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Studies on the Syntheses of Heterocyclic Compounds. CDLXXXVII.[1] Photolytic Synthesis and Rearrangement of Proerythrinadienones

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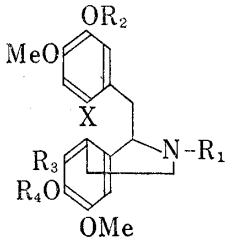
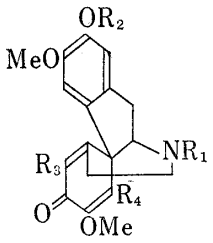
Photolysis of the 1-(2-bromobenzyl)-1,2,3,4-tetrahydro-7-hydroxyisoquinolines(VII, VIII, and X) gave the proerythrinadienones (XIII, XIV, and XV), which would be key precursors for several isoquinoline alkaloids. The acidic treatment of these dienones and the corresponding dienols (XXXII) was investigated under several conditions.

It was proposed by Robinson that sinomenine (XVIII) was biosynthesized from protosinomenine (I).[3] The original proposal involved 1,3-coupling[4] which, although unacceptable,[5] can be expressed in modern terms as oxidation to the "dienone" (XI),[6] followed by acid-induced rearrangement to the carbonium ion (XVII) and by reduction to give sinomenine. Moreover, this dienone type compounds (XI) are proved to be the precursors in biosynthesis of the erythrina (XIX)[7] and the aporphine alkaloids (XX).[8,9] Battersby also suggested that the dienone would be precursor to the hasubanan type alkaloids (XXI).[10]





I: R_1=Me, R_2=R_3=R_4=X=H
II: R_1=CO_2Et, R_2=R_3=R_4=X=H
III: R_1=H, R_2=Me, R_3=OMe, R_4=$CH_2C_6H_5$, X=Br
IV: R_1=R_3=H, R_2=R_4=$CH_2C_6H_5$, X=Br
V: R_1=CO_2Et, R_2=Me, R_3=OMe, R_4=$CH_2C_6H_5$, X=Br
VI: R_1=CO_2Et, R_2=R_4=$CH_2C_6H_5$, R_3=H, X=Br
VII: R_1=CO_2Et, R_2=Me, R_3=OMe, R_4=H, X=Br
VIII: R_1=CO_2Et, R_2=R_3=R_4=H, X=Br
IX: R_1=$COCF_3$, R_2=R_4=$CH_2C_6H_5$, R_3=H, X=Br
X: R_1=$COCF_3$, R_2=R_3=R_4=H, X=Br

XI: R_1=Me, R_2=R_3=R_4=H
XII: R_1=CO_2Et, R_2=R_3=R_4=H
XIII: R_1=CO_2Et, R_2=Me, R_3=OMe, R_4=H
XIV: R_1=CO_2Et, R_2=R_3=R_4=H
XV: R_1=$COCF_3$, R_2=R_3=R_4=H
XVI: R_1=CO_2Et, R_2=R_3=H, R_4=OMe

Chart 1

1) Part CDLXXXVI: T. Kametani, T. Kohno, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1678 (1972).
2) Location: *Aobayama, Sendai.*
3) R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.
4) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, **1931**, 3163; *idem, ibid.*, **1932**, 789.
5) D.H.R. Barton, A.J. Kirby, and G.W. Kirby, *Chem. Commun.*, **1965**, 52; *J. Chem. Soc.* (*C*), **1968**, 929.
6) T. Kametani, R. Charubala, M. Ihara, M. Koizumi, and K. Fukumoto, *Chem. Commun.*, **1971**, 289.
7) D.H.R. Barton, R.B. Boar, and D.A. Widdowson, *J. Chem. Soc.* (*C*), **1970**, 1213 and refs. cited herein.
8) A.R. Battersby, J.L. McHugh, J. Staunton, and M. Todd, *Chem. Commun.*, **1971**, 985.
9) T. Kametani, T. Takahashi, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 3617.
10) A.R. Battersby in "Oxidative Coupling of Phenols," eds. A.R. Battersby and W.I. Taylor, Marcel Dekker, New York, 1967, p. 119.

