

## Studies on Dimethoxyphenylaminoalcohols. II.<sup>1)</sup> Syntheses and Relative Configurations of 1-Dimethoxyphenyl-3-(alkylamino)butanols

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1-Dimethoxyphenyl-3-(alkylamino)butanols were synthesized by the reduction of the corresponding  $\beta$ -aminoketones. 1-Dimethoxyphenyl-3-aminobutanols were synthesized *via* the hydrogenolyses of the corresponding N-benzyl derivatives. Diastereomers were respectively isolated and their relative configurations were determined by extensive nuclear magnetic resonance studies.

The various diphenylalkanolamines possessing the atropine-like spasmolytic activity have been synthesized and the several compounds among them were practically used as drugs. In 1952, K. Takagi and Y. Kasuya demonstrated<sup>3)</sup> that 1,1-diphenyl-3-piperidinobutanol (I) and its homologues possess remarkable spasmolytic activities and that the activity of the dextrorotatory enantiomer of I was about a hundred times more potent than that of its antipode.<sup>4)</sup> J.P. Long, *et al.* also reported that the levo to dextro activity ratios for the optical isomers of 1-cyclohexyl-1-phenyl-3-piperidinopropanol (II) are 1:157 and 1:500 in rabbits and dogs, respectively.<sup>5)</sup> These compounds possess only one asymmetric center, *viz.*, C<sub>3</sub> in I and C<sub>1</sub> in II. Therefore one enantiomer of the similar compound possessing two asymmetric centers is expected to have the stronger spasmolytic activity. Thus the preparations of 1-phenyl-1-(2',5'-dimethoxyphenyl)-3-piperidinobutanol (III) and its homologues, and their pharmacological tests were carried out getting the interesting results. It seems very interesting to us to clarify the stereochemistry and the absolute configurations of the pharmacologically important compounds of these types and to get some informations of relationships between structures and biological activities. For the purposes of searching new biologically active compounds and of confirming their structures, we started the studies of this series.

This paper deals with the syntheses and the stereochemistry of 1-dimethoxyphenyl-3-(alkylamino)butanols and 1-dimethoxyphenyl-3-aminobutanols.

### A) 1-Dimethoxyphenyl-3-(alkylamino)butanols

As shown in Chart 2, dimethoxyphenyl 2-(alkylamino)propyl ketone (V), prepared from dimethoxyphenyl propenyl ketone (IV) by addition of alkylamine, were converted to the desired aminoalcohols (VI) under the various reductive conditions as described below.

1) **Catalytic Hydrogenation**—The catalytic hydrogenations of  $\beta$ -aminoketones (V) were carried out either with platinum in neutral medium or with Raney nickel in acidic medium. Hydrogenation of 2',5'-dimethoxyphenyl 2-piperidinopropyl ketone (VII) with platinum afforded 2,5-dimethoxyphenylpropyl ketone (VIII) and 1-(2',5'-dimethoxyphenyl)-3-piperidinobutanol (IX) in 50% and 42% yields respectively (*cf.* Chart 3). Hydrogenation of such a Mannich type aminoketone in neutral medium is usually accompanied by deamination. However W. Wenner showed that hydrogenation of 2-methyl-2-aminomethylpropional-

1) Part I: Y. Kasuya, M. Watanabe, Y. Kanai and H. Hamano, *Chem. Pharm. Bull.* (Tokyo), **15**, 481 (1967).

2) Location: a) 3-31, Shimo-cho, Kita-ku, Tokyo; b) 1-1-1, Yayoi, Bunkyo-ku, Tokyo.

3) K. Takagi and Y. Kasuya, *J. Japan Pharm. Assoc.*, **71**, 1328 (1951).

4) Y. Kasuya, *Chem. Pharm. Bull.*, (Tokyo), **6**, 147 (1958).

5) J.P. Long, F.P. Laudueno, B.F. Tulla and A.M. Lands, *J. Pharmacol.*, **117**, 29 (1956).

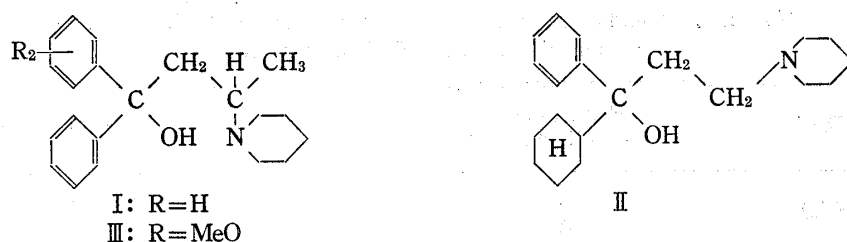


Chart 1

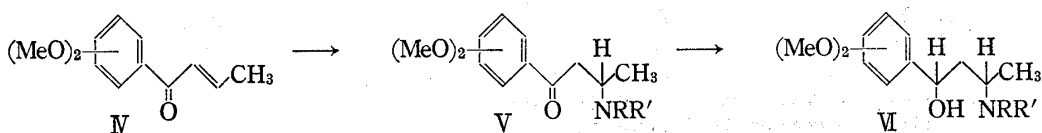


Chart 2

dehyde hydrochloride with Raney nickel gave the corresponding aminoalcohol in high yield.<sup>6)</sup> Thus this undesirable side reaction can be suppressed under the salt-formation of the starting material.

According to the similar conditions, 3,4-dimethoxyphenyl 2-piperidinopropyl ketone (X) was hydrogenated at pH 4.2 with Raney nickel to give aminoalcohol (XIII) in 80% yield. In this case the deamination products, 3',4'-dimethoxyphenyl propyl ketone (XI) and 1-(3',4'-dimethoxyphenyl)butanol (XII), were produced in 14% and 6% yields respectively (*cf.* Chart 4).

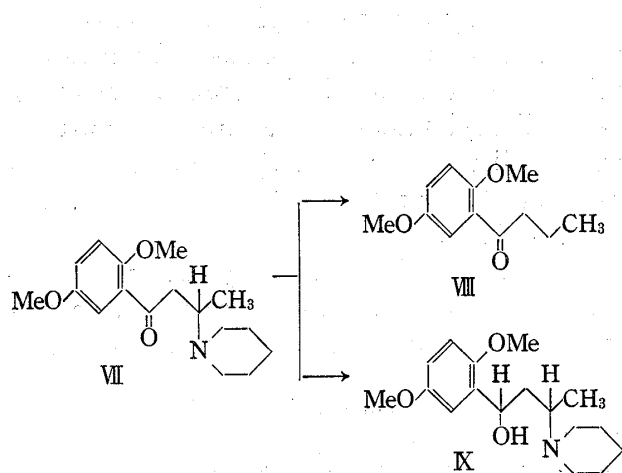


Chart 3

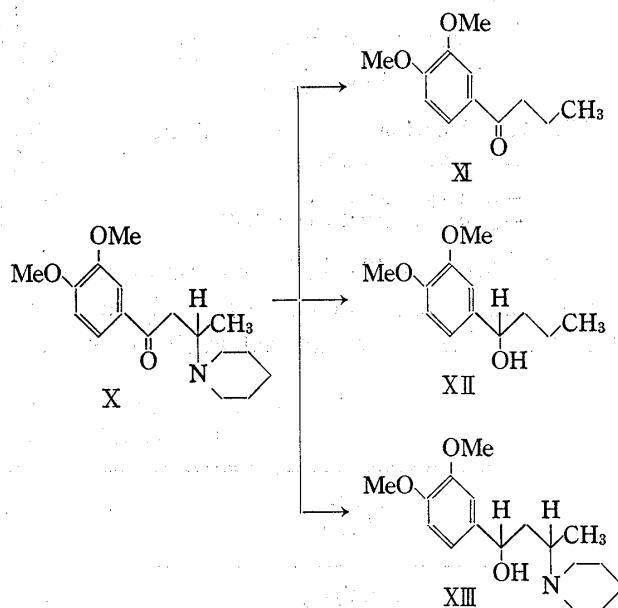



Chart 4

The production ratios of diastereomers were determined by gas liquid chromatography and the results were summarized in Table I. The predominant products were the same as those from metal hydride reductions (*cf.* Section 2) and their stereochemistry was determined as described in Section 3.

