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Azamorphinan and Related Compounds. I. A Synthesis of 3-Hydroxy-N-methyl-9-azamorphinan (Studies on the Syntheses of Heterocyclic Compounds. CCXIV[1])

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In order to examine the analgesic action of azamorphinan attempt to synthesize 3-hydroxy-N-methyl-9-azamorphinan (III) which has an additional nitrogen in morphinan ring was carried out successfully. Hydrolysis of 2-ethoxycarbonylmethyl-2-(3-methoxyphenyl)cyclohexanone (IX), which was obtained by condensation of 2-(3-methoxyphenyl)cyclohexanone (VIII) with ethyl bromoacetate in the presence of sodium amide, was first examined to give 2-carboxymethyl-2-(3-methoxyphenyl)cyclohexanone (X), whose methylhydrazination with methyl hydrazine afforded 3,4,5,6,7,8-hexahydro-2H,4aH-4a-(3-methoxyphenyl)-2-methyl-3-oxocinnoline (XI).

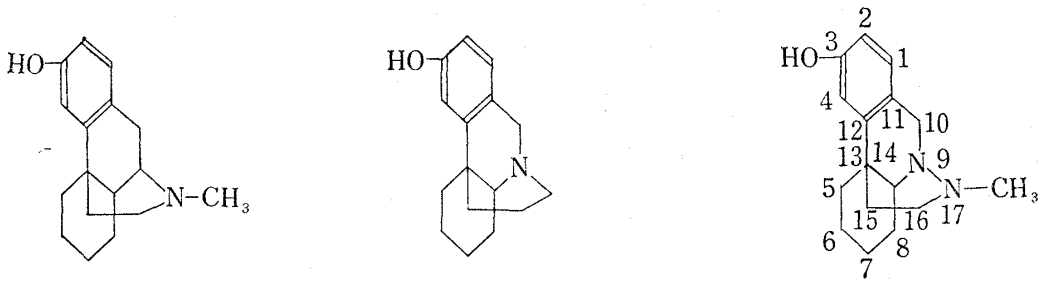
Secondly, reduction of the preceding compound (XI) with lithium aluminum hydride gave 4a-(3-methoxyphenyl)-2-methyldecahydrocinnoline (XII), which was converted into 3-methoxy-N-methyl-9-azamorphinan (XV) by Pictet-Spengler reaction with formalin and hydrochloric acid. Finally, demethylation of XV with hydrobromic acid afforded 3-hydroxy-9-azamorphinan (III), which was characterized as the picrate of its benzoate (XVI). Furthermore, conformation of XV was discussed.

In the previous papers,[3-8] azabenzomorphan derivatives which contained an additional nitrogen atom in the benzomorphan ring were synthesized in order to examine an analgesic action. The purpose of the present investigation was to study the synthesis of azamorphinan derivative (III) which had an additional nitrogen atom in the morphinan ring systesm (I).

In 1952, Schnider, *et al.*[9] reported that 3-hydroxy-N-methylmorphinan (I) caused a marked analgesic action which was about several times stronger than that of morphine, and Sugimoto and Kugita[10] also reported that 3-hydroxy-9-azamorphinan (II) showed analgesic action about equal to that of morphine but with much stronger toxicity. Although both compounds (I) and (II) as above had a strong analgesic action, they were scarcely used as an analgesic agent because of its toxicity. Accordingly, the title compound (III) which had further one nitrogen in morphinan ring system (I) was synthesized for the purpose of expecting an excellent analgesic action without addiction.

Since the structure of III has not yet been known in the literature, 2-(3-methoxyphenyl)-cyclohexanone (VIII) as a starting material was first synthesized as was shown in Chart 2. 3-Hydroxybenzaldehyde was methylated with dimethyl sulfate to give 3-methoxybenzaldehyde

1) Part CCXII : *Yakugaku Zasshi*, **88**,168 (1968); Part CCXIII : *Chem. Comm.*, **1968**, 26.
2) Location: *a)Kita-4-bancho, Sendai. b) Shinmachi-3-chome, Setagaya-ku, Tokyo.*
3) T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, and T. Iwata, *Yakugaku Zasshi*, **84** ,405 (1964).
4) T. Kametani, K. Kigasawa, and T. Hayasaka, *Chem. Pharm. Bull.* (Tokyo), **13**, 300 (1965).
5) T. Kametani, K. Kigasawa, M. Hiiragi, and H. Ishimaru, *Chem. Pharm. Bull.* (Tokyo), **13**, 295 (1965).
6) T. Kametani, K. Kigasawa, and M. Hiiragi, *Yakugaku Zasshi*, **85**, 871 (1965).
7) T. Kametani, K. Kigasawa, and M. Hiiragi, *Chem Pharm. Bull.* (Tokyo), **13**, 1220 (1965).
8) T. Kametani, K. Kigasawa, and T. Hayasaka, *Chem. Pharm. Bull.* (Tokyo), **13**, 1225 (1965).
9) O. Schnider and A. Grusner, *Helv. Chim. Acta*, **35**, 1328 (1952).
10) N. Sugimoto and H. Kugita, *Chem. Pharm. Bull.* (Tokyo), **3**, 11 (1955).



