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# Studies on the Syntheses of Heterocyclic Compounds. CDLVII.[1] Synthesis of O-Benzylhomosalutaridine by Photolysis of Diazotized 1-(2-Aminophenethyl)-1,2,3,4-tetrahydroisoquinoline

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Photolysis of the diazonium salt of 1-(2-amino-3-benzyloxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (VIIIa) gave O-benzylhomosalutaridine (VIIa).

The morphinandienone-type alkaloid, salutaridine (I) found in *Croton salutaris*,[3] is a key intermediate in the biogenesis of morphine,[4] which has already been derived from salutaridine *via* thebaine by the chemical[5a–d] and the biogenetic pathways.[6a–d] Previously we synthesized homoproaporphine (II),[7] homoaporphine (V),[8] homoprotoberberine (III),[9] homocularine (IV),[10] and isosalutaridine (VI)[11] which were expected to occur in nature. The expectation was satisfied partially by the isolation of the naturally occurring alkaloids, kreysiginone (II),[12] multifloramine (V),[13] and pallidine (isosalutaridine).[14] From this point of view, we here wish to report the attempt to synthesize homosalutaridine (VIIa), which might be isolated from plants in the future.

Some years ago, the syntheses of homomorphinandienone-type compounds (VIIb and VIIc) were accomplished by way of phenolic oxidation[15] and the Pschorr reaction.[16] However, the attempted synthesis of VIIa from the aminophenethylisoquinoline (VIIIa) by the latter method resulted in failure.[17] Recently *o*-methylandrocymbine (VIIe), an alkaloid

1) Part CDLVI, T. Kametani, M. Mizushima and S. Takano, *Yakugaku Zasshi*, **92**, 204 (1972).
2) Location: *Aobayama, Sendai*.
3) A.R. Barnes, *Anais. Acad. brasil Cienc.*, **36**, 238 (1964).
4) D.H.R. Barton and T. Cohen, "Festschrift Arthur Stoll," 1957, p. 114.
5) *a*) D.H.R. Barton, G.W. Kirby, W. Steglich, G.M. Thomas, A.R. Battersby, T.A. Dobson and H. Ramuz, *J. Chem. Soc.*, **1965**, 2423; *b*) C. Schöpf and H. Hirsch, *Ann.*, **489**, 224 (1913); *c*) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **74**, 1109 (1952); *d*) T. Kametani, M. Ihara, K. Fukumoto and H. Yagi, *J. Chem. Soc.* (*C*), **1969**, 2030.
6) *a*) A.R. Battersby and B.J.T. Harper, *Tetrahedron Letters*, **1960**, 21; *b*) H. Rapoport, F.R. Stermitz and D.R. Baker, *J. Am. Chem. Soc.*, **82**, 2765 (1960); *c*) F.R. Stermitz and H. Rapoport, *Nature*, **189**, 310 (1961); *d*) G. Blaschke, H.I. Parker and H. Rapoport, *J. Am. Chem. Soc.*, **89**, 1540 (1967).
7) T. Kametani, F. Satoh, H. Yagi and K. Fukumoto, *Chem. Commun.*, **1967**, 878; *J. Org. Chem.*, **33**, 690 (1968).
8) T. Kametani, F. Satoh, H. Yagi and K. Fukumoto, *J. Chem. Soc.* (*C*), **1970**, 382.
9) T. Kametani, T. Terui, T. Ogino and K. Fukumoto, *J. Chem. Soc.* (*C*), **1969**, 874.
10) T. Kametani and T. Terui, *J. Heterocyclic Chem.*, **7**, 55 (1970).
11) *a*) T. Kametani, M. Koizumi and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 2245 (1969); *b*) T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi and M. Koizumi, *J. Chem. Soc.* (*C*), **1969**, 2034.
12) A.R. Battersby, E. McDonald, M.H.G. Munro and R. Ramage, *Chem. Commun.*, **1967**, 934.
13) G.M. Badger and R.B. Bradbury, *J. Chem. Soc.*, **1960**, 445.
14) T. Kametani, M. Ihara and T. Honda, *J. Chem. Soc.* (*C*), **1970**, 1060.
15) T. Kametani, K. Fukumoto, M. Koizumi and A. Kozuka, *Chem. Commun.*, **1968**, 1605; *J. Chem. Soc.* (*C*), **1969**, 1295.
16) T. Kametani, K. Fukumoto, F. Satoh and H. Yagi, *Chem. Commun.*, **1968**, 1001; *J. Chem. Soc.* (*C*), **1968**, 3084.
17) T. Kametani, M. Koizumi and K. Fukumoto, *Yakugaku Zasshi*, **90**, 1331 (1970).

