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Dienone-Phenol Rearrangement of "Procularine-type Compound" and Synthesis of Its Rearranged Cularine-type Compound. (Studies on the Syntheses of Heterocyclic Compounds. CCCVI[1])

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Dienone–phenol rearrangement of dienone (II) with concentrated sulfuric acid gave a cularine–type compound, 9-hydroxy-5,6,10-trimethoxy-1-methyl-1,2,3,12,12a-pentahydrobenzoxepino[2,3,4-*i,j*]isoquinoline (III), whose structure was assigned by spectroscopic method and its alternative synthesis of III from 1-(2-bromo-4-hydroxy-5-methoxybenzyl)-1,2,3,4-tetrahydro-8-hydroxy-6,7-dimethoxy-2-methylisoquinoline (XI). Moreover, this paper described the preparation of XI.

In the previous papers[3,4] we have described that phenolic oxidation of diphenolic isoquinoline (I) with alkaline ferricyanide to dienone type compound (II), followed by rearrangement of II with hydrochloric acid–acetic acid, gave the cularine type compound (III). The structure of the latter compound was tentatively assigned by microanalysis and spectroscopic data, especially depending on the chemical shifts of O-methyl resonances because of the shortage of its sample. We reinvestigated the rearrangement of this dienone (II) with the acid catalysts and confirmed that the rearranged product with sulfuric acid had the structure (III) reported previously. Since the product obtained by treatment with hydrochloric acid–acetic acid of the dienone (II) seems to have an another structure having cularine type skeleton, we hereby wish to report the correct structure for the rearranged compound which was proved by its synthesis.

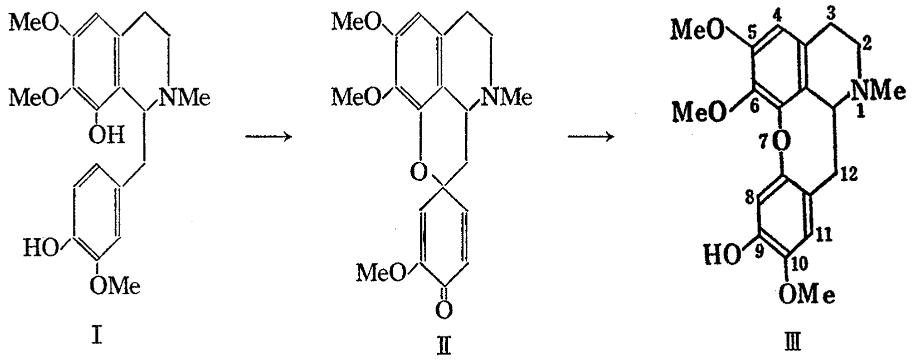

Chart 1

The dienone (II) was treated with an excess of concentrated sulfuric acid in a current of nitrogen at room temperature with stirring for 15 hr to give a phenolic base, mp 145—147°,

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[1] Part CCCV: T. Kametani, S. Hibino, and S. Takano, *Chem. Comm.*, **1969**, 131.
[2] Location: a) *No. 85, Kita-4-bancho, Sendai*; b) *No. 600, Kashiwagi-4-chome, Shinjuku, Tokyo.*
[3] T. Kametani, T. Kikuchi, and K. Fukumoto, *Chem. Comm.*, **1967**, 546.
[4] T. Kametani, T. Kikuchi, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1003 (1968).

which was different from the product by the rearrangement with hydrochloric acid and acetic acid.[3,4] Microanalysis verified the molecular formula of $C_{20}H_{23}O_5N$, whose infrared (IR) spectrum showed an absorption at 3400 cm^{-1} (phenolic hydroxyl). The nuclear magnetic resonance (NMR) (ppm) revealed four methyl resonances at 2.58 (NMe), 3.76 (OMe), 3.80 (OMe), and 3.87 (OMe) as singlets, hydroxyl group at 5.3 as a broad singlet (exchanged with deuterium oxide) and three aromatic protons at 6.49 (2H) and 6.87 (1H) as singlets. Moreover, methine proton in C_{12a} position appeared at 4.35 as a quartet ($J=4$ and 12 cps) coupled with methylene protons at C_{12} position, whose quartet and coupling constants were characteristic for cularine type skeleton.[5,6] The chemical shifts of O-methyl groups were closely similar to those of 6,10-O,O-didemethylcularine[5,7] and the product prepared by the rearrange-