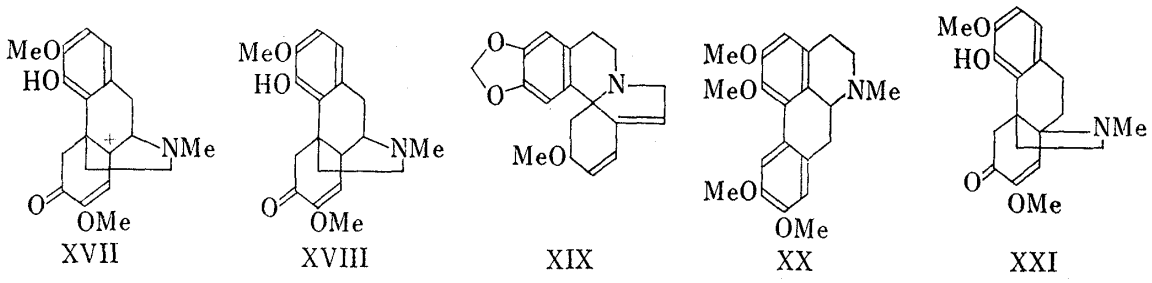


Chart 2

As the dienones (XI), called as "proerythrinadienone,"[6] play an important role in a biosynthesis of the isoquinoline alkaloids described above, we investigated the synthesis of the proerythrinadienone[6,11] and reported the formation of this dienone (XII) in low yield by an oxidative coupling of the diphenolic isoquinoline (II).[6] Therefore, we examined on the modified synthesis of the proerythrinadienone type compounds by photolysis of the phenolic bromoisoquinolines[12] and also on the rearrangement of the dienones into the isoquinoline alkaloids along the biogenetic pattern. Here we wish to report these results.

The fusion of 3-benzyloxy-2,4-dimethoxyphenethylamine (XXII)[13] with methyl 2-bromo-4,5-dimethoxyphenylacetate (XXIV) gave the corresponding amide (XXVI). The same reaction of the phenethylamine (XXIII) and ester (XXV) afforded the second amide (XXVII). Bischler–Napieralski reaction of the amides (XXVI and XXVII) with phosphoryl chloride, followed by sodium borohydride reduction of the resulting 3,4-dihydroisoquinoline hydrochlorides (XXVIII and XXIX), furnished the 1,2,3,4-tetrahydroisoquinolines (III and IV), which were treated with ethyl chloroformate to give the urethans (V and VI). The debenzylation by ethanolic hydrochloric acid gave the phenolic bromoisoquinolines (VII and VIII). Moreover, phenolic N-trifluoroacetylisoquinoline (X) was synthesized from IV by trifluoroacetylation and then debenzylation of IX.

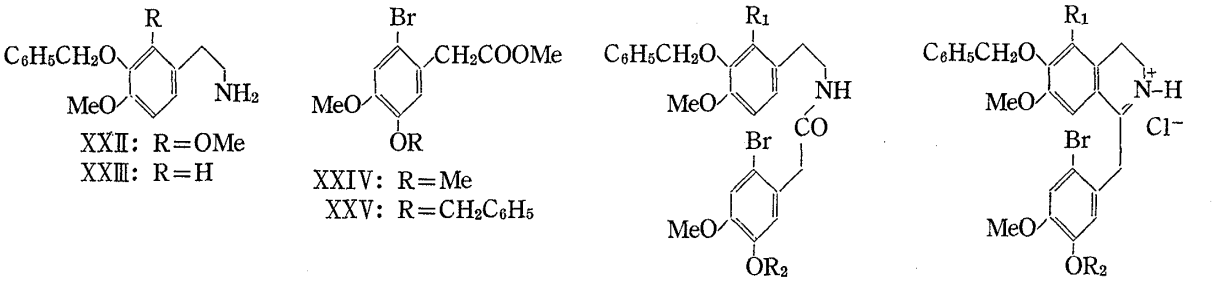


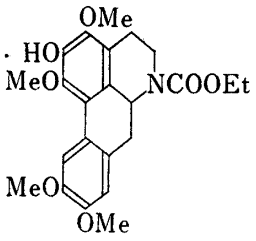
Chart 3

The irradiation of the phenolic bromoisoquinoline (VII) by a Hanovia 450 W mercury lamp with a Pyrex filter in the presence of an excess of sodium hydroxide solution gave the proerythrinadienone (XIII), the structure of which was determined by spectroscopic method. Infrared (IR) spectrum showed cross-conjugated α,α'-dialkoxycyclohexadienone system[14] at 1655 and 1615 cm^{-1} in addition to N-ethoxycarbonyl group (1675 cm^{-1}) but no hydroxy

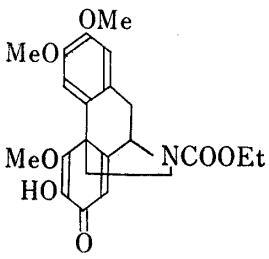
11) T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 1032.
12) T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *Tetrahedron*, **27**, 5441 (1971), and refs. cited herein.
13) S.M. Kupchan, T.-H. Yang, G.S. Vasilikiotis, M.H. Barnes, and M.L. King, *J. Org. Chem.*, **34**, 3884 (1969).
14) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).

group. Nuclear magnetic resonance (NMR) spectrum (δ) revealed an olefinic proton at 5.71 and enolic O-methyls at 3.61 and 3.75 together with an ethoxy-group, two O-methyls and two aromatic protons.

