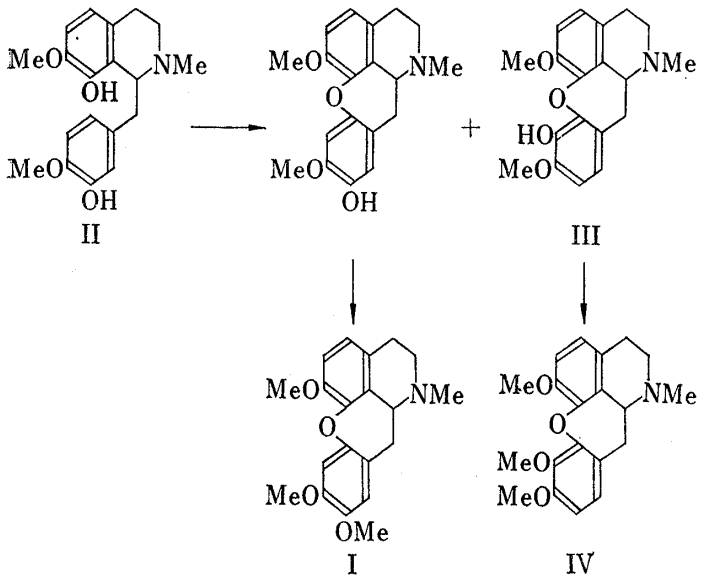


Chart 1

In order to prove this assignment (III) for the oxidation product, we investigated the synthesis of "isocularine", and here wish to report that the synthesis of III and IV was carried out in good yield through two routes by an intramolecular Ullmann reaction[4] and that our assignment for the oxidation product was correct.

Condensation of 3-benzyloxy-2-bromo-4-methoxybenzaldehyde (V)[5] with methyl chloroacetate, followed by hydrolysis, gave sodium glycidate (VII), which on acidic treatment afforded the phenylacetaldehyde (VIII) characterized as its semicarbazone. Pictet-Spengler reaction of sodium bisulfite adduct of the aldehyde (VIII) with 2-bromo-5-hydroxy-4-methoxyphenethylamine hydrochloride[6] was carried out in the presence of ammonia[3] in hot methanol to give the 1,2,3,4-tetrahydroisoquinoline (IX), the structure of which was determined by spectroscopic data described in experimental part. Eschweiler-Clarke reaction of IX with

1) Part CDLXXXVII: T. Kametani, K. Takahashi, T. Honda, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1793 (1972).
2) Location: *a*) *Aobayama, Sendai*; *b*) *2-2-5, Kawagishi, Toda, Saitama.*
3) T. Kametani, K. Fukumoto, and M. Fujihara, *Bioorg. Chem.*, **1**, 40 (1971).
4) T. Kametani, H. Iida, T. Kikuchi, M. Mizushima, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 709 (1969).
5) T. Kametani, H. Nemoto, T. Nakano, S. Shibuya, and K. Fukumoto, *Chem. and Ind.*, **1971**, 788.
6) T. Kametani, S. Shibuya, and M. Satoh, *Chem. Pharm. Bull.* (Tokyo), **16**, 953 (1968).

formalin and sodium borohydride furnished the 1,2,3,4-tetrahydro-2-methylisoquinoline (X), which was subjected to Ullmann reaction.[4] Thus, a mixture of the tetrahydroisoquinoline (X) and potassium carbonate was heated in dry pyridine in the presence of cupric oxide to furnish the cyclization product (XI) in 87% yield. The use of copper powder instead of cupric oxide in this cyclization also gave XI in good yield. The structure of this product [*m/e* 495 (M^+) and 497] was proved by infrared spectrum (IR) showing no hydroxy group and nuclear magnetic resonance spectrum (NMR) (δ) revealed 5a-proton as a quartet (J= 5.5 and 10.0 Hz) at 5.67 ppm which was characteristic of the cularine alkaloids.[7] Hydrogenolysis of XI on 10% palladium-charcoal yielded the phenolic base, and the identity of this product with the oxidative product (III)[3] from the diphenolic base (II) was rigorously established by the full range of physical methods.