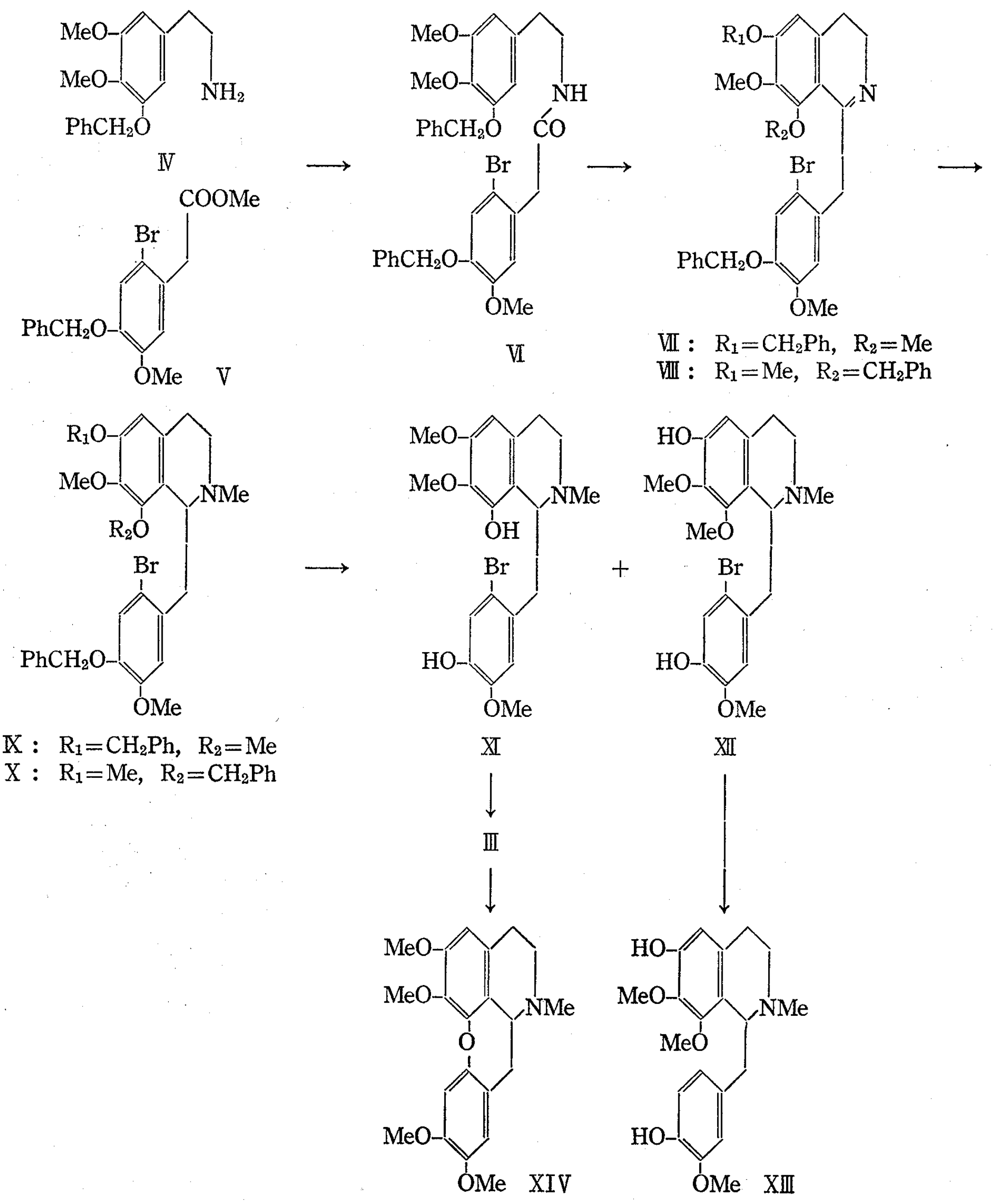

Chart 2

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5) T. Kametani, S. Shibuya, C. Kibayashi, and S. Sasaki, *Tetrahedron Letters*, **1966**, 3215.

6) N.S. Bhacca, J.C. Craig, R.H.F. Manske, S.K. Roy, M. Shamma, and W.A. Slusarchyk, *Tetrahedron*, **22**, 1467 (1960).

