structure (III). In the present series of experiments, it was confirmed that although so far trilobine was considered to possess two N-CH_3 groups, actually one of the two nitrogen atoms is present as N-CH_3, and the other, as an NH group (see Table I). It follows, therefore, that isotrilobine should be represented by the structure of (IX, $R_1=R_2=CH_3$), whereas trilobine by (IX, $R_1=H$, $R_2=CH_3$ or $R_1=CH_3$, $R_2=H$). Furthermore, it was suggested that the stereochemical arrangments about the two asymmetric centers in these bases are both of (−,+) type.

(Received October 26, 1954)

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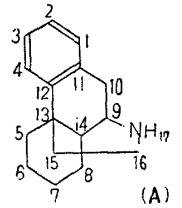
4. **Norio Sugimoto and Hiroshi Kugita** : Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. IV.[1] Synthesis of 3-Hydroxy-9-azamorphinan.

(*Osaka Research Laboratory, Gohei Tanabe & Co., Ltd.**)

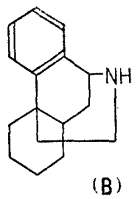
In 1946, Grewe[2] succeeded in synthesizing the parent nucleus of morphine and designated this structure as morphinan (A). Later, various improved methods for the synthesis of morphinan were published and, according to the reports of Gross, Fromberg, Isbell, and Böni,[3] there is no analgesic action in *d*-3-hydroxy-N-methylmorphinan or N-ethylmorphinan while their administration in large doses is effective against rheumatism.

It has, however, been found that *l*-3-hydroxy-N-methylmorphinan causes a marked analgesic action, which is lasting and is about three times stronger than that of morphine. This action is antagonistic to morphine.

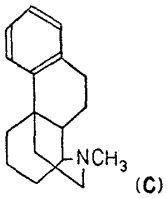
Following the synthesis of morphinan, studies on the syntheses of its allied compounds have been published but these were all allied compounds with identical compositions but with entirely different skeleton. For example, Newmann and others[4] synthesized, in 1947, 1,3,4,9,10,10a-hexahydro-9,4a-2*H*-iminoethanophenanthrene (B) but failed to give its pharmacological effect. Recently, May and others[5] reported on the synthesis of 1,2,3,9,10,10a-hexahydro-11-methyl-1,4a-4*H*-iminoethanophenanthrene (C) but there seemed to be no marked analgesic action in this compound.



(A)



(B)



(C)

The compound which was taken up as the object of our attempt to synthesize the isomers of morphinan is 9-azamorphinan and as can be known from such a designation, it is an isomer of morphinan in which the nitrogen in its skeleton has shifted from 17-

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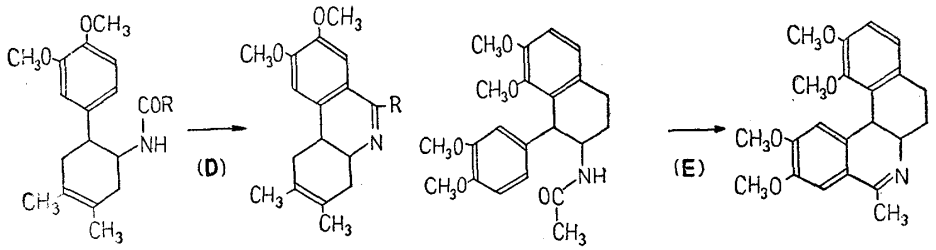
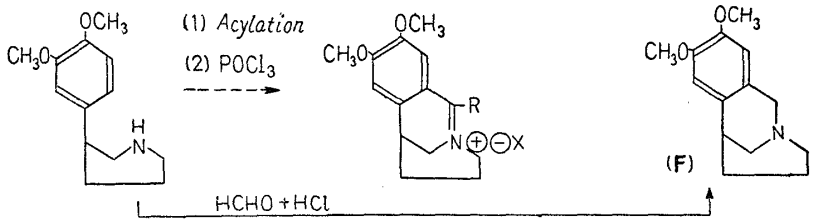
1) Part III : J. Pharm. Soc. Japan, **75**(1955), in press.
2) R. Grewe : Naturwissenschaften, **33**, 333(1946).
3) E. Goss, K. Fromberg, H. Isbell, A. Böni : Feder. Proc., 8, Part I, 297(1949); Arch. Int. Pharm. Therap., **85**, 3871(1952); Experientia, 8, 394(1952); J. Pharmacol. Exptl. Therap., **107**, 524(1953); Zeitsch. Rheumaforschung, **12**, 23(1953).
4) M. S. Newmann, *et al.* : J. Am. Chem. Soc., **69**, 942(1947).
5) E. L. May, *et al.* : J. Org. Chem., **19**, 618(1954).

to 9-position. There has been no report on morphinans in which the position of the nitrogen has been shifted.

Some time ago, Sugasawa and others[6] succeeded in deriving 1,2-dimethyl-4-(3′,4′-dimethoxyphenyl)-5-acylamino-Δ^1-cyclohexene(D) to the corresponding phenanthridine ring, and Walker and others,[7] 1-(3′,4′-dimethoxyphenyl)-2-acetamino-7,8-dimethoxy-1,2,3,4-tetraline (E) to the corresponding one, both by the Bischler-Napieralski reaction. These reactions are successful examples of a cyclization of an acyl compound of a base in which the carbon atoms in the α- and β-positions of phenethylamine are bonded with several numbers of methylene groups.



