Chem. Pharm. Bull. 19(7)1374—1380(1971)

UDC 547.04 : 547.491.04

[4,5-Dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]acetonitrile: A By-Product from the Reaction of 3,4-Dimethoxybenzyl Chloride with Sodium Cyanide[1]

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(Received November 27, 1970)

The formation of [4,5-dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]acetonitrile (IV) as a by-product in the metathesis of 3,4-dimethoxybenzyl chloride (II) with sodium cyanide in dimethyl sulfoxide or N,N-dimethylformamide is reported. The structure of IV has been established by analysis, ultraviolet spectrum, infrared spectrum, nuclear magnetic resonance spectrum, and conversion into 4,5-dimethoxy-2-(3,4-dimethoxybenzyl)-N,N-dimethylphenethylamine (XI) through [4,5-dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]acetic acid (VII) and 2-[4,5-dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]-N,N-dimethylacetamide (VIII). The sample of XI thus obtained was identical with the one produced by catalytic hydrogenolysis of 1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2,2-dimethylisoquinolinium chloride, which was synthesized from 1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (IX) by quaternization with methyl iodide and treatment of the resulting methiodide (X) with silver chloride. The reaction of benzyl chloride with sodium cyanide in dipolar aprotic solvents was found to give a small amount of 2,3-diphenylpropionitrile (XIV) besides benzyl cyanide.

Since 3,4-dimethoxyphenylacetonitrile (III) has served as one of the most important intermediates in the synthesis of a number of pharmacologically active compounds such as benzoquinolizines, isoquinolines,[3] and α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa),[4] considerable effort has been expended in seeking efficient methods for the preparation of III. Among the procedures reported in the literature,[5-7] the metathesis[5,7] of 3,4-dimethoxybenzyl chloride (II) with alkali cyanide seems immensely popular. The chloride (II) is usually prepared from veratrole by chloromethylation,[8] or from 3,4-dimethoxybenzyl alcohol (I) by chlorination with thionyl chloride,[7a,c,9] hydrogen chloride,[10] or concentrated hydrochloric acid.[11] Since its methoxyl groups at the 3- and 4-positions render II very

1) Presented in part at the 31th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, October 17, 1970.
2) Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
3) W.M. Whaley and T.R. Govindachari in R. Adams (Ed. -in- Chief), "Organic Reactions," Vol. VI, John Wiley & Sons, Inc., New York, 1951, p. 74, p. 151.
4) *a*) G.A. Stein, H.A. Bronner, and K. Pfister, III, *J. Am. Chem. Soc.*, **77**, 700 (1955); *b*) H.L. Slates, D. Taub, C.H. Kuo, and N.L. Wendler, *J. Org. Chem.*, **29**, 1424 (1964).
5) Beilstein's, "Handbuch der Organischen Chemie," 10, E I 198, E II 269.
6) *a*) K. Kindler and K. Schrader, *Arch. Pharm.*, **283**, 190 (1950); *b*) R. Trave, *Gazz. Chim. Ital.*, **80**, 502 (1950)[*Chem. Abstr.*, **45**, 7048*c* (1951)].
7) See, for example, *a*) K. Kindler and E. Gehlhaar, *Arch. Pharm.*, **274**, 377 (1936); *b*) F. Dengel, U.S. Patent 2734908 (1956) [*Chem. Abstr.*, **50**, 15587*b* (1956)]; *c*) J. Knabe and J. Kubitz, *Arch. Pharm.*, **296**, 591 (1963).
8) See, for example, *a*) A.E. Bide and P.A. Wilkinson, *J. Soc. Chem. Ind.*, **64**, 84 (1945); *b*) O. Gawron, *J. Am. Chem. Soc.*, **71**, 744 (1949); *c*) F. Dengel, U.S. Patent 2695319 (1954) [*Chem. Abstr.*, **49**, 15963*a* (1955)]; *d*) A.M. Anthony-Barbier, *J. Rech. Centre Natl. Rech. Sci. Lab. Bellevue*, **32**, 319 (1955) [*Chem. Abstr.*, **51**, 1961*h* (1957)].
9) *a*) F. Kröhnke, H. Schmeiss, and W. Gottstein, *Chem. Ber.*, **84**, 131 (1951); *b*) B.C. Pal, *J. Sci. Ind. Res.*, **17A**, 270 (1958) [*Chem. Abstr.*, **53**, 17163 *a* (1959)]; *c*) F. Leonard, A. Wajngurt, M. Klein, and C.M. Smith, *J. Org. Chem.*, **26**, 4062 (1961).
10) *a*) H. Decker and R. Pschorr, *Ber.*, **37**, 3396 (1904); *b*) M.A. Terpstra and F.B. Zienty, U.S. Patent 2796440 (1957) [*Chem. Abstr.*, **51**, 16541*b* (1957)].
11) J.H. Hahn, J.F. Quinn, and M.A. Terpstra, U.S. Patent 2777001 (1957) [*Chem. Abstr.*, **51**, 13922*b* (1957)].

