

**Application of Norphenylephrine Derivatives to the Isoquinoline Syntheses  
(Studies on the Syntheses of Heterocyclic Compounds.  
CCCLII<sup>1)</sup>)**

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A synthesis of 2-amino-(3-hydroxyphenyl)ethanol (I) was investigated as follow. Hydrolysis of 3-acetoxy- $\omega$ -(N,N-dibenzylamino)acetophenone (XVI), which was obtained from 3-acetoxy- $\omega$ -bromoacetophenone and dibenzylamine, gave the corresponding 3-hydroxy-derivative, whose catalytic hydrogenolysis with Pd-C afforded the above compound (I) as shown in Chart 1.

Phenolic cyclization of I and 1-(3-hydroxyphenyl)-2-methylaminoethanol (II) was studied. Cyclization of I with cyclic ketones afforded three kinds of 1,2,3,4-tetrahydro-1,1-spiroheterocycloisoquinolines. Cyclization of amine (II) with carbonyl compounds was also carried out successfully to give five kinds of the corresponding 1,2,3,4-tetrahydroisoquinolines. Furthermore, it was found that the cyclization occurred at the *para* position to phenolic hydroxy group.

Catecholamines have been well known as a sympathomimetic agent and 2-amino-1-(3-hydroxyphenyl)ethanol (I) and 1-(3-hydroxyphenyl)-2-methylaminoethanol (II) have been used for the hypertensive agent. The general synthetic methods of the above compounds have been fully investigated.<sup>3)</sup> The present paper describes an improved method for the preparation of I. Furthermore, although we reported on the syntheses of 1-substituted-1,2,3,4-tetrahydroisoquinoline by the phenolic cyclization of 3-hydroxyphenethylamines with various carbonyl compounds,<sup>4)</sup> we wish to report on the syntheses of the three additional tetrahydroisoquinolines, which may show a pharmacological activity, by phenolic cyclization and on the successful application of phenolic cyclization to secondary amine (II) to afford five kinds of 1,2,3,4-tetrahydro-2-methylisoquinolines.

In the previous paper<sup>5)</sup> one of the authors reported the syntheses of cyanomethyl derivatives by the benzyne reaction of halogenobenzenes with nitriles. First, an alternative preparation of amine (I) was investigated with the use of 3-methoxybenzyl cyanide (IV) which was obtained from the 2-chloroanisole (III) with acetonitrile. The synthesis of 2-amino-1-(3-methoxyphenyl)ethanol (VII) from IV through bromonitrile and acetoxy-derivative (VI)

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- 2) Location: a) *Aobayama, Sendai*; b) *Sakurashinmachi, Setagayaku, Tokyo*; c) *Kamiochiai, Shinjuku-ku, Tokyo*.
- 3) A. D'amico, L. Bertolini, and C. Mornreale, *Chemical e Industria* (Milan), **38**, 93 (1965); O. Hromatka and C. Skopalic, *Monatsh.*, **84**, 919 (1953); H. Brachwits and K.H. Werner, *Ger. Pat. (East)* **50**, 624 (1966).
- 4) T. Kametani, K. Fukumoto, H. Agui, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc. (C)*, **1968**, 112; T. Kametani, K. Kigasawa, M. Hiiragi, and H. Ishimaru, *Chem. Pharm. Bull.* (Tokyo), **17**, 2353 (1969); T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru, and S. Saito, *Yakugaku Zasshi*, **89**, 1482 (1969); T. Kametani, K. Kigasawa, M. Hiiragi, and H. Ishimaru, *J. Heterocyclic Chem.*, **7**, 51 (1970).
- 5) T. Kametani, K. Ogasawara, T. Terui, K. Yamaki, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1584 (1968).

was investigated, but bromination of IV gave no desired compound (VIII), but a mixture of the bromo-derivative (IX) and amide (X) was obtained. Furthermore, the condensation of IV with diethyl oxalate in the presence of sodium ethoxide gave ethyl 3-cyano-3-(3-methoxyphenyl)-2-ketopropionate (V) in 60% yield, whose bromination with bromine in the presence of sodium acetate afforded 1-bromo-1-(3-methoxyphenyl)acetonitrile (VIII) in 68% yield. In case of using no sodium acetate, V was converted to  $\alpha$ -diketone (XIII) because of the presence of hydrobromic acid formed during reaction. Further treatment of V with hydrochloric acid in chloroform yielded the amide (XIV). However, treatment of VIII with sodium acetate did not give the acetyl derivative (VI) in good yield, which was a key intermediate for VII. On the other hand, Wohl-Ziegler reaction of V with N-bromosuccinimide gave no compound (VIII), but keto-ester (XI), which was subsequently hydrolysed to afford the amide (XII). Then, treatment of V with sodium acetate in ethanol gave the acetyl compound (VI) in 45% yield, whose subsequent reaction with lithium aluminum hydride gave 2-amino-1-(3-methoxyphenyl)ethanol (VII). Its infrared (IR) and nuclear magnetic resonance (NMR) spectra were identical with those of the authentic sample (VII), which was synthesized by

