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Studies on the Syntheses of Heterocyclic Compounds. CDXXXIV.[1] The Abnormal Formation of 3-(4-Methoxyphenethyl)-6,7-methylenedioxy-1,2,3-benzotriazin-4-one in Case of Pschorr Reaction

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Recently the synthesis of the Amarylidaceae alkaloid by phenol oxidation has been developed.[3,4] As we reported previously,[4] the galanthamine (I) type ring system could be synthesized by one step oxidation from N-benzylphenethylamine derivatives. Therefore the synthesis of the ring system of lycorine (II) and crinine (III) alkaloids by the following reaction was expected. Although we tried to prepare the lycorine (II) skeleton by a Pschorr reaction of the corresponding indole derivative (VII), which would be formed by oxidative coupling of the phenolic phenethylamine derivative (VI), this attempt was not successful. Therefore we examined the Pschorr cyclization of IX, by the result of which the abnormal formation of 3-(4-methoxyphenethyl)-6,7-methylenedioxy-1,2,3-benzotriazin-4-one (XI) was observed. In this cyclization, oxidation of the methylene group was also recognized. Herein we wish to report these results.

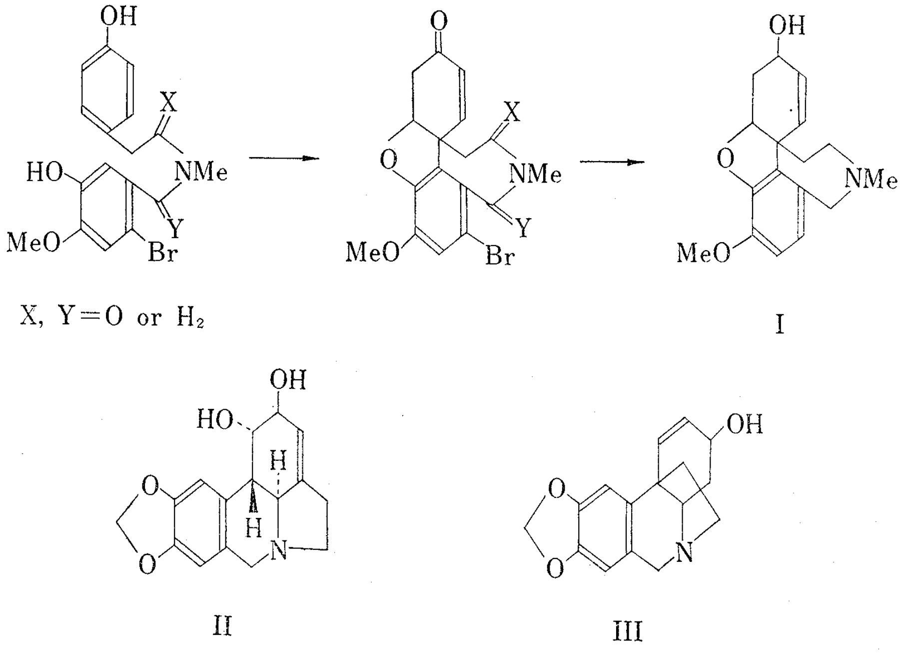

Chart 1

First, the Schiff base (IV), obtained from 2-nitropiperonal and 3-benzyloxy-4-methoxyphenethylamine, was reduced by sodium borohydride to give the amine (V). Debenzyla-

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[1] Part CDXXXIII: T. Kametani, H. Nemoto, T. Nakano, S, Shibuya, and K. Fukumoto, *Chem. Ind.* (London), **1971**, 788.

[2] Location: *Aobayama, Sendai.*

[3] T. Kametani, K. Yamaki, H. Yagi, and K. Fukumoto, *Chem. Commun.*, **1969**, 425.

[4] T. Kametani, K. Shishido, E. Hayashi, C. Seino, T. Kohno, S. Shibaya, and K. Fukumoto, *J. Org. Chem.*, **36**, 1295 (1971).

tion of this amine (V) gave the secondary amine (VI). In order to obtain our desired compound (VII), oxidation of VI with potassium ferricyanide in 5% sodium bicarbonate using a two-phase system of chloroform–water was attempted, but the starting material was recovered. Furthermore, oxidation of VI with potassium ferricyanide in chloroform and 8% ammonium acetate was also examined, but an anomalous product was obtained, the structure of which could not be determined. Oxidation of VI with ferric chloride resulted in the formation of a tar.

