

An Abnormal Formation of Indane from N-Phenethylphenylpropionamide under Bischler-Napieralski Reaction Conditions

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(Received August 9, 1976)

A treatment of N-(3-acetoxy-4-benzyloxyphenethyl)-4-benzyloxy-3-methoxyphenylpropionamide (17) with phosphoryl chloride gave 1-(3-acetoxy-4-benzyloxyphenethyl)-imino-6-benzyloxy-5-methoxyindane (21) instead of the normal product, 3,4-dihydroisoquinoline (20). The structure of 21 was determined by chemical method and by an alternative synthesis of the indane derivative (25) derived from 21.

Keywords—abnormal formation of indane; N-phenethylphenylpropionamide; Bischler-Napieralski reaction; 1-(3-acetoxy-4-benzyloxyphenethyl)imino-6-benzyloxy-5-methoxyindane; kesselringine

In a previous paper,²⁾ we have reported a synthesis of the homoproaporphine (5), which would be a key intermediate to an alkaloid kesselringine (9),³⁾ by a phenol oxidation of the triphenolic phenethylisoquinoline (1). However, this reaction proceeded in poor yield, the result of which would be ascribable to the fact that the starting isoquinoline (1) or the product (5) has an unstable catechol ring system in the air and a tendency to an undesirable coupling reaction. On the other hand, the kreysiginone (6), in which one hydroxyl group in 5 is replaced by methoxyl group, is obtained from the diphenolic isoquinoline (2) in good yield by the same reaction.⁴⁾ Therefore we planned a synthesis of the homoproaporphines (7 and 8) by a phenol oxidation of 6-acetoxy- or 6-meslyoxy-1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-2-methylisoquinolines (3 and 4) in which an unnecessary hydroxyl group to the oxidative coupling in catechol system is protected by acetyl or mesyl group.

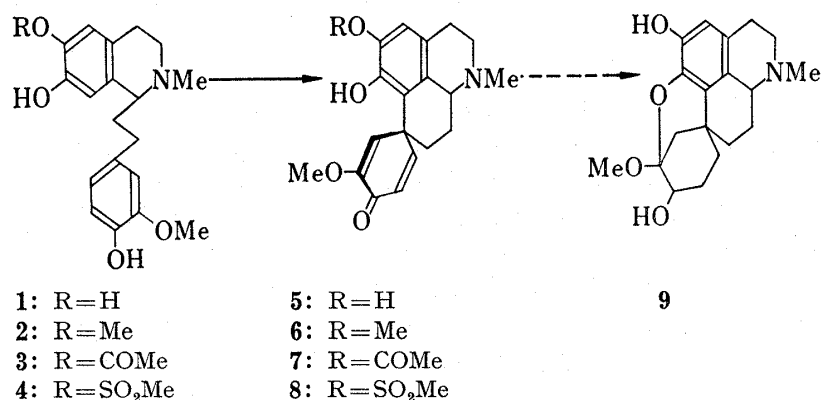


Chart 1

During a synthetic process of the starting isoquinolines (3 and 4), we have found an abnormal formation of the indane (21) in the Bischler-Napieralski reaction of the amide (17), and we here report on this interesting but abnormal result.

1) Location: Aobayama, Sendai 980, Japan.

2) T. Kametani, Y. Satoh, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 922 (1977).

3) M.K. Jusupov, *Chim. Rastitel, Vecčstv, Jaškent*, **1972**, 19; this literature was given by Professor Šantavý as a private communication.

4) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).

three typical indene resonances,⁸⁾ namely C₁-H at 3.31 as triplet having $J=2$ Hz, C₂-H at 6.28—6.47 as multiplet and C₃-H at 6.62—6.82 as multiplet. Moreover, the appearance of two singlets (6.94 and 7.06) assigned to aromatic protons indicated the indene derivative to have the substituents at C₅- and C₆-positions. Thus, the presence of an indane system in **23** is established and, in turn, the structure of the product formed by a reaction of the amide (**17**) with phosphoryl chloride is now also known with certainty.