It is interesting that the stereoselectivity in hydrogenation was higher with platinum than with Raney nickel. The reaction rate in hydrogenation was much slower with Raney nickel than with platinum as shown in Fig. 1. If the aminoalcohol produced sojourns on the catalyst for a prolonged period, dehydrogenation and rehydrogenation accompanied by iso-

6) W. Wenner, *J. Org. Chem.*, **15**, 301 (1950).

TABLE I. Yields and Ratios of Diastereomers of Aminoalcohols Obtained under Hydrogenation

NRR'	Reaction <sup>a)</sup> condition	Yields (%)	<i>erythro</i> : <i>threo</i> <sup>b)</sup>
-NHC <sub>2</sub> H <sub>5</sub>	A	60	83.0 : 17.0
	B	65	76.2 : 23.8
-N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	A	71	97.7 : 2.3
	B	38	65.0 : 35.0
-N 	A	53	100.0 : 0
	B	40	82.5 : 17.5

a) A: hydrogenation over Pt at atmospheric pressure

B: hydrogenation over Ra-Ni at high pressure

b) These ratios were estimated by GLC.

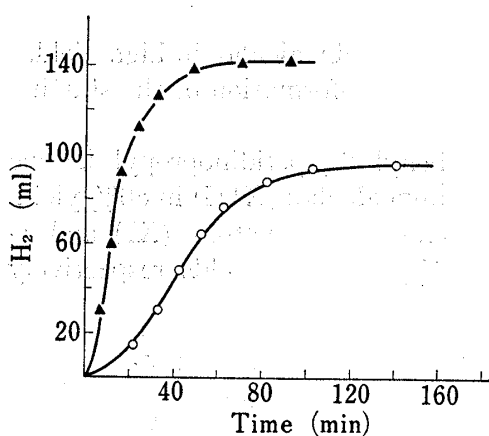





Fig. 1. Reaction Rate on Catalytic Hydrogenation of IX

—▲—: hydrogenation over Pt  
—○—: hydrogenation over Ra-Ni

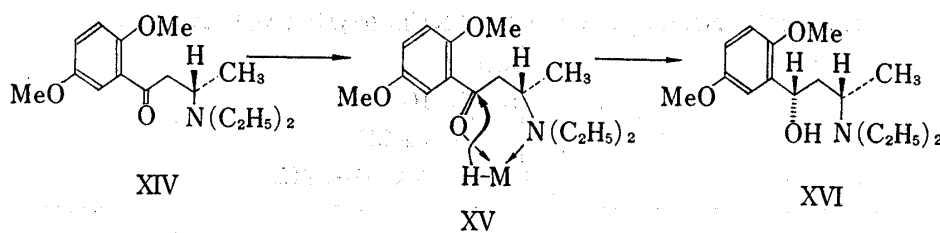
As shown in Table II, the predominant diastereomers in these metal hydride reductions are the same as in the case of catalytic hydrogenation. These phenomena are rationalized as follows. The six-membered cyclic transition state,<sup>7)</sup> shown in Chart 5, plays an important

TABLE II. The Ratios of the Diastereomeric Aminoalcohols Obtained by Metal Hydride Reduction

N 	Metal hydrides	<i>erythro</i> : <i>threo</i> <sup>a)</sup>
NHC <sub>2</sub> H <sub>5</sub>	NaBH <sub>4</sub>	75.3 : 24.7
N(CH <sub>3</sub> ) <sub>2</sub>	NaBH <sub>4</sub>	92.0 : 8.0
N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	LiAlH <sub>4</sub>	80.0 : 20.0
N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	NaBH <sub>4</sub>	92.2 : 7.8
N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	NaAlH <sub>2</sub> (OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ) <sub>2</sub>	65.0 : 35.0
	NaBH <sub>4</sub>	89.3 : 10.7
	NaAlH <sub>2</sub> (OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ) <sub>2</sub>	64.7 : 35.3

a) These were estimated by GLC.

7) The similar transition state was proposed by D.J. Cram and his co-workers for explaining 1,3-asymmetric induction in 2,4-dihydroxy-2,4-diphenylpentane. T.J. Leitery and D.J. Cram, *J. Am. Chem. Soc.*, **90**, 4019 (1968).



role in these reductions. The metal hydride anion is expected to approach to the carbonyl group from the less hindered side opposite to the methyl group (the larger substituent) on the chiral center to furnish diastereomer of the *erythro* type predominantly.

**3) Isolation of Diastereomers and Determination of Their Relative Configurations**—The diastereomers of aminoalcohols are hardly separable by thin-layer chromatography (TLC) and column chromatography, although they are clearly separable on gas-liquid chromatography (GLC). For isolating diastereomers, recrystallizations of crystalline derivatives such as picrate, styphnate or hydrochloride were employed. Usually the salt of predominant compound (*erythro* type) first precipitated and the salt of minor product (*threo* type) precipitated in a different crystal form at a latter stage. The respective crops were cautiously harvested and repeatedly recrystallized. The diastereomers thus isolated are listed in Table III.

TABLE III. Isolated Diastereomers

Compounds	Relative configuration	Styphnates (mp, °C)	M <sup>+</sup> a) (m/e)	t <sub>R</sub> <sup>b)</sup> (min)	Ratios <sup>c)</sup> (%)
 K	A <i>erythro</i>	prisms (128—129)	293	7.6	64.7
	B <i>threo</i>	needles (125—126)	293	6.7	36.7
 XVI	A <i>erythro</i>	needles (102—103)	281	8.5	65.0
	B <i>threo</i>	prisms (133—134)	281	8.0	35.0

a) molecular ion of free base

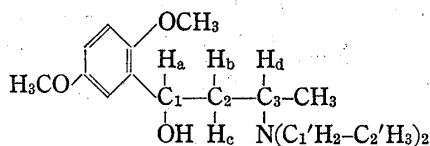
b) Gas-liquid chromatographic conditions are listed in experimental.

c) These ratios were estimated by GLC.

(i) The Determination of the Relative Configurations of 1-(2',5'-Dimethoxyphenyl)-3-(diethylamino)butanols (XVI): To confirm the relative configurations of 1-(2',5'-dimethoxyphenyl)-3-(diethylamino)butanols (XVI), nuclear magnetic resonance (NMR) studies were carried out utilizing spin-spin decoupling techniques. The NMR data of two diastereomers are summarized in Table IV.

In the NMR spectrum of the predominant diastereomer (XVIa), a signal of C<sub>1</sub>-H<sub>a</sub> appeared at  $\delta$  5.16 as a diffused doublet of doublets which changes into a sharp doublet of doublets ( $J=4.8$  and  $7.2$  Hz) under irradiation at  $\delta$  3.25 and into a singlet under irradiation at  $\delta$  1.61 (cf. Fig. 2). The diffused multiplet at  $\delta$  3.25 due to C<sub>3</sub>-H<sub>d</sub> appeared a sharp multiplet under irradiation at  $\delta$  5.16 and a diffused quartet under irradiation at  $\delta$  1.61. The complicated signals, centered at  $\delta$  1.61, corresponding to two protons changed into a AB quartet under double irradiation at  $\delta$  3.25 and 5.16. The chemical shift values and double decoupling data clearly showed that these signals were due to C<sub>2</sub>-H<sub>b</sub> and -H<sub>c</sub>. Nuclear Overhauser effect<sup>8)</sup> (12%

8) This is abbreviated to NOE hereafter.