reactive to electrophilic attack at the 6-position and to solvolysis at the benzylic position, preparation of II is often accompanied by formation[8a,c,d,9a,12] of cyclotriveratrylene, a cyclic trimer,[13] in certain cases, and the choice of suitable solvents for the metathesis of II is rather limited. Especially in the latter reaction, the use of methanol or ethanol has to be avoided;[7a] inert solvents such as dioxane,[7a] benzene,[7a] acetone,[7b] and N,N-dimethylformamide (DMF)[7c] have thus been employed.

In connection with other studies in this laboratory a need for improving the procedure for the preparation of nitrile III led us to apply dimethyl sulfoxide (DMSO)[14] to the metathesis of II as a reaction solvent. The unexpected behavior of II in the reaction with sodium cyanide in such a dipolar aprotic solvent[14] is the main subject of this report.

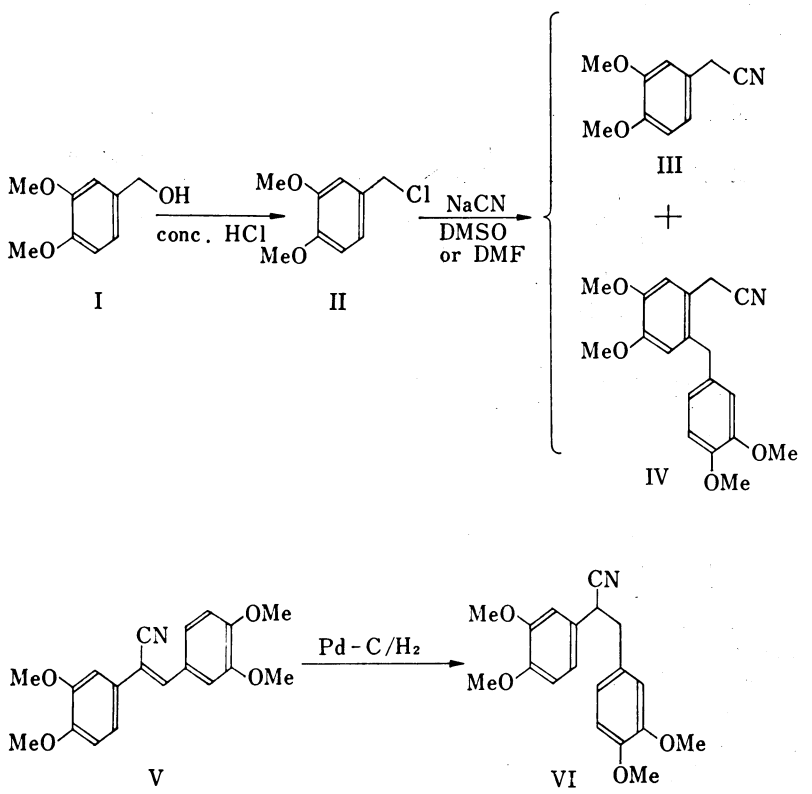
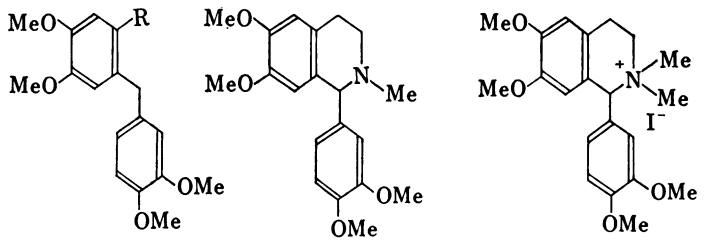


