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The Synthesis of C-nor-Androcymbine (Studies on the Syntheses of Heterocyclic Compounds. CCCXXIV[1])

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The thermal decomposition of the diazonium salt, derived from 1-(2-amino-3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XI) which was prepared by an usual method, by our method gave the morphinandienone type compound (C-nor-androcymbine) (X). This paper also described the approaches to the synthesis of androcymbine (I).

Androcymbine, an alkaloid co-existed with melanthioidine (II)[3–6] and colchicine (III)[7] in *Androcymbium melanthioides* var. *stricta* (Liliaceae),[8] which was used as one of folk medicines in Estern Africa,[9] was assigned to structure (I) by chemical and spectroscopic methods by Battersby and his associates in 1965.[10] Biogenetically, androcymbine (I) is formed with phenolic oxidation[11] of 1-phenethylisoquinoline derivative (IV), and also precursor to colchicine type alkaloids.[12]

In the previous paper,[13] we reported a biogenetic type synthesis of androcymbine-like compound (VI) with phenolic oxidation of diphenolic isoquinoline derivative (VII). However, an application of this method to 1-phenethylisoquinoline derivative (IV) has not yet been succeeded.[14] On the other hand, diazotization of 2′-aminophenethylisoquinoline derivative (VIII), followed by thermal decomposition of the diazonium salt, afforded the second androcymbine type compound (IX)[15] and this method is presumed more useful one than phenolic oxidation method and we are now approaching to the total synthesis of androcymbine by this method. In this paper, we wish to describe a synthesis of C-nor-androcymbine (X) by modified Pschorr reaction[16–18] as a model experiment for the total synthesis of androcymbine (I).

The starting compound, 1-(2-amino-3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XI), was prepared by usual method as follow. Heating of

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1) Part CCCXXIII: T. Kametani, V. Kigasawa, M. Hiiragi, O. Kusama, and K. Wakisaka, *Yakugaku Zasshi*, **89**, 1212 (1969).
2) Location: *Aobayama, Sendai.*
3) A.R. Battersby, R.B. Herbert, and F. Santavy, *Chem. Comm.*, **1965**, 415.
4) A.R. Battersby, R.B. Herbert, L. Mo, and F. Santavy, *J. Chem. Soc.* (*C*), **1967**, 1739.
5) T. Kametani and S. Takano, *Tetrahedron Letters*, **1968**, 121.
6) T. Kametani, S. Takano, and K. Haga, *Chem. Pharm. Bull.* (Tokyo), **16**, 663 (1968).
7) H.G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," 28, Akademie-verlag, Berlin, 1961.
8) J. Hrbek and F. Santavy, *Coll. Czech. Chem. Comm.*, **27**, 255 (1962).
9) J.M. Watt and M.G. Breyer-Brandwijk, "Medicinal and Poisonous Plants of South and Eastern Africa," Livigston, Edinburgh, 1962, p. 687.
10) A.R. Battersby, R.B. Herbert, L. Pijiwska, and F. Santavy, *Chem. Comm.*, **1965**, 228.
11) T. Kametani and K. Fukumoto, *Japanese J. Pharm. Chem.*, **35**, 426 (1963); *Pharmacia*, **4**, 144 (1968).
12) A.C. Baker, A.R. Battersby, E. McDonald, R. Ramage, and J.H. Chements, *Chem. Comm.*, **1967**, 390, and refs. cited therein.
13) T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *Chem. Comm.*, **1968**, 1605.
14) *cf.* T. Kametani, H. Yagi, F. Satoh, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1968**, 271.
15) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, **1968**, 1001.
16) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, **1968**, 1398.
17) T. Kametani, K. Fukumoto, and T. Sugahara, *Tetrahedron Letters*, **1968**, 5459.
18) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc.* (*C*), in press.

