synchronous change in cerebellar activity. With picrotoxin (2.0 mg/kg, *i.v.*), cerebral EEG patterns with high amplitudes occurred and several min later convulsive waves developed in both structures (Fig. 3B).

We have studied a neurotoxic substance, lyoniol-A,[12a,b] which disturbs motor function of animals and causes a peculiar posture. It seems worthwhile to examine the effect of this substance on the chick cerebellum. Lyoniol-A (8.0 mg/kg, *i.v.*) caused a decrease of amplitude and an increase of mean frequency in the cerebellum and a decrease of amplitude in the cerebrum. Approximately 20 min later, peculiar synchronized patterns developed in the cerebellum although no changes could be found in the cerebrum (Fig. 3C). Without gallamine and under restraint, the low amplitude fast waves induced by lyoniol-A in the cerebrum continued even when the chick closed its eyes, indicating the arousal state of the cerebrum. In our previous study in rats,[12c] lyoniol-A accelerated the EEG arousal patterns in the motor cortex while showing no clear modification of electrical activity in the cerebellum, hippocampus and amygdala. In chicks the cerebellum seems to be more sensitive than the cerebrum in contrast to rats. These results suggest the advantage of employing birds for the study on the drugs which affect the motor function or posture regulation.

Acknowledgement We are grateful to Prof. M. Yasue, Faculty of Pharmaceutical Sciences, Nagoya City University, for provision of lyoniol-A.

12) a) H. Fukuda, K. Watanabe, and T. Ito, *Yakugaku Zasshi*, **89**, 382 (1969); *b*) *Idem*, *Japan. J. Pharmacol.*, **19**, 394 (1969); *c*) *Idem*, *Japan. J. Pharmacol.*, **22**, 461 (1972).

[Chem. Pharm. Bull. 20(11)2483—2487(1972)]

UDC 547.566.8.057 : 615.212.011.5

Studies on the Syntheses of Analgesics. XXXIII.[1] Synthesis of N-Methyl-N-[2-(3-methoxyphenyl)-2-phenyl]propylhydrazine (Studies on the Syntheses of Heterocyclic Compounds. CDXCVI.[2])

Tetsuji Kametani,[3a] Kazuo Kigasawa, Mineharu Hiiragi, Toyohiko Aoyama, Kunio Araki, and Setsu Saito[3b]

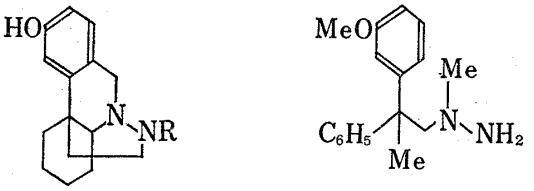
Pharmaceutical Institute, Tohoku University[3a] *and Grelan Pharmaceutical Co., Ltd.*[3b]

(Received March 27, 1972)

In the previous papers, we reported syntheses of ethyl 2-(ω-aminoalkyl)-2-(3-methoxyphenyl)phenylacetates[4] and 1,2,3,4,5,6-hexahydro-2,6-methano-3-methyl-6-phenyl-2,3-benzo[*g*]diazocines,[1] in which one nitrogen was introduced instead of the C_2-carbon of benzomorphan ring, using 1-(3-methoxyphenyl)-1-phenylacetonitrile (III)[5] as a starting material for the purpose of getting the drugs effective to the central nervous system, particularly to analgesic activity. Since the azamorphinan derivative (I),[6] prepared by Kametani, was proved to

1) Part XXXII: T. Kametani, K. Fukumoto, K. Kigasawa, M. Hiiragi, F. Satoh, H. Sugi, and T. Uryu, *J. Heterocyclic Chem.*, in press.
2) Part CDXCV: T. Kametani and K. Fukumoto, *Synthesis*, in press.
3) Location: *a*) *Aobayama, Sendai*; *b*) *Sakurashinmachi, Setagayaku, Tokyo.*
4) T. Kametani, K. Kigasawa, M. Hiiragi, and T. Aoyama, *J. Med. Chem.*, **14**, 1235 (1971).
5) T. Kametani, K. Kigasawa, M. Hiiragi, T. Aoyama, and O. Kusama, *J. Org. Chem.*, **36**, 327 (1971).
6) T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, K. Wakisaka, F. Satoh, and S. Saito, *J. Med. Chem.*, **13**, 1064 (1970).