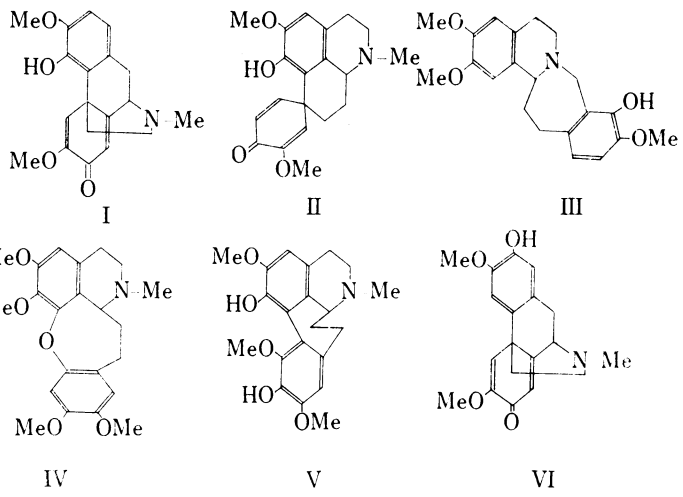


Chart 1


VIIa : $R_1$=OH, $R_2$=OMe, $R_3$=H
VIIb : $R_1$=H, $R_2$=OMe, $R_3$=OH
VIIc : $R_1$=H, $R_2$=$R_3$=OMe
VIId : $R_1$=$R_3$=OMe, $R_2$=OH
VIIe : $R_1$=$R_2$=$R_3$=OMe
VIIf : $R_1$=H, $R_2$=OMe, $R_3$=$OCH_2C_6H_5$
VIIg : $R_1$=$OCH_2C_6H_5$ $R_2$=OMe, $R_3$=H

VIIIa : $R_1$=$R_3$=OMe, $R_2$=H, $R_4$=$OCH_2C_6H_5$, X=$NH_2$
VIIIb : $R_1$=$OCH_2C_6H_5$, $R_2$=$R_3$=$R_4$=OMe, X=$N_2^+$
VIIIc : $R_1$=$OCH_2C_6H_5$, $R_2$=$R_3$=$R_4$=OMe, X=$NH_2$
VIIId : $R_1$=$R_2$=$OCH_2C_6H_5$, $R_3$=OMe, $R_4$=H, X=$NH_2$
VIIIe : $R_1$=$R_3$=OMe, $R_2$=H, $R_4$=$OCH_2C_6H_5$, X=$N_2^+$
VIIIf : $R_1$=$R_3$=OMe, $R_2$=H, $R_4$=$OCH_2C_6H_5$, X=OH

Chart 2

from *Colchicum autumnale*,[18] was synthesized by photolytic decomposition of diazonium salt (VIIIb) derived from 1-(2-aminophenethyl)-1,2,3,4-tetrahydroisoquinoline (VIIIc).[19] We examined the photolysis of diazonium salts from 1-(2-amino-3-benzyloxy-4-methoxyphenethyl)-6,7-dimethoxy-(VIIIa)[17] and 1-(2-amino-5-benzyloxy-4-methoxyphenethyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydro-2-methylisoquinoline (VIIId) in order to obtain our expected homomorphinandienone-type compounds (VIIg and VIIf).

Firstly, nitration of 3-benzyloxy-4-methoxyphenylpropionic acid, which was obtained from 3-hydroxy-4-methoxyphenylpropionic acid,[20] gave the 2-nitrophenylpropionic acid (X), which was fused with 4-benzyloxy-3-methoxyphenethylamine to afford the corresponding amide (XI). A Bischler–Napieralski reaction of the above amide furnished the 3,4-dihydroisoquinoline (XII), the methiodide of which was reduced with zinc and hydrochloric acid to give aminoisoquinoline (VIIId). Diazotization and then photolysis of VIIId was carried out under the conditions describerd later, but failed.

18) R. Ramage, *Ann. Reports*, **64B**, 515 (1967).
19) T. Kametani, M. Koizumi and K. Fukumoto, *Chem. Commun.*, **1970**, 1157.
20) F. Tiemann and N. Nagai, *Ber.*, **11**, 650 (1878).