Chart 1

The chloride (II) used in the present study was prepared in a good yield from alcohol I[7a,15] by shaking it with cold conc. hydrochloric acid. The procedure was modified from that of Hahn, *et al.*,[11] and was virtually identical with that[16] described for the preparation

12) *a*) Beilstein's, "Handbuch der Organischen Chemie," **6**, E III 4520; *b*) Personal communication from Dr. N. Yoneda of Tanabe Seiyaku Co.
13) *a*) A.S. Lindsey, *J. Chem. Soc.*, **1965**, 1685; *b*) T. Sato, T. Akima, S. Akabori, H. Ochi, and K. Hata, *Tetrahedron Letters*, **1969**, 1767; *c*) B. Umezawa, O. Hoshino, H. Hara, and S. Mitsubayashi, *J. Chem. Soc.* (C), **1970**, 465.
14) A.J. Parker, "Advances in Organic Chemistry," Vol. 5, ed. by R.A. Raphael, E.C. Taylor, and H. Wynberg, Interscience Publishers, New York, 1965, pp. 1—46.
15) D. Davidson and M. T. Bogert, *J. Am. Chem. Soc.*, **57**, 905 (1935).
16) S. Yamada, T. Fujii, and T. Shioiri, *Chem. Pharm. Bull.* (Tokyo), **10**, 680 (1962).

of 3,4-methylenedioxybenzyl chloride. Treatment of chloride II with 1.3 equivalnt mole of sodium cyanide in DMSO below 30° for *ca.* 2 hr furnished nitrile III as the major product (77% yield) and compound IV, mp 102—103°, in 11% yield. The by-product (IV) was characterized by mass spectrum [*m/e* 327 (M^+)], correct analysis for $C_{19}H_{21}O_4N$, ultraviolet (UV) spectrum [$\lambda_{max}^{95\%EtOH}$ 282 mμ (ε 6530)], infrared (IR) spectrum [ν_{max}^{Nujol} 2245 cm^{-1} (CN)], and nuclear magnetic resonance (NMR) spectrum. The NMR spectrum in deuterochloroform exhibited a somewhat dull two-proton singlet at 6.45 τ ($ArC\underline{H}_2CN$), fourteen-proton multiple bands in the region of 6.0—6.16 τ (four methoxyl groups and $ArC\underline{H}_2Ar$), and five-proton multiple peaks in the region of 3.0—3.3 τ (aromatic protons). Furthermore, IV was readily distinguishable by unmistakable difference in physical and spectral properties from the side-chain isomer, 2,3-bis(3,4-dimethoxyphenyl)propionitrile (VI), which was prepared for direct comparison from α-(3,4-dimethoxyphenyl)-3,4-dimethoxycinnamonitrile (V)[17] by catalytic hydrogenation.