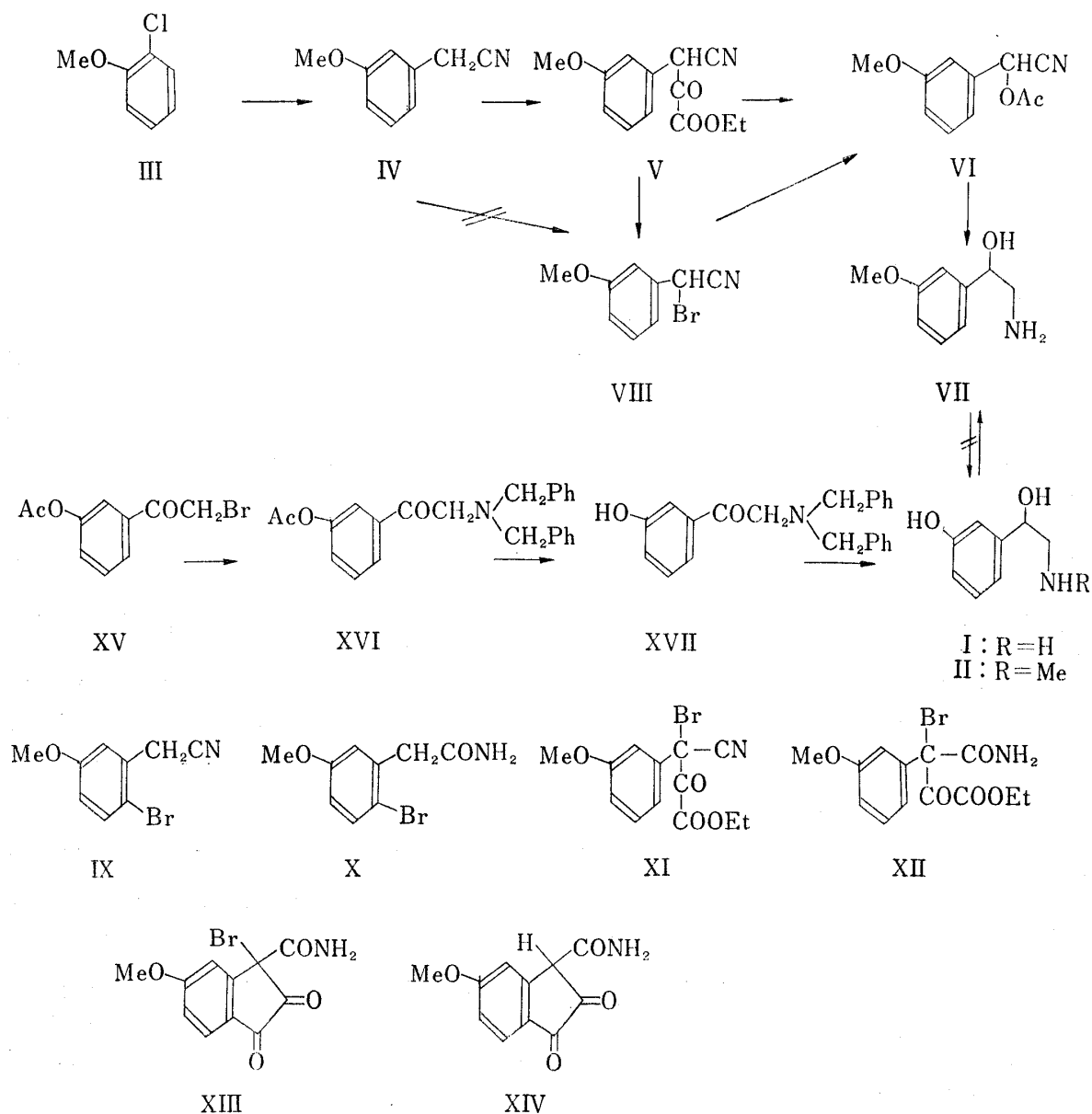


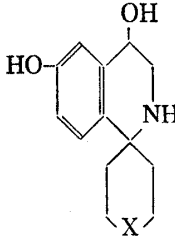
Chart 1

O-methylation of I with diazomethane. Attempts to obtain I by demethylation of methoxyl group with hydrobromic acid, hydroiodic acid, hydrochloric acid, or pyridine hydrochloride were unsuccessful.