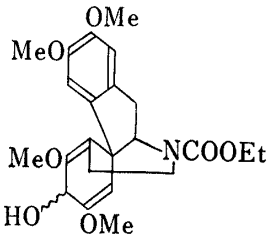
Rearrangement of this dienone (XIII) to thalicsimidine type aporphine (XXX)[9] or the morphinandienone (XXXI) was examined by treatment with boron trifluoride-etherate to afford a negative result. On the other hand, the dienol (XXXII), derived from XIII by sodium borohydride reduction, was treated with boron trifluoride-etherate to give the dienone (XXXIII), which was also obtained by treatment of XXXII with concentrated sulfuric acid or formic acid. The molecular formula $C_{22}H_{25}O_6N$ was determined by microanalysis and mass spectrometry (M^+ 399), and the IR (1648 and 1603 cm^{-1}) and UV (λ_{max} 345, 262, and 234 nm) spectra suggested this product to be cross-conjugated β-methoxy-β'-phenyl-cyclohexadienone.[15-18] NMR spectrum (δ) also supported this system as follow; two α-olefinic protons coupled each other (J=2 Hz) resonanced at 5.65 and 6.33[15,16] and, moreover, the resonances of three methoxyls, two aromatic protons, and ethoxycarbonyl group were observed. This dienone (XXXIII) is analogous to the intermediate (XXXIV) in the biogenetic synthesis of protostephanine (XXXVII) by Battersby.[16] The ring opening of XXXIII with boron trifluoride-etherate[19] under drastic condition ceased in recovery of starting dienone.



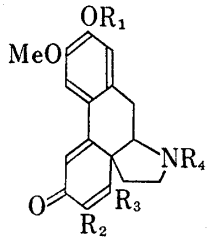
XXX

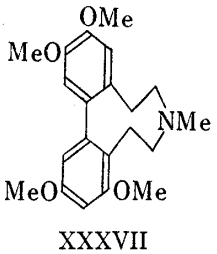


XXXI



XXXII





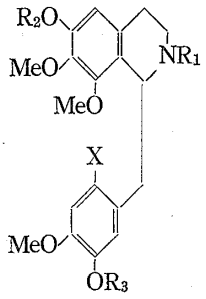
XXXVII

XXXIII : R_1=Me, R_2=H, R_3=OMe, R_4=COOEt
XXXIV : R_1=R_4=Me, R_2=H, R_3=OMe
XXXV : R_1=R_3=H, R_2=OH, R_4=COOEt
XXXVI : R_1=R_3=H, R_2=OH, R_4=$COCF_3$

Chart 4

15) T. Kametani and F. Satoh, *Chem. Pharm. Bull.* (Tokyo), **17**, 814 (1968).
16) A.R. Battersby, A.K. Bhatnagar, P. Hackett, C.W. Thornber, and J. Staunton, *Chem. Commun.*, **1968**, 1214.
17) K.L. Stuart, C. Chambers, and D. Byfield, *J. Chem. Soc.* (*C*), **1969**, 1681.
18) T. Kametani, R. Charubala, M. Ihara, M. Koizumi, K. Takahashi, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 3315.
19) B. Franck and V. Teetz, *Angew. Chem.*, **83**, 409 (1971).

The same photolysis of VIII and X also afforded the proerythrinadienones (XIV[6] and XV), which were subjected to acidic rearrangement with concentrated sulfuric acid or boron trifluoride-etherate to furnish the dienone (XXXV[18] and XXXVI) in moderate yield. The structures of these products (XIV, XV, XXXV, and XXXVI) were determined by spectroscopic methods. Aporphine and morphinandienone type compounds could not be detected on thin-layer chromatography (TLC) in this rearrangement.