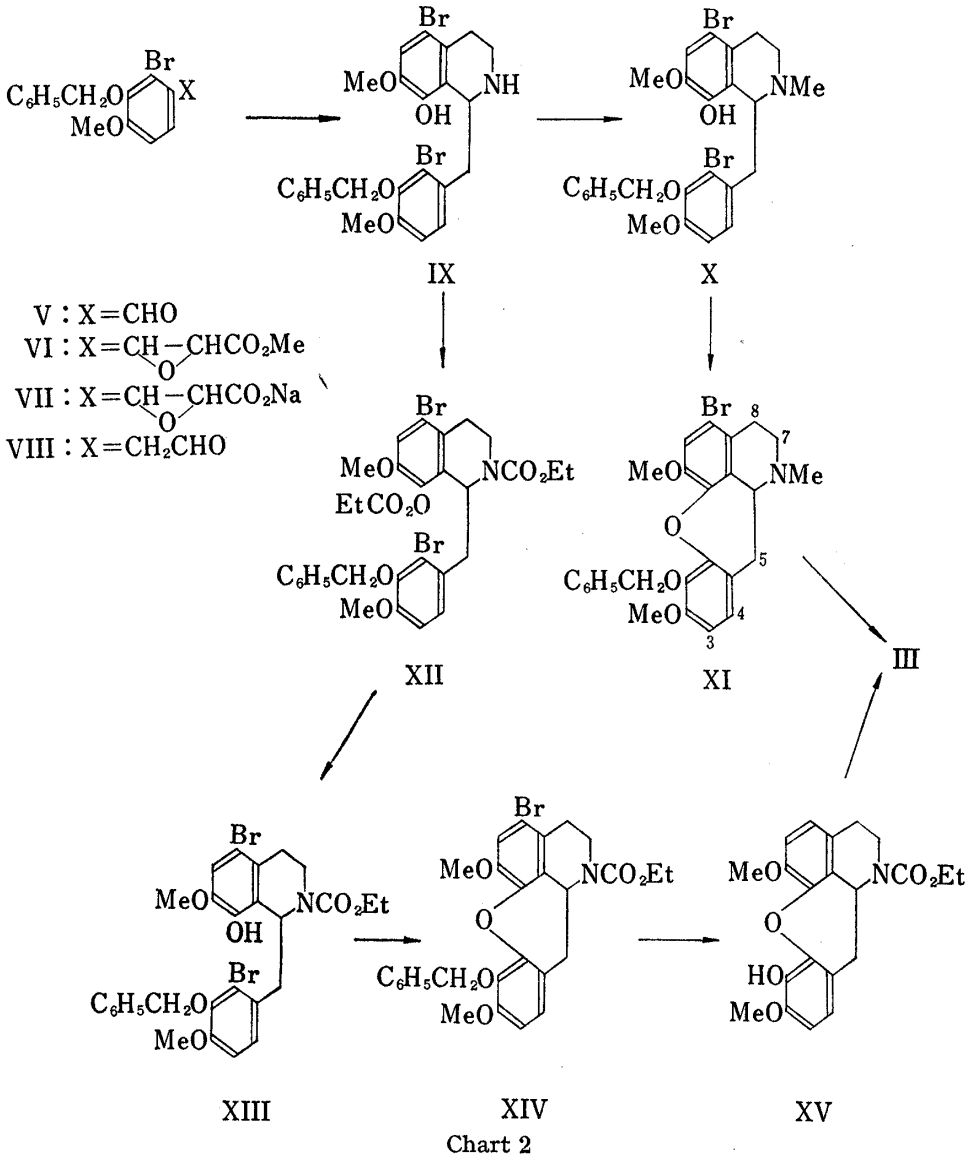


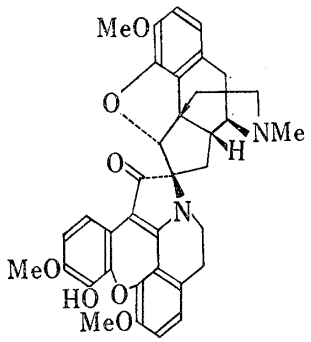
Chart 2

The second method was an approach to a synthesis of III by an intramolecular Ullmann reaction of the N-ethoxycarbonylisoquinoline (XIII), which could be converted into N-methyl group by lithium aluminum hydride reduction.[8] Thus, ethoxycarbonylation of IX with

7) N.S. Bhacca, J.C. Craig, R.H.F. Manske, S.K. Roy, M. Shamma, and W.A. Slusarchyk, *Tetrahedron*, **22**, 1467 (1966).
8) T. Kametani, T. Sugahara, and K. Fukumoto, *Tetrahedron*, **25**, 3667 (1969).

ethyl chloroformate gave the 2-ethoxycarbonyl-8-ethoxycarbonyloxyisoquinoline (XII), which on mild hydrolysis with sodium hydroxide afforded the 2-ethoxycarbonyl-8-hydroxyisoquinoline (XIII). Ullmann reaction of XIII with copper in the presence of potassium carbonate in pyridine gave the cyclization product (XIV) in 65.6% yield, the structure of which was proved by the spectroscopic method. Hydrogenolysis of XIV on platinum oxide in the presence of sodium acetate effected the debromination and debenzylation to give the N-ethoxycarbonyl derivative (XV), which was reduced by lithium aluminum hydride to yield the demethylisocularine (III). The IR and NMR spectra of this product were in distinguishable from those of the above sample.

Recently, cancentrine, an alkaloid from *Dicentra canadensis*,[9,10] was assigned a novel dimeric benzylisoquinoline (XVI) derived from morphine and cularine, which has three interesting facts from biogenetic and chemotaxonomic points of view. Thus, the first is in the manner of its linkage between the