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Reactions of Lactonic Compounds with Nitrogen-containing Reagents. I. Reaction of Byakangelicol with Dimethylamine and Piperidine[1]

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Byakangelicol (I) was treated with dimethylamine or piperidine in benzene below 60° (condition A), in methanol near room temperature (condition B), and in benzene in a sealed tube at 125° (condition C). Amine amides (VIII and IX), neutral amides (X and XII), and neutral amides (XI and XIII) were obtained under conditions A, B, and C, respectively. Results of ultraviolet and nuclear magnetic resonance measurements and chemical treatment showed that X—XI and XII—XIII were in geometrical relationship, X and XII being *cis* isomers and XI and XIII *trans* isomers. An equilibrium between XII and XIII in a 87:13 ratio was established within 25 hr when either XII or XIII in 0.1N NaOH–EtOH was exposed to diffused light.

In 1938, Noguchi, *et al.*[3] isolated two new substances from the ether extract of *Angelica dahurica* var. *dahurica* roots (byakushi) collected at Nara Prefecture and named them byakangelicol and byakangelicin, to which chemical structures (I and II) were assigned, respectively. Noguchi, *et al.*[4] also reported that heating I with alkali gave rise to the formation of iso-byakangelicolic acid (III) in which fission of the lactonic ring took place with simultaneous formation of a fused dioxene ring. It was also reported that heating I with 1% aqueous oxalic acid[4] or treating I by silicic acid column chromatography[5] resulted in conversion of I into II (Chart 1).

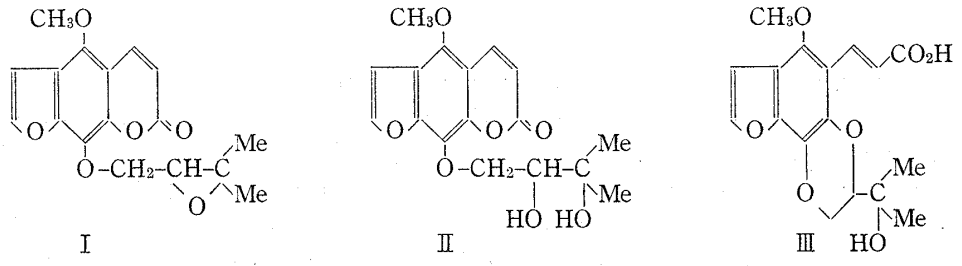


Chart 1

In 1939, Böhme, *et al.*[6] reported that they obtained *cis*- (V) and *trans*-meranzinic acids[7] (VI) by alkaline hydrolysis of meranzin[7] (IV). They also described that reaction of IV with dimethylamine in benzene at 150° led to opening of the epoxy ring and yielded an amino alcohol (VII) which still had the intact lactonic ring (Chart 2).

Though the existence of a furan ring and of an additional oxygen atom in the side chain of I makes the structural difference between I and IV, it was a matter of interest to be informed of those conflicting results given by the above two groups of workers when we looked upon

1) Presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.
2) Location: *Nishioji-hachijo, Minami-ku, Kyoto.*
3) T. Noguchi and M. Kawanami, *Yakugaku Zasshi*, **58**, 370 (1938).
4) T. Noguchi and M. Kawanami, *Yakugaku Zasshi*, **58**, 1052 (1938).
5) K. Hata, M. Kozawa and K. Yen, *Yakagaku Zasshi*, **83**, 606 (1963).
6) H. Böhme and G. Pietsch, *Ber.*, **72**, 773 (1939).
7) The previous names for IV and VI were auraptenic acid and aurapten, respectively.