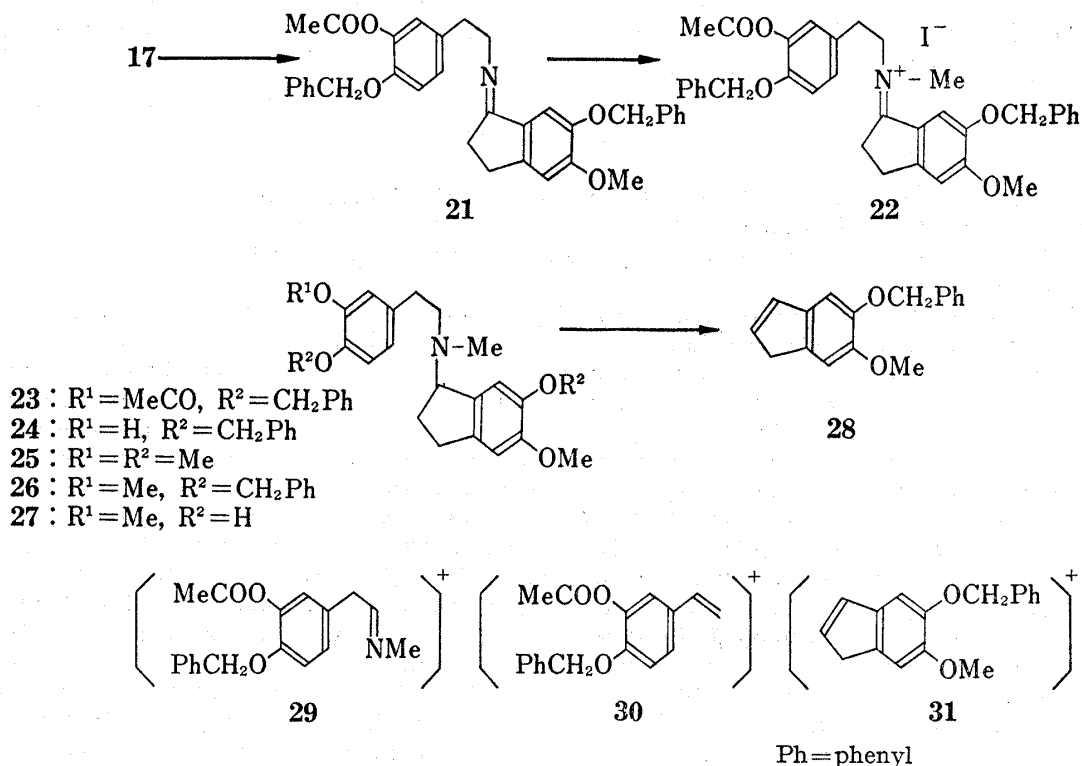


Chart 3

Furthermore, a confirmation of the structure having an indane ring was carried out by an alternative synthesis of **25**, which was prepared from **24** by methylation and then debenzoylation of the nonphenolic base (**26**), followed by methylation of **27** with diazomethane. The Schiff base (**34**), which was obtained by a condensation of the phenethylamine (**32**) with the indanone (**33**), was reduced with sodium borohydride to the secondary amine (**35**).

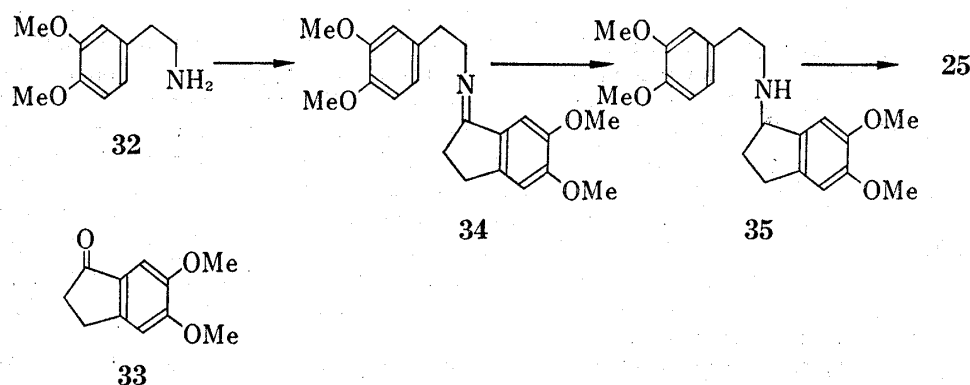


Chart 4

8) N.S. Bhacca, L.F. Johnson, and J.N. Schoolery, "NMR Spectra Catalog," No. 227, Varian Associates, Palo Alto, California, 1962.