Therefore, we investigated an another method for preparation of I with the use of 3-acetoxy-*o*-bromoacetophenone (XV) as a starting material as follow. Treatment of XV with dibenzylamine in absolute ethanol yielded 3-acetoxy-*o*-(*N,N*-dibenzylamino)acetophenone (XVI), whose hydrolysis with methanolic hydrochloric acid, followed by catalytic hydrogenation of XVII in the presence of 5% palladium-charcoal in ethanol, gave the desired amine (I).

Phenolic cyclization of the above amine (I) with 2,3,5,6-tetrahydro-1,4-thiapyrone,<sup>6)</sup> 2,3,5,6-tetrahydro-1,4-pyrone<sup>7)</sup> and 1-methyl-4-piperidone was investigated to afford the corresponding 1,1'-spiroheterocycloalkano-1,2,3,4-tetrahydroisoquinolines (XVIII), (XIX) and (XX), respectively. It has been already reported in the previous paper<sup>4)</sup> that the cyclization occurred at the *para* position to hydroxyl group.

TABLE I. The Reaction of Carbonyl Compounds with 2-Amino-1-(3-hydroxyphenyl)ethanol

Compound No.		Carbonyl compound (g)	Amine (I) (g)	Time (hr)	Yield g (%)	Product	UV $\lambda_{\max}^{\text{EtOH}}$ m $\mu$ (log $\epsilon$ )
XVIII	X=S	2,3,5,6-tetrahydro-1,4-thiapyrone (1.0)	1.32	10	0.82 (38)	colorless needle (iso PrOH) mp 179—181°	282 (3.27)
XIX	X=O	2,3,5,6-tetrahydro-1,4-pyrone (0.8)	1.2	10	0.95 (51)	colorless needles (EtOH) mp 225° (decomp.)	282 (3.59)
XX	X=N Me	1-methyl-4-piperidone (0.7)	0.8	10	1.69 (96)	as 2 HCl salt colorless powder (MeOH) mp 250° (decomp.)	281 (3.30)

Moreover, phenolic cyclization of the secondary amine (II)<sup>8)</sup> was investigated, by the result of which the condensation of II with carbonyl compounds was found to give the corresponding isoquinolines, the cyclization occurring at the *para* position to hydroxyl group. For instance, acetone, cyclopentanone, 1-methyl-4-piperidone, acetophenone, benzaldehyde, 4-chlorobenzaldehyde, and phenylpropionaldehyde were used as one component of starting materials, among which, in case of aldehydes, the reaction was carried out in isopropanol at room temperature to afford the corresponding isoquinolines easily. On the other hand, in case of acetone and cyclopentanone, an isopropanolic solution of the ketone was refluxed for 20 hr to afford the desired isoquinolines. However, 1-methyl-4-piperidone did not give the isoquinoline, but the oxazolidine (XXVI) which could not be converted into the isoquinoline under reflux in ethanol or by fusion at 180°. Moreover, the oxazolidine (XXVI) was treated with hydrochloric acid to give 1-methyl-4-piperidone and the starting phenethylamine (II) by hydrolysis, but the isoquinoline was not obtained. Therefore, the reaction with thiapyrone and pyrone having a similar skeleton to 1-methyl-4-piperidone was not examined. Furthermore, acetophenone did not condense with the amine to recover the starting material under the above condition.

6) G.M. Bennett and L.V.D. Scora, *J. Chem. Soc.*, 1927, 194.

7) S.R. Cawley and S.G.P. Plant, *J. Chem. Soc.*, 1938, 1214.

8) S.I. Sergieuskaya and G.A. Raudel, *J. Gen. Chem.*, 22, 496 (1952).