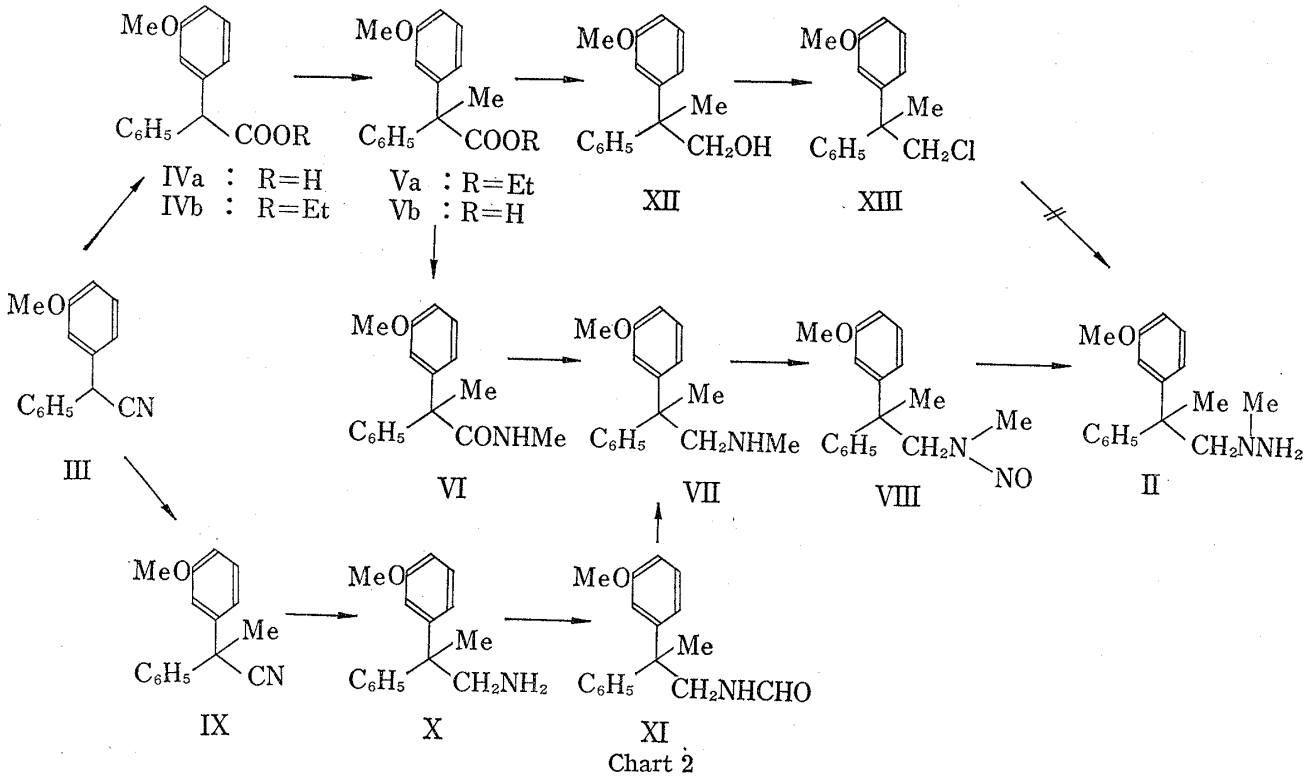
have a strong analgesic activity without addiction, we have investigated the synthesis of N-methyl-N-[2-(3-methoxyphenyl)-2-phenyl]propylhydrazine (II) possessing a partial structure of I, in the expectation that II also would be potent to analgesic activity. Herein we wish to report these results.



