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Modified Synthesis of Isosalutaridine (Studies on the Syntheses of Heterocyclic Compounds. CCCXXXVI[1])

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Diazotization of 1-(2-amino-5-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (V), followed by thermal decomposition without metallic catalyst, afforded the O-benzylisosalutaridine (VIII) in 10% yield, which was debenzylated to give isosalutaridine (IV).

Amurine (I)[3,4] and flavinantine (II)[5–7] would be biosynthesized from reticuline (III); thus, phenolic oxidative coupling[8] of reticuline (III) in *para-para* mode gives a morphinandienone type compound (IV), which will be a hypothetical alkaloid. This compound was named as isosalutaridine by Franck and his co-workers.[9] The cyclization or transmethylation of *o*-methoxyphenolic moiety in isosalutaridine (IV) would afford amurine (I) or flavinantine (II). The present authors have recently synthesized isosalutaridine (IV) by phenolic

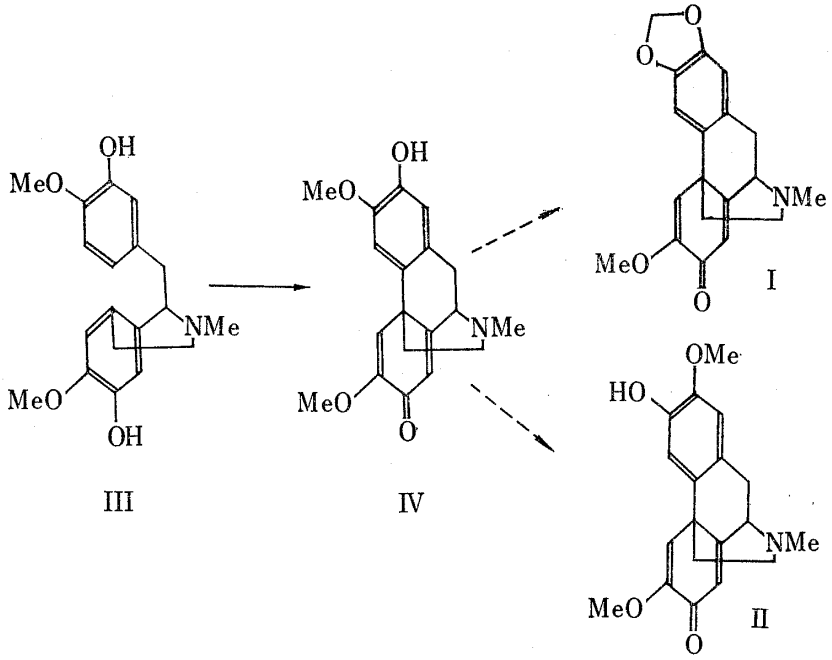

Chart 1

1) Part CCCXXXV: T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru S, Asagi: *Yakugakn Zasshi*, **89**, 1482 (1969).
2) Location: *Aobayama, Sendai.*
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oxidative coupling of reticuline (III) with potassium ferricyanide in poor yield, which would complete the biogenetic type syntheses of amurine (I) and flavinantine (II).[10] On the other hand, we are currently investigating the possibility of Pschorr cyclization on the syntheses of morphinandienone[4,6,7,11,12] and homomorphinandienone[13] (androcymbine)[14,15] type compounds, and here we wish to report a modified synthesis of isosalutaridine (IV) by this method.

1-(2-Amino-5-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (V), which has been already synthesized by Kikkawa,[16] was diazotised as usual and the resulting diazonium salt was decomposed without metallic catalyst at 70° for 1 hr to give three compounds as follows.

The first compound obtained in 17% yield from chloroform eluant was assigned to the deamination product, namely 1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (VI) [(±)-O-benzyllaudanine], on the comparisons of the melting point of its picrate, 153—154°, with that of authentic sample, and on its spectral data of free base.