Eschweiler-Clarke reaction of **35** with formalin and sodium borohydride gave the 1-aminoindane, which was identical with our product (**25**) in all respects in melting point and spectral comparisons. Thus, we confirmed the structure of the abnormal reaction product from the amide (**17**).

The abnormal formation of the indane derivative (**21**) from the amide (**17**) under Bischler-Napieralski reaction conditions would be due to the fact that the methoxylated aromatic ring is more reactive than the acetoxylated one in a reaction with the carbonium cation derived from amide carbonyl function, because an electron-donating effect of methoxyl group is stronger than of acetoxyl group.

Experimental

All melting points are uncorrected and were measured with a Yanagimoto micro melting point apparatus (MP-22). Infrared (IR) spectra were measured with a Hitachi 215 grating spectrophotometer, NMR spectra with a JEOL PMX-60 spectrometer with Me₄Si as an internal standard, and mass spectra with a Hitachi RMU-7 spectrometer.

4-Benzoyloxy-3-methoxymethoxybenzaldehyde (11)—To a suspension of 4-benzoyloxy-3-hydroxybenzaldehyde (**10**)⁵ (53.0 g, 0.23 mole) in refluxing benzene (500 ml) was added 50% sodium hydride (13 g, 0.27 mole) with stirring in a current of nitrogen and the resulting mixture was stirred for 2 hr under reflux. After cooling, chloromethyl methyl ether (21.0 g, 0.26 mole) was added to the above reaction mixture with stirring at 0° in a current of nitrogen. The mixture was stirred at room temperature for 8 hr and then refluxed for 1 hr. After completion of the reaction, the mixture was poured into water and the organic layer was separated, washed with water and dried over Na₂SO₄. Evaporation of the solvent *in vacuo* gave a yellow oil which was distilled to give the aldehyde (**11**) (49.0 g, 78%), bp 181–182° (0.08 mmHg). After solidification on standing in the air, it showed mp 56–57°. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1680 (>CO), NMR (CDCl₃) ppm: 3.43 (3H, s, OMe), 5.09 (2H, s, OCH₂Ph), 5.14 (2H, s, OCH₂O), 6.91 (1H, d, *J*=8 Hz, C₅-H), 7.18–7.60 (2H, m, ArH) and 7.28 (5H, broad s, OCH₂C₆H₅). Anal. Calcd. for C₁₆H₁₆O₄: C, 70.58; H, 5.92. Found: C, 70.61; H, 6.11.

4-Benzoyloxy-3-methoxymethoxy-β-nitrostyrene (12)—To a mixture of the aldehyde (**11**) (49.0 g, 0.18 mole), ethanol (200 ml) and nitromethane (13.4 g, 0.22 mole) was added methylamine [prepared from methylamine hydrochloride (9.0 g)] at 10° and the mixture was allowed to stand at 0° for 2–4 days to give the nitrostyrene (**12**) (32.8 g, 58%) as pale yellow needles, mp 97.5–98°. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1630 (>C=C<), NMR (CDCl₃) ppm: 3.56 (3H, s, OMe), 5.23 (2H, s, OCH₂Ph), 5.28 (2H, s, OCH₂O), 7.13 (1H, d, *J*=16 Hz, -CH=CHNO₂), 7.68 (1H, d, *J*=16 Hz, -CH=CHNO₂) and 6.86–7.65 (8H, m, ArH). Anal. Calcd. for C₁₇H₁₇O₅N: C, 64.75; H, 5.43; N, 4.44. Found: C, 65.11; H, 5.39; N, 4.38.