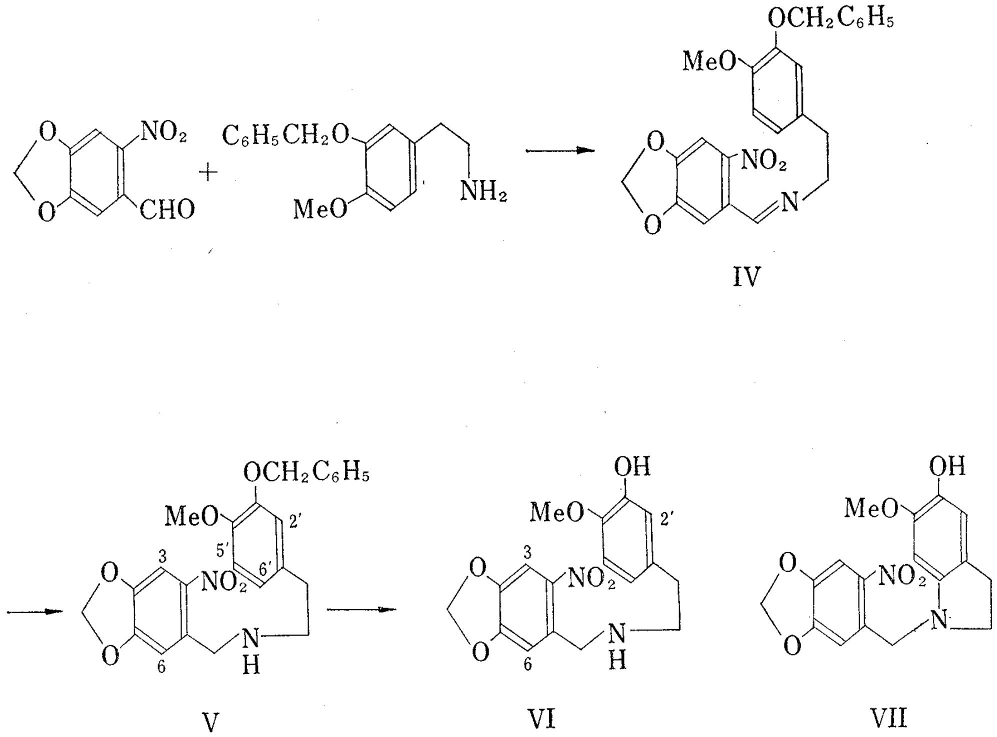

Chart 2

Then, the second starting material was synthesized as follows; the Schiff base (VIII), prepared from 2-nitropiperonal and 4-methoxyphenethylamine, was reduced with zinc powder and hydrochloric acid to give the amine (IX). Diazotization of IX, followed by thermal decomposition[5–9] of the diazonium salt (X), afforded a mixture of piperonal and an unexpected product (XI),[10] the latter of which was determined by an alternative synthesis by Hendrickson's method.[11]

The amide (XII), obtained by a Schotten–Baumann reaction of 4-methoxyphenethylamine with 2-nitropiperonilic acid chloride, was hydrogenated to give the amine (XIII). The diazonium fluoroborate (XIV) of this amine (XIII) was subjected to ring closure with polyphosphoric acid to give XI. The infrared (IR), nuclear magneric resonance (NMR),

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5) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, **1968**, 1398; *idem, J. Chem. Soc.* (*C*), **1969**, 520.

6) T. Kametani, K. Fukumoto, and T. Sugahara, *Tetrahedron Letters*, **1968**, 5459; *idem, J. Chem. Soc.* (*C*), **1969**, 801.

7) T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1969**, 1063.

8) T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 2245 (1969).

9) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc.* (*C*), **1969**, 2030.

10) This compound seems to be formed through oxidation of the methylene group of the reactive benzyl group with nitrous acid during diazotization.