TABLE IV. NMR Spectral Data of XVIa (*erythro*) and XVIb (*threo*)

	Aromatic protons	C <sub>1</sub> -H <sub>a</sub>	OCH <sub>3</sub>	C <sub>3</sub> -H <sub>d</sub>	C <sub>1</sub> '-H	C <sub>2</sub> '-H <sub>b</sub> / H <sub>c</sub>	C <sub>2</sub> '-H	C-Me
XVIa ( <i>erythro</i> )	7.25—6.60	5.16	3.76 3.77	3.25	2.54	1.79—1.43 (centered at δ 1.61)	1.23	0.95
	m	dd <i>J</i> <sub>ab</sub> =4.8 <i>J</i> <sub>ac</sub> =7.2	sx2	m <i>J</i> <sub>bd</sub> =5.0 <i>J</i> <sub>cd</sub> =9.0	m	m <i>J</i> <sub>bc</sub> =12.5	t <i>J</i> =7.2	d <i>J</i> =7.0
XVIb ( <i>threo</i> )	7.35—6.70	5.20	3.80 3.82	2.97	2.75	2.22 1.73	1.15	0.84
	m	dd <i>J</i> <sub>ab</sub> =3.0 <i>J</i> <sub>ac</sub> =5.5	sx2	m <i>J</i> <sub>bd</sub> =3.0 <i>J</i> <sub>cd</sub> =11.0	m	m <i>J</i> <sub>bc</sub> =14.5	t <i>J</i> =7.2	d <i>J</i> =7.0

chemical shifts: δ *J*=Hz, s: singlet, d: doublet, dd: doublet of doublets, m: multiplet

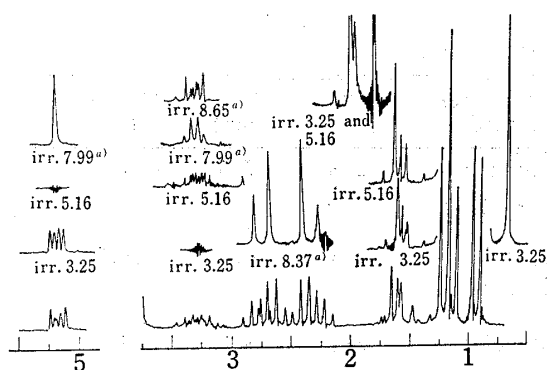


Fig. 2. NMR spectrum of XVIa

a) measured with H<sub>2</sub>SO<sub>4</sub> as external standard

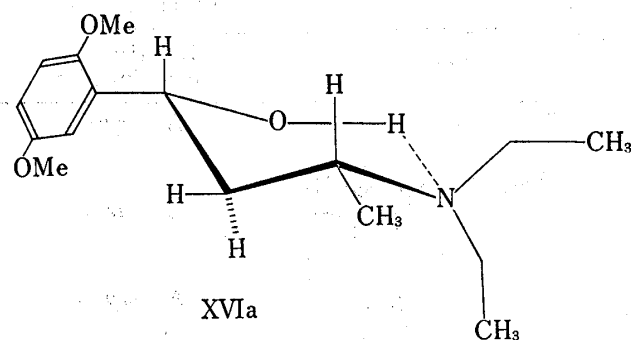


Chart 6

peak intensity increase of H<sub>a</sub> under irradiation at δ 3.25) was observed between H<sub>a</sub> and H<sub>d</sub>. This NOE and clearly observed spin-spin coupling constants of H<sub>a</sub>-H<sub>b</sub>, H<sub>a</sub>-H<sub>c</sub>, H<sub>b</sub>-H<sub>c</sub>, H<sub>b</sub>-H<sub>d</sub>, and H<sub>c</sub>-H<sub>d</sub> demonstrated that this compound possess rather rigid six-membered ring structure formed by intramolecular hydrogen bonding. Furthermore these spin-spin coupling constants are all in quite good agreement with the values expected from the respective H-H dihedral angles in the structure (XVIa) as shown in Chart 6.

On the other hand, infrared (IR) spectrum of this compound exhibited the existence of an intramolecularly hydrogen bonded hydroxyl group (*cf.* Fig. 3).

These results lead to the conclusion that this predominant diastereomer should be the *erythro* type possessing the ring structure in aprotic solution and that the another minor diastereomer the *threo* type. The assignments of these relative configurations were proved to be correct by X-ray crystallographic analysis of the hydrobromide of (–)-XVIa acetate.<sup>9)</sup>

In the NMR spectrum of another diastereomer, the minor product, a signal of C<sub>3</sub>-H<sub>d</sub> appeared at δ 2.97 as a multiplet which was observed as a quartet under double irradiations at δ 1.68 and 2.20 (*cf.* Fig. 4). The multiple signals of C<sub>2</sub>-H<sub>b</sub> and -H<sub>c</sub> appeared at δ 1.68 and 2.20 and changed into two doublets of doublets (*J*=14.5 and 3.0, *J*=14.5 and 11.0 Hz) under

9) Y. Masuda, Y. Iitaka and H. Hamano, *Bull. Chem. Soc. Japan*, **47**, 825 (1974).

irradiation at  $\delta$  5.20. Although the intramolecular hydrogen bonding was also observed in the IR spectrum of this compound, any clear NOE could not be checked between  $C_1$ -Ha and  $C_3$ -Hd or between  $C_1$ -Ha and  $C_3$ -CH<sub>3</sub>. Accordingly the ring conformation is not a true chair but the rather strongly twisted one, if the similar six-membered ring structure of this compound exists.

(ii) The Determination of the Relative Configuration of 1-(2',5'-Dimethoxyphenyl)-3-(dimethylamino)butanol (XVII): The relative configuration of the predominant diastereomer of 1-(2',5'-dimethoxyphenyl)-3-(dimethylamino)butanol (XVII), prepared by the reduction with metal hydride, was similarly determined by NMR analysis. In this compound,

NOE was also observed between Ha and Hd (*cf.* Table V). Then this diastereomer is confirmed to be the *erythro* type.

(iii) The Determination of the Relative Configuration of 1-(2',5'-Dimethoxyphenyl)-3-piperidinobutanol (IX): In the NMR of IX, the signal due to  $C_2$ -Hb, -Hc and  $C_3$ -Hd (the important keys for elucidation of stereochemistry) overlapped on those of piperidine ring protons. To distinguish these signals, 1-(2',5'-dimethoxyphenyl)-3-piperidino-d<sub>10</sub>-butanol (IXd) was prepared

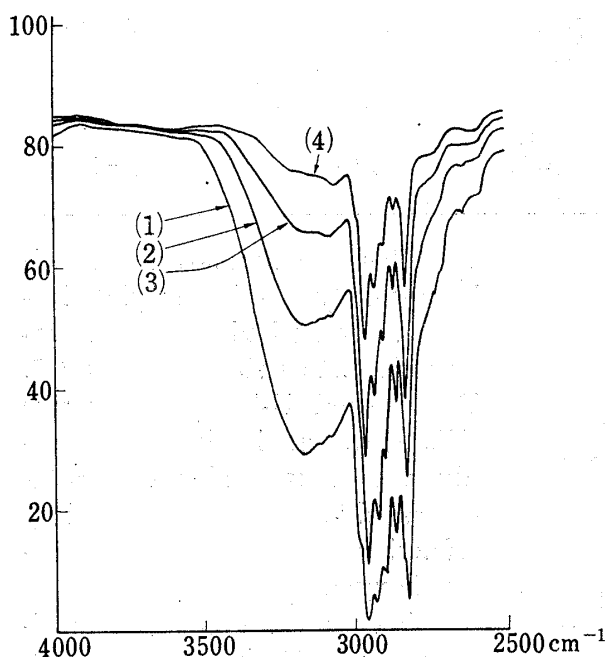


Fig. 3. OH-Stretching Vibration on IR Spectrum of XVIa

solvent: CCl<sub>4</sub>  
 thickness: 5 mm  
 concentration: (1) 11.26 mmole  
 (2) 5.58 mmole  
 (3) 2.79 mmole  
 (4) 1.40 mmole