4-Benzoyloxy-3-methoxyphenethylamine (13)—To a suspension of lithium aluminum hydride (17.0 g, 0.45 mole) in dry tetrahydrofuran (300 ml) was added a solution of the nitrostyrene (**12**) (47.0 g, 0.15 mole) in tetrahydrofuran (300 ml) during 1 hr with stirring in a current of nitrogen. After refluxing for 1 hr with stirring, the reaction mixture was decomposed with an excess of 30% sodium hydroxide. The organic layer was separated and concentrated to leave a residue which was extracted with benzene. The extract was washed with water, dried over Na₂SO₄, and distilled *in vacuo* to leave the amine (**13**) as a pale yellow syrup. NMR (CDCl₃) ppm: 1.80 (2H, broad, -NH₂), 2.48–3.13 (4H, m, 2×CH₂), 3.52 (3H, s, OMe), 5.11 (2H, s, OCH₂Ph), 5.20 (2H, s, OCH₂O), 6.61–7.09 (3H, m, ArH) and 7.21–7.60 (5H, m, OCH₂C₆H₅). This was characterized as oxalate (32.0 g, 57%), colorless needles, mp 151–152°, from methanol-ether. Anal. Calcd. for C₁₇H₂₁O₃N·C₂H₂O₄: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.18; H, 6.27; N, 3.57.

N-(4-Benzoyloxy-3-methoxymethoxyphenethyl)-4-benzoyloxy-3-methoxyphenylpropionamide (15)—A mixture of the amine (**13**) (14.8 g, 52 mmole) and 4-benzoyloxy-3-methoxyphenylpropionic acid (**14**)⁶ (14.3 g, 50 mmole) was heated at 170–180° for 2 hr in a current of nitrogen. After cooling, the reaction mixture was taken up in benzene and the extract was washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, and water, and dried over K₂CO₃. Evaporation of the solvent *in vacuo* gave the amide (**15**) (17.4 g, 63%) as colorless needles, mp 89–90°, from benzene-*n*-hexane. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3450 (>NH) and 1650 (>CO), NMR (CDCl₃) ppm: 2.18–3.10 (6H, m, 3×CH₂), 3.20–3.61 (2H, m, CH₂CH₂N), 3.47 (3H, s, OCH₂-OCH₃), 3.82 (3H, s, ArOMe), 5.06 (4H, s, 2×OCH₂Ph), 5.15 (2H, s, OCH₂O), 5.19–5.54 (1H, m, NH), 6.43–6.98 (6H, m, ArH) and 7.11–7.58 (10H, m, 2×OCH₂C₆H₅). Anal. Calcd. for C₃₄H₃₇O₆N: C, 73.49; H, 6.71; N, 2.52. Found: C, 73.83; H, 6.89; N, 2.61.

N-(4-Benzoyloxy-3-hydroxyphenethyl)-4-benzoyloxy-3-methoxyphenylpropionamide (16)—To a solution of the above amide (**15**) (16.6 g, 30 mmole) in methanol (30 ml) was added dropwise concentrated hydrochloric acid (10 ml) with stirring at 0°. After stirring for 2 hr at room temperature, the reaction mixture was basified with 10% ammonia and the separated oil was extracted with chloroform. The extract was washed with water, dried over Na₂SO₄ and evaporated *in vacuo* to give the phenolic amide (**16**) (12.5 g, 82%) as colorless needles, mp 132–133°, from benzene. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3540 (-OH), 3450 (>NH) and 1650 (>CO), NMR (CDCl₃) ppm: 2.12–3.07 (6H, m, 3×CH₂), 3.18–3.62 (2H, m, CH₂CH₂N), 3.84 (3H, s, OMe), 5.03

(2H, s, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 5.20—5.52 (1H, m, NH), 5.76 (1H, broad s, OH), 6.36—6.91 (6H, m, ArH) and 7.13—7.55 (10H, m, $2 \times \text{OCH}_2\text{C}_6\text{H}_5$). *Anal.* Calcd. for $\text{C}_{32}\text{H}_{33}\text{O}_5\text{N}$: C, 75.12; H, 6.50; N, 2.74. Found: C, 75.20; H, 6.82; N, 2.78.

