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Synthesis of 1,2,3,4,5,6,7,8-Octahydro-1-(4-methoxybenzyl)-2-methylphthalazine Derivative (Studies on the Syntheses of Heterocyclic Compounds. CDXXXI[1])

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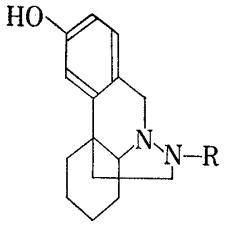
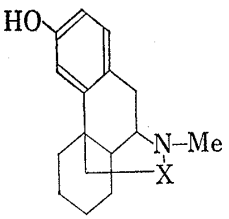
Grignard reaction of 5,6,7,8-tetrahydro-2-methylphthalazinium iodide (IX) with 4-methoxybenzylmagnesium chloride afforded 1,2,5,6,7,8-hexahydro-1-(4-methoxybenzyl)-2-methylphthalazine (X), which was further converted to several kinds of 1-benzyloctahydrophthalazine derivatives (IV, XI, XII, XIII, XIV, XVII, and XIX). Grewe cyclization of IV to yield 16-azamorphinan (III) resulted in failure.

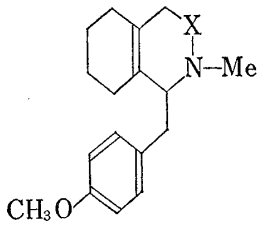
In the previous papers,[3] we have reported on the syntheses and pharmacological activity of a number of 9-azamorphinan derivatives (Ia—e). Morphinan derivatives (II) have been well known to have a strong analgesic activity and the above 9-aza-analogues (Ia—e) were also found to have an appreciable analgesic activity as II. Therefore we have currently examined a synthesis of 16-azamorphinan (III) which is a position isomer of Ia—e by the application of Schnider's method.[4] Herein we wish to report these results.



Ia : R=Me
Ib : R=CH_2CH_2Ph
Ic : R=$CH_2-CH=CH_2$
Id : R=CH_2Ph
Ie : R=$-CH_2-$ 
Ph=C_6H_5



II : X=CH_2
III : X=N—Me



IV : X=N—Me
V : X=CH_2

Chart 1

1) Part CDXXX: T. Kametani, S. Takano, H. Nemoto, and H. Takeda, *Yakugaku Zasshi.* **91**, 966 (1971)
2) Location: *a) Aobayama, Sendai; b) Sakurashinmachi-2-chome, Setagayaku, Tokyo.*
3) T. Kametani, K. Kigasawa, M. Hiiragi, and N. Wagatsuma, *Chem. Pharm. Bull.* (Tokyo), **16**, 296 (1966); T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, and N. Wagatsuma, *ibid.*, **17**, 1096 (1969); T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, K. Wakisaka, F. Satoh, and S. Saito, *J. Med. Chem.*, **13**, 1064 (1970).
4) O. Schnider and A. Grussner, *Helv. Chim. Acta*, **32**, 821 (1949).

Firstly, we investigated a synthesis of 1-benzyloctahydrophthalazine (IV) in the expectation that the Grewe cyclization of IV would give the 16-azamorphinan (III) as in the case of Grewe cyclization of 1-benzyloctahydroisoquinoline (V) to give morphinan (II). The intermediate, 5,6,7,8-tetrahydrophthalazine (VI) was obtained by the reductive dechlorination of 1,4-dichloro-5,6,7,8-tetrahydrophthalazine (VII).[5,6] Since the 2-benzyl-5,6,7,8-tetrahydrophthalazinium iodide (VIII: X=I) obtained from VI through the corresponding chloride (VIII: X=Cl) was unstable, methiodide (IX: X=I) was treated with 4-methoxybenzyl magnesium chloride to give 1,2,5,6,7,8-hexahydro-1-(4-methoxybenzyl)-2-methylphthalazine (X). The microanalysis verified the molecular formula, $C_{17}H_{22}ON_2$, and the nuclear magnetic resonance (NMR) spectrum of X showed two singlets due to NMe and OMe at 3.04 and 3.78 ppm, respectively; and a singlet due to C_4-H was observed at 6.65 ppm. These data indicated that the Grignard reaction product had the structure (X).