The second compound (in 13% yield), which was obtained by elution with chloroform–methanol (99:1 v/v), was characterized as its picrate, mp 209° (decomp.), and assigned to 9-benzyloxy-1,2,10-trimethoxy-6-methylaporphine (VII). Namely, the ultraviolet (UV) spectrum showed a typical 1,2,9,10-oxygenated aporphine absorption at 280 and 303 mμ (log ε 4.23 and 4.20, respectively), whose assignment was also supported by its nuclear magnetic resonance (NMR) spectrum. Both compounds (VI and VII) had been obtained by Kikkawa with catalytic decomposition of the diazonium salt from the aminoisoquinoline (V) in the presence of zinc.[16]

The third fraction showing the carbonyl absorption in the infrared (IR) spectrum, which was eluted with chloroform–methanol (98:2, v/v), gave O-benzylisosalutaridine (VIII) in 10% yield as a pale yellow glass, which was characterized as its methiodide, mp 224—225° [λ_{max}^{MeOH} 237^{sh} and 286.5 mμ; ν_{max}^{KBr} 1665, 1645 and 1622 cm^{-1}]. Furthermore, the structure of this product was confirmed by the following evidences. The microanalysis of its methiodide verified the molecular formular of $C_{26}H_{27}O_4N$, and IR and UV spectra of the free bases showed $\nu_{max}^{CHCl_3}$ 1665, 1644 and 1623 cm^{-1}, and λ_{max}^{MeOH} 236 and 281 mμ (log ε 4.14 and 3.82), which revealed the product to be cross-conjugated α-methoxycyclohexadienone type compound.[4,6,10–13,17] Moreover, the ratio of the molecular extinction coefficient at 236 (ε=13.800) and 281 mμ (ε=6.607) was 2:1, which showed the product to be the morphinandienone type structure.[18] Furthermore, the NMR spectrum of its free base (τ in $CDCl_3$) showed three methyl resonances at 7.57 (3H, NMe), 6.20 (3H, OMe) and 6.12 (3H, OMe) as singlets, methylene protons in the benzyloxy group at 4.91 as singlet, two olefinic protons at 3.14 (1H, C_5–H) and 3.72 (1H, C_8–H) as singlets, and seven aromatic protons at 3.62 (1H, s), 3.33 (1H, s) and 2.64 (5H, broad singlet, OCH_2Ph).

The structure (IX) having another coupling mode was ruled out by the following spectral speculation. Although one β-olefinic proton standing next to methoxy group in orientalinone (X-a) or kreysiginone (X-b) resonanced at 4.08[19] or 4.02[17] τ (4.05),[20] respectively, there ap-