N-(3-Acetoxy-4-benzyloxyphenethyl)-4-benzyloxy-3-methoxyphenylpropionamide (17)—Acetyl chloride (2.0 g, 25 mmole) was added dropwise to a mixture of the phenolic amide (16) (11.2 g, 22 mmole), triethylamine (3.0 g, 30 mmole) and chloroform (40 ml) with stirring at 0° . After stirring for 2 hr at room temperature, the reaction mixture was washed with 10% hydrochloric acid and water, and dried over Na_2SO_4 . Evaporation of the solvent *in vacuo* gave the nonphenolic amide (17) (11.0 g, 90%) as colorless needles, mp $137\text{--}138^\circ$, from ethanol. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3450 ($>\text{NH}$), 1750 ($-\text{OCOMe}$) and 1650 ($-\text{CO-N}<$), NMR (CDCl_3) ppm: 2.24 (3H, s, COMe), 2.15—3.08 (6H, m, $3 \times \text{CH}_2$), 3.21—3.62 (2H, m, $\text{CH}_2\text{CH}_2\text{N}$), 3.82 (3H, s, OMe), 5.02 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 5.28—5.63 (1H, m, NH), 6.41—6.95 (6H, m, ArH) and 7.07—7.56 (10H, m, $2 \times \text{OCH}_2\text{C}_6\text{H}_5$). *Anal.* Calcd. for $\text{C}_{34}\text{H}_{35}\text{O}_6\text{N}$: C, 73.76; H, 6.37; N, 2.53. Found: C, 73.62; H, 6.44; N, 2.42.

Reaction of the Amide (17) with Phosphoryl Chloride—To a solution of the above amide (17) (6.6 g, 12 mmole) in acetonitrile (50 ml) was added phosphoryl chloride (15 g) under reflux and the mixture was further refluxed for 8 hr. After evaporation of the solvent and reagent *in vacuo*, the residue was washed with ether, basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and distilled *in vacuo* to leave the indane (21) as a pale brown syrup, to which was added methyl iodide (20 ml). The mixture was allowed to stand overnight at room temperature and then an excess of methyl iodide was distilled off. The residue was washed with ether to give the methiodide (22) (3.8 g, 48%) as colorless needles, mp $116\text{--}118^\circ$, from acetone. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1760 ($>\text{CO}$) and 1630 ($>\text{C}=\text{N}^+\text{C}<$), Mass Spectrum m/e : 550 $\text{M}^+ - \text{I}^-$, 281, 268, 252 and 226. *Anal.* Calcd. for $\text{C}_{35}\text{H}_{36}\text{O}_5\text{NI}$: C, 62.04; H, 5.36; N, 2.06. Found: C, 62.37; H, 5.43; N, 1.99.

1-[N-(3-Acetoxy-4-benzyloxyphenethyl)-N-methyl]amino-6-benzyloxy-5-methoxyindane (23)—Sodium borohydride (1 g) was added in small portions to a suspension of the methiodide (22) (3.4 g, 5.0 mmole) in methanol (80 ml) with stirring at $0\text{--}5^\circ$ and then stirring was continued for 1 hr at $0\text{--}5^\circ$. After adjusting pH of the reaction mixture to 5—6 by addition of a few drops of concentrated hydrochloric acid, methanol was distilled off *in vacuo*. The residue was taken up in chloroform and the extract was washed with 10% ammonia and sodium chloride solution, and dried over Na_2SO_4 . The solvent was distilled *in vacuo* to leave a residue, which was chromatographed on silica gel (60 g) by elution with chloroform to give the indane (23) (2.0 g, 73%) as a pale yellow viscous syrup. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 2790 ($>\text{NMe}$) and 1755 ($>\text{CO}$), NMR (CDCl_3) ppm: 2.21 (3H, s, COMe), 2.23 (3H, s, NMe), 3.83 (3H, s, OMe), 4.39 (1H, m, $\text{C}_1\text{-H}$), 5.01 (2H, s, OCH_2Ph), 5.10 (2H, s, OCH_2Ph), 6.58—6.96 (5H, m, ArH) and 7.12—7.53 (10H, m, $2 \times \text{OCH}_2\text{C}_6\text{H}_5$), Mass Spectrum m/e : 551 (M^+), 297, 268 and 252 (base peak).