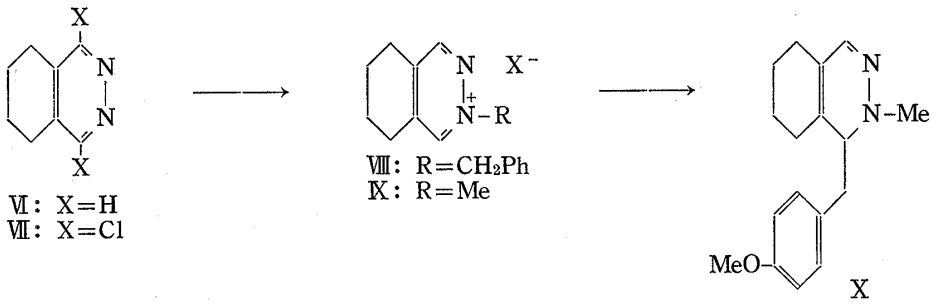


Chart 2

Secondly, we investigated the alkylation on the nitrogen at the 3-position. Reduction of X with lithium aluminum hydride or sodium dihydro-bis-(2-methoxyethoxy)aluminate afforded octahydrophthalazine (XI), whose structure was confirmed by the microanalysis of the hydrochloride and the formation of N-acetyl derivative (XII). Although the hydrochloride of XI was stable in air, the liberated one was transformed readily to X by oxidation with air. The Eschweiler–Clarke reaction of XI gave the expected 1,2,3,4,5,6,7,8-octahydro-

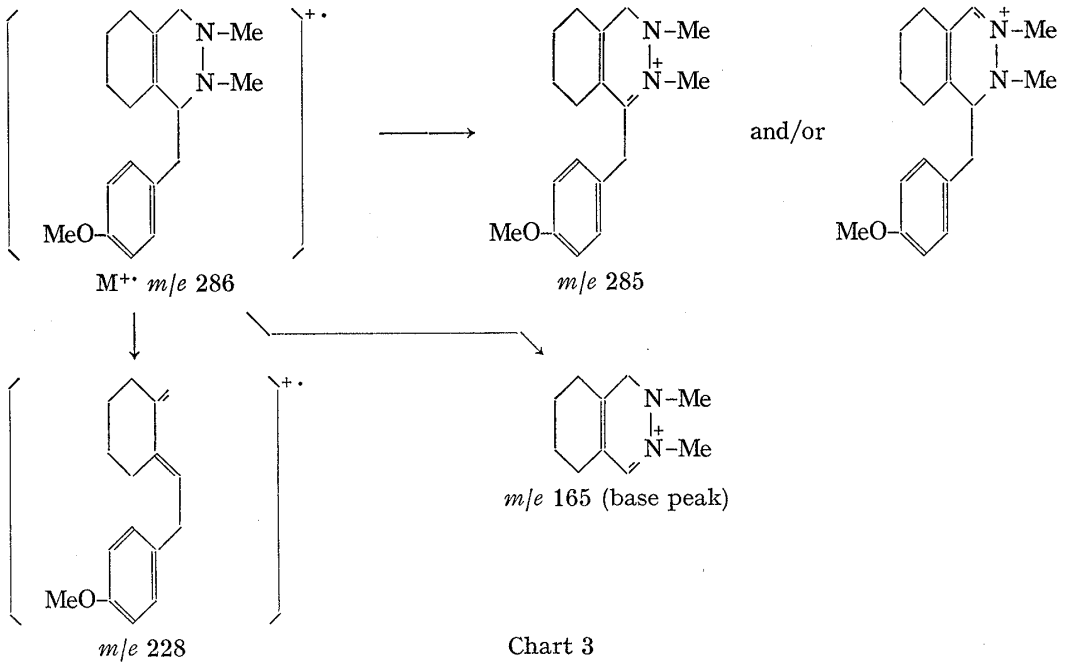


Chart 3

5) R.H. Horning and E.D. Amstutz, *J. Org. Chem.*, **20**, 707 (1955).
6) I. Satoda, F. Kusuda, and K. Mori, *Yakugaku Zasshi*, **82**, 233 (1962).