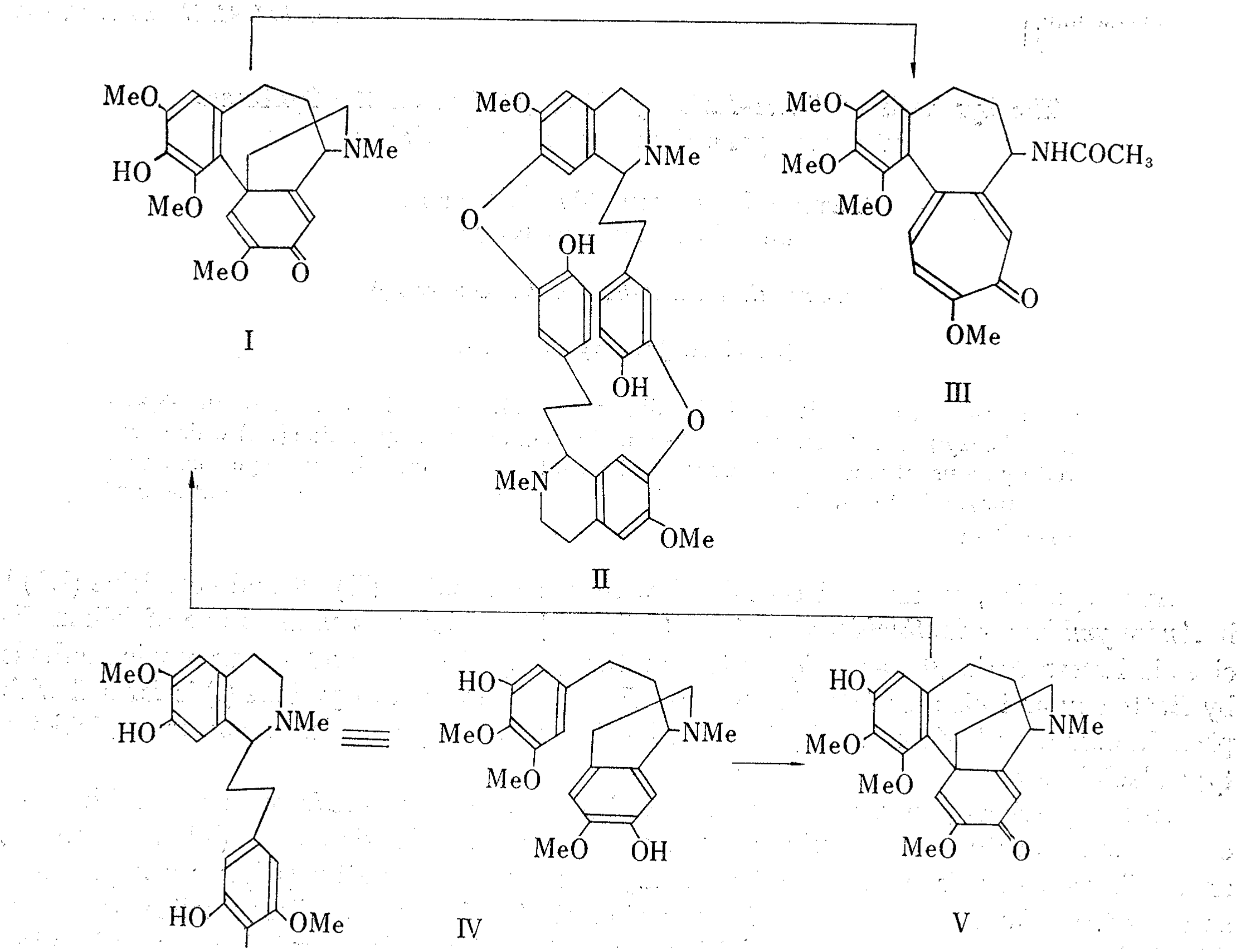

Chart 1

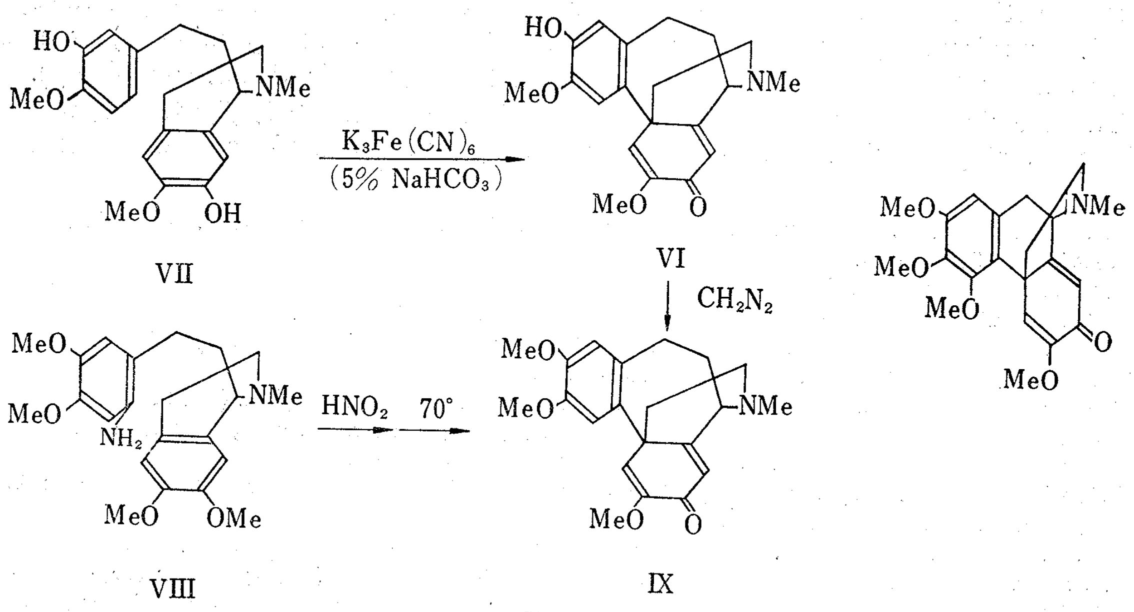

Chart 2

homoveratrylamine (XII) with 3,4,5-trimethoxy-2-nitrophenylacetic acid (XIII)[19] in dry xylene afforded the amide (XIV), which was cyclized with phosphoryl chloride in dry chloroform to give the 3,4-dihydroisoquinoline (XV) characterized as its methiodide (XVI). Reduc-

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[19] K. Hirai and K. Harada, *J. Pharm. Soc. Japan*, **80**, 1429 (1960).

tion of this methiodide (XVI) with zinc and concentrated hydrochloric acid gave the starting aminoisoquinoline (XI), which was unstable in the air and used without purification.