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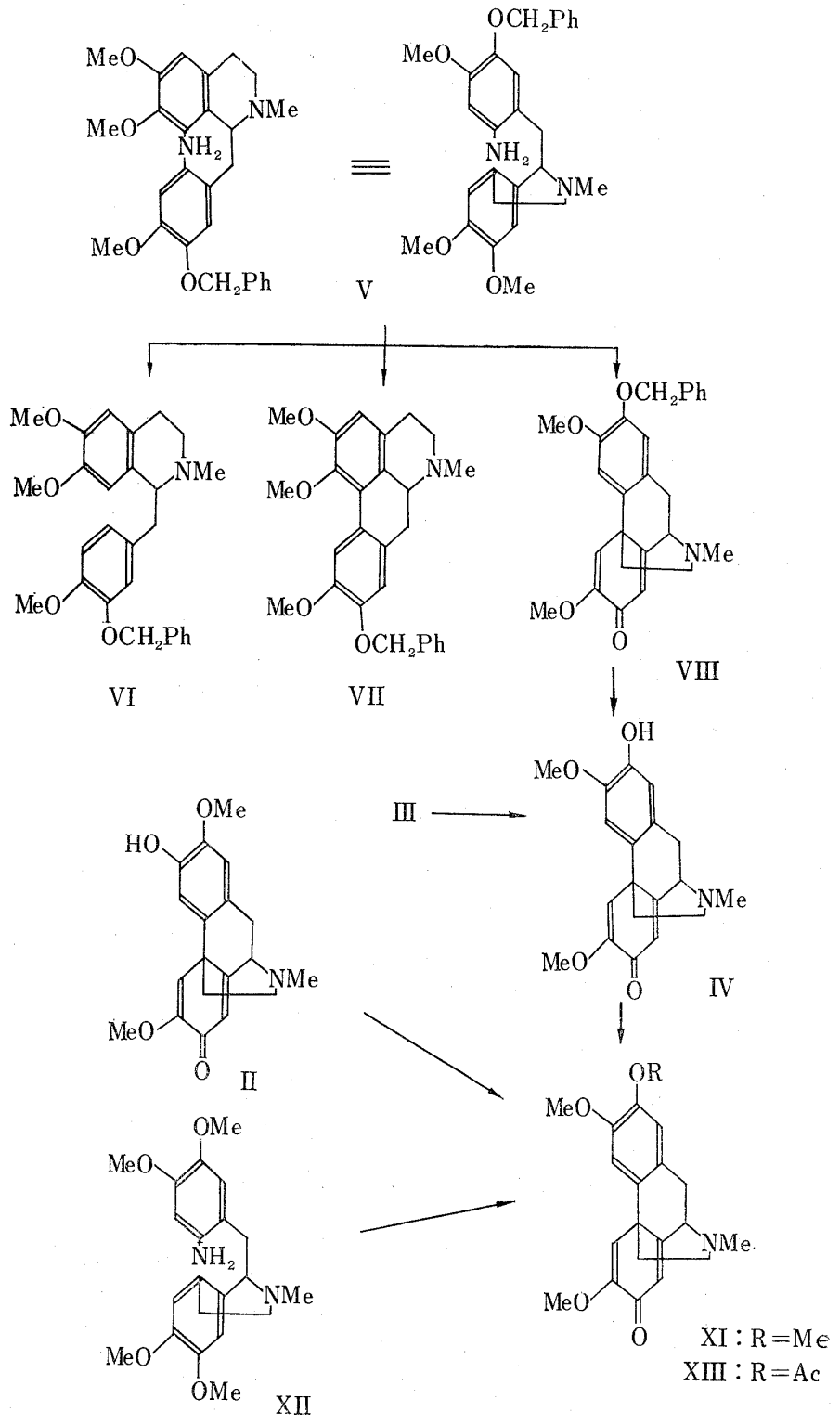
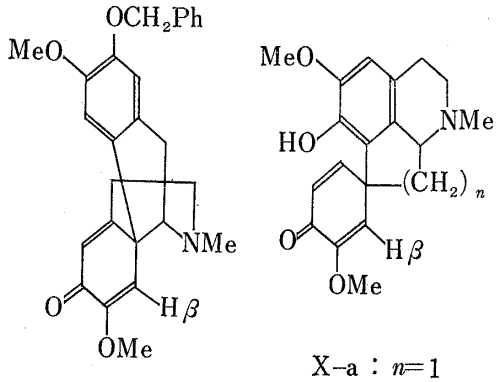


Chart 2

peared no olefinic protons resonanced at higher field than 3.8 τ in our product. This fact denies the product to have the structure (IX).

Debenzylation of O-benzylisosalutaridine (VIII) with concentrated hydrobromic acid gave isosalutaridine (IV) as a pale yellow viscous syrup, which was characterized as its methiodide. This product showed the phenolic hydroxyl group at 3500 cm^{-1} and cross-conjugated α-methoxycyclohexadienone system at 1666, 1643 and 1624 cm^{-1} in its IR spectrum (in $CHCl_3$) and λ_{max}^{MeOH} 235 mμ (log ε 4.08) in its UV spectra, whose data revealed that no rearrangement