1-(4-methoxybenzyl)-2,3-dimethylphthalazine (IV) in poor yield. However the 2,3-dimethyl phthalazine (IV) was also obtained by the reduction of N-ethoxycarbonylphthalazine (XIII), obtained from XI, with lithium aluminum hydride in excellent yield. The NMR spectrum (in deuteriochloroform) showed two singlets due to two N-methyls at 2.06 and 2.39 ppm and one O-methyl signal at 3.71 ppm as shown in Fig. 1. Further structural proof of IV was afforded by the formation of the ions at *m/e* 286 (M^+), 285 (M^+-1), 165 (M^+-$MeOC_6H_4CH_2$), and 288 (formed by the retro Diels–Alder type cleavage) in its mass spectrum. These fragmentation processes were shown in Chart 3.

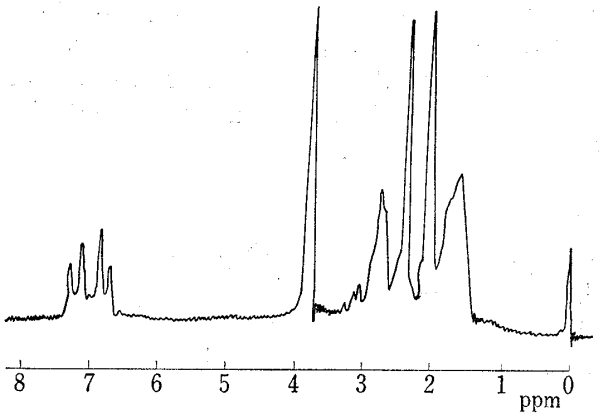
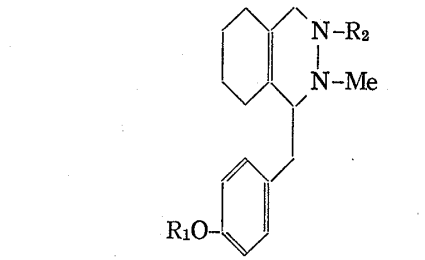
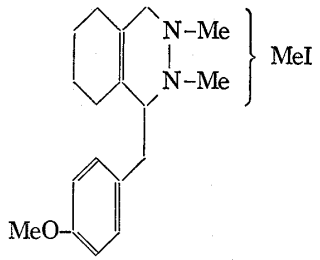


Fig. 1. NMR Spectrum of IV in $CDCl_3$

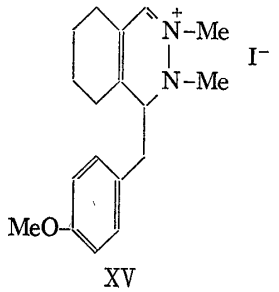
The phthalazine derivative (IV) was treated with methyl iodide to give mono methiodide (XIV). Then we examined the synthesis of IV from X through the methiodide (XVI). The treatment of X with methyl iodide, followed by the reduction of the crude product (XV and XVI) with sodium borohydride, gave IV with the formation of phthalazinium methiodide (XVII) as by-product. Therefore the quaternarization occurred in both nitrogens at the 2- and 3-position to give XV and XVI as intermediates during the above reaction. The structure of XVII was proved by the microanalysis and the spectroscopic data described in the experimental section.