11) J.B. Hendrickson, R.W. Alder, D.R. Dalton, and D.G. Hey, *J. Org. Chem.*, **34**, 2667 (1969).

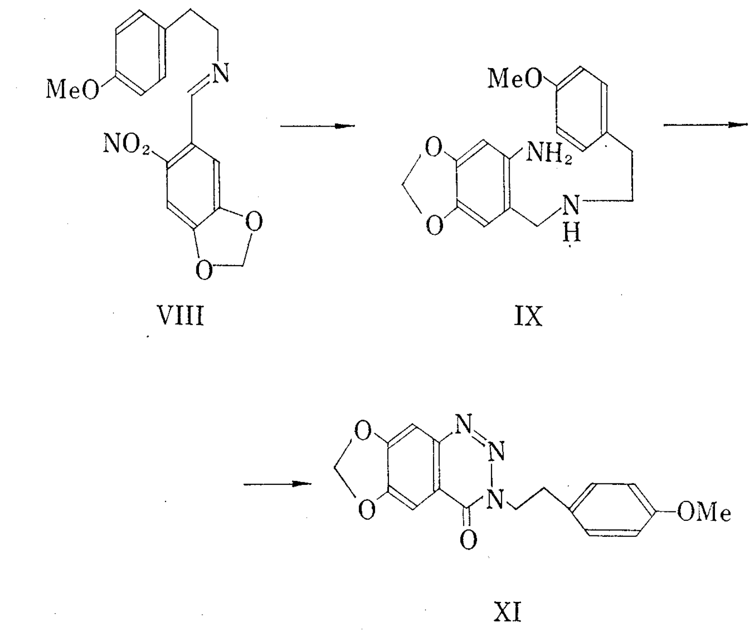

Chart 3

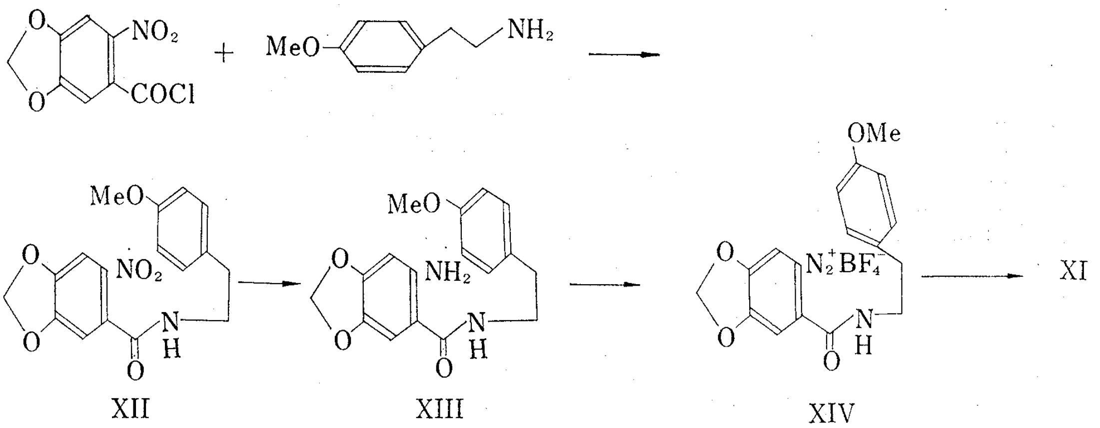

Chart 4

and mass spectra of XI coincided with those of the above specimen, which was prepared by a Pschorr reaction of X.

Although the synthetic approach to lycorine and crinine type alkaloids was not successful, it is interesting that the formation of triazinone (XI) by internal conjugate additions of heteroatoms proceeded more preferentially than our expected Pschorr reaction.