XXXVIII: R_1=H, R_2=R_3=$CH_2C_6H_5$, X=Br
XXXIX: R_1=COOEt, R_2=R_3=$CH_2C_6H_5$, X=Br
XL: R_1=COOEt, R_2=R_3=H, X=Br
XLI: R_1=COOEt, R_2=R_3=X=H

Chart 5

Finally, in order to investigate a steric factor in the formation of the proerythrinadienone, the photolysis of the 8-substituted phenolic isoquinoline (XL) and phenolic oxidation of diphenolic isoquinoline (XLI) were examined. Ethoxycarbonylation of the 1,2,3,4-tetrahydroisoquinoline (XXXVIII),[20] followed by debenzylation of the resulting urethan (XXXIX) in a usual way, gave the phenolic bromoisoquinoline (XL), the irradiation of which in a similar manner as above afforded the dienone (XVI), but the phenolic oxidation of XLI was not successful. Therefore, we could not find the steric factor in the formation of the proerythrinadienone.

Experimental[21]

N-(3-Benzyloxy-2,4-dimethoxyphenyl)-2-bromo-4,5-dimethoxyphenylacetamide (XXVI)——A mixture of 26 g of phenethylamine[13] (XXII) and 24 g of methyl 2-bromo-4,5-dimethoxyphenylacetate (XXIV) was heated at 175° for 2.5 hr under a current of nitrogen, and the cooled mixture was recrystallized from benzene–ether to give 35 g of the amide (XXVI) as needles, mp 113—114°. IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1635 (C=O). *Anal.* Calcd. for $C_{27}H_{30}O_6NBr$: C, 59.55; H, 5.55; N, 2.58. Found: C, 59.46; H, 5.56; N, 2.83.

6-Benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-5,7-dimethoxyisoquinoline (XXVIII)——A solution of 10 g of the amide (XXVI), 10 ml of phosphoryl chloride and 100 ml of toluene was heated at 100° for 1.5 hr. Excess of toluene and phosphoryl chloride was evaporated off and the residue was washed with hot benzene to give a syrup, the perchlorate of which was recrystallized from methanol–ether to afford 8 g of a pale yellow powder (XXVIII), mp 266—268°. *Anal.* Calcd. for $C_{27}H_{28}O_5NBr \cdot HClO_4$: 51.72; H, 4.66; N, 2.24. Found: C, 51.68; H, 4.72; N, 2.48.

6-Benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-5,7-dimethoxyisoquinoline (III)——To a stirred solution of 10 g of the 3,4-dihydroisoquinoline hydrochloride (XXVIII) in 300 ml of methanol 3 g of sodium borohydride was added in portions during 30 min. The mixture was stirred for 1 hr, methanol was evaporated off, and the residue was basified with ammonia and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave 8 g of an orange syrup, the hydrochloride of which was recrystallized from methanol–chloroform–ether to give (III) as needles, mp 230—231° (decomp.). *Anal.* Calcd. for $C_{27}H_{30}O_5NBr \cdot HCl$: C, 57.39; H, 5.53; N, 2.48. Found: C, 57.14; H, 5.79; N, 2.53.

6-Benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-5,7-dimethoxyisoquinoline (V)——To a stirred solution of 10 g of the 1,2,3,4-tetrahydroisoquinoline (III) and 3 g of ethyl chloroformate in 200 ml of chloroform was added dropwise 40 ml of 5% sodium hydroxide solution during 5 min under cooling and the stirring was continued for a further 30 min. The separated organic layer was washed with 10% hydrochloric acid solution and water, dried over Na_2SO_4, and evaporated to leave a pale yellow syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (C=O). NMR δ (in $CDCl_3$): 3.79 (3H, s, OMe), 3.85 (9H, s, 3×OMe), 4.98 (2H, s, $OC\underline{H}_2C_6H_5$).

1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonyl-6-hydroxy-1,2,3,4-tetrahydro-5,7-dimethoxyisoquinoline (VII)——A solution of 6.5 g of compound (V) in 60 ml of concentrated hydrochloric acid and 80 ml of

20) T. Kametani, K. Fukumoto, H. Yagi, H. Iida, and T. Kikuchi, *J. Chem. Soc.* (*C*), **1968**, 1178.
21) Infrared and ultraviolet spectra were taken with Hitachi EPI-3 and Hitachi EPS-3 recording spectrophotometer, respectively. The mass spectra were measured on a Hitachi RMU-7 mass spectrometer. Nuclear magnetic resonance spectra were measured on a Hitachi A-60 using tetramethylsilane as an internal standard.

ethanol was refluxed for 2 hr. After evaporation of solvent, the residue was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to give an orange solid, which was recrystallized from benzene to give 6 g of VII as needles, mp 180—181°. IR ν_{max}^{KBr} cm^{-1}: 3240 (OH), 1655 (C=O). *Anal.* Calcd. for $C_{23}H_{28}O_7NBr$: C, 54.16; H, 5.53; N, 2.75. Found: C, 54.08; H, 5.42; N, 2.91.