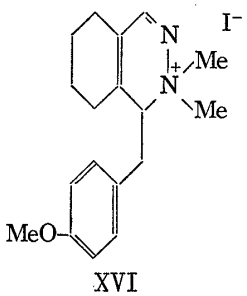
XI: R_1=Me; R_2=H
XII: R_1=Me; R_2=COMe
XIII: R_1=Me; R_2=COOEt
XVIII: R_1=H; R_2=Me
XIX: R_1=COPh; R_2=Me



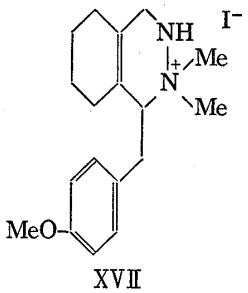
XIV



XV



XVI



XVII

Chart 4

Finally, we investigated, under a variety of conditions, the Grewe cyclization of IV thus obtained. The phthalazine (IV) was heated with 47% hydrobromic acid, 85% phosphoric acid, 35% hydrochloric acid, a mixture of acetic acid and 47% hydrobromic acid (1:1), or a mixture of acetic acid and sulfuric acid (1:1) to give the phenolic phthalazine (XVIII),

in each case. No formation of the cyclized product (III) was observed. The similar reaction on N-acetyl derivative (XII), the phenolic base (XVIII), and the quaternary salt (XIV) also resulted in failure. The phenol base (XVIII) was characterized as O-benzoyl derivative (XIX).

Although the Grewe cyclization of 1-benzyloctahydroisoquinoline derivatives gave the morphinans, no cyclized product was found to form under the same conditions in the case of 1-benzylphthalazine derivatives.

Experimental[7]

5,6,7,8-Tetrahydrophthalazine (VI)——A mixture of 10 g of 1,4-dichloro-5,6,7,8-tetrahydrophthalazine (VII), 250 ml of EtOH, and 10 ml of ethanolic KOH solution was shaken in a current of hydrogen in the presence of 5 g of 10% Pd-C until the cease of the uptake of hydrogen. After the catalyst had been filtered the filtrate was evaporated and resulting residue was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over K_2CO_3, and evaporated to give 6.3 g (95.2%) of pale brownish crystals, mp 83—86°, which were recrystallized from ether–pet. ether to give VI as colorless needles, mp 89—90° (lit.[5] 88.5—89°). *Anal.* Calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.25; H, 7.39; N, 21.33. NMR (in $CDCl_3$) δ: 1.66—2.07 (4H, m, C_6-$\underline{H}_2$ and C_7-$\underline{H}_2$), 2.52—2.90 (4H, m, C_5-$\underline{H}_2$ and C_8-$\underline{H}_2$), 8.78 (2H, s, C$\underline{H}$=N).

2-Benzyl-5,6,7,8-tetrahydrophthalazinium Iodide (VIII)——A solution of 3.5 g of VI and 6.6 g of benzyl chloride in 60 ml of EtOH was refluxed for 3.5 hr in a current of nitrogen. After evaporation of the solvent, the remaining residue was poured into 100 ml of H_2O. The crude product, precipitated on the addition of 4.3 g of KI to the above aqueous solution, was collected to give 5 g (54%) of VIII (X=I), mp 155—157°. NMR (in $CDCl_3$) δ: 1.8—2.2 (4H, m, C_6-$\underline{H}_2$ and C_7-$\underline{H}_2$), 2.9—3.3 (4H, m, C_5-$\underline{H}_2$ and C_8-$\underline{H}_2$), 6.00 (2H, s, PhC$\underline{H}_2$), 9.11 (1H, s,-C$\underline{H}$=N–N=), 10.54 (1H, s, -C$\underline{H}$=N–).

5,6,7,8-Tetrahydro-2-methylphthalazinium Iodide (IX)——To a stirred solution of 6.3 g of VI in a mixture of 20 ml of MeOH and 20 ml of acetone was added 20 ml of MeI under cooling. After the stirring had been continued for 1 hr under cooling and then for an additional 2 hr at room temperature, the solvent was evaporated to leave 12.5 g (99.2%) of a yellowish powder. Recrystallization of the crude product from acetone afforded IX (X=I) as pale yellowish plates, mp 108—110°. *Anal.* Calcd. for $C_9H_{13}N_2I$: C, 39.15; H, 4.74; N, 10.14. Found: C, 39.07; H, 4.59; N, 10.19. NMR (in $CDCl_3$) δ: 1.65—2.10 (4H, m, C_6-$\underline{H}_2$ and C_7-$\underline{H}_2$), 2.70—3.35 (4H, m, C_5-$\underline{H}_2$ and C_8-$\underline{H}_2$), 3.32 (3H, s, N-C$\underline{H}_3$), 9.09 (1H, s, -C$\underline{H}$=N-), 9.79 (1H, s, -C$\underline{H}$=N–).

