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Studies on the Syntheses of Heterocyclic Compounds. DXVI.[1] Total Syntheses of the Aporphine, Morphinandienone, and Tetrahydrodibenzopyrrocoline Alkaloids by Benzyne Reaction

Tetsuji Kametani, Akira Ujiie, Kimio Takahashi, Takuo Nakano, Toshio Suzuki, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University[2]

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Benzyne reaction of 1-(2-bromo-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (III) with sodium amide in liquid ammonia gave domesticine (II), amurine (X), and cryptowoline (XI) in one-step. The same reaction of the phenolic bromoisoquinoline (VI) gave thaliporphine (XV) O-methylflavinantine (XVI), and cryptaustoline (I).

Benzyne reaction[3] has been extensively investigated from the theoretical interests by Wittig and Huisgen and applied to the synthesis of the heterocyclic compounds. Only a few examples[4,5] were reported on the total synthesis of alkaloids by an application of benzyne reaction in a key step, such as synthesis of cryptaustoline (I). Recently, Kametani[6] and Kessar,[7] independently, synthesized domesticine (II), as an aporphine alkaloid by treatment of the phenolic bromoisoquinoline (III) with sodium amide in liquid ammonia, and reported this reaction to proceed through a benzyne intermediate without any evidence. We investigated this type of reaction by use of the phenolic bromoisoquinoline (IV), the reaction of which was found to proceed through a benzyne intermediate by *cine*-substitution method. The formation of the tetrahydrodibenzopyrrocoline type compound (V) by C-N coupling under benzyne reaction was also reported.[8] On the ground of the above fact, we attempted the extension of this intramolecular benzyne reaction to the general synthesis for some isoquinoline alkaloids, and here wish to report a synthesis of three types of alkaloids described in the title.

The starting phenolic isoquinolines (III[6,9] and VI) were synthesized by usual method; thus, the methiodide (VIII), prepared from 7-benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (VII),[4] was reduced with sodium borohydride to afford the 2-methyl-1,2,3,4-tetrahydroisoquinoline (IX), which was debenzylated with hydrochloric acid in ethanol to give the phenolic isoquinoline (VI).

Benzyne reaction of the first phenolic bromoisoquinoline (III) was carried out in liquid ammonia with sodium amide and gave three compounds. The first one, mp 185—186°, showed the 1,2,9,10-tetraoxygenated aporphine system in the ultraviolet (UV) spectrum,[10] the fact of which was supported by the nuclear magnetic resonance (NMR) spectrum.[10] This fact

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2) Location: *Aobayama, Sendai.*
3) Recent Review on benzyne reaction, R.W. Hoffmann, "Dehydrobenzene and cycloalkynes," Academic Press, New York, 1967.
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5) F. Benington and R.D. Morin, *J. Org. Chem.*, **23**, 1050 (1967).
6) T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc.* (*C*), **1971**, 2712.
7) S.V. Kessar, S. Batra, and S.S. Gandhi, *Indian J. Chem.*, **8**, 468 (1970).
8) T. Kametani, K. Fukumoto, and T. Nakano, *Tetrahedron*, **28**, 4667 (1972).
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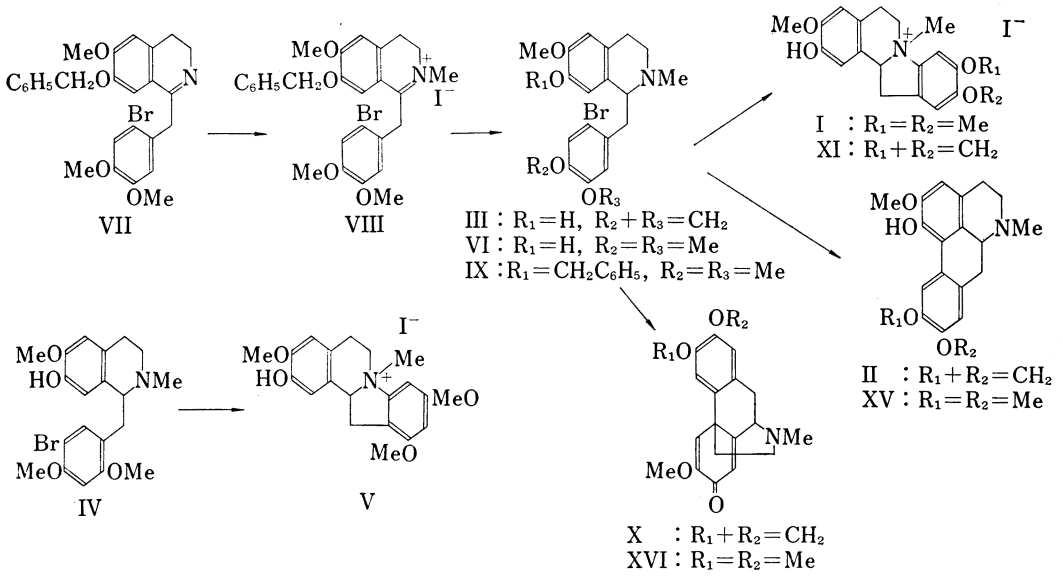