I II

Chart 1

Firstly, benzyne reaction of *o*-chloroanisole with phenylacetonitrile in the presence of sodium amide gave 1-(3-methoxyphenyl)-1-phenylacetonitrile (III)[5] as a starting material, the alkaline hydrolysis of which, followed by esterification of (IVa),[7] afforded the ester (IVb).[4] The reaction of IVb with methyl iodide in dimethylformamide (DMF) in the presence of sodium hydride gave ethyl 2-(3-methoxyphenyl)-2-phenylpropionate (Va), the structure of which was confirmed by infrared (IR) and nuclear magnetic resonance (NMR) spectra. The ester (Va) was hydrolysed in alkaline media to give carboxylic acid (Vb), the chlorination of which with thionyl chloride in benzene, followed by Schotten-Baumann reaction with methylamine, afforded the amide (VI). Reduction of VI with lithium aluminum hydride in dry tetrahydrofuran (THF) gave 2-(3-methoxyphenyl)-2-phenyl-N-methylpropylamine (VII) as its hydrochloride, mp 166—167.5°. After nitrosation of VII as usual, reduction of the nitroso derivative (VIII) with lithium aluminum hydride in dry ether was carried out according to Zimmer's method,[8] by the result of which our expected hydrazine (II) was obtained as its hydrochloride, mp 87—89°. The NMR spectrum of free base (II) showed C-methyl at 1.72,N-methyl at 2.30, N-methylene at 3.27 and O-methyl protons at 3.76 ppm as singlet. This fact proved the structure (II) to be correct.



IVa : R=H, IVb : R=Et; Va : R=Et, Vb : R=H; XII; XIII; III; VI; VII; VIII; II; IX; X; XI

Chart 2

As described as above, although our expected hydrazine (II) was synthesized, there are many synthetic steps and the yield of amine (VII) from nitrile (III) is very poor as 18.9%.

7) T. Kametani, K. Kigasawa, M. Hiiragi, T. Aoyama, and O. Kusama, *J. Med. Chem.*, **14**, 72 (1971).
8) H. Zimmer, L.F. Audrieth, M. Zimmer, and R.A. Rowe, *J. Am. Chem. Soc.*, **77**, 790 (1955).

Therefore a modified synthesis of VII was investigated as follow. Namely, the reaction of III with methyl iodide in benzene–ether in the presence of sodium amide gave 1-(3-methoxyphenyl)-1-phenylpropionitrile (IX), which was hydrogenated in the presence of Raney nickel under high pressure to give 2-(3-methoxyphenyl)-2-phenylpropylamine (X). In the IR spectrum of X, an absorption due to the nitrile group observed in the case of IX disappeared and a primary amino group was observed at 3400 cm^{-1}. Formylation of X with formic acid gave the amide (XI), the IR spectrum of which showed amide-carbonyl band at 1670 cm^{-1}. Reduction of XI with lithium aluminum hydride in ether–benzene gave VII. Thus the yield from III to VII increased to 26.0%.

Secondly, a synthetic approach to II by the reaction of 1-chloro-2-(3-methoxyphenyl)-2-phenylpropane (XIII) with hydrazine derivatives was examined. Namely, lithium aluminum hydride reduction of ester (Va) in ether, followed by chlorination of XII in benzene with thionyl chloride, gave the chloride (XIII) as a colorless oil, which was confirmed by microanalysis, spectral data and positive Beilstein test. The condensation of XIII with hydrazine derivatives was carried out under various conditions, but failed.