1,2,5,6,7,8-Hexahydro-1-(4-methoxybenzyl)-2-methylphthalazine (X)——To a stirred suspension of 4.5 g of IX in 100 ml of tetrahydrofuran was added a solution of 4-methoxybenzylmagnesium chloride (prepared from 6.5 g of 4-methoxybenzyl chloride and 3.0 g of Mg turnings) in dry ether at room temperature. After the stirring had been continued for 0.5 hr at room temperature, the mixture was refluxed for 3.5 hr, and then poured into a mixture of an excess of ice and conc. HCl. The organic layer was extracted with 5% HCl solution and the combined aqueous layers were washed with ether, basified with 28% NH_4OH, and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3 and evaporated to give 2.56 g (58.1%) of X as a pale brownish oil. NMR (in $CDCl_3$) δ: 1.34—1.65 (4H, m, C_6-$\underline{H}_2$ and C_7-$\underline{H}_2$), 1.74—2.25 (4H, m, C_5-$\underline{H}_2$ and C_8-$\underline{H}_2$), 3.04 (3H, s, N–C$\underline{H}_3$), 3.78 (3H, s, OC$\underline{H}_3$), 6.65 (1H, s, –C$\underline{H}$=N), 6.76 (2H, d, J=8.4 Hz, Ar-$\underline{H}$), 7.02 (2H, d, J=8.4 Hz, Ar-$\underline{H}$). The hydrochloride, prepared as usual, was recrystallized from iso-PrOH–ether to give the monohydrochloride as pale yellowish prisms, mp 119—121°. *Anal.* Calcd. for $C_{17}H_{22}ON_2 \cdot HCl$: C, 66.55; H, 7.55; N, 9.13. Found: C, 66.46; H, 7.56; N, 9.31. NMR (in $CDCl_3$) δ: 1.35—2.35 (8H, m, -(C$\underline{H}_2$)$_4$-), 3.29 (3H, s, N-C$\underline{H}_3$), 3.82 (3H, s, OC$\underline{H}_3$), 6.86 (2H, d, J=8.5 Hz, Ar-$\underline{H}$), 7.05 (2H, d, J=8.5 Hz, Ar-$\underline{H}$), 7.21 (1H, s, -C$\underline{H}$=N-). The picrate formed orange needles (from acetone), mp 115—116° (decomp.). *Anal.* Calcd. for $C_{17}H_{22}ON_2 \cdot C_6H_3O_7N_3$: C, 53.59; H, 4.89; N, 13.59. Found: C, 53.96; H, 5.16; N, 13.39.

1,2,3,4,5,6,7,8-Octahydro-1-(4-methoxybenzyl)-2-methylphthalazine (XI)——a) To a stirred suspension of 1.5 g of $LiAlH_4$ in 50 ml of dry ether was added a solution of 5.4 g of X in 150 ml of ether under reflux. After the mixture had been refluxed for 8 hr, the excess of $LiAlH_4$ was decomposed with 10% NaOH in a current of N_2. The organic layer was separated, washed with H_2O and dried over K_2CO_3. The hydrochloride, precipitated on introduction of HCl gas to the above solution, was collected and recrystallized from iso-PrOH to give 5.3 g (88.1%) of colorless needles, mp 213—214° (decomp.). *Anal.* Calcd. for $C_{17}H_{24}ON_2 \cdot HCl$: C, 66.12; H, 8.16; N, 9.07. Found: C, 66.30; H, 8.15; N, 9.08. NMR (in $CDCl_3$) δ: 1.35—2.05 (8H, m, -(C$\underline{H}_2$)$_4$-), 2.81 (3H, s, N-C$\underline{H}_3$), 2.98—3.32 (2H, broad s, Ar-C$\underline{H}_2$-), 3.32—3.59 (2H, broad s, =C-C$\underline{H}_2$-), 3.76 (3H, s, OC$\underline{H}_3$),