I II III

Chart 1

(IV), whose Knoevenagel reaction with nitromethane afforded 3-methoxy-ω-nitrostyrene (V). Diels-Alder reaction[11] of V with 1,3-butadiene in toluene in an autoclave gave 5-(3-methoxyphenyl)-4-nitrocyclohexene (VI), which was converted into 2-(3-methoxyphenyl)-4-cyclohexen-1-one (VII) by Nef reaction.[12] Catalytic hydrogenation of VII in the presence of 30% palladium charcoal gave 2-(3-methoxyphenyl)cyclohexanone (VIII) which was identical with an authentic sample in the literature.[13] Attempt to synthesize the compound (VIII) by Wurtz-Fittig reaction of 3-bromoanisole with 2-chlorocyclohexanone resulted in failure.

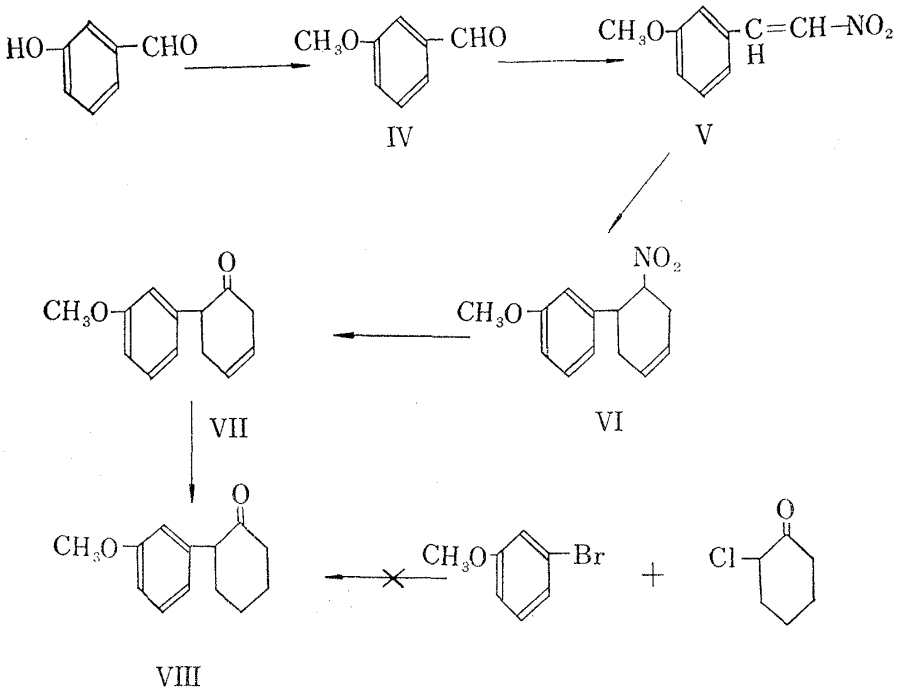


Chart 2

Secondly, the title compound (III) was synthesized as shown in Chart 3. Condensation of VIII with ethyl bromoacetate in a mixed solvent of benzene and ether in the presence of sodium amide[14] gave 2-ethoxycarbonylmethyl-2-(3-methoxyphenyl)cyclohexanone (IX) as a colorless oil, bp 158—160° (0.25 mmHg), whose infrared (IR) spectrum showed carbonyl groups of ester and ketone at 1720 cm^{-1} and 1700 cm^{-1}, respectively. The above compound (IX) was also characterized as its semicarbazone, mp 179—180°. One-step cyclization of

11) O. Schnider and A. Grusner, *Helv. Chim. Acta*, **35**, 1328 (1952).
12) J.U. Nef, *Ann.*, **280**, 263 (1894).
13) W.C. Wildman and R.B. Wildman, *J. Org. Chem.*, **17**, 581 (1952).
14) V. Boekelheide and W.M. Schilling, *J. Am. Chem. Soc.*, **72**, 712 (1950).

IX with methylhydrazine[15] was first tried, but 3,4,5,6,7,8-hexahydro-2H,4aH-4a-(3-methoxyphenyl)-2-methyl-3-oxocinnoline (XI) was not obtained. Hydrolysis of IX with 10% sodium hydroxide solution gave 2-carboxymethyl-2-(3-methoxyphenyl)cyclohexanone (X) as an oil, which was dissolved in sodium bicarbonate aqueous solution with an evolution of carbon dioxide. The IR spectrum (in $CHCl_3$) of X showed a week hydroxyl band of carboxyl group at 3500 cm^{-1} and the bands of carbonyl groups at 1750 cm^{-1} and 1700 cm^{-1}. Cyclization of the above ketone (X) with methylhydrazine sulfate and potassium hydroxide afforded the cinnoline derivative (XI) as a yellow oil, bp 188° (0.4 mmHg), whose IR spectrum (in $CHCl_3$) showed the lactam band at 1675 cm^{-1}. The nuclear magnetic resonance spectrum[16] (NMR) (in $CDCl_3$) of XI showed the protons of N-methyl group at 3.37 ppm and those of O-methyl group at 3.77 ppm as singlets, respectively, and