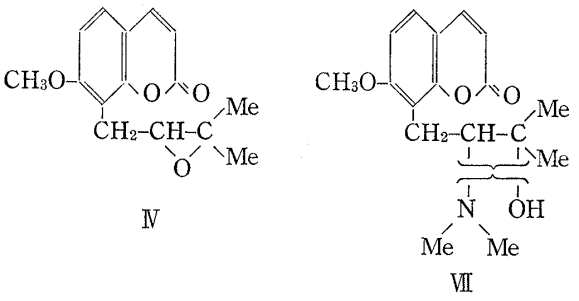


Chart 2

reactivities of the lactonic and the epoxy rings. This, together with the limited number of studies on reactions of coumarins and furocoumarions with nitrogen-containing reagents, stimulated us to carry out an investigation on preparation of nitrogen-containing furocoumarin or benzofuran derivatives which were to be prepared by treating I with secondary amines, dimethylamine and piperidine.

For the reactions, we adopted the following three conditions, (A) standing in benzene below 60°, (B) standing in methanol near room temperature, and (C) heating in benzene in a sealed tube at 125°. As the results, the products obtained were different from condition to condition.

Reactions under condition A, in which I was let stand with dimethylamine (at 2°) and piperidine (at 60°) for 1 to 3 days, afforded amine amides (VIII and IX), respectively, both soluble in 5% HCl, insoluble in 5% aqueous NaOH, and negative in $FeCl_3$ test (Chart 3).

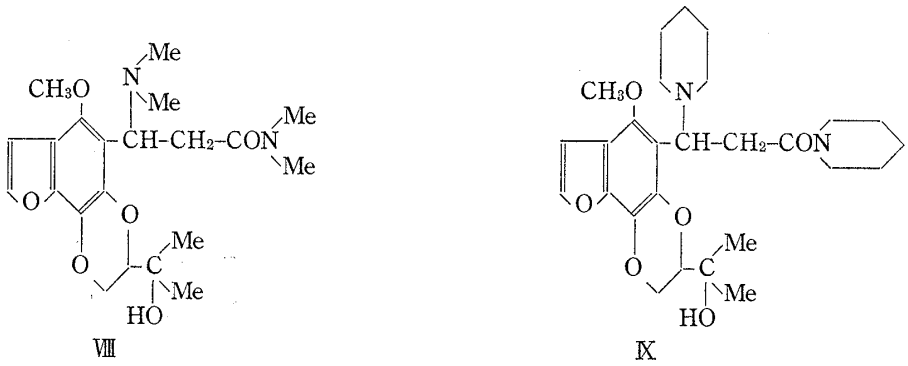


Chart 3

VIII, however, in its oily state or in solvents at 2° to 60° was labile enough to give forth gradually dimethylamine and to be converted into XI, so that it was impossible to obtain VIII in a purified crystalline state. On the other hand, IX was comparatively stable and was able to be isolated as crystals from the reaction mixture by means of silica gel column chromatography and recrystallization. It was also found that IX remained almost unchanged when heated in benzene in a sealed tube at 125° for 7 hr and that the amount of conversion into XIII was unexpectedly small.

Treatment of I under condition B resulted in formation of neutral products. Condition C by use of the same starting materials also gave neutral products, which, however, showed evidently different behaviors on thin-layer chromatography (TLC) plates from those obtained under condition B. These two pairs of products had the same elemental analysis data, $C_{19}H_{23}O_6N$ (in case of dimethylamine) and $C_{22}H_{27}O_6N$ (in piperidine) and showed rather similar infrared (IR) spectra. The ultraviolet (UV) spectral curves, however, were quite different and the compounds produced under condition B did not possess absorption maxima in the vicinity of 300 mμ while those produced under condition C showed marked absorption maxima at 304 mμ.