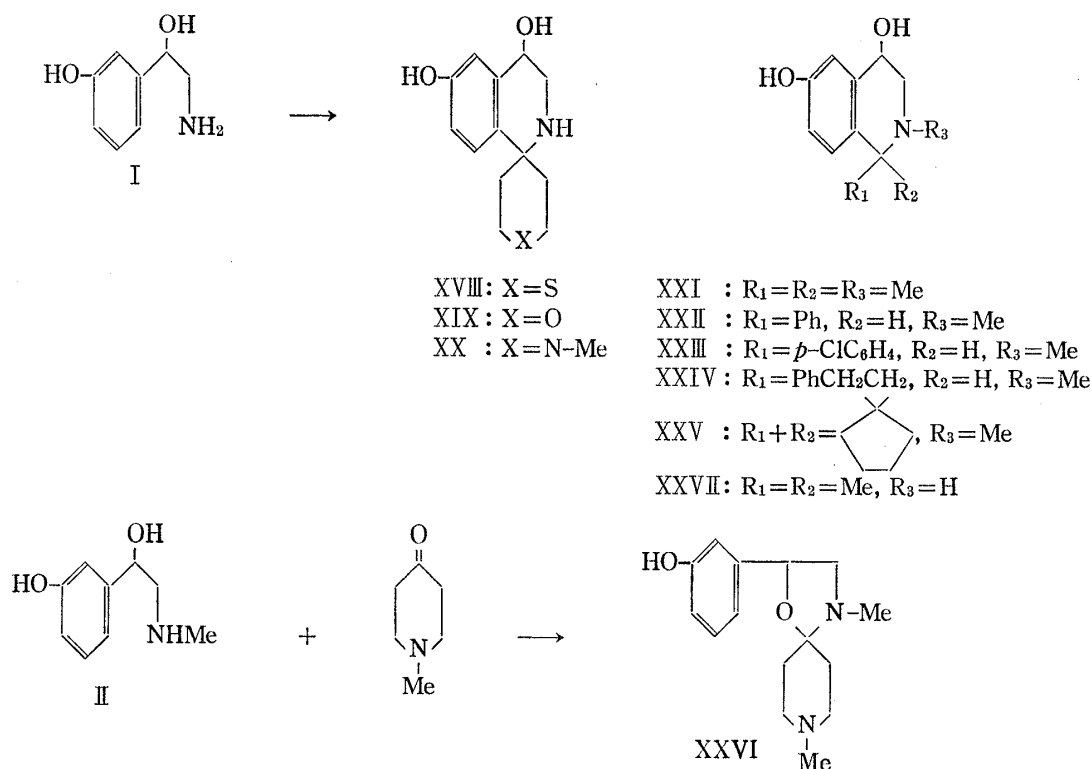


Chart 2

The IR spectrum of XXI was superimposable on that of the authentic sample which was synthesized by N-methylation of 1,2,3,4-tetrahydro-4,6-dihydroxy-1,1-dimethylisoquinoline (XXVII) with formalin and sodium borohydride and no depression was shown on the mixed melting point test. It has been found that phenolic cyclization in case of secondary amine (II) also occurred at the *para* position to hydroxyl group to afford the corresponding 1,2,3,4-tetrahydro-4,6-dihydroxyisoquinolines.

TABLE II. The Reaction of Carbonyl Compounds with 1-(3-Hydroxyphenyl)-2-methylaminoethanol

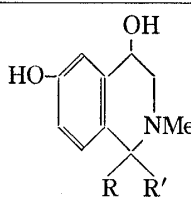

Compound No.		Carbonyl compound (g)	Amine (II) (g)	Time (hr)	Yield g (%)	Product	UV $\lambda_{max}^{EtOH}$ m $\mu$ (log $\epsilon$ )
XXI	R Me, R' Me	acetone (2.0)	0.5	20	0.20 (32)	colorless needles (C <sub>6</sub> H <sub>6</sub> ) mp 162—164°	281 (3.33)
XXII	R Ph, R' H	benzaldehyde (0.5)	0.5	3	0.35 (46)	colorless prisms (cyclohexane) mp 90° (decomp.)	283 (3.88)
XXIII	R <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> , R' H	4-chloro-benzaldehyde (0.5)	0.5	3	0.30 (34)	colorless needles (C <sub>6</sub> H <sub>6</sub> ) mp 163—165°	282.5 (3.39)
XXIV	R PhCH <sub>2</sub> CH <sub>2</sub> , R' H	phenylpropion-aldehyde (0.5)	0.5	3	0.40 (47)	colorless needles (C <sub>6</sub> H <sub>6</sub> ) mp 154—156°	283 (3.23)
XXV	R, R' 	cyclopentanone (0.5)	0.5	20	0.15 (22)	colorless needles (C <sub>6</sub> H <sub>6</sub> ) mp 170—172°	282 (3.30)