VII : R=CH_2CO_2H
VIII : R=CH_2CONMe_2
XI : R=$CH_2CH_2NMe_2$

IX

X

Me=$-CH_3$

Chart 2

For final identification as IV, it seemed adequate to convert IV into 4,5-dimethoxy-2-(3,4-dimethoxybenzyl)phenethylamine (type XI) or its derivatives which could be synthesized unambiguously from a known compound. Thus, we selected the reaction sequence (IV→VII→VIII→XI) shown in Chart 2. On treatment with a mixture of 50% aq. potassium hydroxide and ethanol at reflux, compound IV gave [4,5-dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]acetic acid (VII) in a good yield. Acid VII was converted by thionyl chloride into the corresponding acid chloride, which then reacted with dimethylamine to yield 2-[4,5-dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]-N,N-dimethylacetamide (VIII). Reduction of amide VIII with lithium aluminum hydride afforded 4,5-dimethoxy-2-(3,4-dimethoxybenzyl)-N,N-dimethylphenethylamine (XI) in 74% yield. An alternative synthesis of XI started with quaternization of 1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (IX)[18] with methyl iodide to give 1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2,2-dimethylisoquinolinium iodide (X). The methiodide (X) was treated with an excess amount of silver chloride, and the resulting methochloride was converted into XI by catalytic hydrogenolysis, which was effected over palladium-on-charcoal at room temperature with uptake of one equivalent mole of hydrogen. That the hydrogenolysis had taken place at the $C_{(1)}$—N bond of the 1,2,3,4-tetrahydroisoquinoline ring was evidenced by the NMR spectrum of XI in carbon tetrachloride. It displayed a six-proton singlet at 7.87 τ (NMe_2), two unresolved two-proton multiplets at 7.73 ($CH_2C\underline{H}_2NMe_2$) and 7.48 τ ($ArC\underline{H}_2CH_2$), fourteen-proton signals overlaid in the region of 6.3 τ (four methoxyl

17) J.B. Niederl and A. Ziering, *J. Am. Chem. Soc.*, **64**, 885 (1942).
18) K. Leander, B. Lüning, and E. Ruusa, *Acta Chem. Scand.*, **23**, 244 (1969).

groups and $ArC\underline{H}_2Ar$), and a five-proton multiplet at 3.3—3.55 τ (aromatic protons). The free base of XI thus obtained was identical with the sample derived from IV through VII and VIII. The picrolonates prepared from both samples of XI were also identical. The direct catalytic hydrogenolysis of methiodide X did not proceed even at an elevated temperature. A scheme of cleaving the $C_{(1)}$—N bond of the tertiary base (IX) or its hydrochloride by catalytic hydrogenolysis was also abandoned since the reaction in each case was found not to proceed or too slow under the conditions employed.

In the above-mentioned metathesis of II with sodium cyanide, replacement of DMSO by DMF also resulted in formation of IV as a by-product besides the major product (III); the yields of IV and III were similar to those in DMSO. On the other hand, IV could not be isolated from the reaction mixture of the metathesis[7a] of II carried out in benzene-water.

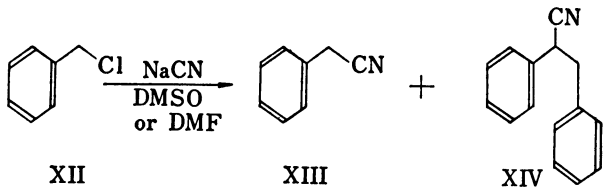


Chart 3

It is well known that primary and secondary halides including substituted benzyl chlorides[19] react rapidly and cleanly with alkali-metal cyanides in dipolar aprotic solvents.[14] The observation of the by-product formation described above, therefore, led us to scrutinize the reported[20] reaction of benzyl chloride (XII) with sodium cyanide in DMSO. When XII