Experimental

N-(4,5-Methylenedioxy-2-nitrobenzyl)-3-benzyloxy-4-methoxyphenethylamine (V)——A solution of 3.35 g of 2-nitropiperonal in 70 ml of MeOH was added to a solution of 4.4 g of 3-benzyloxy-4-methoxyphenethylamine in 80 ml of MeOH, and the mixture was refluxed for 1 hr. After cooling, 400 mg of $NaBH_4$ was added in small portions to the above mixture with stirring at 0—5° during 45 min, and the reaction mixture was allowed to stand at room temperature for 40 min. After evaporation of the solvent below 40° under a current of N_2, the residue was recrystallized from benzene–hexane to give 4.0 g of yellow crystals, mp 111—112.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1585, 1328 (NO_2), 930 (OCH_2O). NMR (in $CDCl_3$) τ: 2.58 (1H, singlet, C_3-H), 2.70 (5H, s, aromatic protons), 3.2 (1H, s, C_6-H), 3.29 (3H, multiplet, C_2'-H, C_5'-H, C_6'-H), 4.2 (2H, s, $OC\underline{H}_2O$), 4.93 (2H, s, $OC\underline{H}_2C_6H_5$), 6.8 (2H, s, $C_6H_5C\underline{H}_2N$), 6.19 (3H, s, OMe), 7.24 (3H, broad t, $C_6H_5CH_2C\underline{H}_2N\underline{H}$), 7.67 (2H, t, $C_6H_5C\underline{H}_2CH_2$). *Anal.* Calcd. for $C_{24}H_{24}O_6N_2$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.14; H, 5.49; N, 6.15.

N-(4,5-Methylenedioxy-2-nitrobenzyl)-3-hydroxy-4-methoxyphenethylamine (VI) Hydrochloride——To a solution of 9 g of I in 180 ml of EtOH was added 180 ml of conc. HCl and the mixture was refluxed for 1 hr. After concentration, the resulting precipitate was collected by filtration and recrystallized from MeOH to give 8.0 g of yellow needles, mp 236—238°. IR $\nu_{\max}^{\text{CHCl}_3}$cm^{-1}: 3530 (OH), 1615, 1587, 1330, 930. NMR (in $CDCl_3$) τ: 2.55 (1H, s, C_3-H), 3.0 (1H, s, C_6-H), 3.30 (3H, m, C_2'-H, C_5'-H, C_6'-H), 3.95 (2H, s, $OC\underline{H}_2O$), 6.03 (2H, s, $C_6H_5C\underline{H}_2N$), 6.17 (3H, s, OMe), 6.28 (2H, broad s, OH and NH), 7.20 (4H, t, $C_6H_5C\underline{H}_2C\underline{H}_2N$). *Anal.* Calcd. for $C_{17}H_{18}O_6N_2 \cdot HCl$: C, 53.34; H, 5.00; N, 7.32. Found: C, 53.31; H, 5.06; N, 7.28.

N-(4-Methoxyphenethyl)-4,5-methylenedioxy-2-nitroaldazine (VIII)——To a solution of 1.5 g of 4-methoxyphenethylamine in 50 ml of EtOH was added a solution of 2.0 g of 2-nitropiperonal in 50 ml of EtOH, and the mixture was refluxed for 3 hr. Evaporation of the solvent gave a solid, which was recrystallized from MeOH to give 3.0 g of VIII as yellow needles, mp 128—130°. IR $\nu_{\max}^{\text{CHCl}_3}$cm^{-1}: 1638 (C=N), 1605, 1585 (shoulder), 1330 (NO_2), 930 (OCH_2O). *Anal.* Calcd. for $C_{17}H_{16}O_5N_2$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.94; H, 4.92; N, 8.43.

N-(2-Amino-4,5-methylenedioxybenzyl)-4-methoxyphenethylamine (IX)——To a mixture of 2.2 g of nitro compound (VIII) in 60 ml of conc. HCl and 16 ml of H_2O was added in small portions 6.8 g of zinc powder during 25 min, and the stirring was continued for 0.5 hr at room temperature. The mixture was heated at 90° for 0.5 hr and then filtered. The filtrate was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 1.1 g of a brown oil. IR $\nu_{\max}^{\text{CHCl}_3}$cm^{-1}: 3400—3200 ($NH_2$, NH), 1600, 1580, 930. NMR (in $CDCl_3$) τ: 3.0—3.52 (4H, m, aromatic protons), 3.53 (1H, s, C_6'-H), 3.84 (1H, s, C_3'-H), 4.25 (2H, s, $OC\underline{H}_2O$), 6.28 (3H, s, $OC\underline{H}_3$).