7) T. Kametani, S. Shibuya, and S. Sasaki, *Yakugaku Zasshi*, **87**, 198 (1967).

ment with acetic acid–hydrochloric acid. Since it was impossible to determine which products had the proposed structure (III), the synthesis[8,9] of an authentic sample was carried out as follow.

A fusion of 3-benzyloxy-4,5-dimethoxyphenethylamine (IV) with methyl 4-benzyloxy-2-bromo-5-methoxyphenylacetate (V) afforded the corresponding amide (VI), which was subjected to Bischler–Napieralski reaction. A mixture of the resulting 3,4-dihydroisoquinolines (VII and VIII) was converted into their methiodides without separation and purification, which were reduced with sodium borohydride to give a mixture of 2-methyl-1,2,3,4-tetrahydroisoquinolines (IX and X). Debenzylation of these products with concentrated hydrochloric acid in ethanol afforded a mixture of diphenolic isoquinolines (XI and XII), which were separated by fractional crystallization from ether; one of them was obtained as colorless prisms, mp 184—186°, and its NMR spectrum showed the following important signals at 2.60 (NMe), 3.82, 3.82, and 3.85 ($3\times$OMe) as singlets, and 6.27 (C_5–H) as a singlet. The other compound was formed as a viscous syrup, whose nuclear magnetic resonance (NMR) spectrum showed four methyl resonances at 2.60 (NMe), 3.76, 3.79, and 3.80 ($3\times$OMe) as singlets, and 6.45 (C_5–H) as a singlet. In general, the chemical shift of C_5-proton of 6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline is known to resonance in a higher field than that of 6-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline.[10] Therefore, the former was assigned to 1-(2-bromo-4-hydroxy-5-methoxybenzyl)-1,2,3,4-tetrahydro-8-hydroxy-6,7-dimethoxy-2-methylisoquinoline (XI) and the latter to 6-hydroxy-7,8-dimethoxy isomer (XII). The latter isoquinoline (XII) was debrominated with zinc and acetic acid to give 1-(4-hydroxy-3-methoxybenzyl)-1,2,3,4-tetrahydro-6-hydroxy-7,8-dimethoxy-2-methylisoquinoline (XIII), whose infrared (IR) spectrum was superimposable on that of an authentic sample.[4]

Ullmann reaction of diphenolic isoquinoline (XI) by using of cupric oxide in the presence of pyridine and potassium carbonate at 150—160° for 3 hr gave a monophenolic isoquinoline (III), mp 145—147°, whose IR spectrum and mp were identical with those of the rearranged product of dienone (II) with sulfuric acid, but differed from those of the product obtained by treatment of the dienone (II) with hydrochloric acid–acetic acid.[11]

Therefore, it is clear that the rearranged product with concentrated sulfuric acid should be assigned to structure (III) and the structure of another rearranged product seems to be cularine–type compound whose substituents would exist in different positions from the structure (III). The structure of the latter compound is under examination.

Experimental[12]

Methyl 4-Benzyloxy-2-bromo-5-methoxyphenylacetate (V)——To a solution of methyl 4-benzyloxy-3-methoxyphenylacetate (15 g) in 200 ml of dry AcOH was added dropwise a solution of 9 g of Br_2 in 50 ml of dry AcOH with stirring. After the stirring was continued for 1 hr at room temperature, the mixture was basified with conc. NaOH aqueous solution and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4, and distilled to leave 15 g of bromo ester (V) as colorless needles, after recrystallization from MeOH, mp 109—110°. *Anal.* Calcd. for $C_{17}H_{17}O_4Br$: C, 56.05; H, 4.70. Found: C, 55.82; H, 4.98.

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[8] H. Iida, T. Kikuchi, K. Sakurai, and T. Watanabe, *Yakugaku Zasshi*, in press.

[9] H. Iida, T. Kikuchi, S. Tanaka, and M. Shinbo, *Yakugaku Zasshi*, in press.

[10] T. Kametani and T. Kikuchi, *Chem. Pharm. Bull.* (Tokyo), **15**, 879 (1967).

[11] Methylation of the compound (III) with diazomethane gave a nonphenolic isoquinoline (XIV), mp 113—115°, whose spectroscopic and chromatographic behaviours were the same as those of authentic sample.[9]

[12] All melting points were not corrected. The nuclear magnetic resonance spectra were measured using JNM–4H 100 Mc spectrometer and the chemical shifts were shown in ppm unit from the internal standard of TMS.