7) Melting points were uncorrected. NMR spectra were measured by Hitachi-R-20 and JNM-MH-60 spectrometers with tetramethylsilane as internal reference. Mass spectra were taken by a Hitachi RMU-7 spectrometer.

6.77 (2H, d, J=8.0 Hz, Ar-H), 7.19 (2H, d, J=8.0 Hz, Ar-H).

b) A mixture of 2 g of X and 0.3 ml of 70% $NaAlH_2(OCH_2CH_2OMe)_2$ solution in benzene was refluxed for 9 hr, and then further 0.3 ml of 70% $NaAlH_2$-$(OCH_2CH_2OMe)_2$ was added to the above mixture. After themixture had been refluxed for 18 hr, the solvent was evaporated, and the resulting residue was decomposed with 10% NaOH and extracted with ether. The extract was worked up as above to give 115 mg (20.5%) of the hydrochloride of XIV as colorless needles, mp 212—213°, whose spectroscopic data were identical with those of the authentic specimen obtained by the procedure (a).

3-Acetyl-1,2,3,4,5,6,7,8-octahydro-1-(4-methoxybenzyl)-2-methylphthalazine (XII)——To a stirred mixture of 0.25 g of XI, 0.5 ml of acetyl chloride, and 10 ml of $CHCl_3$, was added 1 g of $NaHCO_3$ in small portions within 2 hr. After the reaction, water was added to the mixture and the organic layer was separated, washed with H_2O, dried over K_2CO_3, and evaporated to give a solid, which was recrystallized from hexane (or pet. ether) to give 235 mg (92.5%) of XII as colorless prisms, mp 93—94°. *Anal.* Calcd. for $C_{19}H_{26}O_2N_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.95; H, 8.20; N, 8.74. NMR (in $CDCl_3$) δ: 1.98 (3H, s, N-COC$\underline{H}_3$), 2.50 (3H, s, N-C$\underline{H}_3$), 3.75(3H, s, OC$\underline{H}_3$). IR ν_{max}^{KBr} cm^{-1}: 1640 (N-$COCH_3$).

3-Ethoxycarbonyl-1,2,3,4,5,6,7,8-octahydro-1-(4-methoxybenzyl)-2-methylphthalazine (XIII)——To a stirred mixture of 1.5 g of the above hydrochloride (XII), 0.8 g of ethyl chlorocarbonate, and 20 ml of $CHCl_3$ was added 2.0 g of $NaHCO_3$ in small portions within 1 hr. After the stirring had been continued for a further 0.5 hr, the inorganic substance was filtered off, and the solvent was evaporated. The resulting residue was extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and evaporated. The remaining substance was recrystallized from pet. ether to give 1.0 g (60%) of XIII as colorless prisms, mp 79—80°. *Anal.* Calcd. for $C_{20}H_{28}O_3N_2$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.41; H, 7.72; N, 8.34. IR ν_{max}^{KBr} cm^{-1}: 1710 (N-COOEt). NMR (in $CDCl_3$) δ: 1.29 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.50 (3H, s, N-C$\underline{H}_3$), 3.82 (3H, s, OC$\underline{H}_3$), 4.28 (2H, q, J=7.0 Hz, -C$\underline{H}_2CH_3$), 6.89 (2H, d, J=8.0 Hz, Ar-H), 7.38 (2H, d, J=8.0 Hz, Ar-H).