IX

X-a : $n=1$
X-b : $n=2$

Chart 3

in the skeleton of IV occurred in case of debenzylation. The NMR spectrum also supported this structure; three methyl groups resonanced at 7.63 (s, NMe), 6.21 (s, OMe) and 6.11(s, OMe), two olefinic protons at 3.23 (C_5–H) and 3.71 (C_8–H) as singlets, and two aromatic protons at 3.67 and 3.23 τ as singlets were revealed. Moreover, this product was proved to be identical with the authentic isosalutaridine (IV) prepared by phenolic oxidative coupling of reticuline (III)[10] by full IR, UV, NMR spectroscopic and chromatographic [*Rf* 0.25 (Wakogel, 0.2 mm, $CHCl_3$: acetone: MeOH=5:4:1) or *Rf* 0.50 (Wakogel, 0.2 mm, $CHCl_3$,: MeOH =5:1)] comparison.

The methylation of isosalutaridine (IV) with diazomethane afforded O-methylflavinantine (XI) as a colorless glass, which was also characterized as its methiodide, mp 222—223° (decomp.). Spectral data of the free base were superimposable upon those of the authentic sample synthesized from natural flavinantine (II)[6] or from 1-(2-amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XII) by Pschorr cyclization.[6]

Moreover, isosalutaridine (IV) was acetylated with acetic anhydride in pyridine to afford the O-acetylisosalutaridine (XIII), whose mp (203—204°) was identical with that of the reported sample by Franck.[9]

Experimental[21]

Modified Pschorr Reaction of 1-(2-Amino-5-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (V)——To a mixture of 3 g of the amino-derivative[16] (V), 10 ml of AcOH, and 70 ml of 5% H_2SO_4 solution was added dropwise 6 ml of 10% $NaNO_2$ aq. solution at 0—5° with stirring and, after addition, the stirring was continued at the same temperature as above for 1 hr. Further, the reaction mixture was heated gradually on a water-bath until it had been kept at 70°. After heating at 70° for 1 hr, the cooled reaction mixture was basified with ammonia and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a brown oil, which was chromatographed on 75 g of silica gel using $CHCl_3$ and MeOH as eluants; $CHCl_3$ (Fr 1—5), $CHCl_3$–MeOH (99:1; Fr 6—14), $CHCl_3$:MeOH (98:2; Fr 15—20), $CHCl_3$–MeOH (97:3; Fr 21—25).

Evaporation of Fr 3—5 gave 500 mg of a brown oil (VI), whose picrate was recrystallized from acetone–MeOH to give yellow plates, mp 153—154°, identical with the picrate of an authentic (±)-O-benzyllaudanine[16] (VI). UV λ_{max}^{MeOH} 282 mμ (log ε 3.85); NMR (τ in $CDCl_3$) 7.43 (NMe), 6.21 (2×OMe), 6.18 (OMe), 5.10 (OC<u>H</u>$_2$-Ph), 3.59 (3H, aromatic protons), 3.53 (1H, aromatic proton), and 2.69 (5H, -OCH$_2$<u>Ph</u>). Secondly, evaporation of Fr 8—9 gave 380 mg of a brown oil (VII), whose picrate was recrystallized from ethanol to afford yellow prisms, mp 209°, identical with the authentic picrate from (±)-O-benzyl-N-methyllaurotetenine[16] (VII). NMR (τ) ($CDCl_3$) 7.46 (s, NMe), 6.32, 6.12 and 6.10 (3H each, singlets, 3×OMe), 4.82 (s, OC<u>H</u>$_2$Ph), 3.42 (1H, s, C_3–<u>H</u> or C_8–H), 3.20 (s, C_8–<u>H</u> or C_3–<u>H</u>), 2.62 (broad s, OCH$_2$<u>Ph</u>), 1.90 (1H, s, C_{11}–<u>H</u>).