Böhme, *et al.*[8] studied the equilibrium by light between *cis*- and *trans*-isomers using several *o*-hydroxycinnamic acid derivatives and demonstrated that all the *trans*-isomers had absorption maxima in the vicinity of 300 mμ. Generally, a reaction by which both *cis*-

8) H. Böhme and T. Severin, *Arch. Pharm.*, **290**, 448 (1957).

and *trans*-isomers are possible to form would be favorable to formation of *trans*-isomers if the reaction is exercised at elevated temperatures. In consideration of these factors, we assigned structural formulas (X, XI, XII, and XIII) to the products prepared from I by use of dimethylamine and piperidine. This assignement was confirmed by the results of nuclear magnetic resonance (NMR) measurement in which the vinyl protons of X and XII gave coupling constants of 12.7—12.8 cps while those of XI and XIII showed greater values of 16.1—16.8 cps. The geometrically isomeric relationship between X—XI and XII—XIII was finally established by converging them into XIV and XV by hydrogenation on Pd-black. The

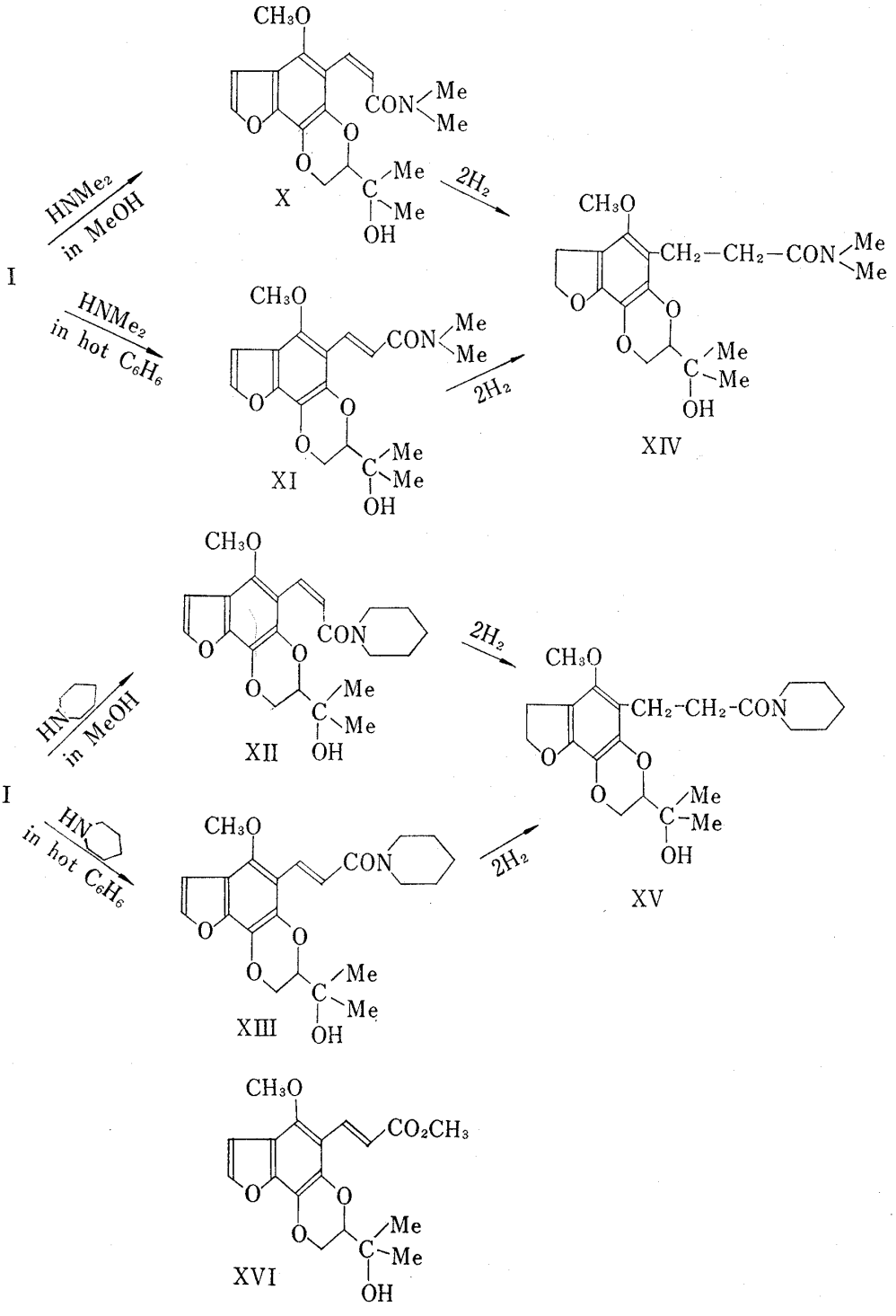


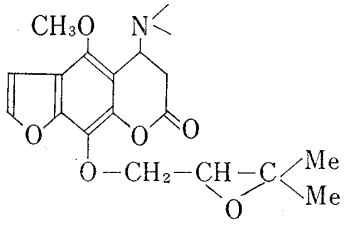
Chart 4

structure of XIII was also supported by converting III to structurally known ester (XVI)[4] using MeOH–H_2SO_4, heating XVI with piperidine in benzene at 180° for a prolonged period of time, and identifying the properties of the product with those of XIII by means of TLC, IR measurement, and admixture test (Chart 4).

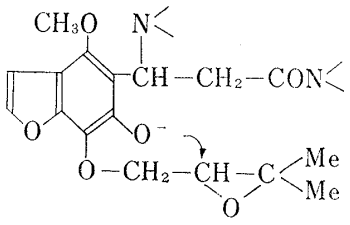
As mentioned above, the conversion rate of IX to XIII in heated benzene was unexpectedly small in consideration of the labile property of VIII, but it was noted by TLC that addition of a few drops of piperidine to the reaction system accelerated the conversion rate. Conversely, the formation of traces of IX was detected on TLC plate after XIII and piperidine had been let stand in benzene at 42° for 9 days.[9]

On applying the conditions of *cis-trans* equilibrium study described by Böhme, *et al.*[8] to XII and XII, *i.e.*, exposure of 0.1 N NaOH/EtOH solutions to diffused light, it was recognized by absorption coefficient calculation at 304 mμ that a rapid equilibrium was achieved with a ratio of 87:13 (XII to XIII).