Finally, an attempt to obtain hydrazine derivative (XV) was examined as follows. Fusion of IVa or IVb with hydrazines gave the hydrazides (XIVa—c), which were reduced with lithium aluminum hydride, but our expected compound (XV) could not be obtained. In this case, Pictet-Spengler reaction of XIVc was investigated in order to obtain benzodiazepine (XVI), by the result of which unexpected tetrazine derivative (XVII) was formed. This would be formed by condensation of two moles of XIVc with two moles formalin. The IR spectrum showed an amidocarbonyl band at 1660 cm^{-1} and mass spectrum showed molecular ion peak at *m/e* 744.

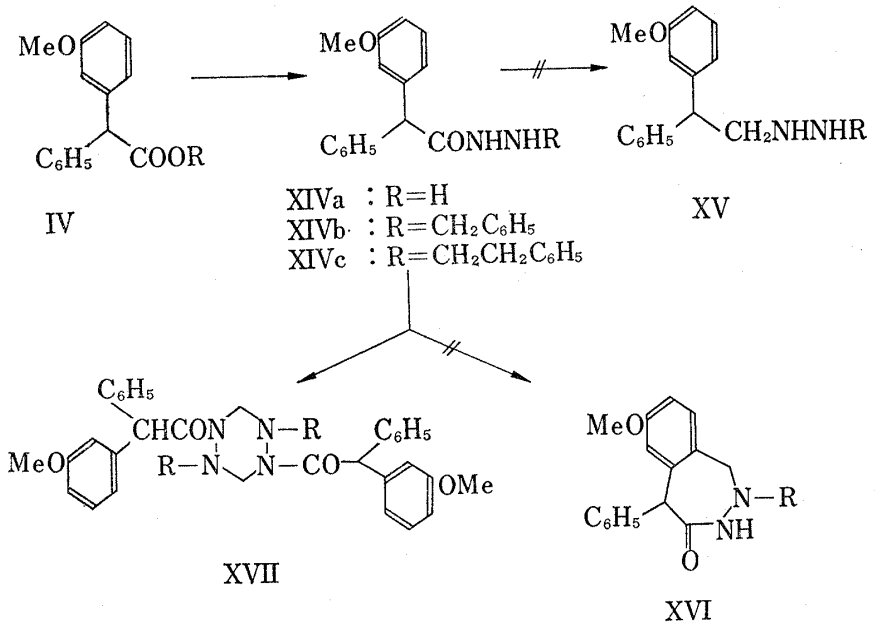


Chart 3

An analgesic activity of II and its derivatives by hot plate procedure is under investigation.

Experimental[9]

Ethyl 2-(3-Methoxyphenyl)-2-phenylpropionate (Va)——To a suspension of 3.2 g of sodium hydride (50% suspension in mineral oil) in 100 ml of dimethylformamide (DMF) was added dropwise 15 g of IVb[5]

9) Melting and boiling points are not corrected. NMR spectra were recorded using JNM-MH-60 spectrometer with tetramethylsilane as an internal standard.

at 40°. After stirring for 1 hr, 16 g of methyl iodide was added dropwise to the above mixture with cooling and then the mixture was stirred at room temperature for 2 hr and then at 40° for 1 hr. The reaction mixture was then poured into ice–water and extracted with ether. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a residue, which was distilled *in vacuo* to give 15 g (85.4%) of Va as a pale yellow oil, $bp_{1.0}$ 160—164°. IR $\nu_{max}^{liq.}$ cm^{-1}: 1720 (C=O). NMR (in CCl_4) δ: 1.05 (3H, t, $CH_2C\underline{H}_3$), 1.78 (3H, s, C-C$\underline{H}_3$), 3.49 (3H, s, OC$\underline{H}_3$), 4.00 (2H, q, C$\underline{H}_2$CH$_3$), 6.45—7.33 (9H, m, Ar-H).