individual benzylisoquinoline units although the usual bisbenzylisoquinolines coupled at the *ortho* or *para* to the phenolic hydroxy group. Secondly, it is unknown when a coupling of two benzylisoquinoline units does occur in this alkaloid. Thirdly, this base is found in *Dicentra* genus which has no morphine alkaloids. Demethylisoquinoline (III), obtained in good yield by an intramolecular Ullmann reaction, forms a part of cancentrine (XVI).



XVI

Chart 3

Thus, we synthesized the key intermediate (III) for the synthesis of cancentrine and also proved the structure of oxidation product of the diphenolic isoquinoline (II). Moreover, an intramolecular Ullmann reaction seems to be an effective method for the synthesis of cularine type alkaloids.[11]

Experimental[12]

Sodium 3-(3-Benzyloxy-2-bromo-4-methoxyphenyl)glycidate (VII)——A mixture of 43 g of 3-benzyloxy-2-bromo-4-methoxybenzaldehyde (V),[5] 24.6 g of methyl chloroacetate and 9 ml of dry MeOH was added dropwise to sodium methoxide solution [prepared from 4.9 g of sodium and 112 ml of dry MeOH] under cooling (−5——15°) and stirring within 1.5 hr. Stirring was continued at −5——10° for 2 hr, and then at room temperature for an additional 3 hr. The reaction mixture was then poured into crushed ice (*ca.* 1 kg) and acidified with 2 ml of AcOH. The separated oil was extracted with benzene. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave methyl 3-(3-benzyloxy-2-bromo-4-methoxyphenyl)glycidate (VI) as a pale brown oil, which was used without purification because this oil was decomposed in vacuum distillation at high temperature.