The results thus far obtained on the reactions of I with dimethylamine and piperidine suggest that, in a non–polar solvent like benzene, the secondary amines initially added to the C-4 of I to give XVII and that a second molecule attacked the carbonyl group, thus giving rise to formation of the phenolate ion (XVIII) which in turn attacked the epoxy ring with a typical intramolecular S_N2 mechanism to give VIII and IX. It followed that the secondary amine on the newly prepared side chain was *trans*–eliminated to afford *trans*–amines XI or XIII. These considerations were supported by the above–mentioned result that the traces of IX were formed on standing XIII with piperidine. The manner in which the *trans*–elimination occured during the formation of XI and XIII was reasonably explained by examining the more preferred conformations of XVIII by use of Newman's projection formulation (Chart 5).



XVII



XVIII

Chart 5

On the other hand, the attack of the secondary amines on I in polar solvents like methanol was assumed to be directed straight to the carbonyl carbon due to the polar effect of the solvent on the carbonyl group. The subsequent mechanism of forming the dioxene ring was probably the same as that in the non–polar solvents. In this case, however, it was noted that the double bond in the side chain was retained in its *cis*–form (X or XII).

Nonexistence of absorption maximum in the vicinity of 300 mμ in X and XII was probably due to the distortion of the carbamoylvinyl chain form the plane of the benzofuran ring. This distortion would be brought about by the oxygen atom at position 4 in the furobenzodioxin ring.

Experimental[10]

2,3-Dihydro-3-(α-hydroxy-α-methyl)ethyl-5-(α-dimethylamino-β-dimethylcarbamoyl)ethyl-6-methoxy-furo[2,3-*f*]-1,4-benzodioxin (VIII)——A 40% C_6H_6 solution (16 ml) of $HNMe_2$ was added to I (1 g) in C_6H_6

9) V.A. Zagorevskii, N.V. Dudykina and V.L. Savel'ev, *Zh. Obshch. Khim.*, 33, 1695 (1963) [*C.A.*, **59**, 11416 (1963)].