2-(3-Methoxyphenyl)-2-phenylpropionic Acid (Vb)——A mixture of 15 g of Va and 100 ml of 60% KOH aq. solution was heated under reflux for 2 hr. After cooling, the reaction mixture was mixed with water and extracted with ether. The resulting aqueous layer was acidified with conc. HCl aq. solution and extracted with ether. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a residue, which was recrystallized from ether–hexane to afford 10.7 g (79.2%) of Vb as colorless prisms, mp 86—89°. IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O). *Anal.* Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.80; H, 6.11.

2-(3-Methoxyphenyl)-2-phenyl-N-methylpropionamide (VI)——After a mixture of 7 g of Vb, 8 g of $SOCl_2$, and 50 ml of dry benzene had been refluxed for 1 hr, the excess of $SOCl_2$ was removed by distillation to give a residue, a solution of which in 50 ml of benzene was added dropwise to 10 g of 40% methylamine aq. solution under cooling. After addition, the mixture was stirred at room temperature for 2 hr. After the reaction, the benzene layer was separated, washed with 5% Na_2CO_3 aq. solution and water, dried over $MgSO_4$, and evaporated to give a residue, which was distilled *in vacuo* to yield 6.3 g (85.7%) of VI as a pale yellow oil, $bp_{0.1}$ 210—215°. IR $\nu_{max}^{liq.}$ cm^{-1}: 3350 (NH), 1650 (C=O). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.69; H, 7.32; N, 5.31.

2-(3-Methoxyphenyl)-2-phenyl-N-methylpropylamine (VII)——a) To a suspension of 2.7 g of $LiAlH_4$ in 70 ml of dry THF was added dropwise a solution of 7 g of VI in 30 ml of THF and the mixture was refluxed under stirring for 3 hr. After the excess of $LiAlH_4$ had been decomposed with 30% NaOH aq. solution, the THF layer was separated, dried over K_2CO_3 and evaporated to give a residue, the hydrochloride of which was recrystallized from EtOH–ether to afford 3.6 g (47.4%) of VII as colorless needles, mp 166—167.5°. *Anal.* Calcd. for $C_{17}H_{21}ON\cdot HCl$: C, 69.97; H, 7.59; N, 4.80. Found: C, 69.66; H, 7.53; N, 5.10. Free base: IR $\nu_{max}^{liq.}$ cm^{-1}: 3400 (NH_2). NMR ($CDCl_3$) δ: 1.73 (3H, s, C-C$\underline{H}_3$), 2.46 (3H, s, NC$\underline{H}_3$), 3.17 (2H, s, C$\underline{H}_2$N), 3.76 (3H, s, OC$\underline{H}_3$), 6.65—7.48 (9H, m, Ar-H).

b) To a mixture of 1.4 g of $LiAlH_4$ in 200 ml of dry ether was added dropwise a solution of 5 g of XI in 100 ml of dry benzene and the mixture was refluxed with stirring for 6 hr. The same work-up as (a) gave 3.6 g (66.7%) of VII as its hydrochloride, which was identical with an authentic sample prepared by method (a).

2-(3-Methoxyphenyl)-2-phenyl-N-methyl-N-nitrosopropylamine (VIII)——To a solution of 1.5 g of hydrochloride of VII in 15 ml of water was added dropwise a solution of 0.42 g of $NaNO_2$ in 5 ml of water at 70° during 1 hr. After stirring for 1 hr, the reaction mixture was cooled and extracted with ether. The extract was washed with water, dried over $MgSO_4$ and evaporated to give 1.4 g of VIII as a yellow oil, which was used in the following reaction without purification.

N-Methyl-N-[2-(3-methoxyphenyl)-2-phenyl]propylhydrazine (II)——A mixture of 6 g of VIII, 0.91 g of $LiAlH_4$, and 115 ml of dry ether was stirred at room temperature for 3 hr and then refluxed for 4 hr. After cooling the excess of $LiAlH_4$ was decomposed with 30% NaOH aq. solution. The ethereal layer was separated, dried over K_2CO_3 and evaporated to give a residue, the hydrochloride of which was recrystallized from iso-PrOH–ether to give 3.2 g (47.0%) of II as colorless needles, mp 87—89°. *Anal.* Calcd. for $C_{17}H_{22}ON_2\cdot HCl$: C, 66.55; H, 7.50; N, 9.13. Found: C, 66.15; H, 7.46; N, 8.75.