Thermal Decomposition of Diazotized IX——A solution of 0.35 g of sodium nitrite in 3.5 ml of water was added dropwise to a solution of 1.0 g of the amino compound (IX) in 31 ml of 5% H_2SO_4, with stirring at 0—5° during 30 min. The mixture was stirred at 5° for 1 hr, and then heated gradually to 70° during 1 hr. The stirring was continued for 1 hr and the mixture was, after cooling, basified with 10% NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with satd. NaCl aq. solution, dried over Na_2SO_4, and evaporated to give 0.7 g of residue, which was chromatographed on 20 g of silica gel using $CHCl_3$ as solvent.

The first fraction gave piperonal, which was identical with an authentic sample, and the second fraction yielded 25.5 mg of triazinone (XI) as a gum, which was crystallized from MeOH to give colorless needles, mp 142—144°. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 1662 (amide C=O), 1605, 935. NMR (in $CDCl_3$) τ: 2.45 (1H, s, C_6-H), 2.64 (1H, s, C_3-H), 2.78—3.30 (4H, m, aromatic protons), 3.83 (2H, s, $OC\underline{H}_2O$), 5.22—5.52 (2H, distorted t, $NC\underline{H}_2$), 6.24 (3H, s, $OC\underline{H}_3$), 6.70—7.02 (2H, distorted t, $C_6H_4C\underline{H}_2$). Mass Spectrum *m/e*: 325 (M^+). *Anal.* Calcd. for $C_{17}H_{15}O_4N_3$: C, 62.76; H, 4.65. Found: C, 62.69; H, 4.95.

N-(3,4-Methylenedioxy-6-nitrobenzoyl)-4-methoxyphenethylamide (XII)——To a suspension of 2.1 g of 6-nitropiperonylic acid in 10 ml of benzene was added 2 g of thionyl chloride in the presence of one drop of piperidine, and the mixture was refluxed for 40 min. After evaporation of the solvent and an excess of thionyl chloride, the residue was dissolved in 20 ml of $CHCl_3$. This solution was added dropwise with stirring to a solution of 1.7 g of 4-methoxyphenethylamine and 22 ml of triethylamine in 40 ml of $CHCl_3$. After stirring for 1 hr, the $CHCl_3$ solution was washed with 1N NaOH aq. solution, 1N HCl aq. solution, and water, and dried over Na_2SO_4. The solvent was evaporated and the resulting solid was recrystallized from MeOH to give 2 g of yellow crystals, mp 160.5—162°. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3360 (NH), 1662 (amide C=O), 1580, 1350, 930. *Anal.* Calcd. for $C_{17}H_{16}O_6N_2$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.05; H, 4.48; N, 8.24.

Diazonium Fluoroborate of XIII——A solution of 472 mg of nitroamide (XII) in 30 ml of ab. EtOH was hydrogenated on 140 mg of PtO_2 at atmospheric pressure. After an uptake of 98 ml of H_2, the catalyst was filtered off and the filtrate was evaporated to give 350 mg of a gum [IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3520 and 3330 (NH), 3650 (amide), 1615, 942], which was treated with 0.6 ml of 50% HBF_4 and 25 ml of water. The resulting clear solution was then cooled at −5°, and a solution of 1.3 g of sodium nitrite in 13 ml of H_2O was added. Then 10 ml of HBF_4 was added to the above mixture to precipitate a yellow solid, which was washed with HBF_4, MeOH and ether, and dried over P_2O_5. This was immediately used in the following reaction without purification.

Decompositon of Diazonium Salt (XIV)——To 5 ml of freshly prepared polyphosphoric acid [prepared from 25 g of P_2O_5 and 10 g of H_3PO_4] was added 100 mg of salt (XIV). The resulting mixture was heated for 1 hr on a water-bath and then poured into water after cooling. The foregoing mixture was extracted with $CHCl_3$ to give 75 mg of a brown gum, the IR, NMR, and Mass spectra of which coincided with those of XI, obtained by a Pschorr reaction of IX.

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