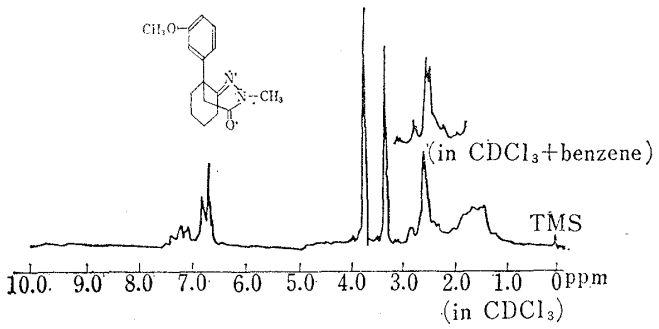


Fig. 1

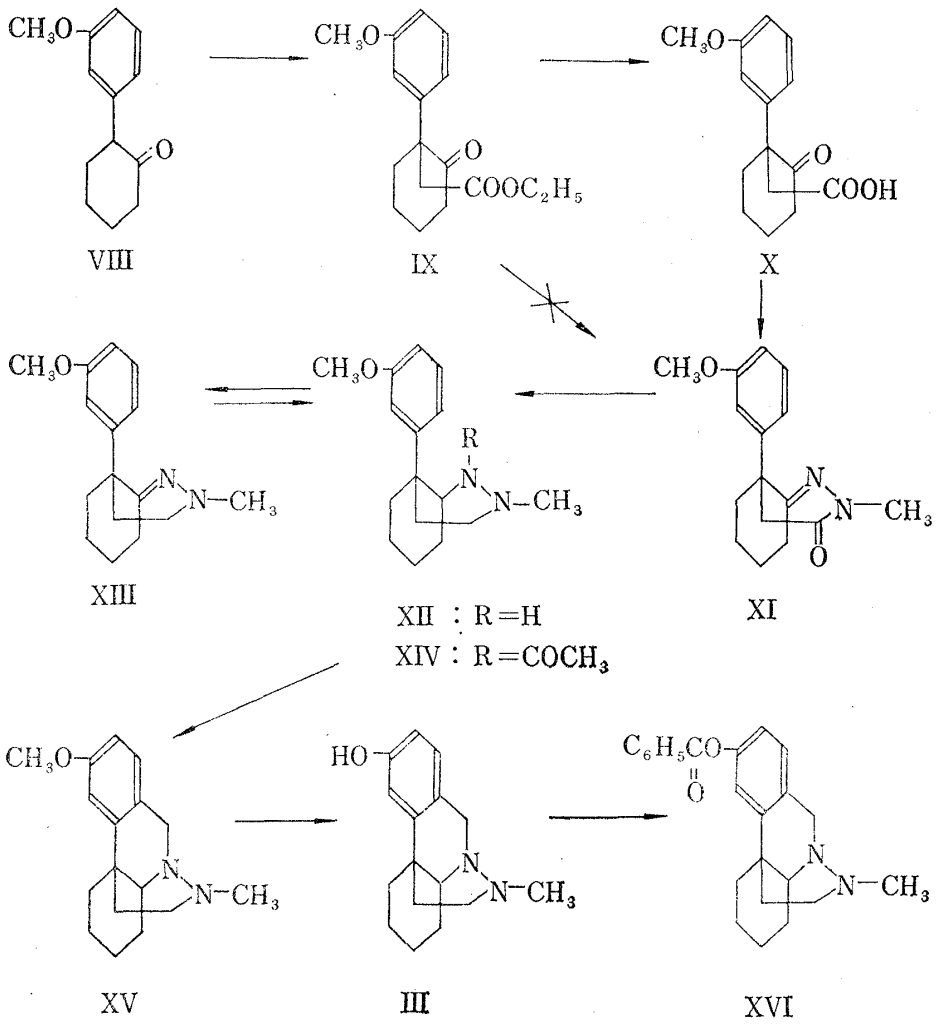


Chart 3

15) *Org. Syntheses*, Coll. Vol. II, 395.
16) The NMR spectra were measured on type H-60 Hitachi and Varian A-60 recording spectrophotometer with deuteriochloroform and trifluoroacetic acid as solvents and tetramethylsilane as an internal reference.

four aromatic protons at 6.73—7.43 ppm (Fig. 1). Furthermore, although the signal of methylene proton at C_4–position was shown at 2.63 ppm as triplet, the signals of the above methylene were converted into quartet (J=15.5 cps) at 2.20 ppm (C_4–*quasi* axial) and at 2.60 ppm (C_4–*quasi* equatorial) when benzene was added to the above solution.