N-(3-Benzyloxy-4,5-dimethoxyphenethyl)-4-benzyloxy-2-bromo-5-methoxyphenylacetamide (VI)——A mixture of 4 g of 3-benzyloxy-4,5-dimethoxyphenethylamine (IV) and 5 g of methyl 2-bromo-4-benzyloxy-5-methoxyphenylacetate (V) was heated at 170—180° for 6 hr. After cooling at room temperature, the reaction mixture was recrystallized from EtOH to give 8 g of the amide (VI) as colorless needles, mp 128—130°. *Anal.* Calcd. for $C_{33}H_{34}O_6NBr$: C, 63.87; H. 5.52; N, 2.26. Found: C, 63.69; H, 5.60; N, 2.10. IR cm^{-1} (KBr): ν_{NH} 3300, $\nu_{C=O}$ 1640 (CO).

Mixture of 6-Benzyloxy-7,8-dimethoxy-(VII) and 8-Benzyloxy-6,7-dimethoxy-1-(2-bromo-4-benzyloxy-5-methoxybenzyl)-3,4-dihydroisoquinoline (VIII)——A mixture of 7 g of the amide (VI), 10 ml of $POCl_3$ and 70 ml of dry benzene was refluxed for 4 hr and the reaction mixture was poured into 1000 ml of cold *n*-hexane. After being allowed to stand overnight, the upper layer was removed by decantation and the residue was washed repeatedly with *n*-hexane and dissolved in MeOH. This solution was poured into 10% NH_4OH aq. solution and the oil separated was extracted with ether. The extract was washed with water, dried over K_2CO_3 and evaporated to leave 6 g of a mixture of 3,4-dihydroisoquinolines (VII and VIII) as a pale yellow viscous syrup, whose recrystallization and separation were so difficult that it was used in the following reaction without purification. IR cm^{-1} ($CHCl_3$): $\nu_{C=N}$ 1630.

Mixture of 6-Benzyloxy-7,8-dimethoxy-(IX) and 8-Benzyloxy-6,7-dimethoxy-1-(2-bromo-4-benzyloxy-5-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (X)——A mixture of 5 g of the above 3,4-dihydroisoquinolines (VII and VIII) and 20 ml of MeI in 200 ml of MeOH–acetone (1:1 v/v) was refluxed gently for 5 hr. The excess of MeI and solvent was distilled off *in vacuo* and the residue was washed with ether. $NaBH_4$ (5 g) was added in small portions to a solution of the crude methiodides in 150 ml of MeOH and the stirring was continued for 0.5 hr at room temperature. The solvent was distilled off and the residue was decomposed with 2% NaOH aq. solution and extracted with ether. The extract was washed with water, dried over K_2CO_3 and evaporated to leave 4 g of a mixture of tetrahydroisoquinolines (IX and X) as a yellow viscous syrup, which could not be purified and used in the following reaction without purification.

8-Hydroxy-6,7-dimethoxy-(XI) and 6-Hydroxy-7,8-dimethoxy-1-(2-bromo-4-hydroxy-5-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (XII)——A solution of 4 g of the above tetrahydroisoquinolines (IX and X) in 40 ml of conc. HCl–EtOH (1:1 v/v) was refluxed for 2 hr and the solvent was then distilled off *in vacuo*. The residue was dissolved in 50 ml of 5% NaOH aq. solution, which was washed with benzene. An excess of solid NH_4Cl was added to the aqueous layer and the resulting ammoniacal alkaline solution was extracted with $CHCl_3$. The extract was washed with water, dried over K_2CO_3, and distilled to leave 2 g of a yellow viscous syrup, which was recrystallized from ether to give 800 mg of diphenolic isoquinoline (XI) as colorless prisms, mp 184—186°. *Anal.* Calcd. for $C_{20}H_{24}O_5NBr$: C, 54.80; H, 5.51; N, 3.20. Found: C, 54.96; H, 5.71; N, 3.10. IR cm^{-1} ($CHCl_3$): ν_{OH} 3450. NMR (ppm) ($CDCl_3$): 2.60 (3H, singlets, N-Me), 3.82 (3H, singlet, O-Me), 3.84 (3H, singlet, O-Me), 3.85 (3H, singlet, O-Me), 6.27 (1H, singlet, C_5-$\underline{H}$), 6.87 (1H, singlet, aromatic proton), 7.00 (1H, singlet, aromatic proton).