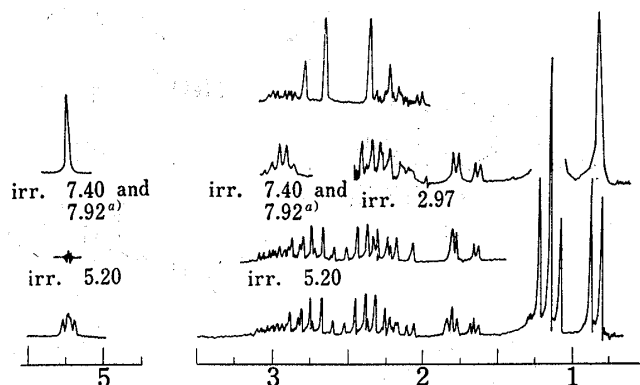


Fig. 4. NMR spectrum of XVIIb

a) measured with H<sub>2</sub>SO<sub>4</sub> as external standard

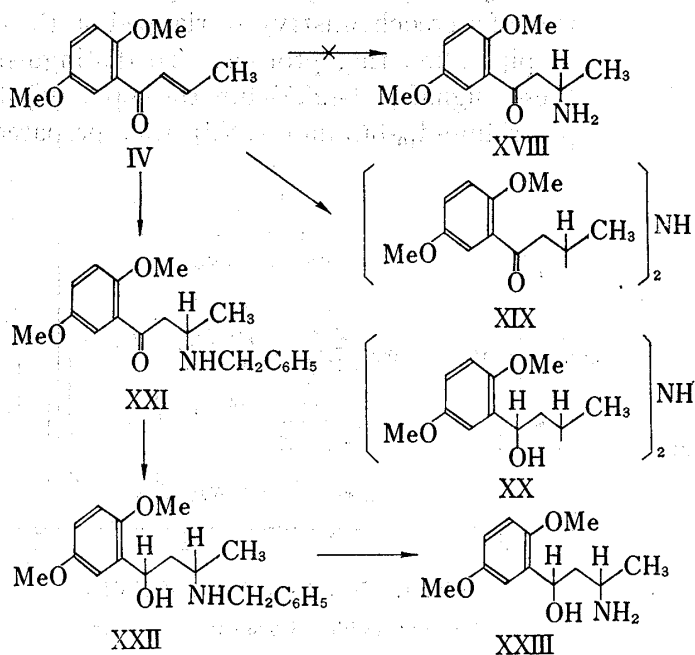
by the stereoselective hydrogenation of the corresponding deuterated  $\beta$ -aminoketone. In the NMR of IXd, NOE (6.9% peak intensity increase of  $C_1$ -Ha under irradiation at  $\delta$  3.06 and 18.7% increase of  $C_3$ -Hd under irradiation at  $\delta$  5.18) was also observed between Ha and Hd (*cf.* Table V). Then the relative configuration of the aminoalcohol (IX) was confirmed to be the *erythro* type.

### B) 1-Dimethoxyphenyl-3-aminobutanol (XXIII)

Although the similar procedures described in Chapter A were first attempted for the preparation of 1-dimethoxyphenyl-3-aminobutanol (XXIII), addition of ammonia to  $\alpha,\beta$ -unsaturated ketone (IV) did not afford the desired primary amine (XVIII) at all. The NMR spectrum of the sole product in this addition reaction showed that the ratio of the signal intensities of CH<sub>3</sub>O and NH was 6/1. The data of elemental analysis of the hydrochloride gave the empirical formula, C<sub>24</sub>H<sub>32</sub>O<sub>6</sub>NCl. Mass spectrum of trimethylsilyl derivative of aminoalcohol (XX), derived by sodium borohydride reduction of this compound, exhibited M<sup>+</sup> ion peak [577: Calcd. for C<sub>24</sub>H<sub>33</sub>O<sub>6</sub>N·2 Si(CH<sub>3</sub>)<sub>3</sub>]. From these data the structure of this sole product was assigned to be  $\alpha,\alpha'$ -bis(2',5'-dimethoxyphenacyl)diethylamine (XIX).

TABLE V. NMR Spectral data of XVII and IXd:

	Aromatic protons	C <sub>1</sub> -H <sub>a</sub>	OMe	C <sub>3</sub> -H <sub>d</sub>	C <sub>2</sub> $\begin{matrix} \nearrow \text{H}_b \\ \searrow \text{H}_c \end{matrix}$	C(Me) <sub>2</sub>	C-Me
XVII	7.15—6.75	4.86	3.86 3.89	3.07	1.45 1.72	2.30	0.93
	m	dd	s × 2	m	m	s	d
		$J_{ab}=3.2$ $J_{ac}=10.0$		$J_{bd}=3.3$ $J_{cd}=10.9$	$J_{bc}=13.7$		$J=6.0$
IXd	7.30—6.70	5.18	3.76 3.78	3.06	1.58 1.64	—	0.95
	m	dd	s × 2	m	m		d
		$J_{ab}=6.0$ $J_{ac}=6.0$		$J_{bd}=7.0$ $J_{cd}=7.0$	$J_{bc}=9.0$		$J=7.0$



Then the alternative route *via* hydrogenolysis of N-benzyl derivative of the desired compound was investigated as shown in Chart 7. The desired N-benzyl derivative (XXII) was easily obtained by addition of benzylamine to  $\alpha,\beta$ -unsaturated ketone (IV), followed by reduction with sodium bis(2-methoxyethoxy)aluminum hydride.

One of these benzylaminoalcohols, 1-(2',5'-dimethoxyphenyl)-3-(benzylamino)butanol (XXII) was separated into the respective diastereomers *via* picrates. The major diastereomer was smoothly cleaved by hydrogenolysis to give one of diastereomer of 1-(2',5'-dimethoxyphenyl)-3-aminobutanol (XXIII).

This product was chemically inter-related to known *erythro*-1-(2',5'-dimethoxyphenyl)-3-(diethylamino)butanol (XVIa) as seen in Chart 8. Consequently the major diastereomer produced by reduction with metal hydride is the *erythro* type, as expected.

The hydrogenolysis of the minor diastereomer of XXII under the similar conditions did not give the expected aminoalcohol but the simultaneous hydrogenolysis of benzyl alcohol also took place to afford 2,5-dimethoxy-3'-aminobutylbenzene as a sole product.

In this case, it may be assumed that the hydroxyl group to be removed by hydrogenolysis is located near to the surface of the catalyst contrary to the case of another diastereomer.

As described above, seventeen new derivatives of dimethoxyphenylaminoalcohol were prepared and their pharmacological tests were made. None of them exhibited any significant spasmolytic activity and this strongly suggests that two phenyl groups are necessary for revelation of spasmolytic activity in this series. However, it is interesting that some of them potentiate the antitussive action of codein phosphate and the details will be presented elsewhere.

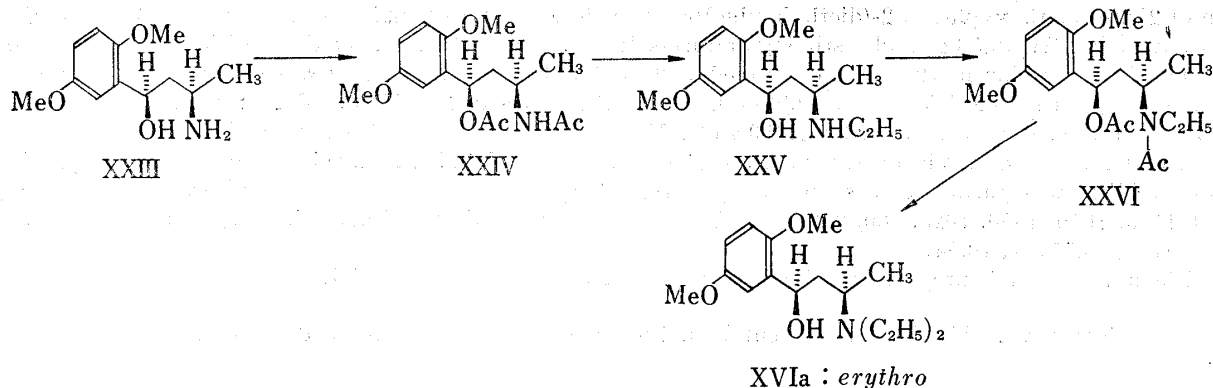


Chart 8

### Experimental

Melting points were determined on a Mitamura micromelting point apparatus and uncorrected. Ultraviolet (UV), IR, NMR and mass spectra were taken on a Hitachi 124 spectrophotometer, JASCO IR-G spectrophotometer, Varian HA-100D (in  $\text{CDCl}_3$  solution with TMS as internal standard), and Shimadzu LKB 9000s (at 70 eV), respectively. All gas-liquid chromatograms (GLC) were measured with a Shimadzu GC-5APTF (hydrogen flame ionization detector).