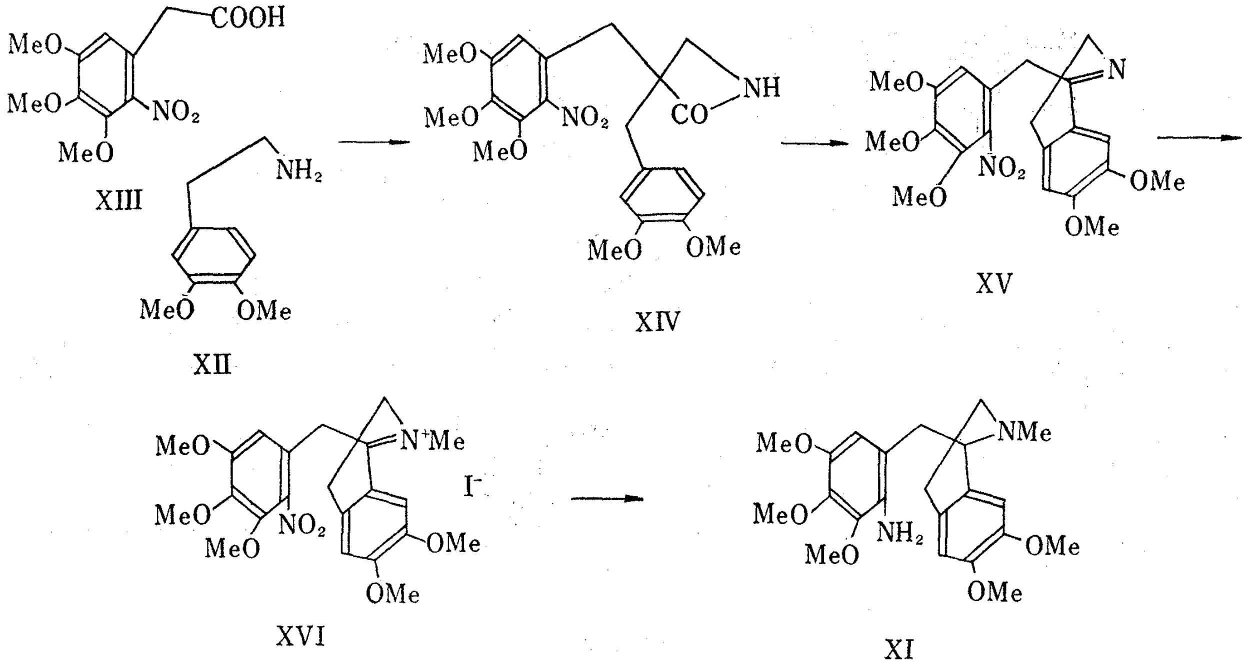

Chart 3

Aminoisoquinoline (XI) was diazotized with a slight excess of sodium nitrite and 1N sulfuric acid–acetic acid with stirring at 0°, and the resulting diazonium salt was decomposed and coupled at 70° for 1 hr with stirring. The careful work up involving silica gel and then alumina chromatographies under investigation by the infrared spectrum afforded many compounds, from which the aimed C-nor-androcymbine (X) was characterized as its methiodide, mp 234—235°, 1.7% yield. The structural assignment was achieved by the spectral method. The molecular formula of $C_{21}H_{25}O_5N$ was verified by the high resolution mass spectrometry of its free base and the microanalysis of its methiodide. The infrared [ν_{max} ($CHCl_3$): 1665, 1641, and 1617 cm^{-1}] and ultraviolet spectra [λ_{max} (MeOH): 234 and 276 mμ] supported well a cross-conjugated α-methoxycyclohexadienone system.[20] The nuclear magnetic resonance (NMR) spectrum (τ in $CDCl_3$) showed the presence of five methyl groups at 7.56 (NMe), 6.22 (OMe), 6.18 (2×OMe) and 6.02 (OMe), two olefinic protons at 3.71 (C_8–H) and 2.78 (C_5–H) as singlets and one aromatic proton at 3.56 as a singlet. These data confirmed unambigously the reaction product to be the structure (X).

Moreover, two products, compound (A) and (B), were obtained in the above reaction as the viscous oily substances in poor yields, but their structures were remained unclear. The former (compound A) revealed the following spectral data; the ultraviolet spectrum showed λ_{max} (MeOH) 281 mμ, and the NMR spectrum showed five methyl resonances at 7.77 (3H), 6.41 (3H), 6.19 (3H), 6.15 (3H) and 6.11 (3H), and four aromatic protons at 3.40 (1H), 3.24 (1H) and 3.18 (2H) as singlets. The latter compound (B) also showed six methyl resonances at 7.45 (3H), 6.42 (3H), 6.21 (3H), 6.13 (6H) and 6.11 (3H) in the NMR spectrum, and the absorption maximum at 278 mμ was shown in the ultraviolet spectrum. These data ruled out both products to be the aporphine type compound (XVII) and they seemed to be the deamination products as XVIII. However, the comparisons of the authentic sample (XVIII), which was obtained by quaternization of 3,4-dihydro-6,7-dimethoxy-1- (3,4,5-trimethoxybenzyl) isoquinoline (XIX)[21] with methyl iodide followed by reduction with sodium borohy-

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[20] T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, 33, 690 (1968).
[21] E. Spath and T. Meinhard, *Ber.*, 75, B, 400 (1942).

dride, with compound A and B by spectral and chromatographic methods proved our assumption to be uncorrect.