TABLE III. Microanalyses of 1,2,3,4-Tetrahydroisoquinoline Derivatives

Compound No.	Formula	Analyses (%)					
		Required			Found		
		C	H	N	C	H	N
XVIII	C <sub>13</sub> H <sub>17</sub> O <sub>2</sub> NS	62.12	6.82	5.57	61.89	6.43	5.38
XIX	C <sub>13</sub> H <sub>17</sub> O <sub>3</sub> N	66.36	7.28	5.95	65.86	7.21	6.07
XX	C <sub>14</sub> H <sub>20</sub> O <sub>2</sub> N <sub>2</sub> ·2HCl·1/2H <sub>2</sub> O	50.91	7.02	8.48	51.12	7.00	8.21
XXI	C <sub>12</sub> H <sub>17</sub> O <sub>2</sub> N	69.54	8.27	6.76	69.48	8.15	6.92
XXII	C <sub>16</sub> H <sub>17</sub> O <sub>2</sub> N	75.27	6.71	5.49	74.96	6.92	5.18
XXIII	C <sub>16</sub> H <sub>16</sub> O <sub>2</sub> NCl	66.32	5.57	4.83	66.18	5.82	4.89
XXIV	C <sub>18</sub> H <sub>21</sub> O <sub>2</sub> N	76.29	7.47	4.94	76.27	7.58	4.88
XXV	C <sub>14</sub> H <sub>19</sub> O <sub>2</sub> N	72.07	8.21	6.00	71.65	8.15	5.54

Furthermore the structure of the products was supported by the ultraviolet (UV) spectrum as follow. The UV spectrum of I and II showed an absorption maximum at 277  $\mu$  and 275.5  $\mu$ , respectively, whereas isoquinolines showed an absorption maximum at 281—283  $\mu$ . A considerable bathochromic shift in case of isoquinolines could be explained by the difference of substituents between 2,3-dimethylphenol and 3,4-dimethylphenol. Namely, 2,3-dimethylphenol exhibited an absorption maximum at 275  $\mu$ , which was similar to that of *m*-cresol by its steric hindrance. However, 3,4-dimethylphenol showed a maximum at 281  $\mu$ . The results support that the isoquinolines have been cyclized at the *para* position to hydroxyl group. The oxazolidine (XXVI) gave an absorption maximum at 276  $\mu$ . Furthermore, the isoquinolines prepared in this paper were stable to hydrochloric acid, but the oxazolidines were hydrolyzed with acid to the starting amines and ketones.

Thus, a modified synthesis of I has been accomplished and it has been revealed that the phenolic cyclization of secondary amine with carbonyl compounds also gave our expected tetrahydroisoquinolines cyclized at the *para* position to hydroxy group.

### Experimental

Melting points were uncorrected. IR spectra were recorded on a type EPI Hitachi recording spectrophotometer in potassium bromide or in chloroform solution. NMR spectra were measured on a Hitachi H-60 spectrometer, examined in deuteriochloroform, carbon tetrachloride or deuteriodimethylsulfoxide using tetramethylsilane as an internal reference.

**Bromination of 3-Methoxybenzyl Cyanide (IV)**—To a cooled solution of 3.3 g of IV in CHCl<sub>3</sub> was added dropwise 3.3 g of bromine in 10 ml of CHCl<sub>3</sub> with stirring. After stirring for 3 hr, the reaction mixture was washed with 60 ml of saturated NaHCO<sub>3</sub> solution and 60 ml of H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give the solid which was recrystallized from benzene to afford 0.4 g (13%) of X as colorless needles, mp 150—152°. IR  $\nu_{\text{max}}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 1680 (C=O), 3400, 3500 (NH). NMR (in CDCl<sub>3</sub>)  $\delta$  (ppm): 3.65 (—CH<sub>2</sub>—CO—), 3.76 (—OCH<sub>3</sub>), 6.63 (C<sub>2</sub>—H, 1H, doublet, *J* = 4 cps), 6.85 (C<sub>4</sub>—H, 1H, a pair of doublet, *J* = 9.0, 4.0 cps), 7.45 (C<sub>5</sub>—H, 1H, doublet, *J* = 9.0 cps). *Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>NBr: N, 5.74. Found: N, 5.92.

On the other hand, evaporation of the mother liquor gave 0.5 g of an oil, which was chromatographed on 15 g of alumina to afford 0.05 g (1.7%) of a brown oil, identical with IX from NMR spectral data.