10) All the mps were uncorrected. Column chromatography was done by use of Merck's silica gel (the grain size 0.2—0.5 mm). Thin–layer chromatography was done on silica gel GF_{254} using AcOEt–$CHCl_3$ (1:1) and MeOH for neutral and basic compounds, respectively. The spots were detected under ultraviolet rays of 2537 Å and 3650 Å and in iodine vapor. IR and UV measurements were carried out on Hitachi EPI-S_2 and EPS-3 spectrophotometers. NMR spectra were taken in $CDCl_3$ on Varian A-60 spectrometer with Me_4Si as internal standard.

(20 ml) and the mixture let stand at 2° for 3 days. After removal of the solvent below 14°, the residue was dried over silica gel in a desiccator. An oil so obtained was soluble in 5% HCl and insoluble in 5% aq. NaOH. Negative in $FeCl_3$ test. The oil was unstable enough to give forth a smell of $HNMe_2$ in ether, EtOH, or C_6H_6 or as it was. IR cm^{-1} (KBr): $\nu_{C=O}$ 1635. *Anal.* Calcd. for $C_{21}H_{34}O_5N_2$: N, 6.92. Found: N, 6.93.

2,3-Dihydro-3-(α-hydroxy-α-methyl)ethyl-5-(α-piperidino-β-piperidinocarbonyl)ethyl-6-methoxy-furo[2,3-*f*]-1,4-benzodioxin (IX)——Piperidine (25 ml) was added to I (4 g) in C_6H_6 (150 ml) and the mixture let stand at 60° for 24 hr. After removal of C_6H_6 and excess of piperidine below 60°, an oily residue (6.7 g) in C_6H_6 was subjected to silica gel chromatography (3.5×50 cm). After a fore run of C_6H_6 (2 liter), an oil was eluted with C_6H_6–MeOH (10:1) (1 liter). The oil was dissolved in (iso-Pr)$_2$O (50 ml), a precipitate (0.1 g) (XIII) filtered off, the filtrate concentrated, and a small amount of ether added to the residue to deposit, after cooling, crystals (1.5 g). Repeated recrystallization from ether–MeOH gave colorless prisms, mp 147—149°. Soluble in 5% HCl, insoluble in 5% aq. NaOH, and negative in $FeCl_3$ test. IR cm^{-1} (KBr): $\nu_{C=O}$ 1623. NMR τ: 2.52, 3.22 (2H, AB q, J=2.3 cps, furan), 6.07 (3H, s, OCH_3), 8.60, 8.67 (6H, s, C–CH_3). *Anal.* Calcd. for $C_{27}H_{38}O_6N_2$: C, 66.64; H, 7.87; N, 5.75. Found: C, 66.62; H, 7.95; N, 5.80.

***dl*-2,3-Dihydro-3-(α-hydroxy-α-methyl)ethyl-5-(*cis*-β-dimethylcarbamoyl)vinyl-6-methoxy-furo[2,3-*f*]-1,4-benzodioxin (X)**——A 40% aq. solution (3.5 g) of $HNMe_2$ was added to I (500 mg) in MeOH (10 ml) and the mixture let stand at 30° for 2 days. After removal of the solvent below 30°, the residue was recrystallized from MeOH to give colorless pillars, mp 169—171°. Yield 450 mg. IR cm^{-1} (KBr): $\nu_{C=O}$1639. UV λ_{max}^{EtOH} mμ (log ε): 252 (4.52). NMR τ: 2.49, 3.15 (2H, AB q, J=2.3 cps, furan), 3.23, 3.88 (2H, AB q, J=12.8 cps, *cis*–vinyl), 5.99 (3H, s, OCH_3), 7.16, 7.40 (6H, s, N–CH_3), 8.56, 8.75 (6H, s, C–CH_3). *Anal.* Calcd. for $C_{19}H_{23}O_6N$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.12; H, 6.52; N, 3.98.