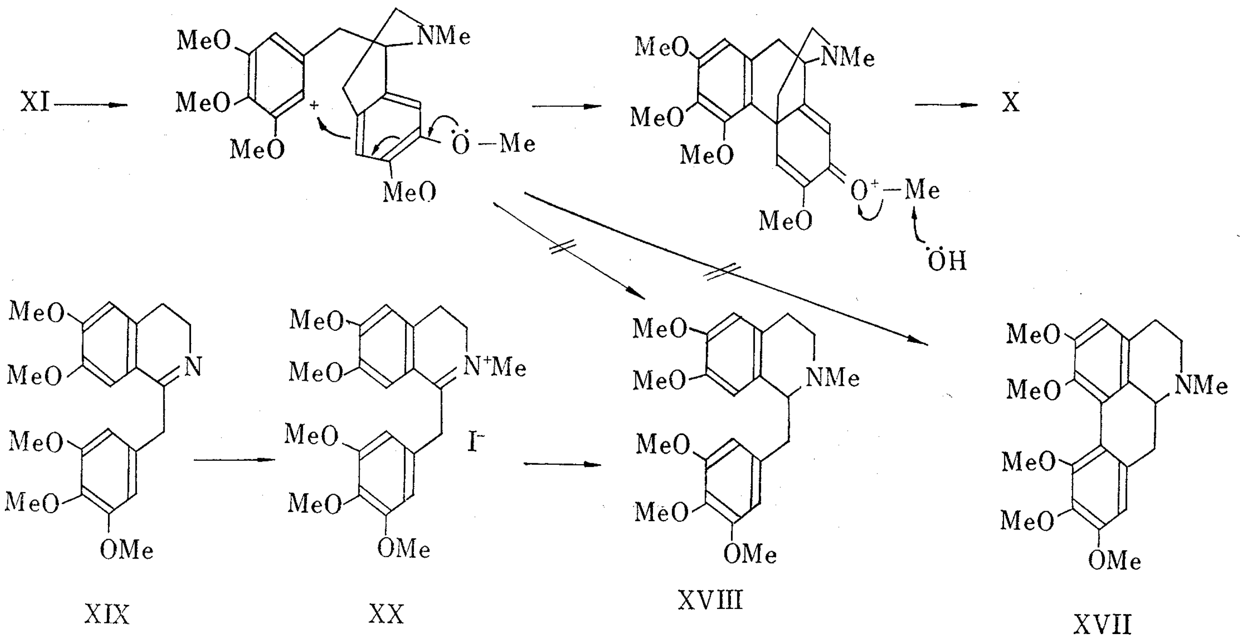

Chart 4

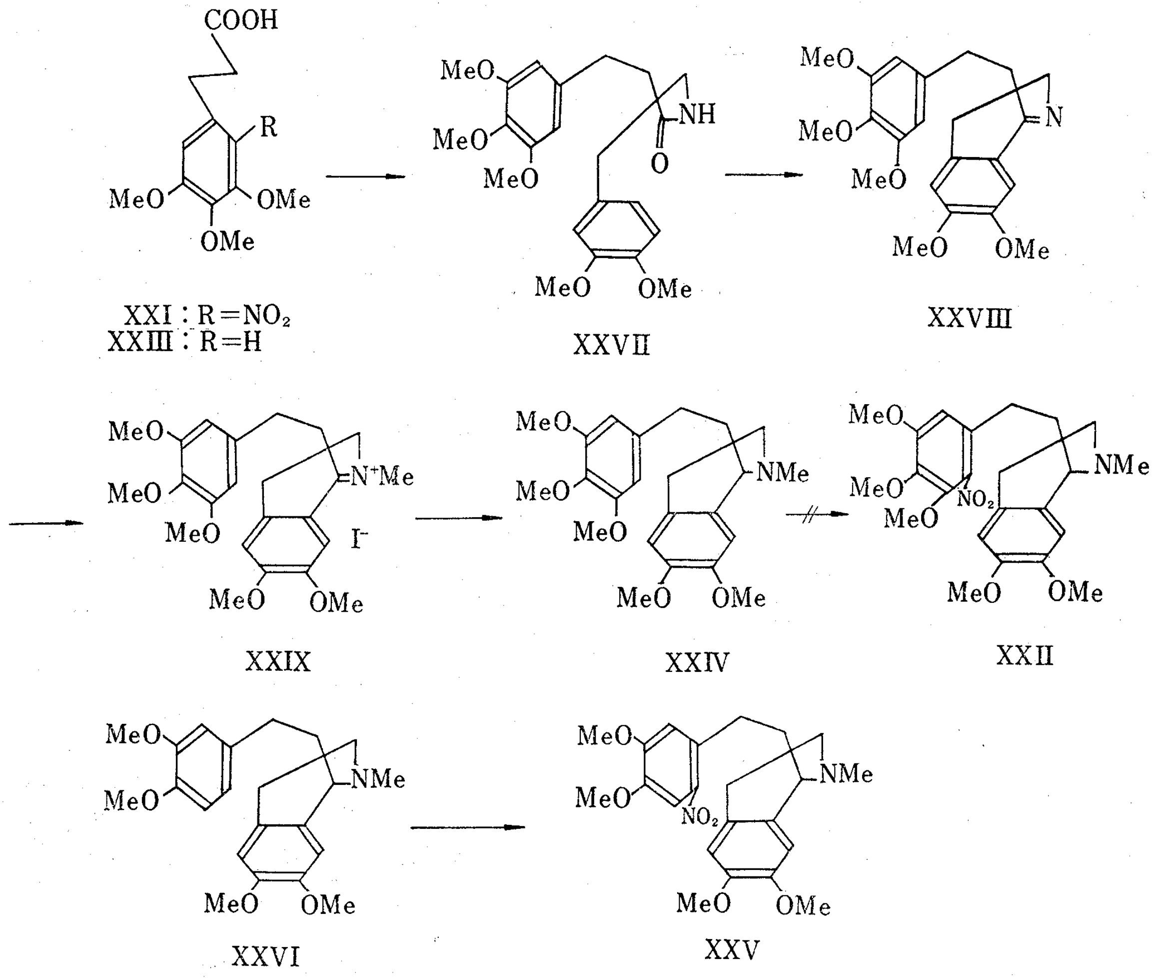

Chart 5

Secondly, we have tried to homologize 2-nitrophenylacetic acid (XIII) to 2-nitrophenylpropionic acid (XXI) by several methods in order to prepare 2'-nitrophenethylisoquinoline (XXII), but ceased in unsuccess. Nitration of 3,4,5-trimethoxyphenylpropionic acid (XXIII) also resulted in failure.

Finally, nitration of 1-phenethylisoquinoline (XXIV) was examined since we have already obtained 2'-nitrophenethylisoquinoline (XXV) by nitration of 1-phenethylisoquinoline (XXVI).[22] Thus, the amide (XXVII) obtained by the fusion of the homoveratrylamine (XII) with 3,4,5-trimethoxyphenylpropionic acid (XXIII) was subjected to Bischler–Napieralski reaction to give 3,4-dihydroisoquinoline (XXVIII), whose methiodide (XXIX) was reduced with sodium borohydride to afford 1,2,3,4-tetrahydroisoquinoline (XXIV). An attempt to introduce the nitro-group to the phenethyl moiety was also unsuccessful. Further studies to synthesize androcymbine by modified Pschorr reaction or phenolic oxidation are in progress.

Experimental[23]

N-(3,4-Dimethoxyphenethyl)-3,4,5-trimethoxy-2-nitrophenylacetamide (XIV)——A mixture of 6.4 g of homoveratrylamine (XII) and 8.0 g of 3,4,5-trimethoxy-2-nitrophenylacetic acid (XIII)[19] in 110 ml of dry xylene was refluxed for 3.5 hr under removal of water formed in this reaction. After evaporation of the solvent, the residue was dissolved in chloroform, whose