To a solution of 53 g of the glycidate in 320 ml of dry benzene, sodium methoxide solution [prepared from 4 g of sodium and 65 ml of dry MeOH] was added dropwise at 5° with stirring during 1 hr, and then 3.5 ml of water was added. After stirring at 5° for 10 min, 300 ml of ether was added and the mixture was stirred for an additional 2 hr at room temperature to precipitate a solid, which was collected, washed with ether and dried to give 24 g (44.6%) of the sodium glycidate (VII) as a colorless powder, mp 191—193° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1660 (CO).

3-Benzyloxy-2-bromo-4-methoxyphenylacetaldehyde (VIII)——To a suspension of 28 g of sodium glycidate (VII) in 280 ml of dry benzene was added 5.6 ml of AcOH with stirring, and the mixture was refluxed

9) R.H.F. Manske, *Can. J. Res.*, **B, 7,** 258 (1932); **B, 16,** 81 (1938).
10) G.F. Clark, R.H.F. Manske, G.J. Palenik, R. Rodrigo, D.B. MacLean, L. Baczynskyj, D.E.F. Gracey, and J.K. Saunders, *J. Am. Chem. Soc.*, **92,** 4998 (1970).
11) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Hirokawa Publishing Inc. Co., Tokyo, Japan, 1968, p. 74 and 239.
12) IR and UV spectra were recorded on type EPI-3 and EPS-2 Hitachi recording spectrometers, respectively. Mass spectra were measured with a Hitachi RMS-4 mass spectrometer, and NMR spectra were taken with JNM-60 and JNM-100 photometers with tetramethylsilane as an internal standard.

for 3 hr. After cooling, the benzene solution was washed with water, dried over Na_2SO_4, and evaporated to leave a pale brown oil, whose solution in 300 ml of ether was stirred vigorously with a solution of 12 g of sodium bisulfite in 24 ml of water to separate 25 g (80%) of the adduct of the aldehyde (VIII) with bisulfite. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (CO) (free aldehyde). The semicarbazone of the aldehyde (VIII) gave colorless needles, mp 166—167° (from MeOH). *Anal.* Calcd. for $C_{17}H_{18}O_3N_3Br$: C, 52.05; H, 4.63; Br, 20.38. Found: C, 52.32; H, 4.86; Br, 20.41.

1-(3-Benzyloxy-2-bromo-4-methoxybenzyl)-5-bromo-1,2,3,4-tetrahydro-8-hydroxy-7-methoxyisoquinoline (IX)——A mixture of 10 g of 2-bromo-5-hydroxy-4-methoxyphenethylamine hydrochloride,[6] 16.5 g of sodium bisulfite adduct of 3-benzyloxy-2-bromo-4-methoxyphenylacetaldehyde (VIII), 200 ml of MeOH, and 50 ml of conc. NH_4OH was heated at 50° for 3 hr, and then refluxed for 17 hr. After cooling, the separated solid was collected, washed with water and MeOH and recrystallized from $CHCl_3$–AcOEt to give 5.0 g (24.7%) of the tetrahydroisoquinoline (IX) as pale brown prisms, mp 191—193°. IR ν_{max}^{Nujol} cm^{-1}: 3320 (OH) and 3200—2400 (betaine). UV λ_{max}^{EtOH} nm (log ε): 287 (4.00). NMR ($CDCl_3$–CF_3CO_2H) ppm: 2.7—3.7 (6H, m, $3\times CH_2$), 3.81 (6H, s, $2\times OCH_3$), 4.97 (2H, s, $OC\underline{H}_2C_6H_5$), 6.81 (1H, d, J=9 Hz, 5′-H), 7.03 (1H, s, 6-H), 7.05 (1H, d, J=9.0 Hz, 6′-H), 7.7—7.2 (5H, m, $OCH_2C_6\underline{H}_5$). Mass Spectrum *m/e*: 561 (M^+), 563 and 565 (M^++2, M^++4, isotope peaks), 256 (base), 258. *Anal.* Calcd. for $C_{25}H_{25}O_4NBr_2\cdot 0.5\,H_2O$: C, 52.47; H, 4.58; N, 2.46; Br, 27.94. Found: C, 52.64; H, 4.53; N, 2.49; Br, 27.98.