Chart 1

revealed the first product to be domesticine (II), which was proved by direct comparison with an authentic sample.[6,9] The second product, which was easily characterized as methiodide, mp 222—224°, revealed the α-methoxylated cross-conjugated cyclohexadienone system in the infrared (IR) spectrum[11] which showed no hydroxy function. These data indicated the product to be amurine (X), the IR spectrum of which was superimposable upon that of the authentic amurine.[12]

The third product was a hygroscopic quaternary ammonium salt, and characterized easily as its iodide, mp 245—247° (decomp.). The IR spectrum showed the quaternary ammonium salt system and was identical with that of the authentic cryptowoline (XI) prepared by Kametani's method.[4] For the standard synthesis[4,5] of the tetrahydrodibenzopyrrocoline alkaloids, the benzyne reaction of nonphenolic brominated secondary amine (XII), followed by quaternization of the resulting tetrahydrodibenzopyrrocoline (XIII) and then debenzylation, seemed to be convenient, but, in this synthesis, there is a fatal defect that 2,3-dihydroindole system was easily dehydrogenated to give the non-alkaloid type of the dihydrodibenzopyrrocoline (XIV).[4] Moreover, the standard synthesis needs many steps and the yield in debenzylation is not so high. On the other hand, since our synthetic method was carried out in one-step, the unstable tetrahydrodibenzopyrrocoline (XIII) was not formed, whose facts were characteristic in our synthesis.

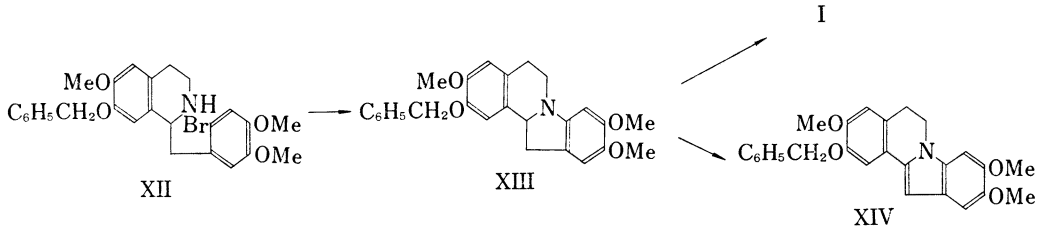

Chart 2

11) T. Kametani and K. Fukumoto, *J. Heterocyclic Chem.*, **8**, 341 (1971).
12) T. Kametani, K. Fukumoto, and T. Sugahara, *J. Chem. Soc.* (*C*), **1969**, 801.

Benzyne reaction of the second phenolic bromoisoquinoline (VI) in a same reaction condition as the case of III gave thaliporphine (XV),[13] O-methylflavinantine (XVI),[14] and cryptaustoline (I),[4] which were identical with the authentic specimens by IR spectral comparison, respectively.

Thus, we have accomplished the coupling reaction at all the possible positions in an intramolecular benzyne reaction of the 1-(2-bromobenzyl)-1,2,3,4-tetrahydro-7-hydroxy-2-methylisoquinolines, the facts of which led to the total syntheses of the aporphine, morphinandienone, and tetrahydrodibenzopyrrocoline alkaloids.