The free base: NMR (CCl_4) δ: 1.72 (3H, s, C-C$\underline{H}_3$), 2.30 (3H, s, NC$\underline{H}_3$), 3.27 (2H, s, C$\underline{H}_2$N), 3.76 (3H, s, OC$\underline{H}_3$), 6.56—7.40 (9H, m, Ar-H).

1-(3-Methoxyphenyl)-1-phenylpropionitrile (IX)——To a refluxed mixture of 3 g of $NaNH_2$, 100 ml of benzene, and 50 ml of dry ether was added dropwise 15 g of III under stirring. After addition the mixture was heated under reflux for 4 hr. To the above mixture was added 10 g of methyl iodide at room temperature and then the stirring was continued for 5 hr. After the excess of $NaNH_2$ had been decomposed with sat. NH_4Cl aq. solution, the reaction mixture was poured into ice–water. The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated to give a residue, which was distilled *in vacuo* to give 12.5 g (81.7%) of IX as a pale yellow oil, $bp_{0.2}$ 145—148° [lit.,[1] $bp_{0.3}$ 140—151°].

2-(3-Methoxyphenyl)-2-phenylpropylamine (X)——A mixture of 20.3 g of IX, 12 ml of Raney Ni, and 150 ml of EtOH saturated with NH_3 gas was hydrogenated in an autoclave under shaking at an initial pressure of 42 kg/cm^2 of hydrogen. After an absorption of H_2 had ceased, the catalyst was removed by filtration and the filtrate was condensed to give a residue, the hydrochloride of which was recrystallized from EtOH–ether to give 15 g (62.9%) of X as colorless needles, mp 142—143°. *Anal.* Calcd. for $C_{16}H_{19}ON\cdot HCl$: C, 69.17; H, 7.26; N, 5.04. Found: C, 69.33; H, 7.11; N, 5.20.

2-(3-Methoxyphenyl)-2-phenyl-N-formylpropylamine (XI)——A solution of 10.5 g of X in 30 ml of formic acid was heated under reflux for 5 hr and the excess of formic acid was then evaporated *in vacuo* to give a residue, which was extracted with ether. The extract was washed with 5% Na_2CO_3, 5% HCl and water, dried over $MgSO_4$, and evaporated to give a residue, which was recrystallized from benzene–pet. ether to

give 10 g (75.8%) of XI as a colorless powder, mp 94—95°. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1670 (C=O). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.94; H, 7.20; N, 5.18.

2-(3-Methoxyphenyl)-2-phenylpropanol (XII)——To a refluxed mixture of 2 g of $LiAlH_4$ and 100ml of dry ether was added dropwise 10 g of Va and the stirring was continued under reflux for 2 hr. After cooling, the excess of $LiAlH_4$ was decomposed with 30% NaOH aq. solution and the ethereal layer was separated and dried over $MgSO_4$. Evaporation of the solvent gave a syrup, which was chromatographed on silicic acid. After removal of the pet. ether eluate, evaporation of the ether eluate gave 6.5 g (76.4%) of XII as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400 (OH). NMR (CCl_4) δ: 1.58 (3H, s, C-C$\underline{H}_3$), 3.62 (3H, s, OC$\underline{H}_3$), 3.84 (2H, s, C$\underline{H}_2$OH), 6.45—7.35 (9H, m, Ar-H). *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.16; H, 7.41.