Photolysis of Bromo-compound (VII)——A solution of 2.5 g of bromo-compound (VII) and 1 g of sodium hydroxide in 800 ml of water and 10 ml of ethanol was irradiated with a Hanovia 450 W mercury lamp using a Pyrex filter for 7 hr at room temperature with stirring. This was basified with crystalline ammonium chloride and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 2 g of a brown syrup, which was chromatographed on 40 g of silica gel. The first chloroform eluant gave 600 mg of a crude dienone, and the second eluant recovered 500 mg of a starting material. The crude dienone was chromatographed on 20 g of alumina eluting with benzene–chloroform (85:15 v/v) to give 200 mg of the dienone as a yellowish solid, recrystallization of which from benzene–hexane gave (XIII) as prisms, mp 102—103°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675, 1655, 1615. NMR δ (in $CDCl_3$) 1.25 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2$), 3.61, 3.75, 3.82, 3.88 (12H, each s, OMe), 5.71 (1H, s, olefinic proton), 6.27, 6.80 (2H, each s, Ar-H). *Anal.* Calcd. for $C_{23}H_{27}O_7N$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.28; H, 6.54; N, 3.24.

Rearrangement of Dienol (XXXII)——To a cooled solution of 100 mg of the dienone (XIII) in 10 ml of methanol, 50 mg of sodium borohydride was added in portions with stirring and stirring was continued for 1 hr. After evaporation, the residue was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 80 mg of the dienol (XXXII) as a yellow syrup, which was used as follows.

a) A mixture of 60 mg of the dienol (XXXII) and 3 ml of 98% sulfuric acid was set aside at room temperature for 1.5 hr. The mixture was then poured into ice–water and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave a brown syrup, which was chromatographed on silica gel with chloroform as eluant to give 17 mg of the dienone (XXXIII) as prisms, mp 167—168° (from benzene–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1672, 1648, 1603. NMR δ (in $CDCl_3$): 1.33 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2$), 3.84 (3H, s, OMe) 3.92 (6H, s, $2\times$OMe), 4.24 (2H, q, $J=7$ Hz, $CH_3C\underline{H}_2$), 5.65, 6.33 (2H, each d, $J=2$ Hz, olefinic protons), 6.74, 6.97 (2H, each s, Ar-H). UV λ_{max}^{MeOH} nm: 345, 262, 234. Mass Spectrum *m/e*: 399 (M^+, 100%), 381, 371, 284, 255. *Anal.* Calcd. for $C_{22}H_{25}O_6N$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.0; H, 6.16; N, 3.57.

b) A mixture of 70 mg of dienol (XXXII) and 20 ml of formic acid was stirred for 2.5 hr at room temperature and then for 1 hr at 100°. After evaporation of formic acid, the residue was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave an orange syrup, which was chromatographed on silica gel with chloroform as eluant to give 30 mg of the dienone (XXXIII) as prisms, mp 167—168°, identical (spectroscopic data) with the specimen obtained by procedure (a).

c) To a solution of 80 mg of dienol (XXXII) in 10 ml of methanol was added 0.3 ml of boron trifluoride-etherate during 10 min at room temperature and the stirring was continued for a further 1 hr. An excess of boron trifluoride-etherate and methanol was evaporated off and the residue was extracted with chloroform. The extract was washed with 5% sodium hydrogen carbonate solution and water, dried over Na_2SO_4, and evaporated to leave a yellow syrup, which was chromatographed on silica gel with chloroform as eluant to give 50 mg of the dienone (XXXIII) as prisms, mp 167—168°, identical with the specimen obtained by procedure (a).

N-(3-Benzyloxy-4-methoxyphenethyl)-5-benzyloxy-2-bromo-4-methoxyphenylacetamide (XXVII)——Fourteen grams of 3-benzyloxy-4-methoxyphenethylamine (XXIII) and 20 g of methyl 5-benzyloxy-2-bromo-4-methoxyphenylacetate (XXV) were heated at 170—180° for 3 hr. After cooling, a usual work-up afforded 30 g of the amide (XXVII) as needles, mp 138—139° (from ethanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (NH), 1675 (C=O). *Anal.* Calcd. for $C_{32}H_{32}O_5NBr$: C, 65.08; H, 5.46; N, 2.37. Found: C, 64.71; H, 5.32; N, 2.49.