Experimental[15]

Benzyne Reaction of 1-(2-Bromo-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (III)[9]——To a stirred suspension of $NaNH_2$ [prepared from 1.6 g of Na metal and NH_3] in 300 ml of liq. NH_3 was added 2.5 g of phenolic bromoisoquinoline (III) in 50 ml of tetrahydrofuran (THF), and stirring was continued for 2 hr. The excess of $NaNH_2$ was decomposed with 4.5 g of NH_4Cl. After evaporation of liq. NH_3, the dark brown residue was diluted with 100 ml of H_2O and extracted with 1 liter of $CHCl_3$. The extract was washed with 200 ml of H_2O, dried over Na_2SO_4 and evaporated. The resulting brownish residue was chromatographed on 60 g of silica gel.

Elution with $CHCl_3$–MeOH (99: 1) afforded a solid, which was rechromatographed on 5 g of silica gel with $CHCl_3$–MeOH (98: 2) as eluant to give 20 mg of domesticine (II). This product was identical with an authentic domesticine[9] in spectroscopic comparisons. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH). NMR ($CDCl_3$) δ: 2.52 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 5.92 (2H, s, OCH_2O), 6.53 and 6.74 (2H, each s, ArH) and 7.94 (1H, s, 11–H).

Elution with $CHCl_3$–MeOH (98: 2) gave an oil, which was rechromatographed on 5 g of silica gel with $CHCl_3$–MeOH (98: 2) as eluant to give 5 mg of amurine (X), identical with an authentic amurine[9] in spectroscopic comparison. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670, 1645, and 1620 (C=O and C=C).

Elution with MeOH in the first chromatography was acidified with 10% HCl and evaporated under reduced pressure to leave a brownish solid. The residue was dissolved in water and the separated solid was filtered off. To the filtrate was added a saturated aqueous solution of KI, and the mixture was set aside for 10 min and then heated on a water bath for a few minutes. The separated substance was removed by decantation while warm and the resulting solution was cooled with ice. The precipitate was collected by filtration, washed with H_2O, *n*-hexane and ether, and then recrystallized from EtOH–ether to give cryptowoline iodide (XI), mp 245—247° (decomp.) which was identical, in its IR spectroscopic comparison, with an authentic cryptowoline iodide synthesized *via* an alternative pathway.[4,5]

7-Benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (VIII)——A mixture of 3,4-dihydroisoquinoline (VII) [prepared from 24 g of the hydrochloride[4] of VII by usual method] and 25 ml of MeI was allowed to stand at room temperature for 2 hr. A yellowish precipitate separated was collected by decantation to give a solid, which was triturated with ether. Collection by filtration, followed by recrystallization from MeOH–ether, afforded 19 g of VIII as yellowish needles, mp 232—233°. IR ν_{max}^{KBr} cm^{-1}: 1629 ($\overset{+}{>}C=\overset{+}{N}-$). *Anal.* Calcd. for $C_{27}H_{29}O_4NBrI$: C, 51.04; H, 4.12; N, 2.20. Found: C, 51.00; H, 4.46; N, 2.15.

7-Benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (IX)——To a stirred solution of 18 g of VIII in 500 ml of MeOH was added 18 g of $NaBH_4$ in small portions under cooling. After the addition, the stirring was continued at room temperature for 0.5 hr, and the mixture was refluxed on a water-bath for 0.5 hr. Removal of the solvent gave a residue, which was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 14 g of IX as a brown oil. Recrystallization from MeOH gave 13 g of IX as colorless prisms, mp 113—115°. *Anal.* Calcd. for $C_{27}H_{30}O_4NBr$: C, 63.28; H, 5.90; N, 2.73. Found: C, 63.42; H, 5.77; N, 2.70. NMR ($CDCl_3$) δ: 2.47 (3H, s, NCH_3), 2.66—3.55 (7H, m, methylene and methine protons), 3.68 (3H, s, OCH_3), 3.81 (6H, each s, $2\times OCH_3$), 4.79 (2H, s, $C_6H_5\underline{CH_2}O$), 6.13, 6.49. 6,57, 6.97 (4H, each s, Ar-H), 7.28 (5H, s, $\underline{C_6H_5}CH_2O$).