solution was washed with 5% HCl, 5% K_2CO_3 and water. The extract was dried over Na_2SO_4 and evaporated to leave a brown viscous syrup, which was subjected to alumina (200 g) chromatography. Evaporation of the appropriate $CHCl_3$ eluant gave 10.8 g of the amide (XIV) as an orange viscous syrup. IR cm^{-1} ($CHCl_3$): ν_{NH} 3380, $\nu_{C=O}$ 1664, ν_{NO_2} 1340. NMR (τ) ($CDCl_3$): 6.19 (6H, singlet, $2\times OC\underline{H}_3$), 6.12 (6H, singlet, $2\times OC\underline{H}_3$), 6.03 (3H, singlet, $OC\underline{H}_3$), 3.30 (4H, broad singlet, aromatic protons).

3,4-Dihydro-6,7-dimethoxy-1-(3,4,5-trimethoxy-2-nitrobenzyl)isoquinoline (XV)——A mixture of 10.8 g of the amide (XIV), 12.2 ml of $POCl_3$ and 210 ml of dry $CHCl_3$ was heated under reflux for 3.5 hr. After evaporation of one-half volume of $CHCl_3$, the reaction mixture was poured into 800 ml of hexane and allowed to stand for 2 hr at room temperature. The precipitate was collected and dissolved in $CHCl_3$, whose solution was washed with 10% NH_4OH solution, water and dried over Na_2SO_4. The solvent was evaporated to leave 8.7 g of the 3,4-dihydroisoquinoline (XV) as a pale brown viscous syrup, which was characterized as 7.5 g of its methiodide (XVI). Recrystallization from MeOH–ether gave pale yellow needles, mp 157—158°. *Anal.* Calcd. for $C_{22}H_{27}O_7N_2I\cdot 1/2H_2O$: C, 46.57; H, 4.97. Found: C, 46.48; H, 4.96. IR cm^{-1} ($CHCl_3$): 3335 (water of crystallization), $\nu_{C=N^+}$ 1620.