6-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-3,4-dihydro-7-methoxyisoquinoline (XXIX)——A mixture of 8 g of the amide (XXVII), 12 ml of phosphoryl chloride and 200 ml of dry benzene was heated on a water-bath for 3 hr. The mixture was poured into an excess of *n*-hexane. The precipitate afforded 7.2 g of the 3,4-dihydroisoquinoline (XXIX) oxalate as needles, mp 205—206° (from ethanol). *Anal.* Calcd. for $C_{34}H_{32}O_8NBr$: C, 61.63; H, 4.87; N, 2.12. Found: C, 61.74; H, 4.72; N, 2.26.

6-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxyisoquinoline (IV)——To a solution of 8 g of the isoquinoline (XXIX) hydrochloride in 400 ml of methanol and 100 ml of chloroform 4 g of sodium borohydride was added in portions at room temperature with stirring. The mixture was stirred at the same temperature for further 2 hr. The solvent was then distilled off and the residue was treated with 5% sodium hydroxide solution. The resulting alkaline solution was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 6.4 g of the 1,2,3,4-tetrahydroisoquinoline (IV) as needles, mp 155—156° (from chloroform–methanol). NMR δ (in $CDCl_3$): 3.68 (3H, s, OMe), 3.73 (3H, s, OMe), 4.98 (4H, s, $OC\underline{H}_2C_6H_5$), 6.48 (2H, s, Ar-H), 6.57 (1H, s, Ar-H), 6.93 (1H, s, 3′-H). *Anal.* Calcd. for $C_{32}H_{32}O_4NBr$: C, 66.51; H, 5.61; N, 2.44. Found: C, 66.83; H, 5.76; N, 2.48.

6-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-7-methoxyisoquinoline (VI)——To a solution of 3 g of the above compound (IV) and 1 g of triethylamine in 300 ml of

benzene, 1.2 g of ethyl chloroformate was added dropwise with stirring at room temperature. After the stirring had been continued for 3 hr, the mixture was then washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 3 g of the isoquinoline derivative (VI) as needles, mp 139—140° (from methanol). *Anal.* Calcd. for $C_{35}H_{36}O_6NBr$: C, 65.01; H, 5.61; N, 2.17. Found: C, 65.15; H, 5.37; N, 2.37.

6-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-trifluoroacetylisoquinoline (IX)——A solution of 4 g of the isoquinoline (IV), 2 g of trifluoroacetic anhydride in 80 ml of dry pyridine was allowed to stand overnight at room temperature. After removal of the solvent by evaporation, the residue was poured into 3% hydrochloric acid and then extracted with chloroform. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent afforded 3.2 g of the trifluoroacetate (IX) as needles, mp 150—151° (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (C=O). NMR δ (in $CDCl_3$): 3.64 (3H, s, OMe), 3.78 (3H, s, OMe), 4.93 (2H, s, $OC\underline{H}_2C_6H_5$), 5.03 (2H, s, $OC\underline{H}_2C_6H_5$), 6.28, 6.53, 6.59, 6.90 (4H, each s, Ar-H). *Anal.* Calcd. for $C_{34}H_{31}O_5NBrF_3$: C, 60.90; H, 4.66; N, 2.04. Found: C, 60.61; H, 4.63; N, 2.27.

6-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-7,8-dimethoxyisoquinoline (XXXIX)——To a solution of 3 g of the tetrahydroisoquinoline (XXXVIII), 0.7 g of triethylamine and 200 ml of benzene, 0.9 g of ethyl chloroformate was added at room temperature with stirring. The solution was worked up as usual. Evaporation of the solvent gave 2.6 g of the N-ethoxycarbonyl derivative (XXXIX) as needles, mp 127—128° (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (C=O). NMR δ (in $CDCl_3$): 3.79, 3.82, 3.94 (9H, each s, 3×OMe), 5.01 (4H, s, 2×$OC\underline{H}_2C_6H_5$), 6.40 (1H, s, 5-H), 6.59 (1H, s, 6′-H), 6.95 (1H, s, 3′-H). *Anal.* Calcd. for $C_{36}H_{39}O_7NBr$: C, 63.81; H, 5.80; N, 2.07. Found: C, 63.76; H, 5.68; N, 2.14.