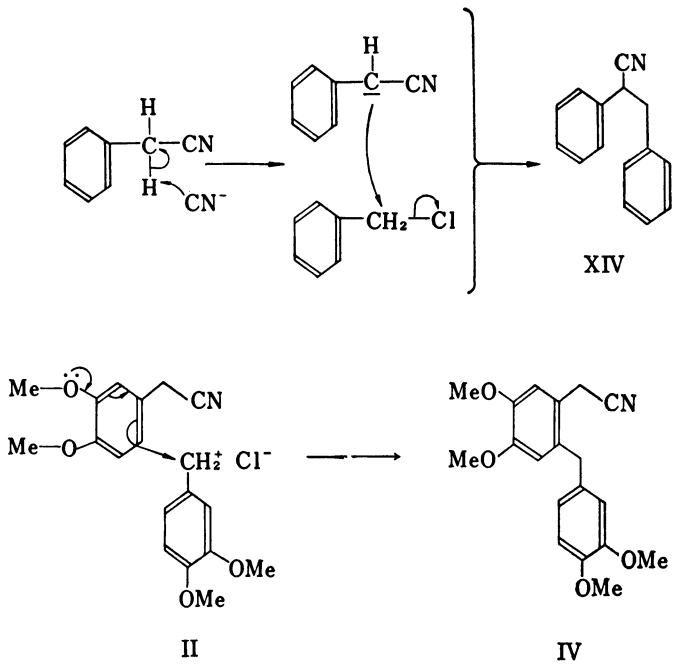


Chart 4

19) A. Parulkar, A. Burger, and D. Aures, *J. Med. Chem.*, **9**, 738 (1966).
20) L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

was treated with a slight excess of sodium cyanide in DMSO at a temperature below 50° for 30 min, 2,3-diphenylpropionitrile (XIV) was obtained in *ca.* 1.5% yield besides benzyl cyanide (XIII) (93%). The minor product (XIV) was characterized by mass spectrum [*m/e* 207 (M^+)], IR spectrum [ν_{max}^{Nujol} 2240 cm^{-1} (CN)], and NMR spectrum, and finally it was identified by direct comparison with the sample of XIV synthesized by the method given in the literature.[21] The reaction using DMF instead of DMSO also gave a similar pattern of formation of products.

For a probable mechanism of the formation of XIV, it is supposed that the poorly solvated CN^- in a dipolar aprotic solvent abstracts a benzylic proton from the benzyl cyanide(XIII) that has formed normally, as shown in Chart 4, and the carbanion thus produced reacts with the unaltered benzyl chloride in an S_N2 manner to give the by-product (XIV). In the case of 3,4-dimethoxy-substituted series, however, the 4-methoxyl group is favorable to the ionized form of II and unfavorable for the abstraction of a benzylic proton from nitrile III by CN^-. The 3-methoxyl group of III renders the reaction with an electrophile easier at the 6-position. These effects would thus prefer the formation of IV, as shown in Chart 4, rather than that of the isomer (VI) of a XIV-type.

Experimental[22]

3,4-Dimethoxybenzyl Chloride (II)——To cooled 3,4-dimethoxybenzyl alcohol (I)[7a,15] (21.05 g, 0.125 mole) was added ice-cooled conc. HCl (31 ml), and the mixture was vigorously shaken in a separatory funnel for 20 min to separate a colorless heavy oil, which was extracted with benzene. The benzene solution was washed successively with H_2O, satd. aq. $NaHCO_3$, and satd. aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to dryness to leave the crude chloride (II) as colorless needles, mp 45—49° (lit.[10a] mp 51°); NMR (CCl_4) τ: 6.27 and 6.25 (6H, two CH_3O's), 5.57 (2H, s, $ArCH_2Cl$), 3.1—3.45 (3H, m, aromatic protons). Yield, almost quantitative. The IR and NMR spectra of this sample were virtually identical with those of the one prepared from I and $SOCl_2$[7a,7c] in the presence of pyridine. The crude sample of II thus obtained was immediately used in the next step without purification.