**2-Bromo-5-methoxybenzyl Cyanide (IX)**—To a solution of a 3 g of IV in 50 ml of CCl<sub>4</sub> was added 3.6 g of N-bromosuccinimide and the mixture was refluxed for 5 hr. After removal of the precipitated succinimide by filtration, the filtrate was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give 0.86 g (3.5%) of IX as a colorless oil, bp<sub>5</sub> 100—110°, which solidified immediately as colorless needles, mp 45°. IR  $\nu_{\text{max}}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 2230 (C≡N). NMR (in CDCl<sub>3</sub>)  $\delta$  (ppm): 3.75 (—CH<sub>2</sub>CN), 3.78 (—OCH<sub>3</sub>), 7.06 (C<sub>2</sub>—H, 1H, doublet, *J* = 2.6 cps), 6.66 (C<sub>4</sub>—H, 1H, a pair of doublet, *J* = 9.6, 2.6 cps), 7.46 (C<sub>5</sub>—H, 1H, doublet, *J* = 9.6 cps). *Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>ONBr: C, 47.79; H, 3.54; N, 6.19. Found: C, 48.07; H, 3.72; N, 6.16.

**Ethyl 3-Cyano-3-(3-methoxyphenyl)-2-ketopropionate (V)**—To a mixture of 20 g of IV and 22 g of diethyl oxalate in EtOH was added an ethanolic solution of EtONa [prepared from 3.1 g of Na and 41 ml of absolute EtOH] and the mixture was heated for 30 min at 50°. After being allowed at room temperature for 12 hr, the reaction mixture was acidified with 10% H<sub>2</sub>SO<sub>4</sub> to give a yellow precipitate which was collected

and recrystallized from benzene-*n*-hexane to afford 20 g of V as pale yellow needles, mp 79—82°. IR  $\nu_{\max}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 1695 (C=O), 2200 (C≡N). *Anal.* Calcd. for C<sub>13</sub>H<sub>13</sub>O<sub>4</sub>N: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.09; H, 5.42; N, 5.85.

**Bromination of Ethyl 3-Cyano-3-(3-methoxyphenyl)-2-ketopropionate (V) with N-Bromosuccinimide**—A mixture of 2.5 g of V and 1.8 g of N-bromosuccinimide in CCl<sub>4</sub> was refluxed for 10 hr. After the succinimide formed during the reaction had been filtered off from the hot reaction mixture, the crystals precipitated on cooling were collected and recrystallized from CCl<sub>4</sub> to give 2.3 g of XI as yellow prisms, mp 125—128°. IR  $\nu_{\max}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 1710 (C=O). *Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>O<sub>4</sub>NBr: C, 47.89; H, 3.71; N, 4.30. Found: C, 48.04; H, 3.86; N, 4.68.

**Hydrolysis of Ethyl 1-Bromo-1-cyano-1-(3-methoxyphenyl)-2-ketopropionate (XI)**—A mixture of 1.8 g of XI and 0.9 g of NaOH in 7.5 ml of EtOH was shaken for 10 hr at room temperature and the resulting precipitate was filtered off. The filtrate was acidified with 10% HCl solution. After removal of the inorganic precipitate by filtration, the filtrate was extracted with CHCl<sub>3</sub>. The extract was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give a solid, which was recrystallized from ether to afford 1 g of XII as colorless needles, mp 133—135°. IR  $\nu_{\max}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 1644 (—CONH<sub>2</sub>), 1725 (C=O), 3350, 3450 (NH). *Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>5</sub>NBr: C, 45.35; H, 4.07. Found: C, 45.47; H, 4.47.

**Bromination of V with Bromine**—To a stirred and cooled solution of 5 g of V in CHCl<sub>3</sub> was added dropwise a solution of 3.2 g of Br<sub>2</sub> in 30 ml of CHCl<sub>3</sub>. The reaction mixture was stirred for 10 hr to give a yellow precipitate, which was collected and recrystallized from MeOH to afford 1.2 g of XIII as a yellow powder, mp 240°. Beilstein test was positive. IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 1660 (—CONH<sub>2</sub>), 1714, 1768 (C=O). NMR [in (CD<sub>3</sub>)<sub>2</sub>SO]  $\delta$  (ppm): 3.82 (OCH<sub>3</sub>), 6.40—7.06 (NH<sub>2</sub>), 7.45—7.80 (aromatic protons). *Anal.* Calcd. for C<sub>11</sub>H<sub>8</sub>O<sub>4</sub>NBr: C, 44.31; H, 2.71; N, 4.70. Found: C, 43.95; H, 3.12; N, 4.28.