5-Benzyloxy-6-methoxyindene (28)—A mixture of the indane (23) (820 mg, 1.5 mmole), 2N potassium hydroxide (1 ml) and methanol (5 ml) was refluxed for 10 min, and then methanol was evaporated *in vacuo*. The residue was treated with saturated ammonium chloride solution and extracted with chloroform. The extract was washed with saturated ammonium chloride solution, dried over Na_2SO_4 and evaporated to give the phenolic indane (24) as a pale yellow syrup. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3550 ($-\text{OH}$) and 2800 ($>\text{NMe}$), NMR (CDCl_3) ppm: 2.25 (3H, s, NMe), 3.80 (3H, s, OMe), 4.45 (1H, m, $\text{C}_1\text{-H}$), 4.95 (2H, s, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 6.42—7.01 (5H, m, ArH) and 7.12—7.92 (10H, m, $2 \times \text{OCH}_2\text{C}_6\text{H}_5$).

To a solution of 24 and triethylamine (400 mg, 4 mmole) in chloroform (30 ml) was added slowly mesyl chloride (400 mg, 3.5 mmole) with stirring at 0° and the stirring was continued for 5 hr at room temperature. The reaction mixture was washed with saturated sodium bicarbonate solution and water, dried over Na_2SO_4 and distilled off *in vacuo* to leave a syrup, which was subjected to silica gel (15 g) chromatography. The chloroform eluate gave 5-benzyloxy-6-methoxyindene (28) (150 mg) as colorless prisms, mp $83\text{--}85^\circ$ (lit.⁹⁾ mp $81\text{--}82^\circ$, from ethanol. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1610 ($>\text{C}=\text{C}<$), NMR (CDCl_3) ppm: 3.31 (2H, t, $J=2$ Hz, $\text{C}_1\text{-H}$), 3.88 (3H, s, OMe), 5.16 (2H, s, OCH_2Ph), 6.28—6.47 (1H, m, $\text{C}_2\text{-H}$), 6.62—6.82 (1H, m, $\text{C}_3\text{-H}$), 6.94 (1H, s, ArH), 7.06 (1H, s, ArH) and 7.18—7.56 (5H, m, $\text{OCH}_2\text{C}_6\text{H}_5$).

1-[N-3,4-(Dimethoxyphenethyl)imino]-5,6-dimethoxyindane (34)—A solution of 3,4-dimethoxyphenethylamine (32) (1.9 g, 11 mmole) and 5,6-dimethoxyindanone (33)⁹⁾ (1.9 g, 11 mmole) in dry toluene (30 ml) was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid for 5 hr. After cooling, the separated solid was collected by filtration and recrystallized from ether to give the Schiff base (34) (2.2 g, 79%) as colorless prisms, mp $121\text{--}122^\circ$, IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1640 ($>\text{C}=\text{N}-$), NMR (CDCl_3) ppm: 2.31—2.69 (2H, m, $\text{C}_2\text{-H}$), 2.72—3.22 (4H, m, $2 \times \text{CH}_2$), 3.34—3.95 (2H, m, $\text{CH}_2\text{CH}_2\text{N}$), 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 3.86 (3H, s, OMe), 3.89 (3H, s, OMe), 6.74 (4H, m, ArH) and 7.31 (1H, s, $\text{C}_7\text{-H}$). *Anal.* Calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.93; H, 6.98; N, 3.81.

1-[N-(3,4-Dimethoxyphenethyl)amino]-5,6-dimethoxyindane (35)—To a solution of the above Schiff base (34) (2.0 g, 5.6 mmole) in methanol (30 ml) was added in small portions sodium borohydride (500 mg) with stirring at 0° and the resulting mixture was stirred for 1 hr at room temperature. After evaporation

9) J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953).

of the solvent *in vacuo*, the residue was extracted with chloroform, and the extract was washed with water and dried over K_2CO_3 . Removal of the solvent by distillation *in vacuo* gave the amine (35) (1.9 g, 94%) as colorless prisms, mp 87–88°, from ether. NMR ($CDCl_3$) ppm: 2.14–3.08 (8H, m, $4 \times CH_2$), 3.82 (12H, s, $4 \times OMe$), 4.21 (1H, m, C_1-H), and 6.64–6.86 (5H, m, ArH). Anal. Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.31; H, 7.72; N, 3.88.