1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (VI)——A mixture of 13 g of IX, 130 ml of conc. HCl and 130 ml of EtOH was refluxed for 0.5 hr. Removal of the solvent under reduced pressure gave a residue, which was made basic with 10% NH_4 OH and extracted with

13) T. Kametani, K. Fukumoto, and T. Nakano, *J. Heterocyclic Chem.*, **9**, 1363 (1972).
14) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *J. Chem. Soc.* (*C*), **1969**, 520.
15) IR and UV spectra were taken with type EPI–2 and EPS–3 Hitachi recording spectrophotometers, respectively. Mass spectra were measured with a Hitachi RMU–7 mass spectrometer, and NMR spectra were taken with a Hitachi H–60 with tetramethylsilane as internal standard.

$CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 8 g of VI as a brown syrup, which was converted into the hydrochloride as cubes, mp 148—150°. *Anal.* Calcd. for $C_{20}H_{24}O_4NBr \cdot HCl \cdot H_2O$: C, 50.38; H, 5.71; N, 2.94. Found: C, 50.66; H, 5.85; N, 2.92. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH). NMR ($CDCl_3$) δ: 2.43 (3H, s, NCH_3), 2.57—3.60 (7H, m, methylene and methine protons), 3.68 (3H, s, OCH_3), 3.77 (6H, s, $2 \times OCH_3$), 5.42 (1H, s, OH), 6.28, 6.51, 6.53, 6.96 (4H, each s, ArH).

Benzyne Reaction of VI——To a stirred solution of $NaNH_2$ [prepared from 1.6 g of Na metal and NH_3] in 300 ml of liq. NH_3 was added a solution of 2.6 g of the above isoquinoline (VI) in 20 ml of dry THF. Stirring was continued for 2 hr, and then the excess of $NaNH_2$ was decomposed with 7 g of crystalline NH_4Cl. The mixture was kept aside overnight to give a brown solid, which was diluted with 100 ml of water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 2 g of a brown solid, which was chromatographed on 80 g of silica gel. Eluant with $CHCl_3$ (fractions 1—30; each fraction 100 ml) and $CHCl_3$–MeOH (99: 1) (fractions 31—55) was discarded. Elution with $CHCl_3$–MeOH (98: 2) (fractions 64—67) gave 30 mg of a brown solid, which was recrystallized from EtOH to give 15 mg of (±)-thaliporphine (XV) as colorless prisms, mp 189—190°. The spectral data of XV were identical with the authentic sample.[13] *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.03; H, 7.05; N, 4.07. UV λ_{max}^{MeOH} nm (log ε): 305 (4.12), 280 (4.12), and 220 (4.52). NMR ($CDCl_3$) δ: 2.56 (3H, s, NCH_3), 2.65—3.75 (7H, m, methylene and methine protons), 3.85 (3H, s, OCH_3), 3.88 (6H, each s, $2 \times OCH_3$), 6.50, 6.74, 8.02 (3H, each s, ArH). Elution with $CHCl_3$–MeOH (98:2) (fractions 69—76) gave 200 mg of a brown solid, which was rechromatographed on 2 g of neutral alumina and then 1 g of active alumina to give the dienone compound. Further purification was carried out by washing with alkali (10% NH_4OH, 5% NaOH, and 10% NaOH) to give 2 mg of (±)-O-methylflavinantine (XVI), which was homogeneous on TLC and identical with an authentic sample.[14] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665, 1642, 1620, 1508. After removal of the eluant with $CHCl_3$–MeOH (97:3) and $CHCl_3$–MeOH (95:5), eluant with 1 liter of MeOH was evaporated to give a brown solid, which was extracted with water. This aqueous solution was acidified with conc. HCl and evaporated under reduced pressure to give 30 mg of a brown solid, to which a solution of KI was added to yield a precipitate. Recrystallization from EtOH afforded 20 mg of (±)-cryptaustoline (I) as colorless prisms, mp 254—255°, which was identified by the mixed melting point test and its IR spectral comparison with that of an authentic sample.[4] *Anal.* Calcd. for $C_{20}H_{24}O_4NI \cdot 1/2H_2O$: C, 50.22; H, 5.27; N, 2.93. Found: C, 49.90; H, 5.04; N, 2.88. NMR δ (DMSO-d_6): 3.50 (3H, s, NCH_3), 3.78, 3.84 (9H, each s, $3 \times OCH_3$), 5.30 (1H, t, $J=9$ Hz, 12a–H), 6.73, 6.81, 7.07, 7.55 (4H, each s, ArH).

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