**1-Bromo-1-(3-methoxyphenyl)acetonitrile (VIII)**—To a cooled solution of 65 g of V in 200 ml of CHCl<sub>3</sub> was added dropwise a solution of 41.6 g of Br<sub>2</sub> in 100 ml of CHCl<sub>3</sub> in the presence of 65 g of AcONa·3H<sub>2</sub>O with stirring. After the stirring had been continued for 10 hr, the mixture was washed with 100 ml of saturated NaHCO<sub>3</sub> and 100 ml of saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give the residue which was distilled *in vacuo* to yield 45.4 g of VIII as a pale yellow oil, bp<sub>6</sub> 130—140°. Beilstein test was positive. NMR (in CDCl<sub>3</sub>)  $\delta$  (ppm): 3.80 (OCH<sub>3</sub>), 5.44 (—CH<), 6.80—7.47 (aromatic protons). *Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>ONBr: N, 6.19. Found: N, 5.99.

**1-Acetoxy-1-(3-methoxyphenyl)acetonitrile (VI)**—a) Preparation from V: A mixture of 20 g of V, 18 g of AcONa·3H<sub>2</sub>O and 50 ml of EtOH was refluxed for 6 hr. After an inorganic substance formed during the reaction was filtered off, 20 ml of H<sub>2</sub>O was added to the filtrate. After evaporation of EtOH, the resulting aqueous layer was extracted with 100 ml of CHCl<sub>3</sub>. The extract was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give an oil, which was distilled *in vacuo* to afford 7.5 g of VI as a pale yellow oil, bp<sub>5-6</sub> 140—143°. IR  $\nu_{\max}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 1740 (C=O). NMR (in CDCl<sub>3</sub>)  $\delta$  (ppm): 2.10 (—CO—CH<sub>3</sub>), 3.78 (—OCH<sub>3</sub>), 6.34 (>CH—), 6.80—7.50 (aromatic protons). *Anal.* Calcd. for C<sub>11</sub>H<sub>11</sub>O<sub>3</sub>N: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.83; H, 5.61; N, 6.44.

b) Preparation from VIII: A mixture of 0.5 g of VIII and 0.5 g of AcONa·3H<sub>2</sub>O was heated at 100—130° in an oil bath for 5 hr. After the reaction, 10 ml of H<sub>2</sub>O was added to the reaction mixture, whose solution was extracted with CHCl<sub>3</sub>. An usual work-up of the extract gave 0.1 g of VI.

**2-Amino-1-(3-methoxyphenyl)ethanol (VII)**—a) To a stirred suspension of 3 g of LiAlH<sub>4</sub> in dry tetrahydrofuran (THF) was added dropwise a solution of 7 g of VI in 100 ml of THF at room temperature and the reaction mixture was stirred for 12 hr at room temperature. The excess of LiAlH<sub>4</sub> was decomposed with 30% NaOH solution, and the organic layer was separated by decantation and evaporated to give a syrup, whose benzene extract was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give 3 g of VII as a pale yellow oil. IR  $\nu_{\max}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 3250—3350 (OH, NH<sub>2</sub>), NMR (in CDCl<sub>3</sub>)  $\delta$  (ppm): 2.81 (>CH—CH<sub>2</sub>, 2H, doublet, *J*=7 cps), 3.77 (—OCH<sub>3</sub>), 3.83 (OH, NH<sub>2</sub>, 3H, broad), 4.57 (>CH—CH<sub>2</sub>, 1H, triplet, *J*=7 cps), 6.70—7.30 (aromatic protons).

b) Methylation of 2-Amino-1-(3-hydroxyphenyl)ethanol (I) with Diazomethane: An excess of ethereal solution of diazomethane was added to a methanolic solution (10 ml) of 0.3 g of I. The reaction mixture was allowed to stand at room temperature for 38 hr. Evaporation of the solvent afforded VII as a pale yellow oil, whose IR and NMR spectra were identical with those of the above sample.