[4,5-Dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]acetonitrile (IV)——To sodium cyanide (8.1 g, 0.165 mole) in partial solution in DMSO (40 ml) was added dropwise with stirring a solution of the whole amount of the chloride (II) described above in DMSO (24 ml) at such a rate that the inner temperature did not exceed 30°. After the addition was complete, the mixture was kept stirring at room temperature for 1.5 hr, and poured into H_2O (300 ml) to separate an oil, which was extracted with benzene. The benzene solution was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave a yellowish oil. Distillation of the oil gave 3,4-dimethoxyphenylacetonitrile (III) (17.1 g, 77% based on the alcohol I used), bp 151—152° (5 mmHg) and mp 61—64° (lit.[7a] mp 68°), identified with the sample prepared by the reported method[7a] by mixed melting-point test and comparison of their IR spectra, and a viscous brownish oil (*ca.* 3.2 g) as a distillation residue, which solidified on trituration with a small amount of ether. Recrystallization of the solid from MeOH afforded IV (2.3 g, 11% based on the alcohol I used) as colorless prisms, mp 102—103°. *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.41; H, 6.43; N, 4.21. For UV, IR, NMR, and mass spectral data, see Theoretical Part.

In the metathesis described above, replacement of DMSO with DMF also gave IV as a by-product.

2,3-Bis(3,4-dimethoxyphenyl)propionitrile (VI)——A solution of α-(3,4-dimethoxyphenyl)-3,4-dimethoxycinnamonitrile (V)[17] (1.63 g, 5 mmoles) in tetrahydrofuran (100 ml) was hydrogenated over 10% palladium-on-charcoal (1 g) at room temperature (18°) and atmospheric pressure for 3.5 hr, taking up one equivalent mole of H_2. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to dryness, leaving a colorless solid. The solid was dissolved in benzene (50 ml), and the benzene solution was washed successively with 10% aq. HCl and H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to dryness to afford the crude VI (1.39 g, 85%), mp 114—118°. Recrystallizations from MeOH gave an analytical sample of VI as colorless needles, mp 127—128° (lit.[23] mp 120°); UV $\lambda_{max}^{95\%EtOH}$ 279 mμ (ε 6110); IR ν_{max}^{Nujol} 2230 cm^{-1}

21) H. Jannsen, *Ann. Chem.*, **250**, 125 (1889).

22) All melting points are corrected, and boiling points are uncorrected. The UV spectra were recorded on a Hitachi Model 356 spectrophotometer. The IR spectra were obtained with a JASCO-DS-402G spectrophotometer. The mass spectra were measured with a JEOL-JMS-01SG mass spectrometer. The NMR spectra were determined with a JEOL-JNM-C-60H spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: b=broad, d=doublet, m=multiplet, s=singlet, t=triplet.

23) J. Knabe, P. Herbort, and N. Ruppenthal, *Arch. Pharm.*, **299**, 534 (1966).

(CN); NMR ($CDCl_3$) τ: 6.92 (2H, d, J=7.5 cps, $ArCH_2CH$), 6.19, 6.17, 6.14, and 6.12 (s each, four CH_3O's), 6.04 (t, J=7.5 cps, CH_2CHCN), 3.1—3.4 (6H, m, aromatic protons); Mass Spectrum *m/e*: 327 (M^+). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.60; H, 6.42; N, 4.45.

[4,5-Dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]acetic Acid (VII)——A mixture of IV (3.25 g, 9.93 mmoles) in EtOH (20 ml) and KOH (3.0 g) in H_2O (3 ml) was heated under reflux for 10 hr. The EtOH was evaporated *in vacuo*, and H_2O (30 ml) was added to the residue. The aq. solution was washed with benzene and acidified (pH 2) with 10% aq. HCl to separate slightly yellowish leaflets (3.17 g, 90% as a hemihydrate of VII), mp 97—100°. Recrystallization from benzene–hexane furnished colorless leaflets, which were dried over P_2O_5 *in vacuo* (3 mmHg) at 40° for 11 hr, mp 97—100°. *Anal.* Calcd. for $C_{19}H_{22}O_6 \cdot 1/2\ H_2O$: C, 64.21; H, 6.52. Found: C, 64.34; H, 6.80.