1-(2-Bromo-5-hydroxy-4-methoxybenzyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-6-hydroxy-7-methoxyisoquinoline (VIII)——A solution of 3 g of the isoquinoline (VI) and 40 ml of concentrated hydrochloric acid in 50 ml of ethanol was refluxed for 4 hr. After evaporation of the solvent, the residue was diluted with water, and then extracted with chloroform. The extract was washed with water, and dried over Na_2SO_4. The solvent was evaporated to give the phenolic isoquinoline (VIII) as needles, mp 138—139° (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1670 (C=O). *Anal.* Calcd. for $C_{21}H_{24}O_6NBr$: C, 54.08; H, 5.19; N, 3.00. Found: C, 54.46; H, 5.35; N, 3.35.

1-(2-Bromo-5-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-trifluoroacetylisoquinoline (X)——A mixture of 4 g of the isoquinoline (IX), 200 ml of concentrated hydrochloric acid, 300 ml of ethanol and 300 ml of methanol was refluxed for 6 hr. After evaporation of the solvent, the residue was extracted with chloroform. The extract was washed with water, and dried over Na_2SO_4. Evaporation of the solvent afforded 1.6 g of the phenolic trifluoroacetate (X) as needles, mp 162—163° (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1680 (C=O). NMR δ (in $CDCl_3$): 3.72, 3.80 (6H, each s, 2×OMe), 6.43, 6.58, 6.62, 6.89 (4H, each s, Ar-H). *Anal.* Calcd. for $C_{20}H_{19}O_5NBrF_3$: C, 48.58; H, 3.91; N, 2.81. Found: C, 48.78; H, 4.07; N, 3.06.

1-(2-Bromo-5-hydroxy-4-methoxybenzyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-6-hydroxy-7,8-dimethoxyisoquinoline (XL)——A solution of 2.5 g of the isoquinoline (XXXIX) and 20 ml of concentrated hydrochloric acid in 40 ml of ethanol was refluxed for 3 hr. The solvent was evaporated and the residue was extracted with chloroform. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent afforded 1.2 g of the phenolic isoquinoline (XL) as needles, mp 136—137° (from methanol–ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1675 (C=O). NMR δ (in $CDCl_3$): 3.81 (6H, s, 2×OMe), 3.92 (3H, s, OMe), 6.45, 6.74 and 6.91 (3H, each s, Ar-H). *Anal.* Calcd. for $C_{22}H_{26}O_7NBr$: C, 53.24; H, 5.28; N, 2.82. Found: C, 53.46; H, 5.03; N, 2.85.

2-Ethoxycarbonyl-1,2,3,4-tetrahydro-6-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-7,8-dimethoxyisoquinoline (XLI)——A solution of 3 g of the isoquinoline (XXXIX) in 80 ml of ethanol was hydrogenated in the presence of 500 mg of 30% palladium charcoal until a hydrogen uptake ceased. After filtration, the filtrate was evaporated to dryness to give a gum which was mixed with water. The mixture was extracted with chloroform. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 1.3 g of the corresponding phenolic isoquinoline (XLI) as needles, mp 157—158° (from ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1675 (C=O). NMR δ (in $CDCl_3$): 3.80, 3.85, 3.92 (9H, each s, 3×OMe), 6.45 (1H, s, 5-H), 6.65 (2H, s, Ar-H) and 6.78 (1H, s, Ar-H). *Anal.* Calcd. for $C_{22}H_{27}O_7N$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.26; H, 6.29; N, 3.40.

Photolysis of VIII——A mixture of 1 g of VIII, 900 ml of 0.15% sodium hydroxide solution and 100 ml of ethanol was irradiated for 9 hr with a 450 W Hanovia mercury lamp equipped with a Pyrex filter under stirring. The solution was then treated with an excess of crystalline ammonium chloride and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 0.8 g of a reddish gum, which was chromatographed on 20 g of silica gel with chloroform as eluant. Fractions 5—12 (each 50 ml) were collected and rechromatographed on 5 g of alumina. Elution with chloroform–benzene (30:70 v/v) gave 150 mg of a pale yellowish oil (XII), which was identical with the authentic sample.[6]