Reduction of XI with lithium aluminum hydride gave 4a–(3–methoxyphenyl)–2–methyldecahydrocinnoline (XII) as its monohydrochloride, mp 236—237.5°, whose thin–layer chromatogram in various solvents showed one spot. The IR spectrum of XII showed NH band at 3150 cm^{-1}, and the lactam band which was shown at 1675 cm^{-1} in case of XI disappeared. The NMR spectrum (in $CDCl_3$) showed the signal of N_2–methyl group at 3.07 ppm as doublet ($J_{N_2H\cdot CH_3}$=5.2 cps), by the result of which the hydrochloride was found to be formed at N_2–position (Fig. 2).

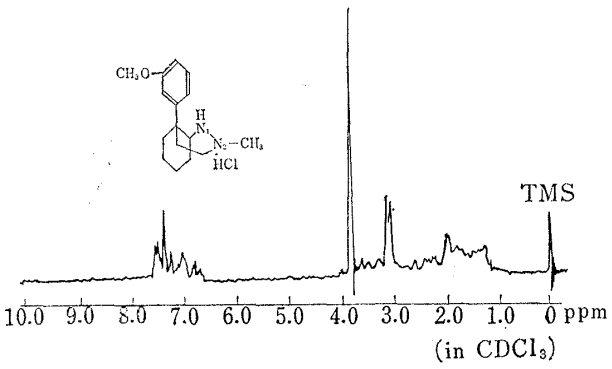


Fig. 2

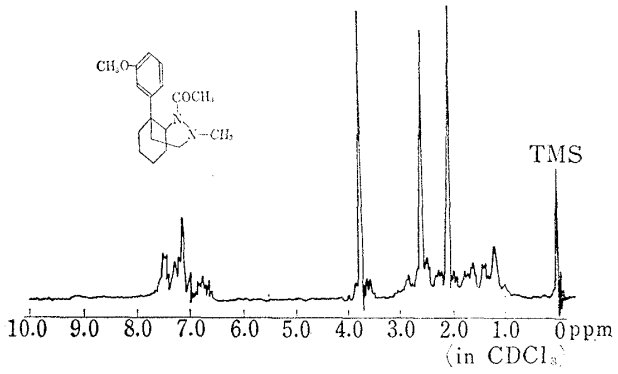


Fig. 3

Furthermore, acetylation of the monohydrochloride of XII with acetic anhydride in the presence of sodium acetate afforded acetyl derivative (XIV) as colorless plates, mp 113°, in the IR spectrum of which the band of NH disappeared and the band of C=O of amidocarbonyl group was observed at 1645 cm^{-1}. The NMR spectrum of XIV showed the protons of methyl of acetyl group at 2.12 ppm as singlet, N–methyl at 2.72 ppm as singlet, and methyl of methoxy group at 3.80 ppm as singlet. In this case the proton at C_{8a}–position was observed at 3.70 ppm as quartet, one of which was overlapped on the signal of O–methyl group (Fig. 3).

When the free base of XII was allowed to stand in the air, dehydro–base (XIII) was formed and the IR spectrum lacked the absorption of NH band. The NMR spectrum of XIII showed the protons of N–methyl group at 2.85 ppm as singlet and those of O–methyl group at 3.80 ppm as singlet, but the signal of the methine at C_{8a}–position could not be observed. Furthermore, no change of the signals as above was recognized by substitution with deuterium oxide (Fig. 4). Although this compound (XIII) could not be acetylated, catalytic hydrogenation of XIII was carried out in the presence of platinum oxide, one molar equivalent of hydrogen being absorbed to give the above hydrochloride of XII, which was identical with the above sample by mixed melting point test and IR spectrum (in KBr). This fact seems to be similar to the easier conversion of 1,2,3,4,5,6–hexahydro–4–methyl–1,5–methanobenzo[*e*][1,2]diazocine into 1,4,5,6–tetrahydro–4–methyl–

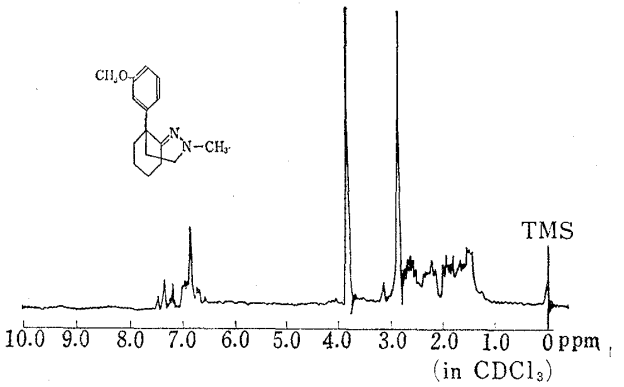


Fig. 4

1,5-methanobenzo[*e*][1,2]diazocine by dehydrogenation in the air reported by Mitsuhashi, *et al.*[17,18] According to the facts that both reductions, namely, lithium aluminum hydride reduction of XI and catalytic hydrogenation of XIII, afforded the same compound (XII), stereospecific reduction seems to have proceeded in this case as was shown in Chart 4.