2-[4,5-Dimethoxy-α-(3,4-dimethoxyphenyl)-*o*-tolyl]-N,N-dimethylacetamide (VIII)——To a solution of the hemihydrate of VII (500 mg, 1.41 mmoles) in abs. $CHCl_3$ (6 ml) was added $SOCl_2$ (1.5 g, 12.6 mmoles), and the mixture was kept at room temperature for 20 hr. Evaporation *in vacuo* of the $CHCl_3$ and excess of $SOCl_2$ left the crude acid chloride as a reddish brown liquid. The acid chloride was dissolved in abs. benzene (8 ml), and the benzene solution was added to a chilled 40% aq. dimethylamine (3 g) with stirring. The mixture was kept stirring at room temperature for 4 hr. The organic layer was separated from the aq. layer, washed successively with H_2O, 10% aq. HCl, H_2O, satd. aq. $NaHCO_3$, and H_2O, and dried over anhyd. Na_2SO_4. Removal of the benzene *in vacuo* left a pale brownish solid (470 mg, 89% based on the acid VII used), mp 117—120°. Recrystallizations from benzene–hexane provided an analytical sample of VIII as colorless prisms, mp 121—123°; IR ν_{max}^{KBr}: 1640 cm^{-1} ($CONMe_2$); NMR ($CDCl_3$) τ: 7.17 and 7.08 (6H, s each, $CONMe_2$), 6.47 (2H, s, $ArCH_2CO$), 6.0—6.2 (14H, four CH_3O's and $ArCH_2Ar$), 3.2—3.35 (5H, m, aromatic protons); Mass Spectrum *m/e*: 373 (M^+). *Anal.* Calcd. for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.84; H, 7.30; N, 3.91.

4,5-Dimethoxy-2-(3,4-dimethoxybenzyl)-N,N-dimethylphenethylamine (XI)——i) Catalytic Hydrogenolysis of the Methochloride derived from X: A mixture of AgCl, which was prepared freshly from $AgNO_3$ (2.3 g, 13.5 mmoles) and 10% aq. HCl, and the monohydrate (2.43 g, 4.83 mmoles) of methiodide X, which was prepared by the procedure described below, in 50% aq. EtOH (40 ml) was heated under reflux with stirring for 4 hr. The silver halides were filtered off and washed with hot 50% aq. EtOH. The filtrate and washings were combined and evaporated *in vacuo* to dryness, leaving the methochloride as an almost colorless solid. A solution of the crude chloride in 50% aq. EtOH (60 ml) was hydrogenated over 10% palladium–on–charcoal (1.5 g) at room temperature (25°) and atmospheric pressure; the reaction ceased after taking up one equivalent mole of H_2 during 1.5 hr. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to leave a colorless oil, which was dissolved in H_2O (50 ml). The aq. solution was rendered strongly basic with NaOH pellets, and an oil separated was extracted with benzene. The benzene solution was dried over KOH and evaporated *in vacuo* to leave a slightly yellowish solid (1.50 g, 87% based on the monohydrate of X), mp 58—61°. Recrystallization from benzene–petroleum ether (1:20) afforded an analytical sample of XI, mp 59—61°; NMR (see Theoretical Part); Mass Spectrum *m/e*: 359 (M^+). *Anal.* Calcd. for $C_{21}H_{29}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.07; H, 8.37; N, 4.00.