1,2,3,4,5,6,7,8-Octahydro-1-(4-methoxybenzyl)-2,3-dimethylphthalazine (IV)——a) To a stirred suspension of 0.5 g of $LiAlH_4$ in 15 ml of dry tetrahydrofuran was added a solution of XIII in 20 ml of tetrahydrofuran, and the mixture was refluxed for 6.5 hr. After an excess of $LiAlH_4$ had been decomposed with 10% NaOH under cooling, the inorganic precipitate was filtered off and the filtrate was evaporated. The remaining residue was extracted with ether. The extract was washed with water, dried over K_2CO_3 and evaporated to give 0.52 g (89.3%) of IV as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2800 (N-CH_3). UV λ_{max}^{MeOH} mμ: 205, 225, 277, 283 (shoulder). NMR (in $CDCl_3$) δ: 1.36—2.05 (8H, m, -($C\underline{H}_2$)$_4$-), 2.06 (3H, s, N-C$\underline{H}_3$), 2.39 (3H, s, N-C$\underline{H}_3$), 3.71 (3H, s, OC$\underline{H}_3$), 6.73 (2H, d, J=8.0 Hz, Ar-H), 7.12 (2H, d, J=8.0 Hz, Ar-H). Mass Spectrum (*m/e*): 286 (M^+), 285 (M^+-1), 228, 213, 165 (base peak). Recrystallization of the picrate from EtOH afforded yellowish prisms, mp 158—159° (decomp.). *Anal.* Calcd. for $C_{18}H_{26}ON_2 \cdot C_6H_3O_7N_3$: C, 55.91; H, 5.67; N, 13.59. Found: C, 56.02; H, 5.63; N, 13.68.

b) To a stirred mixture of 2.1 g of the hydrochloride (XI), 3.0 ml of 37% HCHO, and 30 ml of MeOH was added 1.2 g of $NaHCO_3$ within 1 hr. After the stirring had been continued for 2.5 hr, the mixture was refluxed for 0.5 hr. To the above stirred solution was added 2 g of $NaBH_4$ in small portions within 0.5 hr under cooling. After the stirring had been continued for an additional 1 hr, the mixture was refluxed for 0.5 hr. After an addition of water to the remaining residue, which was obtained on the evaporation of the solvent, the resulting solution was extracted with ether. The extract was washed with saturated NaCl solution, dried over K_2CO_3, and evaporated to give 1.8 g of IV as a pale brownish syrup, whose picrate was recrystallized to afford 1.4 g (40.0%), mp 158—159° (decomp.) (from EtOH). This was identical with the authentic specimen obtained by the procedure a) by comparison of the spectroscopic data and mixed melting point test.

c) A mixture of 0.2 g of XI hydrochloride, 1 ml of 37% HCHO and 1 ml of 98% HCOOH was heated on a water-bath for 4 hr. The crude product obtained by the usual work-up was chromatographed on silica gel. Evaporation of the solvent from the pet. ether eluate afforded 75 mg (44.1%) of IV as a pale brownish oil, whose spectroscopic data were identical with those of the authentic IV obtained as above.

d) A mixture of 0.5 g of X, 5 ml of CH_3I and 5 ml of MeOH was refluxed for 7 hr. After evaporation of the solvent, to a stirred solution of 0.7 g of the resulting residue in 8 ml of MeOH was added 0.35 g of $NaBH_4$ in small portions. After the mixture had been refluxed for 0.5 hr, the solvent was evaporated, and the remaining residue was poured into water, and extracted with ether and then $CHCl_3$. The each of the extracts was washed with saturated NaCl solution, and dried over Na_2SO_4. Evaporation of the ethereal extract afforded 220 mg of a brownish oil, which was chromatographed on silica gel with pet. ether as an eluant to give 110 mg (20.8%) of IV. Removal of the chloroform extract afforded 340 mg of a pale brownish powder, which was recrystallized from acetone to give 207 mg (27.1%) of XVII as colorless prisms, mp 178—179°. *Anal.* Calcd. for $C_{17}H_{24}ON_2 \cdot CH_3I$: C, 52.18; H, 6.57; N, 6.76. Found: C, 52.61; H, 6.57; N, 7.21. IR ν_{max}^{KBr} cm^{-1}: 3150 (NH). NMR (in $CDCl_3$) δ: 3.65 (3H, s, N-C$\underline{H}_3$), 3.74 (3H, s, N-C$\underline{H}_3$), 3.88 (3H, s, OC$\underline{H}_3$).