1-(3-Benzyloxy-2-bromo-4-methoxybenzyl)-5-bromo-1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-2-methylisoquinoline (X)——To a suspension of 600 mg of the above isoquinoline (IX) in 60 ml of MeOH was added 0.3 ml of 37% formalin, and the mixture was stirred at 5° for 7 hr. Sodium borohydride (500 mg) was added to this mixture at 5° with stirring during 15 min, and the stirring was continued for 2 hr at room temperature. After being set aside overnight at room temperature, the separated solid was filtered off and the filtrate was concentrated *in vacuo*. The residue was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave 470 mg (76.9%) of the 2-methylisoquinoline (X) as a pale brown oil, which was homogeneous on TLC ($CHCl_3$: MeOH=10:1). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH). NMR ($CDCl_3$) ppm: 2.31 (3H, s, NCH_3), 3.81 (6H, s, $2\times OCH_3$), 4.27 (1H, t, J=6.2 Hz, 1-H), 5.0 (2H, s, $OC\underline{H}_2C_6H_5$), 6.79 (1H, d, J=8.5 Hz, 5′-H), 6.97 (1H, s, 6-H), 7.07 (1H, d, J=8.5 Hz, 6′-H), 2.8—2.3 (5H, m, $OCH_2C_6\underline{H}_5$). Recrystallization of the picrolonate from EtOH gave yellow prisms, mp 201—203°. *Anal.* Calcd. for $C_{26}H_{27}O_4NBr_2\cdot C_{10}H_8O_5N_4$: C, 51.38; H, 4.20; N, 8.33; Br, 19.00. Found: C, 51.25; H, 4.39; N, 8.44; Br, 18.65.

Ullmann Reaction of the Phenolic Bromoisoquinoline (X)——a) A mixture of 300 mg of the phenolic bromoisoquinoline (X), 500 mg of K_2CO_3 and 10 ml of pyridine was heated at 130°, and to this was added 150 mg of cupric oxide. This mixture was heated under reflux at 160° for 4 hr, and filtered after cooling. The solid was washed with benzene, and benzene layer and filtrate were combined and distilled *in vacuo* to leave the residue, which was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave 280 mg of a brown oil, which was chromatographed on 3 g of silica gel and $CHCl_3$ eluant gave 227 mg (87.5%) of the benzo[*b*]oxepino[7,6,5-*ij*]isoquinoline (XI) as a pale yellow syrup. Mass Spectrum *m/e*: 495 (M^+), 497 (M^++2, isotope peak), and 404, 406, (base peaks, $M^+ - CH_2C_6H_5$). NMR ($CDCl_3$) ppm: 2.51 (3H, s, NCH_3), 3.62 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.33 (1H, q, J=5.5, 10.0 Hz, 5a-H), 5.19 (2H, s, $OC\underline{H}_2C_6H_5$), 6.53 (1H, d, J=9.0 Hz, 3-H), 6.74 (1H, d, J=9.0 Hz, 4-H), 6.99 (1H, s, 10-H), 7.2—7.7 (5H, m, $OCH_2C_6\underline{H}_5$).

b) A mixture of 100 mg of X, 150 mg of K_2CO_3, 100 mg of Cu powder, and 3 ml of pyridine was heated under reflux for 4 hr and worked up as above to give 50 mg (71%) of XI, which was identical with the product prepared by method (a).