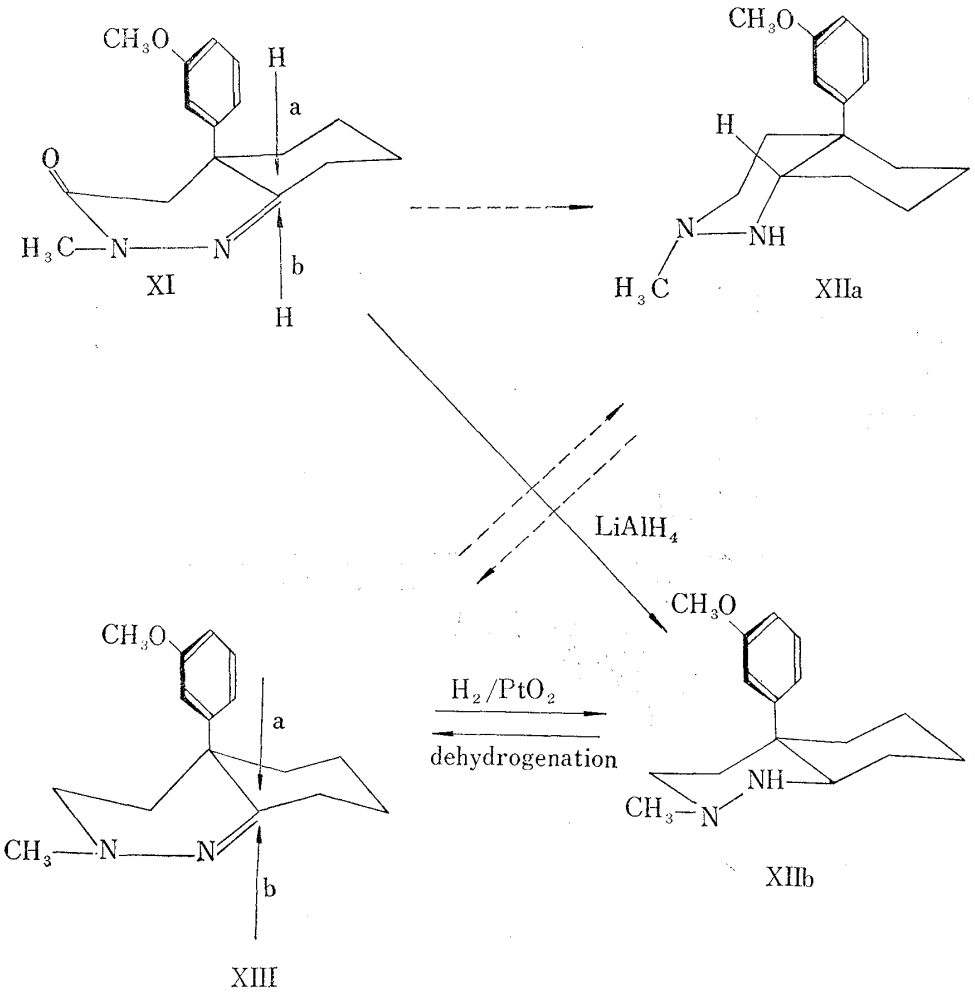


Chart 4

In case of reduction of XI with lithium aluminum hydride, there seems to be two directions of hydrogen-attack against C=N double bond, but the hydrogen-attack from the direction (a) would be hindered because of steric repulsion by the influence of the bulky phenyl group. On the other hand, the hydrogen would be introduced from sterically non-hindered direction

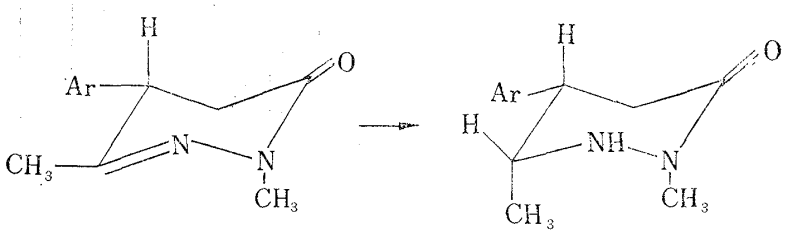


Chart 5

17) Proceedings of the Pharmaceutical Society of Japan, the 23rd Annual Meeting in Sendai, October, 1966, p. 75.
18) S. Shiotani, T. Hori, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **15**, 88 (1967).