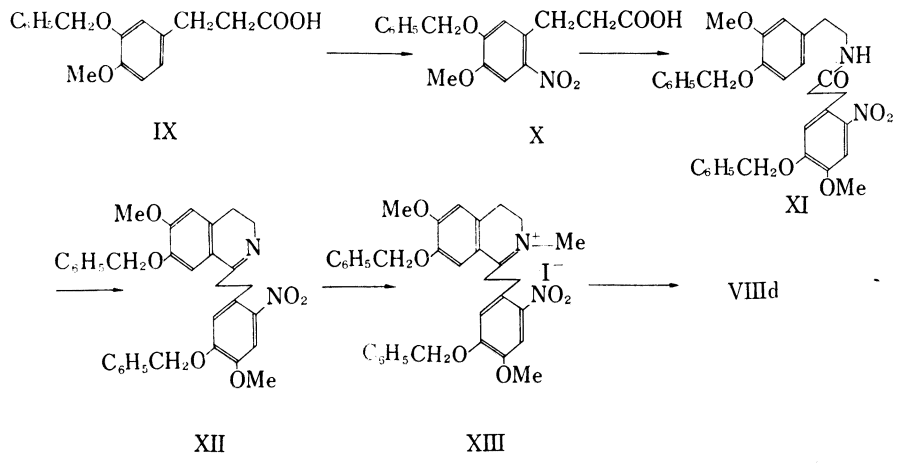

Chart 3

Secondly, diazotization of 2'-aminophenethylisoquinoline (VIIIa) was carried out in the usual way, and the resulting diazonium salt (VIIIe) was irradiated with a Hanovia 450 W mercury lamp using a pyrex filter at 5—10° until the evolution of nitrogen gas had ceased. Two compounds were obtained after separation and purification by silica gel column chromatography.

The first compond in 29% yield had the molecular formula, $C_{28}H_{33}O_5N$, by mass spectrometry, and its infrared (IR) spectrum revealed the presence of hydroxy absorption due to the phenolic isoquinoline at 3470 $cm^{-1}$. The ultraviolet (UV) spectrum also showed this compound to be a 1,2,3,4-tetrahydroisoquinoline derivative. Moreover, the nuclear magnetic resonance (NMR) ($CDCl_3$) spectrum revealed the aromatic protons having *ortho*-coupling at 3.65 and 3.62 $\tau$ together with the resonances of four methyls, an *o*-benzyl and two aromatic protons. Therefore, this compound was assigned to 1-(3-benzyloxy-2-hydroxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (VIIIf).

The second compound in 6.1% yield was assigned *o*-benzylhomosalutaridine (VIIg) by the following evidence. The microanalysis of its methiodide and mass spectrometry of its free base verified the molecular formula, $C_{27}H_{29}O_4N$, and it had an $\alpha$-alkoxylated cross-conjugated cyclohexadienone system as revealed by its IR spectrum. The NMR spectrum ($CDCl_3$) showed the presence of three methyl groups at 7.68, 6.60, and 6.18 $\tau$ each as singlet. Moreover, the methylene protons of benzyl ether moiety at 4.93 and 4.62 each as doublet ($J$=12 Hz), two olefinic and two aromatic protons at 3.78 (1H), 3.29 (2H) and 3.15 (1H) respectively were observed.

Debenzylation of VIIg with trifluoroacetic acid or 48% hydrobromic acid-methanol (1:2 v/v) gave a homomorphinandienone-type compound, the structure of which was strongly suggested from the spectral data as follows. The molecular formula, $C_{20}H_{23}O_4N$, was supported by mass spectrometry. Its IR spectrum ($CHCl_3$) showed absorption bands due to OH at 3500 $cm^{-1}$ and the cyclohexadienone system at 1660, 1637, and 1612 $cm^{-1}$. The NMR spectrum ($CDCl_3$) revealed three methyl groups at 7.66, 6.20, and 6.14 each as singlet, and, moreover, two olefinic and two aromatic protons appeared at 3.74 (1H), 3.26 (2H), and 3.13 (1H) $\tau$, respectively each as singlet. The above data were closely similar to those of *o*-methylandrocymbine (VIIe) rather than to those of salutaridine (I).

Thus *o*-benzylhomosalutaridine (VIIg) was synthesized as one of the phenethylisoquinoline series. Further studies on the photolysis of various diazotized isoquinolines are in progress, particularly concerning the synthesis of androcymbine (VIId).