**3-Acetoxy- $\omega$ -(N,N-dibenzylamino)acetophenone (XVI)**—To a solution of 13 g of 3-acetoxy- $\omega$ -bromoacetophenone (XV)<sup>9)</sup> in 50 ml of absolute EtOH was added 24 g of dibenzylamine and the mixture was heated at 60—70° for 3 hr. After dibenzylamine hydrobromide had been filtered off, the filtrate was evaporated and the residue was extracted with benzene. The benzene extract was washed with water dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give 16 g of XVI as pale yellow needles, which were recrystallized from benzene to give colorless needles, mp 67°. *Anal.* Calcd. for C<sub>24</sub>H<sub>23</sub>O<sub>3</sub>N: C, 77.19; H, 6.21; N, 3.75. Found: C, 76.98; H, 6.44; N, 4.03.

**$\omega$ -(N,N-Dibenzylamino)-3-hydroxyacetophenone (XVII)**—To a solution of 16 g of XVI in 50 ml of MeOH was added 10 ml of conc. HCl and the mixture was refluxed for 3 hr. On cooling, there formed

9) R. Sachs, French Patent, 866, 570 (1941).

crystals, which were collected and recrystallized from EtOH to afford 13 g of hydrochloride of XVII as colorless needles, mp 196°. The  $\text{CHCl}_3$  solution of the above hydrochloride was neutralized with 1N NaOH, washed with water dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to give a solid which was recrystallized from MeOH to afford 11 g of XVII as colorless needles, mp 123°. *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{21}\text{O}_2\text{N}$ : C, 79.73; H, 6.39; N, 4.23. Found: C, 79.85; H, 6.53; N, 4.07.

**2-Amino-(3-hydroxyphenyl)ethanol (I)**—An ethanolic solution (130 ml) of 10 g of XVII·HCl was shaken in a current of  $\text{H}_2$  in the presence of 22 g of 5% Pd-C at 40–60°. After the reaction, the catalyst was removed and the solvent was evaporated to give a syrup, to whose ethanolic solution was introduced a stream of HCl gas. The precipitate was collected and recrystallized from EtOH to give 4.5 g of I as colorless needles, mp 160°. Its IR and NMR spectra were identical with those of an authentic sample and no depression was shown by the mixed melting point test.

**The Reaction between 2-Amino-1-(3-hydroxyphenyl)ethanol (I) or 1-(3-Hydroxyphenyl)-2-methylaminoethanol (II) and Carbonyl Compounds**—An isopropanolic solution of I (or II) and carbonyl compound was refluxed and the solvent was then evaporated to give the residue, which was basified with 28%  $\text{NH}_4\text{OH}$  solution and extracted with  $\text{CHCl}_3$ . The extract was dried over  $\text{Na}_2\text{SO}_4$  and evaporated to give the corresponding 1-substituted-1,2,3,4-tetrahydroisoquinoline as shown in Table I and II.

**1,2,3,4-Tetrahydro-4,6-dihydroxy-1,1,2-trimethylisoquinoline (XXI)**—To a solution of 200 mg of 1,2,3,4-tetrahydro-4,6-dihydroxy-1,1-dimethylisoquinoline (XXVII) in 20 ml of MeOH was added 0.5 ml of 37% formalin and the reaction mixture was stirred for 30 min, to which was added 2.5 g of  $\text{NaBH}_4$  within 15 min. After the stirring had been continued for 45 min, the mixture was acidified with 10% HCl solution. After removal of the solvent, the residue was basified with ammonia and extracted with benzene. The extract was dried over  $\text{Na}_2\text{SO}_4$  and evaporated to leave 80 mg of XXI as colorless needles, mp 162–164°, whose structure was identified with IR spectral comparison and by mixed melting point test with that prepared by the above phenolic cyclization.

**5-(3-Hydroxyphenyl)-3-methyloxazolidine-2-spiro-4'-1'-methylpiperidine (XXVI)**—A mixture of 0.5 g of II and 0.5 g of 1-methyl-4-piperidone in 10 ml of isopropanol was refluxed for 20 hr. The solvent was evaporated and the crude product was recrystallized from isopropanol to yield 0.5 g of XXVI as colorless cubes, mp 176–178°. UV  $\lambda_{\text{max}}^{\text{EtOH}}$  m $\mu$  (log  $\epsilon$ ): 276 (3.28). *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{22}\text{O}_2\text{N}_2$ : C, 68.68; H, 8.45; N, 10.68. Found: C, 68.91; H, 8.21; N, 10.58.

On the other hand, 100 mg of XXVI was refluxed with several drops of conc. HCl for 1 hr. The residue obtained, after evaporation of the solvent, was identified as a mixture of II and 1-methyl-4-piperidone by IR spectrum and thin-layer chromatography.

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