**Catalytic Hydrogenation of 2',5'-Dimethoxyphenyl 2-Piperidinopropyl Ketone (VI)**—VI (1.040 g)<sup>1)</sup> was dissolved in EtOH (20 ml) and hydrogenated over Pt (100 mg) under atmospheric pressure of hydrogen and at room temperature. After absorption of 1 mole of  $\text{H}_2$ , the reaction mixture was filtered and the filtrate was concentrated to dryness *in vacuo* to give pale yellow oil. The oil was dissolved in ether and extracted with  $3 \times 15$  ml of 1N HCl. The HCl-layer was washed with ether and basified with 10%  $\text{NH}_4\text{OH}$ . The oil precipitated was extracted with  $3 \times 20$  ml of ether, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated *in vacuo* to give an oily 1-(2',5'-dimethoxyphenyl)-3-piperidinobutanol (VIIa) (440 mg, 43%),<sup>10)</sup> which showed a single peak in GLC (3% OV-17 on Chromosorb W-HP, 80—100 mesh, 2 m, column temp. 235°).

Mass Spectrum  $m/e$ : 293 ( $\text{M}^+$ ). IR  $\nu_{\text{max}}^{\text{film}}$   $\text{cm}^{-1}$ : 3400—3050, 1500, 1275, 1240, 1210, 1155, 1050. Styphnate, mp 128—129° (EtOH). Anal. Calcd. for  $\text{C}_{23}\text{H}_{30}\text{O}_4\text{N}_4$ : C, 51.29; H, 5.61; N, 10.40. Found: C, 51.28; H, 5.41; N, 10.67.

The ethereal solution, from which the base removed, was washed with  $\text{H}_2\text{O}$ , and dried over  $\text{Na}_2\text{SO}_4$ . The ether was evaporated to give an oily 2',5'-dimethoxyphenyl propyl ketone (VII) (370 mg, 50%). Mass Spectrum  $m/e$ : 208 ( $\text{M}^+$ ). IR  $\nu_{\text{max}}^{\text{film}}$ : 1675  $\text{cm}^{-1}$ . 2,4-Dinitrophenylhydrazone, mp 154—159°. Anal. Calcd. for  $\text{C}_{18}\text{H}_{20}\text{O}_6\text{N}_4$ : C, 55.66; H, 5.19; N, 14.43. Found: C, 55.46; H, 5.26; N, 14.32.

**Catalytic Hydrogenation of 3',4'-Dimethoxyphenyl 2-Piperidinopropyl Ketone (IX)**—The mixture of IX (3.480 g), and W-7 Raney nickel (freshly prepared from 2 g of alloy)<sup>11)</sup> in a mixture of EtOH (30 ml) and 5% HCl (15 ml). The hydrogenation was carried out at 40—50° under initial hydrogen pressure of 100  $\text{kg}/\text{cm}^2$  (27°) for 3 hr. The catalyst was filtered off. GLC of the filtrate indicated the presence of 1-(3',4'-dimethoxyphenyl)-3-piperidinobutanol (X), 3',4'-dimethoxyphenyl propyl ketone (XI) and 1-(3',4'-dimethoxyphenyl)-butanol (XII) in ratios (80:14:6). The usual work-up afforded basic oil (2.943 g, 84%). To a solution of the base in EtOH (10 ml) was added the solution of picric acid (2.400 g) in EtOH (15 ml). The picrate precipitated was filtered, and recrystallized from EtOH to yield 4.680 g (75% based on IX) of X, mp 150—151°. Anal. Calcd. for  $\text{C}_{23}\text{H}_{30}\text{O}_4\text{N}_4$ : C, 57.50; H, 5.47; N, 8.94. Found: C, 57.21; H, 5.32; N, 8.80.

The neutral residue (400 mg) was fractionated by column chromatography on silica gel (20 g) using petr. ether—benzene (1:1) as eluent. The first fraction was XI (220 mg), and the second was XII (125 mg). XI: mp 52—53° (petr. ether). IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1675, 1495, 1380, 1220, 1150, 1050. NMR ( $\text{CDCl}_3$ ),  $\delta$  ( $J=\text{Hz}$ ): 0.96 (3H, t,  $J=7.0$ ,  $-\text{CH}_2\text{CH}_3$ ), 1.70 (2H, m,  $-\text{CH}_2-\text{CH}_2-\text{CH}_3$ ), 2.84 (2H, t,  $J=7.0$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ), 3.86 (6H, s,  $-\text{OCH}_3 \times 2$ ), 6.72 (1H, d,  $J=9.0$ , aromatic proton), 7.43 (2H, m, aromatic protons). Anal. Calcd. for  $\text{C}_{12}\text{H}_{16}\text{O}_3$ : C, 69.21; H, 7.74. Found: C, 69.39; H, 7.48. XII: mp 64—65° (petr. ether). NMR,  $\delta$  ( $J=\text{Hz}$ ): 0.95 (3H, t,  $J=6.0$ ,  $-\text{CH}_2-\text{CH}_3$ ), 1.07—1.83 (4H, m,  $-\text{CH}_2-\text{CH}_2-\text{CH}_3$ ), 1.97 (1H, s,  $-\text{OH}$ ), 3.83 (6H, s,  $-\text{OCH}_3 \times 2$ ), 4.53 (1H, t,  $J=6.0$ ,  $-\text{CH}-\text{OH}$ ), 6.73—6.86 (3H, m, aromatic protons). Anal. Calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_3$ : C, 68.54; H, 8.63. Found: C, 68.59; H, 8.46.

10) This procedure for extraction of base was generally used in the following experiments.

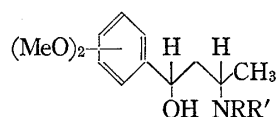
11) H.R. Bilica and H. Adkins, *Org. Syn.*, Coll. Vol. 3, 176 (1955).



**1-(2',5'-Dimethoxyphenyl)-3-(diethylamino)butanol (XIV)**—(a) Reduction with  $\text{NaBH}_4$ : To a solution of 2',5'-dimethoxyphenyl 2-(diethylamino)propyl ketone (XIII)<sup>1)</sup> (3.625 g) in MeOH (50 ml) was added portionwise  $\text{NaBH}_4$  (0.58 g) under stirring and ice-salt cooling at  $-10^\circ$ . After the addition was completed, stirring of the reaction mixture was continued at  $0-3^\circ$  for 1 hr<sup>12)</sup> (the reaction was monitored by following disappearance of ketone UV band at 330 nm). After the excess of  $\text{NaBH}_4$  was decomposed by addition of AcOH (1 ml), usual work-up afforded 2.359 g of XIV as a pale yellow oil. This was estimated as a 92.2:7.8 mixture of XIVa and XIVb by GLC (3% OV-17 on Chromosorb W-HP, 2 m, column temp.  $220^\circ$ ). *Erythro* isomer (XIVa) was purified as a styphnate, mp  $102-103^\circ$  (EtOH). IR (free base)  $\nu_{\text{max}}^{\text{film}}$ ,  $\text{cm}^{-1}$ : 3150, 1495, 1220, 1155, 1070, 1050, 1028, 880, 800. *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{30}\text{O}_{11}\text{N}_4$ : C, 50.19; H, 5.74; N, 10.64. Found: C, 50.04; H, 5.77; N, 10.54.

The aminoalcohols prepared by the similar method were listed in Table VI.

TABLE VI. Yields and Elemental Analysis of Aminoalcohols Obtained by Reduction



No.	Position of methoxy group	NRR'	Yield (%)		mp of free base or derivative	Analysis (%)		
						Found. (Calcd.)		
						C	H	N
1	2',5'	$-\text{N}(\text{CH}_3)_2$	75 <sup>a)</sup>	63 <sup>b)</sup>	S <sup>c)</sup> 136—137	48.00 (48.19)	5.04 (5.26)	11.48 (11.24)
2	2',5'	$-\text{NH}(\text{iso-Pr})$	80	77	S 151—152	49.35 (49.22)	5.61 (5.51)	10.90 (10.93)
3	2',5'		85	70	F 70—71	68.90 (68.78)	8.93 (9.02)	5.02 (5.01)
4	2',5'		95	85	S 149—150	48.81 (48.89)	5.03 (5.22)	10.61 (10.37)
5	2',4'	$-\text{NH}(\text{iso-Pr})$	95	60	F 75—76	67.31 (67.38)	9.23 (9.43)	5.18 (5.24)
6	2',4'		88	65	F 69—70	69.81 (69.59)	9.33 (9.28)	4.82 (4.77)
7	2',4'		90	60	P 143—144	50.74 (50.38)	5.59 (5.38)	10.78 (10.68)
8	3',4'	$-\text{N}(\text{CH}_3)_2$	75	65	P 132—133	49.53 (49.79)	5.50 (5.92)	11.68 (11.61)
9	3',4'	$-\text{N}(\text{C}_2\text{H}_5)_2$	80	57	P 133—134	51.39 (51.76)	5.85 (5.92)	10.96 (10.98)
10	3',4'		90	63	F 76—77	69.01 (68.78)	9.06 (9.02)	5.13 (5.01)
11	3',4'		89	80	P 150—151	57.21 (57.50)	5.32 (5.47)	8.80 (8.94)
12	3',4'		90	60	S 157—158	49.19 (48.89)	5.50 (5.22)	10.39 (10.37)