## Experimental

All melting points are uncorrected. IR and NMR spectra were measured on a type EPI-3 Hitachi recording spectrometer and Hitachi R-20 spectrometer with tetramethylsilane as internal reference, respectively. The mass spectra were determined with a Hitachi RMU-7 spectrometer.

**3-Benzyloxy-4-methoxyphenylpropionic Acid (IX)**——A mixture of 20 g of 3-hydroxy-4-methoxyphenylpropionic acid, [20] 2 ml of conc. $H_2SO_4$, and 20 ml of dry MeOH was refluxed for 5 hr, and the solvent was distilled off. The residue was extracted with $CHCl_3$ and the extract was washed with water, dried over $Na_2SO_4$, and evaporated to leave the crude methyl ester [IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 3498 (OH) and 1730 (CO)], to which solution in 100 ml of MeOH was added 15 g of benzyl chloride and 20 g of $K_2CO_3$. After the mixture had been refluxed for 5 hr, the inorganic substance separated was filtered off, and the filtrate was treated as usual to give 21 g of 3-benzyloxy-4-methoxyphenylpropionic acid (IX) as pale yellow prisms (from MeOH), mp 124—126°. *Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.01; H, 6.21.

**5-Benzyloxy-4-methoxy-2-nitrophenylpropionic Acid (X)**——Conc. $HNO_3$ (*d*: 1.42) (40 ml) was added to a stirred solution of 30 g of phenylpropionic acid (IX) in 200 ml of glacial AcOH under cooling during 0.5 hr, and the reaction mixture was poured into an excess of ice–water. The crystals separated were collected and recrystallized from MeOH to afford 19 g of the nitrophenylpropionic acid as pale yellow prisms, mp 139—141°. IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 1705 (CO), 1328 ($NO_2$). *Anal.* Calcd. for $C_{17}H_{17}O_6N$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.41; H, 5.13; N, 4.42.

**N-(4-Benzyloxy-3-methoxyphenyl)-5-benzyloxy-4-methoxy-2-nitrophenylpropionamide(XI)**——The fusion of 11.5 g of 4-benzyloxy-3-methoxyphenethylamine with 10.7 g of 2-nitrophenylpropionic acid (X) at 170—180° for 1.5 hr gave 13.2 g of the amide as colorless needles, mp 137—138° (from MeOH). IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 3400 (NH), 1660 (CO), 1328 ($NO_2$). *Anal.* Calcd. for $C_{33}H_{34}O_7N_2$: C, 69.46; H, 6.01; N, 4.91. Found: C, 69.75; H, 6.12; N, 4.83.

**7-Benzyloxy-1-(5-benzyloxy-4-methoxy-2-nitrophenethyl)-3,4-dihydro-6-methoxyisoquinoline (XII)**——A mixture of 4 g of the amide (XI), 4 ml of $POCl_3$ and 80 ml of dry $CHCl_3$ was refluxed for 1 hr, and worked up as usual to afford 3.8 g of the 3,4-dihydroisoquinoline (XII) hydrochloride as pale yellow needles, mp 209—210.5° (from MeOH). IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 1648 ($\rangle C{=}\overset{+}{N}-$). *Anal.* Calcd. for $C_{33}H_{32}O_6N_2 \cdot HCl$: C, 67.28; H, 5.65; N, 4.72. Found: C, 67.45; H, 5.77; N, 4.65. The free base (XII) gave the methiodide (XIII) as pale yellow needles, mp 205—207° (from MeOH). IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 1625 ($\rangle C{=}\overset{+}{N}\langle$). *Anal.* Calcd. for $C_{34}H_{35}N_2O_6I$: C, 58.79; H, 5.08; N, 4.03. Found: C, 58.43; H, 5.19; N, 4.39.

**1-(2-Amino-5-benzyloxy-4-methoxyphenethyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (VIIId)**——To a stirred mixture of 4 g of the methiodide (XIII), 100 ml of AcOH, 100 ml of conc. HCl, and 24 ml of water was added in small portions 30 g of zinc at 0—2°. The resulting mixture was stirred for 5 hr at 0—2° and worked up as usual to give 2.2 g of the tetrahydroisoquinoline (VIIId) as a pale brown viscous syrup. IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 3400—3250 (NH). NMR ($CDCl_3$)$\tau$: 7.62 (3H, s, NMe), 6.28 (3H, s, OMe), 6.22 (3H, s, OMe), 5.02 (2H, s, $OCH_2C_6H_5$), 4.98 (2H, s, $OCH_2C_6H_5$), 3.81 (1H, s, 3′-H), 3.49 (2H, s, Ar-H), 3.46 (1H, s, Ar-H), and 2.70 (10H, m, $2\times OCH_2C_6H_5$).