The picrolonate of XI was prepared from a portion of the free base (XI) by dissolving it in a small amount of EtOH and adding a satd. solution of picrolonic acid in EtOH. Recrystallization from EtOH gave yellow minute needles, mp 132—135° (decomp.). *Anal.* Calcd. for $C_{31}H_{37}O_9N_5$: C, 59.70; H, 5.98; N, 11.23. Found: C, 59.81; H, 6.10; N, 10.98.

ii) The $LiAlH_4$ Reduction of VIII: Amide VIII (680 mg, 1.82 mmoles) was placed in the thimble of a Soxhlet extractor, which was connected to a flask containing a stirred slurry of $LiAlH_4$ (1.0 g) in abs. ether (180 ml). By refluxing the ether for 24 hr, all the amide was carried into the flask. The mixture was further refluxed with stirring for 24 hr and treated successively with H_2O (1 ml), 15% aq. NaOH (1 ml), and H_2O (3 ml) under ice–cooling. The precipitates that resulted were filtered off and washed with ether. The filtrate and washings were combined and evaporated *in vacuo* to leave an oil, which was dissolved in 10% aq. HCl (25 ml). The aq. solution was washed with benzene, made strongly alkaline with NaOH pellets to separate an oil, which was extracted with benzene. The benzene solution was dried over KOH and evaporated *in vacuo* to give a yellowish solid (485 mg, 74%), mp 56—60°. Recrystallazation from benzene–petroleum ether furnished a pure sample of XI, mp 59—61°, undepressed upon mixture with the sample derived from X by the above–mentioned hydrogenolysis. The IR spectra of both samples were also identical. The picrolonate prepared from a small portion of the free base was also identified, by mixed melting–point test and comparison of the IR spectra, with the one obtained by method-(i).

1-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2,2-dimethylisoquinolinium Iodide (X)——A mixture of methyl iodide (20 ml) and 1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (IX)[18] (4.00 g, 11.6 mmoles) in benzene (100 ml) was refluxed with stirring for 1 hr. The colorless crystals that separated were filtered, washed with benzene, and recrystallized from EtOH to give X (5.6 g) as colorless prisms. The sample started to sinter at *ca.* 130° and melted at 145°. For analysis it was dried over P_2O_5 at 60° and 4 mmHg for 6 hr. *Anal.* Calcd. for $C_{21}H_{28}O_4NI \cdot H_2O$: C, 50.11; H, 6.01; N, 2.78. Found: C, 50.45; H, 6.07; N, 2.83.

2,3-Diphenylpropionitrile (XIV)——To a stirred suspension of sodium cyanide (8.0 g, 0.163 mole) in DMSO (20 ml) was added dropwise a solution of benzyl chloride (15.8 g, 0.125 mole) in DMSO (16 ml) at such a rate that the inner temperature did not exceed 50°. After the addition was complete, the mixture was kept stirring at room temperature for 30 min and poured into H_2O (250 ml) to separate an oil, which was extracted with benzene. The benzene solution was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo*, leaving a yellowish oil. Distillation of the oil provided benzyl cyanide (13.7 g, 93%), bp 114—115° (20 mmHg), identified with an authentic sample by comparison of the IR spectra, and XIV (0.2 g, *ca.* 1.5% based on the benzyl chloride used), bp 180° (bath temp.) (5 mm Hg) and mp 48°. Recrystallization of the crude XIV from EtOH gave an analytical sample as colorless needles, mp 54—55°; IR ν_{max}^{Nujol} 2240 cm^{-1}(CN); Mass Spectrum *m/e*: 207 (M^+); NMR (CCl_4)τ: 6.93 (2H, d, J=7.5 cps, $ArCH_2CH$), 6.11 (1H, t, J=7.5 cps, CH_2CHCN), 2.6—3.0 (10H, m, aromatic protons). Identity of this sample with the authentic XIV prepared according to the reported procedure[21] was established by mixed melting-point test. The IR spectra of both samples were also identical.

Replacement of DMSO with DMF in this reaction also gave XIV as a by-product.

Acknowledgement We are grateful to Dr. N. Yoneda of Tanabe Seiyaku Co. for a generous gift of 3,4-dimethoxyphenethylamine and to Mr. Y. Itatani and his associates at the Kanazawa University for the microanalyses and NMR and mass spectral data.