1-(2-Amino-3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XI)——To a solution of 7.5 g of the above methiodide (XVI) in 280 ml of 24% HCl solution was added portionwise 56g of zinc powder at 100° within 1 hr with stirring and the stirring was continued for further 1 hr at the same temperature as above. Undissolved zinc powder was filtered off, and the filtrate was basified with 10% ammonia solution, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave 4.8 g of the aminoisoquinoline as a brown viscous syrup. IR cm^{-1} ($CHCl_3$): ν_{NH_2} 3325 and 3125. NMR (τ) ($CDCl_3$): 7.47 (3H, singlet, $NC\underline{H}_3$), 6.31 (6H, singlet, $2\times OC\underline{H}_3$), 6.19 (3H, singlet, $OC\underline{H}_3$), 6.18 (6H, singlet, $2\times OC\underline{H}_3$), 3.78 (2H, singlet, $N\underline{H}_2$), 3.48 (1H, singlet, aromatic proton), 3.30 (2H, singlet, aromatic proton), 3.30 (2H, singlet, aromatic protons).

C-nor-Androcymbine (X)——To a solution of 4.8 g of the aminoisoquinoline (XI) in 125 ml of 5% H_2SO_4 and 1.5 ml of acetic acid was added dropwise 10 ml of 10% aqueous sodium nitrite solution with stirring at 0—5° during 15 min and the mixture was stirred for 1 hr at 0—5° and then heated at 70° for 1 hr with stirring. After cooling to room temperature, the reaction mixture was basified with 10% NH_4OH solution and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 4.5 g of a dark brown gum, which was chromatographed on 100 g of silica gel using chloroform [fractions 1—13, each fraction (200 ml) was collected], chloroform–methanol (99:1, v/v; fractions 14—22) as eluants by IR and UV spectra control. Fractions 11—19 were combined to leave 540 mg of the crude dienone, which was rechromatographed on 15 g of alumina and eluted successively with benzene [fractions 1—4, each fraction (30 ml) was collected], benzene–chloroform [95:5 v/v; fractions 5—21], benzene–chloroform (90:10 v/v; fractions 22—29), benzene–chloroform(85:15 v/v; fractions 30—35), benzene–chloroform

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[22] T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *J. Chem. Soc.* (*C*), **1968**, 3084.

[23] All melting points were uncorrected. NMR spectra were determined on a Hitachi H-60 spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectrum was determined on a Hitachi RMU-7 spectrometer.

(80:20 v/v; fractions 36—43], benzene–chloroform (65:35 v/v; fractions 44—51) and benzene–chloroform (50:50 v/v, fractions 52—67]. Fractions 5—8 (controlled by UV spectra) were combined and evaporated to give 6 mg of the compound A as a pale yellow viscous syrup, and the same treatment of fractions 11—13 gave 10 mg of the compound B as a pale yellow viscous syrup. Furthermore, fractions 15—63 were combined and the solvent was distilled to give 75 mg of C-nor-androcymbine (X) as a yellow viscous syrup, which was characterized as its methiodide, whose recrystallization from MeOH–ether gave yellow needles, mp 234—235°. *Anal.* Calcd. for $C_{22}H_{28}O_5NI \cdot 1/3H_2O$: C, 50.87; H, 5.56. Found: C, 51.13; H, 5.91. UV mμ (MeOH): 234 and 276. IR cm^{-1} ($CHCl_3$): 3335 (water of crystallization), $\nu_{C=O}$ 1665, $\nu_{C=C}$ 1641, $\nu_{C=C}$ 1617. NMR [free base (X)] (τ) ($CDCl_3$): 7.56 (3H, singlet, $NC\underline{H}_3$), 6.22 (3H, singlet, $OC\underline{H}_3$), 6.18 (6H, singlet, $2\times OC\underline{H}_3$), 6.02 (3H, singlet, $OC\underline{H}_3$), 3.71 (1H, singlet, C_8-$\underline{H}$), 3.56 (1H, singlet, C_1-$\underline{H}$), 2.78 (1H, singlet, C_5-H).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)-2-methylisoquinoline (XVIII)——A mixture of 4.5 g of 3,4-dihydro-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)isoquinoline (XIX)[21] and 10 ml of methyl iodide was set aside overnight at 10° and the excess of methyl iodide was distilled off. The residue was recrystallized from MeOH to give 3.2 g of the methiodide (XX) as yellow needles, mp 216—217° (decomp.). *Anal.* Calcd. for $C_{22}H_{28}O_5NI$: C, 51.47; H, 5.5; N, 2.73. Found: C, 51.41; H, 5.42; N, 2.82. IR cm^{-1} (KBr): $\nu_{C=N^+}$ 1631. To a solution of 2.0 g of the methiodide (XX) in 100 ml of MeOH was added portionwise 2.0 g of $NaBH_4$ during 0.5 hr with stirring at 5—10° and the mixture was stirred for 0.5 hr at room temperature and then refluxed for 0.5 hr. The methanol was then distilled off and the residue was decomposed with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave 1.4 g of the tetrahydroisoquinoline (XVIII) as a pale brown viscous syrup, NMR (τ) ($CDCl_3$) 7.41 (3H, singlet, $NC\underline{H}_3$), 6.39 (3H, singlet, $OC\underline{H}_3$), 6.20 (6H, singlet, $2\times OC\underline{H}_3$), 6.18 (3H, singlet, $OC\underline{H}_3$), 6.16 (3H, singlet, $OC\underline{H}_3$), 3.89 (1H, singlet, aromatic proton), 3.65 (2H, single, aromatic protons), 3.38 (1H, singlet, aromatic proton). The free base was characterized as its picrate, mp 177—178°, after recrystallization from EtOH. *Anal.* Calcd. for $C_{28}H_{32}O_{12}N_4$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.09; H, 5.20; N, 8.75.