a) yield in catalytic hydrogenation

b) yield in  $\text{NaBH}_4$ -reduction

c) F: free base, S: styphnate, P: picrate

(b) Reduction with  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ : To a solution of  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$  (20 g, 67% solution of benzene) in anhydrous ether (100 ml) was added dropwise a solution of XIII (20 g) in anhydrous ether (50 ml) under vigorous stirring and ice-salt cooling (at  $-10^\circ$ ) during period of 30 min. After the addition was completed the stirring was continued for further 1 hr at  $-10-5^\circ$ , then  $\text{H}_2\text{O}$  (10 ml) was dropwise added to decompose the excess of  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$  and 10% NaOH (30 ml) was added. The organic layer was separated, and the aqueous layer was extracted with ether ( $3 \times 50$  ml). The combined organic layer was treated as usual to give crude aminoalcohol (14.0 g, 69%), a 65:35 mixture of XIVa and XIVb (GLC). To the solution of this mixture in EtOH (50 ml) was added a solution of styphnic acid (12.2 g) in EtOH (50 ml) under stirring, and allowed to stand overnight at  $5^\circ$ . The first crop (15.5 g), fine needles,

12) When  $\text{NaBH}_4$  was added at room temp., and the reaction was carried out at  $25-30^\circ$ , 1-(2',5'-dimethoxyphenyl)butanol was obtained as a sole product.

mp 95—98°, mainly consisted of XIVa-styphnate, and the second crop (8.0 g) precipitated after concentration of the filtrate into 1/2 volume mainly consisted of XIVb-styphnate. Recrystallizations from EtOH gave pure styphnates, mp 102—103° (XIVa-styphnate,<sup>13</sup> 12.4 g), and mp 133—134° (XIVb-styphnate, 6.0 g). XIVb: Mass Spectrum (free base)<sup>14</sup> *m/e*: 281 (M<sup>+</sup>). IR (free base)  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 3150, 1495, 1215, 1180, 1080, 1050, 980. *Anal.* Calcd. for C<sub>22</sub>H<sub>30</sub>O<sub>11</sub>N<sub>4</sub>: C, 50.19; H, 5.74; N, 10.64. Found: C, 50.31; H, 5.84; N, 10.73.

**1-(2',5'-Dimethoxyphenyl)-3-piperidinobutanol (VIIIa and VIIIb)**—To a solution of NaAlH<sub>2</sub>(OCH<sub>2</sub>CH<sub>2</sub>-OCH<sub>3</sub>)<sub>2</sub> (17.2 g, 70% solution of benzene) in anhydrous ether (70 ml) was added dropwise a solution of VI (14.6 g) in anhydrous ether (50 ml) at -10° under ice-salt cooling and vigorous stirring during period of 30 min. After the addition was completed, the reaction mixture was stirred at -10—5° for further 1.5 hr (the reaction was monitored by the preceding method), H<sub>2</sub>O (10 ml) was dropwise added to decompose the excess of reducing agent, and then 10% NaOH (30 ml) was added. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 70 ml). The combined organic layer was treated as usual to give crude aminoalcohol (13.5 g, 92.5%), 64.5:35.5 mixture of VIIIa and VIIIb by GLC (3%, OV-17, on chromosorb W-HP, 2 m, column temp. 235°).

To a solution of the base in EtOH (70 ml) was added a solution of styphnic acid (12.4 g) in EtOH (50 ml), and allowed to stand overnight at 5°. The first crop (12.6 g, orange yellow prisms) mainly consisted of VIIIa-styphnate. The yellow needles (6.3 g) precipitated after concentration of the filtrate into 1/2 volume mainly consisted of VIIIb-styphnate. Recrystallization from EtOH gave pure styphnates, mp 128—129° (VIIIa-styphnate, *vide supra*), mp 125—126° (VIIIb-styphnate), respectively. VIIIb: IR (free base)  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 3400—3050, 1500, 1280, 1245, 1160, 1060. *Anal.* Calcd. for C<sub>23</sub>H<sub>30</sub>O<sub>11</sub>N<sub>4</sub>: C, 51.29; H, 5.61; N, 10.40. Found: C, 51.40; H, 5.58; N, 10.32.

**1-(2',5'-Dimethoxyphenyl)-3-piperidino-d<sub>10</sub>-butanol (IX-d)**—(i) Piperidine-d<sub>10</sub>: Pyridine-d<sub>5</sub> (4 ml) (Merck) in cyclohexane (15 ml) was hydrogenated under D<sub>2</sub> atmosphere (6 kg/cm<sup>2</sup>) over Pt-Rh (1:3) (Kawaken Fine Chemicals Co. Ltd.) (100 mg) at room temperature. After absorption of D<sub>2</sub> completed, catalyst was filtered off, and the filtrate was stirred with H<sub>2</sub>O (1 ml) containing trace of *p*-toluenesulfonic acid monohydrate at room temperature for 20 hr. The reaction mixture was dried over molecular sieve-4A, and the resulted piperidine-d<sub>10</sub> in cyclohexane was employed for following investigation without further purification.

(ii) 2,5-Dimethoxyphenyl 2'-piperidino-d<sub>10</sub>-propyl Ketone (VI-d<sub>10</sub>): To the above solution of piperidine-d<sub>10</sub> in cyclohexane was added a solution of IV (10 g) in cyclohexane (10 ml), and the mixture was stirred at room temperature overnight. Work-up as usual afforded 7.372 g of VI-d<sub>10</sub>. IR  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 2200, 2100, 1680, 1500, 1285, 1228. Picrate, mp 140—141°. *Anal.* Calcd. for C<sub>23</sub>H<sub>18</sub>D<sub>10</sub>O<sub>10</sub>N<sub>4</sub>: C, 52.07; H+D, 7.22; N, 10.56. Found: C, 52.10; H+D, 7.28; N, 10.66.

(iii) 1-(2',5'-Dimethoxyphenyl)-3-piperidino-d<sub>10</sub>-butanol (IX-d): VI-d (1.933 g) in EtOH (20 ml) was hydrogenated over PtO<sub>2</sub> (200 mg) under atmospheric pressure at room temperature for 40 min. Usual work-up afforded IX-d (1.44 g). Mass Spectrum *m/e*: 303 (M<sup>+</sup>). IR  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 3200—3050, 2350, 2250, 2200, 1595, 1495, 1280, 1210, 1050. Styphnate, mp 135—136° (EtOH). *Anal.* Calcd. for C<sub>23</sub>H<sub>20</sub>D<sub>10</sub>O<sub>11</sub>N<sub>4</sub>: C, 50.36; H+D, 7.30; N, 10.22. Found: C, 50.44; H+D, 7.48; N, 10.23.