5,5a,6,7,8-Pentahydro-1-hydroxy-2,11-dimethoxy-6-methylbenzo[*b*]oxepino[7,6,5-*ij*]isoquinoline (III)——a) A solution of 85 mg of the above benzo[*b*]oxepino[7,6,5-*ij*]isoquinoline (XI) in 20 ml of EtOH and aqueous AcONa solution [prepared from 16 mg of AcONa and 4 ml of water] was shaken at room temperature and low pressure (hydrogen pressure 45 lb) by using Parr Pressure Reaction Apparatus on 50 mg of 10% Pd-C. After absorption of H_2 the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 51 mg (90.6%) of the 1-hydroxybenzo[*b*]oxepino[7,6,5-*ij*]isoquinoline(III) as colorless needles, mp 127—129° (from ether), which was completely identical with the oxidation product[3] from the diphenolic isoquinoline(II) in IR and NMR spectral comparison and mixed mp test.

b) To a suspension of 40 mg of $LiAlH_4$ in 10 ml of tetrahydrofuran was added 120 mg of the phenolic oxepine(XV) in 3 ml of tetrahydrofuran within 10 min, and the mixture was refluxed for 3 hr. After the reaction, an excess of $LiAlH_4$ was decomposed with water and the separated material was collected by filtration, and dissolved in 1 ml of conc. HCl, which was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave 65 mg of a pale yellow oil. On the other hand, the mother liquor of lithium salt was evaporated to leave 25 mg of a pale yellow oil. Both oil was combined and purified on silica gel (1 g) chromatography eluted with chloroform to give 65 mg (63.7%) of the demethylisocularine(III), which was identical with the sample prepared by method (a) in spectral comparison.

1-(3-Benzyloxy-2-bromo-4-methoxybenzyl)-5-bromo-2-ethoxycarbonyl-8-ethoxycarbonyloxy-1,2,3,4-tetrahydro-7-methoxyisoquinoline(XII)——To a suspension of 1 g of the phenolic isoquinoline(IX) in 250 ml of $CHCl_3$ and 600 mg of triethylamine was added 600 mg of ethyl chloroformate in 10 ml of $CHCl_3$ with stirring below 5° within 15 min, and the mixture was stirred for 0.5 hr below 5° and then for further 1 hr at room temperature. After the reaction, the mixture was washed with 5% hydrochloric acid and water, dried over Na_2SO_4, and evaporated to give 1.0 g (80.0%) of the 2-ethoxycarbonyl-8-ethoxycarbonyloxyisoquinoline (XII) as colorless needles, after recrystallization from EtOH, mp 119—120°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (OCO_2Et), 1683 (NCO_2Et). UV λ_{max}^{EtOH} nm (log ε): 281 (3.71), 286 (3.72). NMR ($CDCl_3$) ppm: 0.97 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.37 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.80 (6H, 2×OCH_3), 4.7—2.5 (6H, m, 3×CH_2), 4.34 (4H, q, J=7.0 Hz, 2×$C\underline{H}_2CH_3$), 4.97 (2H, s, $OC\underline{H}_2C_6H_5$), 6.8 (2H, s, 5′-H and 6′-H), 7.15 (1H, s, 7-H), 7.7—7.2 br (5H, $OCH_2C_6\underline{H}_5$). *Anal.* Calcd. for $C_{31}H_{33}O_8NBr_2$: C, 52.63; H, 4.70; N, 1.98; Br, 22.59. Found: C, 52.56; H, 4.74; N, 1.98; Br, 22.36.

1-(3-Benzyloxy-2-bromo-4-methoxybenzyl)-5-bromo-2-ethoxycarbonyl-1,2,3,4-tetrahydro-8-hydroxy-7-methoxyisoquinoline (XIII)——A mixture of 3.88 g of the above isoquinoline (XII), 19 ml of 10% NaOH, and 300 ml of EtOH was heated at 60° for 2 hr, and then set aside at room temperature overnight. After evaporation of EtOH, the residue was diluted with water, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 3.25 g (93.2%) of the phenolic isoquinoline (XIII) as colorless prisms, after recrystallization from EtOH, mp 149—151°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1680—1690 (CO). NMR ($CDCl_3$) ppm: 1.4—0.8 (3H, m, $CH_2C\underline{H}_3$), 3.82 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.5—2.5 (6H, m, 3×CH_2), 4.5—3.9 (2H, m, $C\underline{H}_2CH_3$), 5.0 (2H, s, $OC\underline{H}_2C_6H_5$), 6.1—5.5 (2H, m, OH and 1-H), 6.8 (1H, d, J=9.0 Hz, 5′-H), 6.97 (1H, d, J=9.0 Hz, 6′-H), 7.0 (1H, s, 6-H). *Anal.* Calcd. for $C_{28}H_{29}O_6NBr_2$: C, 52.93; H, 4.60; N, 2.21; Br, 25.16. Found: C, 53.16; H, 4.69; N, 2.30; Br, 25.16.