N-(3,4-Dimethoxyphenethyl)-3,4,5-trimethoxyphenylpropionamide (XXVII)——A mixture of 2.0 g of homoveratrylamine (XII) and 2.5 g of 3,4,5-trimethoxyphenylpropionic acid (XXIII) was heated at 180° for 2 hr in a current of N_2. The reaction mixture was extracted with $CHCl_3$, and the extract was washed with 5% $NaHCO_3$, 10% HCl and water, and dried over Na_2SO_4. The solvent was evaporated to leave a yellow solid, which was recrystallized from benzene–hexane to give 3.2 g of the amide (XXVII) as colorless needles, mp 113—114°. *Anal.* Calcd. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.25. Found: C, 65.39; H, 7.02. IR cm^{-1} (KBr): ν_{NH} 3270, $\nu_{C=O}$ 1647.

3,4-Dihydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenethyl)isoquinoline (XXVIII)——A mixture of 3.0 g of the amide (XXVII), 4 ml of $POCl_3$ and 40 ml of dry benzene was refluxed for 2.5 hr, and the cooled mixture was poured into 200 ml of hexane and kept at room temperature for 3 hr. The solvent layer was removed by decantation, and the residue was dissolved in $CHCl_3$ and washed with 5% $NaHCO_3$, water, and dried over Na_2SO_4. The solvent was distilled to leave 2.5 g of 3,4-dihydroisoquinoline (XXVIII) as a pale brown viscous syrup, whose methiodide (XXIX) was recrystallized from MeOH to give pale yellow needles, mp 214—215°. *Anal.* Calcd. for $C_{23}H_{30}O_5NI$: C, 52.38; H, 5.73; N, 2.66. Found: C, 52.45; H, 5.87; N, 2.41. IR cm^{-1} (KBr): $\nu_{C=N^+}$ 1621.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenethyl)-2-methylisoquinoline (XXIV)——To a suspension of 2.65 g of the methiodide in 40 ml of MeOH was added portionwise 1.8 g of $NaBH_4$ with stirring at 0—5° during 1 hr and the stirring was continued for 1 hr at room temperature. The solvent was evaporated and the residue was decomposed with water. The separated gum was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and distilled to leave 2.2 g of the tetrahydroisoquinoline (XXIV) as a pale orange viscous syrup. IR cm^{-1} ($CHCl_3$): ν_{NCH_3} 2810. NMR (τ) ($CDCl_3$): 7.56 (3H, singlet, $NC\underline{H}_3$), 6.22 (3H, singlet, $OC\underline{H}_3$), 6.20 (12H, singlet, $4\times OC\underline{H}_3$), 3.62 (2H, singlet, aromatic protons), 3.48 (1H, singlet, aromatic proton), 3.46 (1H, singlet, aromatic proton).

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