(b) to give the compound (XIIb) of *trans*-type. This fact also seems to be similar to stereospecific catalytic hydrogenation of 5-(3-methoxyphenyl)-2,6-dimethyl-4,5-dihydropyridazine-3-(2*H*)-one.[18]

Pictet-Spengler reaction of XII with formalin and hydrochloric acid afforded 3-methoxy-N-methyl-9-azamorphinan (XV) as its hydrochloride, mp 219—220°, whose IR spectrum (in KBr) lacked the NH absorption band and showed the absorption of 1,2,4-trisubstituted benzene at 800—880 cm^{-1}. This fact shows that the cyclization would be held at the *para*-position to the methoxyl group. Furthermore, the NMR spectrum of XV (in $CDCl_3$) showed the aromatic protons at 6.58—7.10 ppm as ABX type signal (J_{ortho}=8.0 cps, J_{meta}=2.5 cps) and the protons of the methylene group at C_{10}-position as doublet (J_{AB}=19 cps) (AB type) at 3.86 and 4.10 ppm, respectively. The former signals also support the cyclization to the *para*-position (Fig. 5).

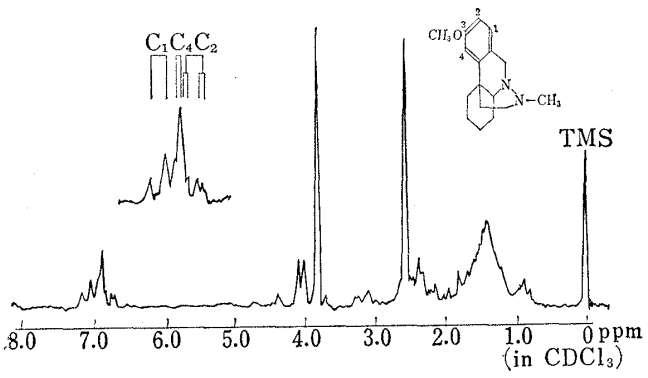


Fig. 5

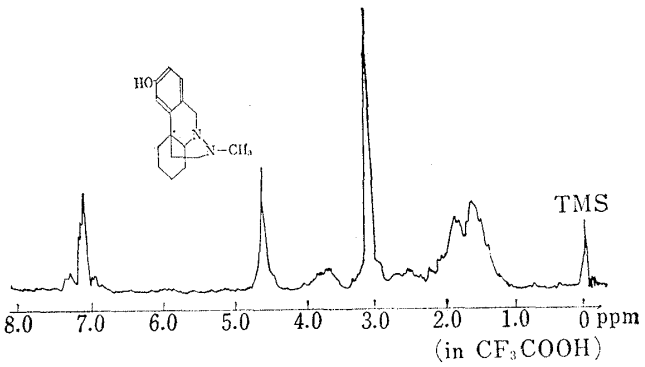
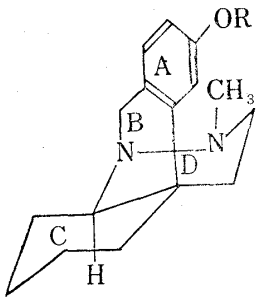


Fig. 6

Finally, demethylation of the above compound (XV) with 47% hydrobromic acid gave our expected compound (III) as colorless needles, mp 265—267° (decomp.), whose IR spectrum (in KBr) showed the absorption bands due to the formation of the intramolecular ammonium salt at 2200—2700 cm^{-1}. In the NMR spectrum of III the signal of the methoxyl group of XV, which was observed at 3.77 ppm, disappeared (Fig. 6). Furthermore, the IR spectrum of its acetyl derivative showed the C=O band of acetyl group at 1760 cm^{-1}. Attempts to crystallize various salts were examined, but resulted in failure. Accordingly, benzoylation of III was tried to give 3-benzoyloxy-N-methyl-9-azamorphinan (XVI) as an oily free base, whose IR spectrum showed the band of ester at 1738 cm^{-1}. This compound was characterized as its picrate, mp 191—192° (decomp.).



XVa : R=CH_3
IIIa : R=H

Chart 6

After all, if there would be no inversion in case of Pictet-Spengler reaction and demethylation, the stereochemical structure of compound (XV and III) may be assumed to be *trans*-type compounds as XVa and IIIa.

Experimental[19]

2-Ethoxycarbonyl-2-(3-methoxyphenyl)cyclohexanone (IX)——To a refluxed suspension of 2.3 g of $NaNH_2$ in 40 ml of dry benzene and 40 ml of dry ether was added dropwise with stirring a solution of 10.2 g of VIII in 50 ml of ether, and the mixture was heated under reflux until no gas evolution of NH_3 had been observed. To the above mixture was added drop by drop 12.5 g of ethyl bromoacetate in 50 ml of dry ether, and further refluxing was continued for 3 hr. After cooling, the excess of $NaNH_2$ was decomposed with

19) All melting points were not corrected.

water and the solvent layer was separated. The solvent was washed with water, dried on K_2CO_3, and distilled to give a pale yellow oil, whose distillation *in vacuo* gave 5 g (34.5%) of IX as a colorless oil, bp 158—160° (0.25 mm Hg). IR cm^{-1} (liquid): $\nu_{C=O}$ 1720 (ester), $\nu_{C=O}$ 1700 (ketone).