Finally, removal of the eluate, Fr 12—22, by distillation gave 280 mg of a brown oil (VIII), which was again chromatographed on alumina using benzene and $CHCl_3$ as eluants. Evaporation of benzene–$CHCl_3$ (1:1 and 1:3) eluate gave 140 mg of O-benzylisosalutaridine (VIII), whose attempts to crystallize resulted in failure. Therefore, recrystallization of the methiodide from MeOH gave colorless needles, mp 224—225° (decomp.). *Anal.* Calcd. for $C_{27}H_{30}O_4NI \cdot \frac{1}{2}H_2O$; C, 57.05; H, 5.49; N, 2.46. Found: C, 56.94; H, 5.80; N, 2.83. IR cm^{-1} (KBr): 3340 (water of crystallization).

Isosalutaridine (IV)——A mixture of 90 mg of O-benzylisosalutaridine (VIII), 9 ml of 48% HBr, and 18 ml of MeOH was heated at 50—55° for 0.5 hr. After cooling, the reaction mixture was basified with 10% ammonia and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give a brown oil, which was chromatographed on silica gel using $CHCl_3$ and MeOH. Evaporation of $CHCl_3$–MeOH (99:1) gave 34 mg of starting material (VIII) and the second $CHCl_3$–MeOH (98:2)

21) All melting points were uncorrected.

afforded 16 mg of isosalutaridine (IV) as a colorless oil, M^+ 327, *m/e* 312, 298, 284, 270, 268, 242, whose IR spectrum was superimposable on that of our authentic sample.[10] During repeated recrystallization of this methiodide (brown prisms, mp 214—216°) from MeOH–ether, it changed brown and therefore was converted to the following O-methylflavinantine.

O-Methylflavinantine (XI)——To a solution of 30 mg of the above isosalutaridine (IV) in ether was added an ethereal solution of diazomethane [prepared from 15 g of *p*-toluenesulfonyl-N-methyl-N-nitrosoamide as usual] and the mixture was set aside at room temperature for 24 hr. Evaporation of the reaction mixture gave a brown oil, which was chromatographed on silica gel. Evaporation of the chloroform eluate gave 18 mg of O-methylflavinantine (XI), whose methiodide was recrystallized from MeOH–ether to give colorless prisms, mp 222—223° (decomp.), identical with an authentic sample.[6] UV λ_{max}^{MeOH} 238 and 282 mμ IR $\nu_{max}^{CHCl_3}$ 1666, 1642 and 1621 cm^{-1}. NMR (τ) ($CDCl_3$) 7.58 (s, NMe), 6.23 (s, OMe), 6.17 (s, OMe), 6.15 (s, OMe), 3.18 (C_8–H), 3.73 (C_5–H), 3.53 and 3.40 (aromatic protons).

O-Acetylisosalutaridine (XIII)——A mixture of 10 mg of isosalutaridine, 0.1 ml of acetic anhydride and 0.1 ml of pyridine was set aside for 15 hr at 10°, and the excess of reagents was distilled off under reduced pressure. The residue was dissolved in $CHCl_3$, whose solution was washed with 10% ammonia and water, and dried over Na_2SO_4. The solvent was evaporated to give a yellow viscous syrup, which was chromatographed on 1 g of silica gel. The $CHCl_3$ eluant gave a colorless viscous syrup, which was recrystallized from ether–hexane to give 4 mg of O-acetylisosalutaridine as colorless prisms, mp 203—204° (lit.,[9] 203°). UV λ_{max}^{MeOH} 233 and 284 mμ. IR $\nu_{max}^{CHCl_3}$ 1753, 1663, 1642 and 1611 cm^{-1}; NMR (τ in $CDCl_3$) 7.70 (COMe), 7.55 (NMe), 6.20 (OMe), 6.18 (Ome), 3.69 (C_5–H), 3.65 (C_1–H), 3.17 (C_4–H) and 3.08 (C_8–H). *Anal.* Calcd. for $C_{21}H_{23}O_5N$: mol. wt., 369.1576. Found (Mass spectrometry) 369.1560.

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