**Addition Reaction of NH<sub>3</sub> to 2,5-Dimethoxyphenyl Propenyl Ketone (IV)**—A solution of IV (10.3 g) in toluene (20 ml) was saturated with gaseous NH<sub>3</sub> under ice-cooling. The reaction mixture was allowed to stand at room temperature overnight. Usual work-up afforded crude crystals. Recrystallization from EtOH gave 6.4 g (60%) of  $\alpha,\alpha'$ -bis(2',5'-dimethoxyphenacyl)diethylamine (XIX), mp 149—150°. UV  $\lambda_{\max}^{\text{EtOH}}$  m $\mu$  (log  $\epsilon$ ): 262 (3.85), 295 (3.80), 340 (3.75). IR  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 3460, 1650, 1460, 1375, 1230, 1050. NMR (CDCl<sub>3</sub>)  $\delta$  (*J*=Hz): 1.10 (3H, d, *J*=6.0, -CH-CH<sub>3</sub>), 1.17 (3H, d, *J*=6.0, -CH-CH<sub>3</sub>), 1.48—2.25 (4H, m, -CO-CH<sub>2</sub>-CH-CH<sub>3</sub> × 2), 3.57 (6H, s, -OCH<sub>3</sub> × 2), 3.70 (3H, s, -OCH<sub>3</sub>), 3.76 (3H, s, -OCH<sub>3</sub>), 3.40—3.80 (2H, m, -CH<sub>2</sub>-CHN-CH<sub>3</sub> × 2), 4.32 (1H, s, NH), 6.27—6.86 (6H, m, aromatic protons). Hydrochloride, mp 232—233° (MeOH-ether). *Anal.* Calcd. for C<sub>24</sub>H<sub>32</sub>O<sub>6</sub>NCl: C, 61.86; H, 6.92; N, 3.01. Found: C, 61.59; H, 6.82; N, 2.98. To a solution of XIX (200 mg) in EtOH (20 ml) was added NaBH<sub>4</sub> (200 mg). The mixture was stirred at 70° for 15 hr. Usual work-up afforded a pale yellow viscous oil. IR  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 3350—2500. This crude reductant was heated with *N,O*-bis(trimethylsilyl)acetamide in pyridine at 60° for 30 min, and the trimethylsilyl thus obtained was used as the sample of GC-MS. Mass Spectrum *m/e*: 577 (M<sup>+</sup>).

**2,5-Dimethoxyphenyl 2'-(Benzylamino)propyl Ketone (XXI)**—To a solution of IV (20.6 g) in toluene (50 ml) was added a solution of benzylamine (16.0 g) in toluene (20 ml) at 5—10° under ice-cooling. The reaction mixture was stirred at room temperature overnight. Usual work-up afforded an oily base, which was purified as hydrochloride, mp 129—130.5° (26.6 g, 73%). NMR (free base) (CDCl<sub>3</sub>)  $\delta$  (*J*=Hz): 1.18 (3H, d, *J*=6.5, -CH-CH<sub>3</sub>), 1.94 (1H, broad s, -NH-), 3.05 (1H, d, *J*=14.0, -CH-CH<sub>2</sub>-CH-), 3.25 (1H, d, *J*=14.0, -CH-CH<sub>2</sub>-CH), 3.55 (1H, m, CH<sub>2</sub>-CHN-CH<sub>3</sub>), 3.66 (1H, d, *J*=13.0, -CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>), 3.95 (1H, d, *J*=

13) *Vide supra*.

14) Styphnate or Picrate was dissolved in CHCl<sub>3</sub> and shaken repeatedly with dil. NH<sub>4</sub>OH and then washed with H<sub>2</sub>O. Usual work up of the CHCl<sub>3</sub> layer gave free base.

13.0,  $-\text{CH}_2-\text{C}_6\text{H}_5$ ), 3.77 (3H, s,  $-\text{OCH}_3$ ), 3.81 (1H, s,  $-\text{OCH}_3$ ), 7.17—7.80 (8H, m, aromatic protons). *Anal.* Calcd. for  $\text{C}_{19}\text{H}_{24}\text{O}_3\text{NCl}$ : C, 65.22; H, 6.91; N, 4.00. Found: C, 65.18; H, 6.78; N, 4.20.

**1-(2',5'-Dimethoxyphenyl)-3-(benzylamino)butanol (XXII)**—To a solution of  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$  (30.3 g, 67% solution of benzene) in anhydrous ether (60 ml), was added dropwise a solution of XXI (50 g) in anhydrous ether (240 ml) at  $-5^\circ$  during a period of 1 hr under ice-salt cooling. The reaction mixture was stirred at room temperature further for 1.5 hr and then poured carefully into ice- $\text{H}_2\text{O}$ . After 10% NaOH was added, the organic layer was separated. Usual work-up afforded 46.0 g (91%) of crude XIX, a 30.2:69.8 mixture of XXIIa and XXIIb by GLC (OV-17.3%. Chromosorb W-HP, 1 m, column temp.  $230^\circ$ ). To a solution of XIX in EtOH (200 ml) was added a solution of picric acid (33.6 g) in EtOH (120 ml). The mixture was allowed to stand at room temperature overnight to give pale yellow needles of the picrate of the diastereomer A (XXIIa), mp  $177\text{--}179^\circ$  (11.9 g). Analytical sample was recrystallized from EtOH to give fine needles, mp  $179.5\text{--}180.5^\circ$ . NMR (free base) ( $\text{CDCl}_3$ )  $\delta$  ( $J=\text{Hz}$ ): 1.18 (3H, d,  $J=6.0$ ,  $-\text{CH}-\text{CH}_3$ ), 1.43 (1H, m,  $J=14.0$ , 10.0, 10.0,  $-\text{CH}-\text{CH}_2-\text{CH}-$ ), 1.87 (1H, m,  $J=14.0$ , 10.0, 10.0,  $-\text{CH}-\text{CH}_2-\text{CH}$ ), 3.11 (1H, m,  $-\text{CH}_2-\text{CHN}-\text{CH}_3$ ), 3.73 (3H, s,  $-\text{OCH}_3$ ), 3.76 (3H, s,  $-\text{OCH}_3$ ), 3.80 (1H, d,  $J=13.0$ ,  $-\text{CH}_2-\text{C}_6\text{H}_5$ ), 3.98 (1H, d,  $J=13.0$ ,  $-\text{CH}_2-\text{C}_6\text{H}_5$ ), 4.11 (2H, broad s,  $-\text{NH}$ , OH), 5.19 (1H, dd,  $J=2.5$ , 10.0,  $-\text{CHOH}-\text{CH}_2-$ ), 6.81—7.45 (8H, m, aromatic protons). Mass Spectrum (free base)  $m/e$ : 315 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{25}\text{H}_{28}\text{O}_{10}\text{N}_4$ : C, 55.14; H, 5.18; N, 10.29. Found: C, 55.10; H, 5.09; N, 10.64.

From the mother liquor, orange yellow prisms, the picrate of the diastereomer B (XXIIb), mp  $145\text{--}146^\circ$ , were obtained. Analytical sample was recrystallized from EtOH to give prisms, mp  $148\text{--}149^\circ$ . NMR (free base) ( $\text{CDCl}_3$ )  $\delta$  ( $J=\text{Hz}$ ): 1.23 (3H, d,  $J=6.5$ ,  $-\text{CHN}-\text{CH}_3$ ), 1.87 (2H, m,  $J_{\text{gem}}=11.0$ ,  $-\text{CHOH}-\text{CH}_2-\text{CHN}-$ ), 3.03 (1H, m,  $J=5.1$ , 4.9,  $-\text{CH}_2-\text{CHN}-\text{CH}_3$ ), 3.76 (3H, s,  $-\text{OCH}_3$ ), 3.82 (3H, s,  $-\text{OCH}_3$ ), 4.10 (2H, broad s,  $-\text{NH}$ ,  $-\text{OH}$ ), 5.33 (1H, dd,  $J=5.1$ , 5.5,  $-\text{CHOH}$ ), 6.74—7.38 (8H, m, aromatic protons). Mass Spectrum (free base)  $m/e$ : 315 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{25}\text{H}_{28}\text{O}_{10}\text{N}_4$ : C, 55.14, H, 5.18; N, 10.29. Found: C, 55.06; H, 5.10; N, 10.59.