A mixture of 0.2 g of the preceding ketone (IX), 0.2 g of semicarbazide, 0.2 g of NaOAc, and dilute EtOH was allowed to stand at room temperature for 2 days.

Filtration and recrystallization from EtOH gave 0.1 g of the semicarbazone of IX as colorless needles, mp 179—180°. IR cm^{-1} (KBr): 1718, 1685. *Anal.* Calcd. for $C_{18}H_{25}O_4N_3$: C, 62.23; H, 7.25; N, 12.10. Found: C, 61.86; H, 6.19; N, 12.42.

2-Carboxymethyl-2-(3-methoxyphenyl)cyclohexanone (X)——A solution of 9.8 g of IX in a small amount of EtOH was added to 50 ml of 10% NaOH aq. solution, and the mixture was heated on a water-bath for 2 hr. After cooling, the reaction mixture was extracted with ether. The resultant aqueous layer was acidified with conc. HCl solution, and extracted with ether. The extract was washed with 5% $NaHCO_3$ solution. The above alkaline extract was again acidified with conc. HCl solution and extracted with ether. The solvent was washed with saturated NaCl aq. solution, dried on Na_2SO_4, and distilled to give 7.2 g (81.4%) of X as a colorless oil. IR cm^{-1} ($CHCl_3$): ν_{OH} 3500, $\nu_{C=O}$ 1750 (ester), $\nu_{C=O}$ 1700 (ketone).

3,4,5,6,7,8-Hexahydro-2H,4aH-4a-(3-methoxyphenyl)-2-methyl-3-oxocinnoline (XI)——To a mixture of 2.6 g of X, 1.7 g of KOH, and 20 ml of water was added a solution of 1.4 g of $CH_3NHNH_2 \cdot H_2SO_4$ in a small amount of water, and the mixture was heated on a water-bath for 1 hr. After cooling, the reaction mixture was made with dil. H_2SO_4 aq. solution as pH 7.2—7.4 and then heated on a water-bath for 2 hr. An oil separated was extracted with ether. The extract was washed with 5% $NaHCO_3$ solution and then water, dried on K_2CO_3, and evaporated to give a yellowish-brown oil, whose distillation *in vacuo* afforded 1 g (37%) of a yellow oil. *Anal.* Calcd. for $C_{16}H_{20}O_2N_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.32; H, 7.51; N, 10.05. IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1675. NMR (ppm) ($CDCl_3$): 2.63 (2H, triplet, C_4–$\underline{H}_2$), 3.37 (3H, singlet, N–$C\underline{H}_3$), 3.77 (3H, singlet, $OC\underline{H}_3$), 6.73—7.43 (4H, multiplet, aromatic protons). NMR (ppm) ($CDCl_3$+benzene): 2.20 (1H, doublet, J=15.5 cps, C_4-*quasi* axial proton), 2.60 (1H, doublet, J=15.5 cps, C_4-*quasi* equatorial proton).

4a-(3-Methoxyphenyl)-2-methyldecahydrocinnoline (XII) and 3,4,5,6,7,8-hexahydro-2H,4aH-4a-(3-methoxyphenyl)-2-methylcinnoline (XIII)——To a heated suspension of 4 g of $LiAlH_4$ in 100 ml of dry dioxane, and the mixture was heated under reflux for 5 hr. After cooling, the excess of $LiAlH_4$ was decomposed carefully with 40 ml of 10% aq. solution. The solvent layer was separated by decantation, dried on K_2CO_3, and saturated with HCl gas. Removal of the solvent gave a colorless powder, whose recrystallization from iso-PrOH afforded 1.5 g (53.6%) of XII as colorless scales, mp 236—237.5°. *Anal.* Calcd. for $C_{16}H_{24}ON_2 \cdot HCl$: C, 64.74; H, 8.49; N, 9.44. Found: C, 64.49; H, 8.56; N, 9.42. IR cm^{-1} (KBr): ν_{NH} 3150. NMR (ppm) ($CDCl_3$): 3.07 (3H, doublet, $J_{N_2^+H-2CH_3}$=5.2 cps, N–$C\underline{H}_3$), 3.80 (3H, singlet, $OC\underline{H}_3$), 6.60—7.60 (4H, multiplet, aromatic protons).

After the compound (XII) had been allowed to stand in the air as its free base, the compound (XIII) was formed as a yellow oil, whose IR spectrum lacked the absorption of NH band. Recrystallization of the picrate from EtOH gave yellow pillars, mp 152—153° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}ON_2 \cdot C_5H_3O_7N_3$: N, 14.37. Found: N, 14.34. NMR (ppm) ($CDCl_3$): 2.85 (3H, singlet, N–$C\underline{H}_3$), 3.80 (3H, singlet, O–$C\underline{H}_3$), 6.63—7.40 (4H, multiplet, aromatic protons).