Photolysis of X——A mixture of 1 g of X, 85 mg of sodium hydroxide and 10 ml of ethanol was diluted to a volume of 11 with water. The mixture was irradiated for 7 hr at 10—20° under the same conditions as above. After addition of an excess of crystalline ammonium chloride, the mixture was extracted with

chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 0.8 g of a brownish gum, which was chromatographed on 20 g of silica gel with chloroform as eluant. Fractions 7—11 (each 50 ml) were collected and rechromatographed on alumina. After the elution with benzene, chloroform–benzene (1:99 v/v) and chloroform–benzene (3:97 v/v) had been discarded, elution with chloroform–benzene (15:85 v/v) gave 80 mg of XV as needles, mp 222—223° (from methanol–ethanol–ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680sh, 1665, 1645sh, 1620: NMR δ (in $CDCl_3$): 3.60, 3.80 (6H, each s, OMe), 5.66, 6.27, 6.38, 6.85 (4H, each s, aromatic and olefinic protons). *Anal.* Calcd. for $C_{20}H_{18}O_5NF_3$: C, 58.68; H, 4.43. Found: C, 58.40; H, 4.21.

Photolysis of XL——A mixture of 1.2 g of XL, 900 ml of 0.15% sodium hydroxide solution and 100 ml of ethanol was irradiated for 17 hr under the same conditions as above. After addition of an excess of crystalline ammonium chloride, the mixture was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 1 g of a brown gum, which was chromatographed on 20 g of silica gel with chloroform as eluant. Fractions 6—12 (each 50 ml) were collected and rechromatographed on alumina. After elution with chloroform–benzene (10:90 v/v) had been discarded, elution with chloroform-benzene (30:70 v/v) gave 100 mg of XVI as an oil, which was recrystallized from ether to give needles, mp 101—102°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680sh, 1675, 1660sh, 1635. UV λ_{max}^{MeOH} nm: 236, 285. NMR δ (in $CDCl_3$): 1.24 (3H, t, $J=7$ Hz, $CO_2CH_2\underline{CH}_3$), 3.72, 3.75, 3.84 (9H, each s, $3\times$OMe), 4.11 (2H, q, $J=7$ Hz, $CO_2\underline{CH}_2CH_3$), 6.11, 6.24, 6.76 (3H, each s, aromatic and olefinic protons). *Anal.* Calcd. for $C_{22}H_{25}O_7N$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.45; H, 6.38; N, 3.30.

Rearrangement of XIV with Boron Trifluoride-etherate——A mixture of 50 mg of dienone (XIV), 10 ml of methylene chloride, and 2 ml of boron trifluoride-etherate was stirred under nitrogen at room temperature for 2 hr. After the solution had been diluted with methylene chloride to 50 ml, the solution was washed with water, 10% ammonia and water, and dried over Na_2SO_4. Evaporation of the solvent gave a pale yellowish oil, which was chromatographed on 5 g of silica gel with chloroform as eluant. Fractions 10—12 (each 10 ml) gave 5 mg of XXXV, which was identical with the authentic sample.[6,18]

Rearrangement of XV with Concentrated Sulfuric Acid——A mixture of 50 mg of XV and 1 ml of concentrated sulfuric acid was stirred under nitrogen at room temperature for 1 hr. The resulting reddish solution was poured into ice–water and adjusted with 10% sodium hydroxide solution to pH 7.0. The solution was then extracted with chloroform, and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a reddish gum, which was chromatographed on 3 g of silica gel with chloroform as eluant. Fractions 3—10 (each 10 ml) gave 30 mg of XXXVI as a pale yellowish gum. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685, 1638. UV λ_{max}^{MeOH} nm (log ε): 358 (3.71), 394 (3.60), 264 (3.70), 243 (3.77). NMR δ (in $CDCl_3$): 3.96 (3H, s, OMe), 6.20, 6.65, 6.75, 7.00 (4H, each s, aromatic and olefinic protons).

Methylation of XXXVI with diazomethane gave the trimethoxy derivative as needles, mp 247—248° (from methanol). *Anal.* Calcd. for $C_{21}H_{20}O_5NF_3$: C, 59.57; H, 4.76. Found: C, 59.78; H, 4.52.

Rearrangement of XV with Boron Trifluoride-etherate——A mixture of 50 mg of XV in 100 ml of methylene chloride and 12 ml of boron trifluoride-etherate was stirred under nitrogen at room temperature for 2 hr. After the solution had been diluted with methylene chloride to 50 ml, the resulting mixture was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a pale reddish gum, which was chromatographed on 5 g of silica gel with chloroform as eluant. Fractions 2—12 (each 10 ml) gave 40 mg of XXXVI which was identical with the rearrangement product of XV with concentrated sulfuric acid.

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