***dl*-2,3-Dihydro-3-(α-hydroxy-α-methyl)ethyl-5-(*trans*-β-dimethylcarbamoyl)vinyl-6-methoxy-furo[2,3-*f*]-1,4-benzodioxin (XI)**——A 40% C_6H_6 solution (3 g) of $HNMe_2$ was added to I (500 mg) in C_6H_6 (10 ml) and the mixture heated in a sealed tube at 125° for 10 hr. Romoval of the solvent and recrystallization from AcOEt gave colorless prisms, mp 181—183°. Yield 400 mg. IR cm^{-1} (KBr): $\nu_{C=O}$1629. UV λ_{max}^{EtOH} mμ (log ε): 253 (4.40), 304 (4.17). NMR τ: 2.55, 3.22 (2H, AB q, J=2.3 cps, furan), 2.00, 2.67 (2H, AB q, J=16.1 cps, *trans*–vinyl), 6.06 (3H, s, OCH_3), 6.89, 6.97 (6H, s, N–CH_3), 8.58 (6H, s, C–CH_3). *Anal.* Calcd. for $C_{19}H_{23}O_6N$: C, 63.13; H, 6.41; N, 3.88. Found: C, 62.85; H, 6.40; N, 3.79.

The Acetate of (XI)——A mixture of XI (250 mg), Ac_2O (3 ml), and AcONa (250 mg) was refluxed, worked up in a usual manner, and recrystallized from EtOH to give colorless needles, mp 158—161°, yield 230 mg. *Anal.* Calcd. for $C_{21}H_{25}O_7N$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.54; H, 6.25; N, 3.39.

***dl*-2,3-Dihydro-3-(α-hydroxy-α-methyl)ethyl-5-(*cis*-β-piperidinocarbonyl)vinyl-6-methoxy-furo[2,3-*f*]-1,4-benzodioxin (XII)**——Piperidine (4 g) was added to I (0.7 g) in MeOH (30 ml) and the mixture let stand at 42° for 45 hr. After removal of MeOH and excess of piperidine below 45°, the residue in C_6H_6 was subjected to silica gel column chromatography (2×16 cm). After a fore run of C_6H_6 (50 ml), fractions (total 300 ml) of C_6H_6 and C_6H_6–ether (7:3) yield a yellow oil (0.66 g). Recrystallization from (iso-Pr)$_2$O gave colorless prisms, mp 126—127°. IR cm^{-1} (KBr): $\nu_{C=O}$1642. UV λ_{max}^{EtOH} mμ (log ε): 252 (4.24). NMR τ: 2.49, 3. 15 (2H, AB q, J=2. 3 cps, furan), 3.27, 3.92 (2H, AB q, J=12.7 cps, *cis*–vinyl): 5.99 (3H, s, OCH_3), 8.54, 8.75 (6H, s, C–CH_3). *Anal.* Calcd. for $C_{22}H_{27}O_6N$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.88; H, 6.78; N, 3.46.

***dl*-2,3-Dihydro-3-(α-hydroxy-α-methyl)ethyl-5-(*trans*-β-piperidinocarbonyl)vinyl-6-methoxy-furo[2,3-*f*]-1,4-benzodioxin (XIII)**——Piperidine (1 g) was added to I (0.2 g) in C_6H_6 (10 ml) and the mixture heated in a sealed tube at 115° for 7 hr. After removal of C_6H_6 and excess of piperidine, the residue was recrystallized from iso-PrOH to give colorless needles, mp 221—223°, yield 160 mg. IR cm^{-1} (KBr): $\nu_{C=O}$1631. UV λ_{max}^{EtOH} mμ (log ε): 254 (4.52), 304 (4.31). NMR τ: 2.51, 3.18 (2H, AB q, J=2.3 cps, furan), 2.01, 2.62 (2H, AB q, J=16.8 cps, *trans*–vinyl), 6.05 (3H, s, OCH_3), 8.56, 8.60 (6H, s, C–CH_3). *Anal.* Calcd. for $C_{22}H_{27}O_6N$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.88; H, 6.78; N, 3.46.