**Hydrogenolysis of XXIIa**—The benzylaminoalcohol XXIIa (2.102 g) in a mixture of EtOH (10 ml) and conc. HCl (0.1 ml) was hydrogenated over 10% Pd-C (0.800 g) at  $75\text{--}80^\circ$  under initial hydrogen pressure of  $110\text{ kg/cm}^2$  ( $27^\circ$ ) for 2 hr. Usual work-up afforded a pale yellow oil (1.320 g), which was chromatographed with elution by benzene-EtOH (9:1) to yield a colorless oil, 1-(2',5'-dimethoxyphenyl)-3-aminobutanol (XXIII) (1.238 g, 82%). IR  $\nu_{\text{max}}^{\text{film}}$   $\text{cm}^{-1}$ : 3350, 3300, 1500, 1210, 1050. NMR ( $\text{CDCl}_3$ )  $\delta$  ( $J=\text{Hz}$ ): 1.11 (3H, d,  $J=6.0$ ,  $-\text{CH}-\text{CH}_3$ ), 1.54—1.96 (2H, m,  $J=14.5$ , 4.5, 5.5, 5.5, 7.0,  $-\text{CHOH}-\text{CH}_2-\text{CHN}-$ ), 2.95 (3H, s,  $\text{NH}_2$ ,  $-\text{OH}$ ), 3.08 (1H, m,  $J=5.5$ , 5.5,  $-\text{CH}_2-\text{CHN}-\text{CH}_3$ ), 4.76 (6H, s,  $-\text{OCH}_3 \times 2$ ), 5.24 (1H, dd,  $J=7.0$ , 4.5,  $-\text{CHOH}-$ ), 6.72—7.15 (3H, m, aromatic protons). Mass Spectrum  $m/e$ : 225 ( $\text{M}^+$ ). Picrate, mp  $129.5\text{--}130^\circ$  (EtOH). *Anal.* Calcd. for  $\text{C}_{18}\text{H}_{22}\text{O}_{10}\text{N}_4$ : C, 47.54; H, 4.88; N, 12.33. Found: C, 47.32; H, 4.98; N, 12.58.

**Hydrogenolysis of XXIIb**—The benzylaminoalcohol (XXIIb) (4.500 g) in a mixture of EtOH (70 ml) and conc. HCl (0.3 ml) was hydrogenated over 10% Pd-C (2 g) at  $78\text{--}90^\circ$  under initial hydrogen pressure of  $120\text{ kg/cm}^2$  ( $27^\circ$ ) for 3 hr. Usual work-up afforded a yellow oil (2.288 g), which was chromatographed on silica gel (40 g) to give 2,5-dimethoxy-3'-aminobutylbenzene (1.533 g, 52%), by elution with benzene-EtOH (9:1). NMR ( $\text{CDCl}_3$ )  $\delta$  ( $J=\text{Hz}$ ): 1.06 (3H, d,  $J=6.5$ ,  $-\text{CH}-\text{CH}_3$ ), 1.48 (2H, m,  $-\text{CH}_2-\text{CH}_2-\text{CHN}-$ ), 1.60 (2H, t,  $J=6.8$ ,  $-\text{CH}_2-\text{CH}_2-$ ), 2.30 (1H, m,  $-\text{CH}_2-\text{CHN}-\text{CH}_3$ ), 3.70 (6H, s,  $-\text{OCH}_3 \times 2$ ), 6.55—6.70 (3H, m, aromatic protons). Mass Spectrum  $m/e$ : 209 ( $\text{M}^+$ ). Styphnate, mp  $138\text{--}140^\circ$ . *Anal.* Calcd. for  $\text{C}_{18}\text{H}_{22}\text{O}_{10}\text{N}_4$ : C, 47.58; H, 4.78; N, 12.53. Found: C, 47.53; H, 4.88; N, 12.44.

**1-(2',5'-Dimethoxyphenyl)-3-aminobutanol O, N-Diacetate (XXIV)**—XXIII (900 mg) was stirred with  $\text{Ac}_2\text{O}$  (1.2 ml) in pyridine (5 ml) at room temperature for 10 hr. The reaction mixture was poured into ice- $\text{H}_2\text{O}$ , extracted with ether, washed with  $\text{H}_2\text{O}$ , and dried over  $\text{Na}_2\text{SO}_4$ . Ether was evaporated to give the crude product (XXIV), which was recrystallized from benzene to give colorless needles, mp  $127\text{--}128.5^\circ$ , (1.100 g, 90%). IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3330, 1740, 1660, 1500, 1230, 1220. NMR ( $\text{CDCl}_3$ )  $\delta$  ( $J=\text{Hz}$ ): 1.15 (3H, d,  $J=7.0$ ,  $-\text{CH}-\text{CH}_3$ ), 1.85 (3H, s, OAc), 2.00 (2H, m,  $-\text{CHOH}-\text{CH}_2-\text{CHN}-$ ), 2.05 (3H, s, NAc), 3.70 (3H, s,  $-\text{OCH}_3$ ), 3.72 (3H, s,  $-\text{OCH}_3$ ), 3.95 (1H, m,  $-\text{CH}_2-\text{CHN}-\text{CH}_3$ ), 5.55 (1H, broad s,  $-\text{NH}-$ ), 6.07 (1H, t,  $J=6.0$ ,  $-\text{CHOH}-\text{CH}_2-$ ), 6.64—6.80 (3H, m, aromatic protons). *Anal.* Calcd. for  $\text{C}_{16}\text{H}_{23}\text{O}_5\text{N}$ : C, 62.12 H, 7.49, N, 4.53. Found: C, 62.10; H, 7.50; N, 4.57.

**Reduction of XXIV**—To a suspension of  $\text{LiAlH}_4$  (300 mg) in THF (10 ml) a solution of XXIV (846 mg) in THF (10 ml) was dropwise added. The reaction mixture was refluxed for 3 hr. After cooling and addition of moistened ether, the reaction mixture was poured into ice- $\text{H}_2\text{O}$ , extracted with ether, washed with  $\text{H}_2\text{O}$ , and dried over  $\text{Na}_2\text{SO}_4$ . Ether was evaporated to give XXV (540 mg, 80%), as a pale yellow oil. IR  $\nu_{\text{max}}^{\text{film}}$   $\text{cm}^{-1}$ : 3250, 3200, 1495, 1215. Styphnate, mp  $121\text{--}122^\circ$ , undepressed on admixture with an authentic sample. XXV (free base) was identified with the authentic sample by comparison of IR,  $R_f$  value on TLC, and  $t_R$  on GLC.

**1-(2',5'-Dimethoxyphenyl)-3-(ethylamino)butanol Diacetate (XXVI)**—To a solution of XXV (540 mg) in pyridine (3 ml) was added  $\text{Ac}_2\text{O}$  (0.3 ml). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into ice- $\text{H}_2\text{O}$ , extracted with ether, washed with  $\text{H}_2\text{O}$ , and dried over  $\text{Na}_2\text{SO}_4$ . Ether was evaporated to give an oil (656 mg, 91%), which was chromatographed on silica gel. Elution with benzene-EtOH (95:5) gave XXVI. Mass Spectrum  $m/e$ : 337 ( $\text{M}^+$ ). IR  $\nu_{\text{max}}^{\text{film}}$   $\text{cm}^{-1}$ : 1740, 1640, 1235. NMR

(CDCl<sub>3</sub>)  $\delta$  ( $J$ =Hz): 1.08 (3H, d,  $J$ =7.0, -CH-CH<sub>3</sub>), 1.15 (3H, t,  $J$ =7.0, -NCH<sub>2</sub>CH<sub>3</sub>), 1.88 (3H, s, OAc), 1.79—1.89 (2H, m, -CHOH-CH<sub>2</sub>-CHN-), 2.05 (3H, s, NAc), 3.35 (2H, q,  $J$ =7.0, -NCH<sub>2</sub>-CH<sub>3</sub>), 3.55 (1H, m, -CH<sub>2</sub>-CHN-CH<sub>3</sub>), 3.68 (3H, s, OCH<sub>3</sub>), 3.72 (3H, s, -OCH<sub>3</sub>), 6.00 (1H, t,  $J$ =7.0, -CHOH-CH<sub>2</sub>-), 6.60—6.80 (3H, m, aromatic protons).

**Reduction of XXVI**—To a suspension of LiAlH<sub>4</sub> (300 mg) in ether (10 ml) was added a solution of XXVI (600 mg) in ether (5 ml). The reaction mixture was refluxed for 3 hr. After excess of LiAlH<sub>4</sub> was decomposed with moistened ether, the reaction mixture was poured into ice-H<sub>2</sub>O, extracted with ether, washed with H<sub>2</sub>O, and dried over Na<sub>2</sub>SO<sub>4</sub>. Ether was evaporated to give XVIa (400 mg, 81%). XVIa (400 mg) and styphnic acid (350 mg) in EtOH (5 ml) gave styphnate (660 mg), mp 108—109°, which was undepressed on admixture with authentic sample. XVIa (free base) was identified with the authentic sample by comparison of IR,  $R_f$  value on TLC, and  $t_R$  on GLC.

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