A solution of 1.7 g of the preceding compound (XIII) in 150 ml of dry MeOH was hydrogenated in the presence of 1.5 g of conc. HCl and 200 mg of PtO_2, 1 molar equivalent of H_2 being absorbed. Filtration and removal of the solvent gave a colorless powder whose recrystallization from iso-PrOH gave 1.8 g (92.3%) of XII as colorless scales, mp 236—237.5°. This was identical with an authentic sample as above by mixed melting point and infrared spectral comparison.

1-Acetyl-4a-(3-methoxyphenyl)-2-methyldecahydrocinnoline (XIV)——A mixture of 0.5 g of HCl salt of XII, 2 g Ac_2O, and 2g of AcONa was heated under reflux in an oil-bath for 2 hr. Removal of the excess of Ac_2O gave the residue, which was mixed with water and allowed to stand. The crystals (0.35 g, 68.6%) were separated. Recrystallization from dilute acetone afforded colorless plates, mp 113°. *Anal.* Calcd. for $C_{18}H_{26}O_2N_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.59; H, 8.88; N, 9.27. IR cm^{-1} (KBr): $\nu_{C=O}$ 1645 (acetyl C=O). NMR (ppm) ($CDCl_3$): 2.12 (3H, singlet, N–$C\underline{H}_3$), 2.72 (3H, singlet, N–$C\underline{H}_3$), 3.80 (3H, singlet, $OC\underline{H}_3$), 3.70 (1H, quartet, C_8–$\underline{H}$), 6.63—7.45 (4H, multiplet, aromatic protons).

3-Methoxy-N-methyl-9-azamorphinan (XV)——A mixture of 0.1 g of HCl-salt of XII, 3 g of H_2O, 3 g of 37% CH_2O, and one drop of conc. HCl solution was heated on a water-bath for 1 hr. After the reaction, the reaction mixture was evaporated to 2 ml of its volume, and extracted twice with 50 ml of ether. After being dried on K_2CO_3, the extract was introduced with HCl gas and distilled to give a colorless oil, which solidified on being triturated with EtOH. Collection by filtration and recrystallization from EtOH afforded 50 mg (50%) of HCl salt of XV as colorless prisms, mp 219—220°. *Anal.* Calcd. for $C_{17}H_{22}ON_2 \cdot HCl$: C, 66.11; H, 8.16; N, 9.07. Found: C, 66.07; H, 7.96; N, 8.98. NMR (ppm) ($CDCl_3$): 2.56 (3H, singlet, N–$C\underline{H}_3$), 3.78 (3H, singlet, $OC\underline{H}_3$), 3.86 and 4.10 (2H, quartet, J=19 cps, C_{10}–$\underline{H}_2$), 6.58—7.10 (3H, multiplet, J_{ortho}=8.0 cps, J_{meta}=2.5 cps, aromatic protons).

3-Hydroxy-N-methyl-9-azamorphinan (III)——To a solution of 0.1 g of HCl salt of XV in 1.5 g of AcOH was added 1.25 g of 47% HBr solution, and the mixture was heated under reflux for 1 hr. Removal

of the solvent *in vacuo* gave the residue, which was made basic with 28% NH_4OH aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried on K_2CO_3, and distilled to give a syrup, which was crystallized on being triturated with EtOH. Recrystallization from EtOH afforded 33 mg (39.3%) of III as colorless needles, mp 265—267°(decomp.). *Anal.* Calcd. for $C_{16}H_{22}ON_2$: C, 74.38; H, 8.58; N, 10.84. Found: C, 73.88; H, 8.54; N, 10.80. IR cm^{-1} (KBr): $\nu^{+}_{N\text{-}H}$ 2200—2700. NMR (ppm) (CF_3COOH): 3.12 (3H, singlet, N–C$\underline{H}_3$), 4.65 (2H, singlet, C_{10}–$\underline{H}_2$).

3-Benzoyloxy-N-methyl-9-azamorphinan (XVI)——To a suspension of 0.2 g of III in 6 ml of 10% NaOH aq. solution was added 0.16 g of benzoyl chloride in the presence of benzene, and the mixture was shaken. The solvent layer was separated, dried on Na_2SO_4, and introduced with HCl gas to separate the HCl salt of XVI, which was made basic with 10% NaOH aq. solution under cooling and extracted with ether. The extract was dried on K_2CO_3 and distilled to give 1.5 g (53.6%) of XVI as a colorless viscous substance. IR cm^{-1} (liquid): $\nu_{C=O}$ 1738. Recrystallization of the picrate from AcOH gave yellow prisms, mp 191—192° (decomp.). *Anal.* Calcd. for $C_{29}H_{29}O_9N_5$: C, 58.88; H, 4.94; N, 11.84. Found: C, 58.70; H, 5.10; N, 11.53.

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