2,3,7,8-Tetrahydro-3-(α-hydroxy-α-methyl)ethyl-5-(β-dimethylcarbamoyl)ethyl-6-methoxy-furo[2,3-*f*]-1,4-benzodioxin (XIV)——Pd-black (0.5 g) was added to X (0.35 g) in 80% aq. MeOH (80 ml) and the mixture vigorously stirred under H_2 current at room temperature to absorb 2 molar equivalents of H_2 in 2 hr. After filtration and removal of MeOH, the residue was recrystallized from iso-PrOH to give colorless small needles, mp 93—94°. Yield 0.35 g. IR cm^{-1} (KBr): $\nu_{C=O}$1622. NMR τ: 6.22 (3H, s, OCH_3), 7.11, 7.20 (6H, s, N–CH_3), 8.59, 8.73 (6H, s, C–CH_3). *Anal.* Calcd. for $C_{19}H_{27}O_6N$: C, 62.44; H, 7.44; N, 3.83. Found: C, 62.34; H, 7.37; N, 4.06. The same treatment of XI gave a product identical with XIV in admixture test, IR measurement, and thin-layer chromatography.

2,3,7,8-Tetrahydro-3-(α-hydroxy-α-methyl)ethyl-5-(β-piperidinocarbonyl)ethyl-6-methoxy-furo[2,3-*f*]-1,4-benzodioxin (XV)——The same hydrogenation treatment as with XIV was applied to XII to obtain a colorless crystalline powder. Recrystallization from AcOEt gave small needles, mp 119—121°, yield being almost quantitatively. IR cm^{-1} (KBr): $\nu_{C=O}$1610. *Anal.* Calcd. for $C_{22}H_{31}O_6N$: C, 65.16; H, 7.71; N, 3.45. Found: C, 64.93; H, 7.81; N, 3.76. The same treatment of XIII gave a product identical with XV in admixture test, IR measurement, and thin-layer chromatography.

The Methyl Ester of Isobyakangelicolic Acid (XVI)——Conc. H_2SO_4 (1.5 ml) was added to III (1.7 g) in MeOH (300 ml) and the mixture let stand at room temperature for 1 week. Concentration to three-fourths

of its volume and addition of H_2O deposited a white precipitate. The precipitate was extracted with ether, the ether layer washed with 1% aq. KOH and H_2O, dried over anhydrous Na_2SO_4, and the ether removed to leave yellow crystals (1.6 g). Recrystallization from MeOH gave slightly yellow needles, mp 122—124° (*lit.*[4] mp 125°).

Reaction of XVI with Piperidine——A mixture of XVI (250 mg), C_6H_6 (13 ml), and piperidine (1.2 g) was heated in a sealed tube at 125° for 17 hr and at 180° for 7 hr. After removal of C_6H_6 and excess of piperidine, the residue in $CHCl_3$ was chromatographed on silica gel (2 × 20 cm) to elute, after a fore run of $CHCl_3$ containing XVI (120 mg), needles (25 mg) with $CHCl_3$–AcOEt (1:1). Recrystallization from iso-PrOH yielded colorless needles, mp 222—223°. The product was identical with XIII in IR measurement, thin-layer chromatography, and admixture test.

Equilibrium between XII and XIII in 1/10N NaOH–EtOH by diffused Light——Each 40 μg of XII and XIII in 1/10N NaOH–EtOH was kept standing in the dark at 37° for 24 hr to show no changes in the UV absorption spectra. Next, the solutions were let stand in diffused light at room temperature for 25 hr to reach an equilibrium and the UV absorption was measured after 5-fold dilution. The ratio of XII to XIII was found to be 87:13 by the calculation of the absorption coefficients at 304 mμ.

Acknowledgement Thanks are due to the members of Analytical Section of this Laboratory who undertook the elemental analysis and NMR measurement.