1-Chloro-2-(3-methoxyphenyl)-2-phenylpropane (XIII)——To a stirred solution of 2.4 g of XII, 0.95 g of pyridine, and 10 ml of dry benzene was added dropwise a solution of 1.2 g of $SOCl_2$ in 5 ml of dry benzene under cooling with ice. After stirring for 1 hr, the stirring was continued at room temperature for 2.5 hr, and then at 40—50° for 1 hr. The reaction mixture was poured into ice-water and extracted with benzene. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silicic acid using pet. ether–ether (2: 1) to afford 2.2 g (84.6%) of XIII as a colorless oil. NMR (CCl_4) δ: 1.58 (3H, s, C-C$\underline{H}_3$), 3.60 (3H, s, OC$\underline{H}_3$), 3.95, 4.18 (1H, each, d, d, -C$\underline{H}_2$Cl, J=10 Hz), 6.50—7.30 (9H, m, Ar-H). *Anal.* Calcd. for $C_{16}H_{17}OCl$: C, 73.70; H, 6.57. Found: C, 73.63; H, 6.66.

2-(3-Methoxyphenyl)-2-phenylacetylhydrazine (XIVa)——A mixture of 5 g of IVb and 2 g of hydrazine hydrate was heated at 150—160° for 15 hr. The reaction mixture was crystallized on being triturated with EtOH and pet. ether to give 2.5 g (47%) of XIVa as a solid, which was recrystallized from EtOH–pet. ether to afford colorless needles, mp 117—118.5°. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH_2NH), 1660 (C=O). *Anal.* Calcd. for $C_{15}H_{16}O_2N_2$: C, 70.29; H, 6.29; N, 10.98. Found: C, 70.05; H, 6.14; N, 11.05.

N'-Benzyl-N-[2-(3-methoxyphenyl)-2-phenyl]acetylhydrazine (XIVb)——A mixture of 2.4 g of IVa and 2.5 g of benzylhydrazine was heated at 165—180° for 30 min. After the reaction mixture had been triturated with ether–pet. ether, collection of crystals by filtration, followed by recrystallization from ether–*n*-hexane, gave 0.9 g (25.7%) of XIVb as colorless needles, mp 90—93°. IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1640 (C=O). *Anal.* Calcd. for $C_{22}H_{22}O_2N_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.12; H, 6.55; N, 8.21.

N-[2-(3-Methoxyphenyl)-2-phenyl]acetyl-N'-phenethylhydrazine (XIVc)——A mixture of 4.8 g of IVa and 5 g of phenethylhydrazine was heated at 160—170° for 4 hr. The reaction mixture was extracted with ether. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a residue, which was recrystallized from benzene–*n*-hexane to afford 4.8 g (66.7%) of XIVc as colorless needles, mp 87—89°. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1640 (C=O). *Anal.* Calcd. for $C_{23}H_{24}O_2N_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 77.11; H, 6.67; N, 8.00.

1,2,3,4,5,6-Hexahydro-2,5-bis[2-(3-methoxyphenyl)-2-phenylacetyl]-1,4-diphenethyl-1,2,4,5-tetrazine (XVII)——A mixture of 340 mg of XIVc, 2 ml of 37% formalin, 2 ml of conc. HCl, 4 ml of water and 12 ml of EtOH was refluxed for 70 hr. The solvent was distilled off from the reaction mixture and the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a yellow oil, which was crystallized on being triturated with EtOH. Collection and recrystallization from EtOAc gave 100 mg (28.6%) of XVII as colorless needles, mp 175—177°. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O). Mass Spectrum *m/e*: 744 (M^+), 372 (1/2 M^+). *Anal.* Calcd. for $C_{48}H_{48}O_4N_4$: C, 77.39; H, 6.50; N, 7.52. Found: C, 77.71; H, 6.50; N, 7.18.

Acknowledgement We thank President A. Yanagisawa and Director O. Takagi, Grelan Pharmaceutical Co., Ltd., for their encouragements. We also thank Miss C. Yoshida, Miss A. Kawakami, Miss T. Yoshida, and Miss R. Kato, Pharmaceutical Institute, Tohoku University, for microanalyses and spectral measurements.