1,2,3,4,5,6,7,8-Octahydro-1-(4-methoxybenzyl)-2,3-dimethylphthalazine Methiodide (XIV)——A mixture of 1.0 g of IV, 2.0 ml of MeI and 10 ml of ether was kept aside at room temperature. The precipitate collected was recrystallized from acetone–ether to give 1.35 g (90.2%) of XIV as colorless needles, mp 195—197° (decomp.). *Anal.* Calcd. for $C_{18}H_{26}ON_2 \cdot CH_3I$: C, 53.28; H, 6.82; N, 6.54. Found: C, 53.22; H, 6.35; N, 6.35.

1,2,3,4,5,6,7,8-Octahydro-1-(4-hydroxybenzyl)-2,3-dimethylphthalazine (XVIII)——A solution of 1.0 g of IV in 10 ml of 35% HCl was heated under reflux for 66 hr. After the reaction, a mixture of 50 ml of H_2O and 5 ml of MeOH was added to the above solution. After an insoluble substance had been filtered off, the filtrate was washed with ether, made basic with 28% NH_4OH, and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The resulting residue was chromatographed on silica gel with pet. ether as an eluant. Removal of the eluant afforded 0.7 g (73.6%) of XVIII as a pale yellowish oil. NMR (in $CDCl_3$) δ: 1.45—2.05 (8H, m, -($C\underline{H}_2$)$_4$-), 2.20 (3H, s, N-$C\underline{H}_3$), 2.48 (3H, s, N-$C\underline{H}_3$), 6.71 (2H, d, J=8.4 Hz, Ar-$\underline{H}$), 7.11 (2H, d, J=8.4 Hz, Ar-$\underline{H}$), 8.02 (1H, s, O$\underline{H}$, disappeared with D_2O).

1-(4-Benzoyloxybenzyl)-1,2,3,4,5,6,7,8-octahydro-2,3-dimethylphthalazine (XIX)——To a stirred mixture of 0.5 g of XVIII, 3 ml of 5% NaOH, 3 ml of H_2O and 10 ml of ether was added dropwise 1 ml of benzoyl chloride at room temperature. The stirring was continued until the reaction mixture changed to acidic, and then 10 ml of 5% NaOH was added to the above mixture. After 1 hr, the mixture was extracted with ether. The extract was washed with 10% NaOH and H_2O, and dried over Na_2SO_4. Evaporation of the solvent afforded 0.58 g (85.0%) of XIX as a brownish oil. IR ν_{max}^{liq} cm^{-1}: 2800 (N-CH_3), 1745 (-OCO-). Recrystallization of the picrate from EtOH afforded yellowish needles, mp 139—140° (decomp.). *Anal.* Calcd. for $C_{24}H_{28}O_2N_2 \cdot C_6H_3O_7N_3$: C, 59.50; H, 5.16; N, 11.57. Found: C, 59.29; H, 4.81; N, 11.71.

Grewe Cyclization of IV——A solution of 1.0 g of IV in 8 ml of 47% HBr was refluxed for 18 hr at 150—160°. The solution was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give a brownish oil, which was chromatographed on silica gel with ether, benzene, $CHCl_3$, 1% MeOH–$CHCl_3$, and 5% MeOH–$CHCl_3$ as eluants. Removal of the solvent from the chloroform eluant afforded a pale yellowish oil, which was identical with XVIII by comparison of spectroscopic data, and no formation of the cyclized product III was observed from any of the above fractions. The heat of IV with 85% H_3PO_4, H_2SO_4–AcOH(1:1), or 47% HBr–AcOH under the similar condition as above afforded the same result as with 47% HBr.

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