The above mother liquor in case of recrystallization was concentrated to afford 1.0 g of the second diphenolic isoquinoline (XII) as a pale yellow syrup, which could not be crystallized. IR cm^{-1} ($CHCl_3$): ν_{OH} 3450. NMR (ppm) ($CDCl_3$): 2.60 (3H, singlet, N-Me), 3.76 (3H, singlet, O-Me), 3,79 (3H, singlet, O-Me), 3.80 (3H, singlet, O-Me), 6.45 (1H, singlet, C_5-$\underline{H}$), 6.88 (1H, singlet, aromatic proton), 6.99 (1H, singlet, aromatic proton).

1,2,3,4-Tetrahydro-6-hydroxy-1-(4-hydroxy-3-methoxybenzyl)-7,8-dimethoxy-2-methylisoquinoline (XIII)——To a solution of 800 mg of the above isoquinoline (XII) in 20 ml of 98% AcOH was added 2 g of Zn and the mixture was refluxed for 3 hr. After removal of insoluble material by filtration, the filtrate was basified with 10% NH_4OH aq. solution and extracted with ether. The extract was washed with water, dried over K_2CO_3, and evaporated to give 500 mg of (XIII) as a pale yellow syrup, whose hydrochloride was purified by recrystallization from MeOH to give colorless needles, mp 198—200° (decomp.). The melting point of this hydrochloride and IR spectrum of free base were identical perfectly with those of the authentic sample.[4]

9-Hydroxy-5,6,10-trimethoxy-1-methyl-1,2,3,12,12a-pentahydrobenzoxepino[2,3,4-*i,j*]isoquinoline (III)—a) Dienone–Phenol Rearrangement: A mixture of 20 mg of dienone (II) and 20 ml of conc. H_2SO_4 was stirred for 15 hr at room temperature in a current of N_2. After addition of 20 ml of water, the reaction mixture was basified with conc. NH_4OH aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried over K_2CO_3, and evaporated to leave 10 mg of a brown viscous syrup, which was chromatographed on silica gel (5 g) and eluted with $CHCl_3$ to give 8 mg of monophenolic isoquinoline (III). Recrystallization from ether gave colorless needles, mp 145—147°. *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.82; H, 6.40; N, 3.71. IR cm^{-1} ($CHCl_3$): ν_{OH} 3400. NMR (ppm) ($CDCl_3$): 2.58 (3H, singlet, N-Me), 3.76 (3H, singlet, O-Me), 3.80 (3H, singlet, O-Me), 3.87 (3H, singlet, O-Me), 4.35 (1H, quartet, $J=4$ and 12 cps, C_{12a}-$\underline{H}$), 6.49 (2H, singlet, aromatic protons), 6.87 (1H, singlet, aromatic proton).

b) Ullmann Reaction: A mixture of 600 mg of diphenolic isoquinoline (XI), 20 ml of dry pyridine and 1 g of anhydrous K_2CO_3 was heated at 130° and then 300 mg of CuO was added to the reaction mixture. The resulting mixture was heated at 160° for 3 hr in a current of N_2 and filtered. The filtrate was concentrated to dryness and the residue was subjected to silicagel (20 g) chromatography. Elution with chloroform gave 400 mg of monophenolic isoquinoline, after recrystallization from ether, as colorless needles, mp 145—147°, whose IR spectrum was superimposable on that of the sample prepared by the method (a). Furthermore, there appeared no depression on admixed melting point test with the sample prepared by method (a).

5,6,9,10-Tetramethoxy-1-methyl-1,2,3,12,12a-pentahydrobenzoxepino[2,3,4-*i,j*]isoquinoline (XIV)—— Diazomethane (prepared from 10 g of nitrosomethylurea) in 100 ml of ether was added to a solution of 100 mg of monophenolic isoquinoline (III) in 50 ml of ether. After the mixture had been allowed to stand for 3 days at room temperature, the solvent was removed by distillation and the residue was subjected to alumina (5 g) chromatography. Elution with benzene gave 80 mg of a pale yellow viscous syrup, which was recrystallized from ether to give 5,6,9,10-tetramethoxy-compound (XIV) as colorless needles, mp 113—115°, whose IR and NMR spectra were identical with those of the authentic sample.[9]