1-[N-(3,4-Dimethoxyphenethyl)-N-methylamino]-5,6-dimethoxyindane (25)—a) N-Methylation of 35: A mixture of the above amine (35) (1.5 g, 4.2 mmole), 37% formalin (1 ml) and methanol (20 ml) was stirred for 1 hr at room temperature and to this solution was added sodium borohydride (500 mg) with stirring at 0°. Stirring was continued for further 1 hr at room temperature and then the solvent was distilled off *in vacuo*. The residue was extracted with chloroform and the extract was washed with water, dried over K_2CO_3 and evaporated *in vacuo* to give the 1-(N-methylamino)indane (25) as colorless needles, mp 91–92°, from methanol. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2795 (NMe), NMR ($CDCl_3$) ppm: 1.81–2.28 (2H, m, C_2-H), 2.26 (3H, s, NMe), 2.41–3.06 (6H, m, $3 \times CH_2$), 3.78 (12H, s, $4 \times OMe$), 4.39 (1H, m, C_1-H) and 6.58–6.85 (5H, m, ArH). Anal. Calcd. for $C_{22}H_{29}O_4N$: C, 71.13; H, 7.89; N, 3.77. Found: C, 70.94; H, 7.91; N, 3.75.

b) A Conversion from the Abnormal Reaction Product: An excess of diazomethane in ether was added to the monophenolic indane (24) (700 mg, 1.4 mmole) in methanol (5 ml) and the mixture was allowed to stand for 3 hr at room temperature. Evaporation of the solvent *in vacuo* afforded the nonphenolic indane (26) as a pale yellow syrup. NMR ($CDCl_3$) ppm: 1.88–2.34 (2H, m, C_2-H), 2.24 (3H, s, NMe), 2.42–3.07 (6H, m, $3 \times CH_2$), 3.80 (6H, s, $2 \times OMe$), 4.35 (1H, m, C_1-H), 5.03 (4H, s, $2 \times OCH_2Ph$), 6.48–6.91 (5H, m, ArH) and 7.18–7.54 (10H, m, $2 \times OCH_2C_6H_5$).

A mixture of this nonphenolic indane (26) (600 mg, 1.1 mmole) and 10% palladium on charcoal (200 mg) in methanol (30 ml) was shaken under a current of hydrogen at room temperature and at atmospheric pressure. After filtration of catalyst, the filtrate was concentrated to leave a residue, which was extracted with chloroform. The extract was washed with 10% ammonia and saturated ammonium chloride solution, dried over Na_2SO_4 and evaporated *in vacuo* to give the diphenolic indane (27) (250 mg) as a yellow syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3550 ($-OH$), NMR ($CDCl_3$) ppm: 1.85–2.42 (2H, m, C_2-H), 2.29 (3H, s, NMe), 2.52–3.12 (6H, m, $3 \times CH_2$), 3.81 (6H, s, $2 \times OMe$), 4.46 (1H, m, C_1-H) and 6.48–6.92 (5H, m, ArH).

To a solution of the diphenolic indane (27) (250 mg, 0.7 mmole) in methanol (3 ml) was added an excess of diazomethane in ether and the mixture was allowed to stand at room temperature overnight. Evaporation of the solvent gave the tetramethoxylated indane (25) (190 mg), colorless needles, mp 91–92° (from methanol), which was identical with the above sample in mixed melting point test and IR and NMR spectral comparisons.

Acknowledgement We thank Mrs. C. Koyanagi, Mrs. R. Kobayashi, Miss R. Suenaga, Miss E. Nagaoka, Miss M. Tanno, and Mr. K. Kawamura, Pharmaceutical Institute, Tohoku University, for microanalyses and spectral measurements.