1-Benzyloxy-9-bromo-6-ethoxycarbonyl-5,5a,6,7,8-pentahydro-2,11-dimethoxybenzo[*b*]oxepino[7,6,5-*ij*]-isoquinoline(XIV)——A mixture of 1.0 g of the phenolic isoquinoline(XIII), 700 mg of K_2CO_3, 27 ml of pyridine, and 700 mg of copper was refluxed for 6 hr, and then the separated inorganic substance was filtered off. The filtrate was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The extract was washed with 5% HCl, and water, dried over Na_2SO_4, and evaporated to leave a brown syrup. The chromatography on 5 g of silica gel eluted with $CHCl_3$ gave 573 mg (65.6%) of the cyclized product(XIV) as a colorless viscous syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (CO). NMR ($CDCl_3$) ppm: 1.27 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$) 3.5—2.5 (5H, m, 2×CH_2 and 7-H), 3.63 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.20 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 4.7—4.0 (1H, m, 7-H), 5.12, 5.25 (each 1H, each d, J=11.0 Hz, $OC\underline{H}_2C_6H_5$), 6.0 (1H, distorted t, J=9.0 Hz, 5a-H), 6.59 (1H, d, J=9.0 Hz, 3-H), 6.77 (1H, d, J=9.0 Hz, 4-H), 7.05 (1H, s, 10-H), 7.8—7.2 (5H, m, $OCH_2C_6\underline{H}_5$). Mass Spectrum *m/e*: 553 (M^+), 555 (M^++2, isotope peak), 462 (base peak), 464.

6-Ethoxycarbonyl-5,5a,6,7,8-pentahydro-1-hydroxy-2,11-dimethoxybenzo[*b*]oxepino[7,6,5-*ij*]isoquinoline (XV)——A mixture of 220 mg of the above oxepine(XIV), 40 mg of NaOAc, and 20 ml of EtOH in the presence of 25 mg of PtO_2 was shaken in a current of H_2 at room temperature. After absorption of two moles of H_2, the catalyst was filtered off and the filtrate was evaporated to leave an oil, which was extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 153 mg of a colorless oil, which was purified by silica gel column chromatography using $CHCl_3$ as an eluant to give 121 mg (76.7%) of the phenolic oxepine(XV) as a colorless viscous syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (OH), 1680—1690 (CO). NMR ($CDCl_3$) ppm: 1.26 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.5—2.5 (5H, m, 2×CH_2 and 7-H), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.21 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 6.05 br (1H, 5a-H), 6.46 (1H, d, J=8.0 Hz, 3-H), 6.65 (1H, d, J=8.0 Hz, 4-H), 6.74 (1H, d, J=8.5 Hz, 10-H), 6.94 (1H, d, J=8.5 Hz, 9-H). Mass Spectrum *m/e*: 385 (M^+, base peak).

Acknowledgement We thank Mr. M. Yamazaki and Dr. M. Kawazu, Tanabe Seiyaku Co. Ltd., for their encouragements, and the Analytical Center of Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd., for microanalyses and spectral measurements. We also thank Miss T. Yoshida and Miss R. Kato, Pharmaceutical Institute, Tohoku University for technical assistance.