**Photolysis of Diazonium Salt of VIIIa**——To a solution of 4 g of aminoisoquinoline (VIIIa),[17] 200 ml of 1N $H_2SO_4$, and 40 ml of glacial AcOH was added dropwise 6.4 ml of 10% $NaNO_2$ solution during 20 min at 0—3° and the stirring was continued for a further 1 hr at the same temperature. After decomposition of the excess of $HNO_2$ with urea, followed by dilution to a volume of 1 liter with water, the reaction mixture was irradiated with a Hanovia 450 W mercury lamp using a pyrex filter at 5—10° for 4 hr. After irradiation, the reaction mixture was basified with conc. $NH_4OH$ and extracted several times with $CHCl_3$. The extract was washed with water, dried over $Na_2SO_4$ and evaporated to afford a dark brown gum, which was chromatographed on 100 g of silica gel with $CHCl_3$ ($F_{1-18}$, each 200 ml), $CHCl_3$–MeOH (99:1) ($F_{19-34}$, each 200 ml) as eluant inspecting with thin-layer chromatography (TLC), IR and UV spectra.

Fractions 8—27 gave 1.095 g of 1-(3-benzyloxy-2-hydroxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (VIIIf) as a pale brown viscous syrup. UV $\lambda_{max}^{MeOH}$ nm: 282. IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 3470 (OH). NMR ($CDCl_3$) $\tau$: 7.62 (3H, s, $NCH_3$), 6.23 (9H, s, $3\times OCH_3$), 4.92 (2H, s, $OCH_2C_6H_5$), 3.65 and 3.62 (2H, each d, $J$=8 Hz, $C_5'$-H and $C_6'$-H), 3.57 and 3.49 (2H, each s, $C_5$-H and $C_8$-H). Mass Spectrum *m/e*: 463 ($M^+$).

Fractions 31—34 gave 229 mg of *o*-benzylhomosalutaridine (VIIg) as a pale brown viscous syrup. IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 1660, 1635, 1614 (cyclohexadienone system). NMR ($CDCl_3$)$\tau$: 7.68 (3H, s, $NCH_3$), 6.60 (3H, s, enolic $OCH_3$), 6.18 (3H, s, $OCH_3$), 4.93 and 4.02 (2H, each d, $J$=12 Hz, $OCH_2C_6H_5$), 3.78 (1H), 3.29 (2H) and 3.15 (1H) (each s, two olefinic and two aromatic protons). Mass Spectrum (m/*e*): 431 ($M^+$), 340. This was then converted to the methiodide with methyl iodide. The solid was collected and recrystallized from MeOH-ether to give yellow plates, mp 193—194°. *Anal.* Calcd for $C_{27}H_{29}O_4N \cdot CH_3I \cdot H_2O$: C, 56.86; H, 5.79. Found: C, 56.53; H, 5.94.

**Debenzylation of VIIg**——(a) A solution of 70 mg of *o*-benzylhomosalutaridine (VIIg) in 1 ml of trifluoroacetic acid was allowed to stand at room temperature for 5 hr and then evaporated *in vacuo* at less

than 40°. 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 50 mg of the crude compound as a pale brown viscous syrup, which was purified by preparative thick layer chromatography on silica gel using $CHCl_3$–MeOH (10:1) to give 3 mg of homomorphinandienone-type compound as a pale yellow viscous syrup, but it could not be crystallized. IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$): 3500 (OH), 1660, 1647, 1612 (cyclohexadienone system). NMR ($CDCl_3$) $\tau$: 7.66 (3H, s, $NCH_3$), 6.20 (3H, s, $OCH_3$), 6.14 (3H, s, $OCH_3$), 3.78 (1H), 3.26 (2H), and 3.13 (1H) (each s, two olefinic and two aromatic protons). Mass Spectrum *m/e*: 341 ($M^+$).

(b) A mixture of 130 mg of *o*-benzylohomosalutaridine, 13 ml of 48% HBr and 26 ml of MeOH was heated at 55° on a water-bath for 45 min. After evaporation of the solvent *in vacuo*, the residue was treated with 10% $NH_4OH$ and extracted with $CHCl_3$. The extract was washed with water, dried over $Na_2SO_4$, and evaporated to give 100 mg of the crude compound, which was purified in a similar manner as above to give 2.5 mg of the same dienone as above.

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