The present writer showed in Part III of this series[1] that the attempted Bischler-Napieralski reaction of the acyl compound of phenethylamine in which the carbon atom in β-position and the amino group is bonded with several numbers of methylene groups had been unsuccessful and that the condensation-cyclization was effected with formaldehyde solution and hydrochloric acid to benzo-1-azabicyclo[3 : 3 : 1]nonane (F).



In the present series of experiments, studies were made on the Bischler-Napieralski cyclization of 10-phenyldecahydroquinoline, a compound in which the carbon atoms in the α- and β-positions of phenethylamine are bonded with some methylene groups, and the carbon at β-position and the amino group are also bonded with a few numbers of methylene groups in between.

3-Methoxy-9-azamorphinan (II) was obtained from 10-(*m*-anisyl)decahydroquinoline (I)[8] by deriving it to N-hydroxymethyl compound with formaldehyde and sodium hydrogen carbonate, and by ring closure on heating with hydrochloric acid. It formed a hydrochloride as colorless needles, m.p. 249~250°.

On the other hand, 10-(*m*-anisyl)decahydroquinoline (I) was heated in a sealed tube with formaldehyde and formic acid to effect N-methylation but the base obtained formed a hydrochloride of colorless needles, m.p. 248~250°, undepressed on admixture with 3-methoxy-9-azamorphinan hydrochloride prepared by the formaldehyde-hydrochloric acid method. Since the infrared absorption curves of these two substances were completely identical** the two compounds must be the same (Fig. 2). A base obtained from the mother liquor in the latter case is a colorless liquid of $b.p_4$ 157~160° and failed to give any crystalline derivatives. Since its infrared absorption spectrum

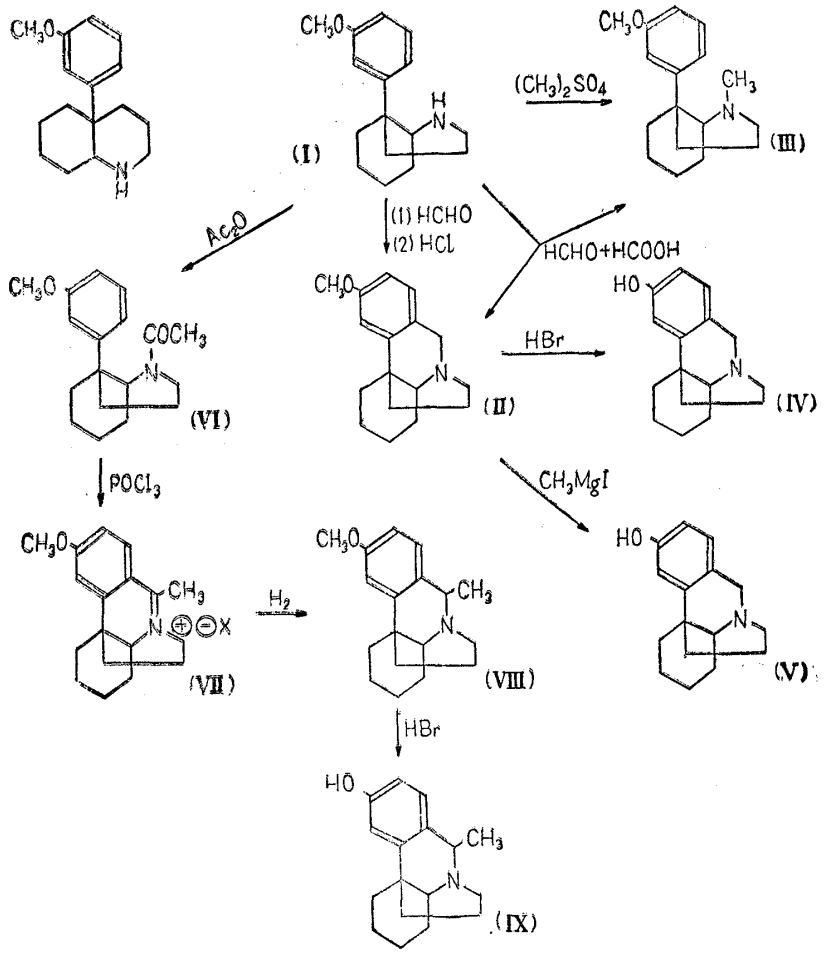
6) S. Sugasawa, *et al.*: Ber., **72**, 675(1939).
7) G. N. Walker, *et al.*: J. Am. Chem. Soc., **76**, 3999(1954).
8) Part I: J. Pharm. Soc. Japan, **75**(1955), in press.
** Infrared spectral measurements were carried out by Mr. K. Kodera of this Laboratory.

is almost identical with that of 10-(*m*-anisyl)-N-methyldecahydroquinoline (III),[8] obtained by methylation of (I) with dimethyl sulfate, with the exception of a small absorption at 10.3 μ in the former (Fig. 1), it is thought that the two are the same compounds and that the N-methylation had also occurred as anticipated.

Examples of such a cyclization with formaldeyde and organic acid has never been published in literatures and is here recorded as a specific case.

In order to examine the Bischler-Napieralski reaction of the acetyl compound (VI) of 10-(*m*-anisyl)decahydroquinoline, (VI) was heated with phosphoryl chloride by which hydrochloric acid evolved vigorously and the reaction seemed to proceed. After the reaction, the solvent was distilled off, the residue was extracted with water, and the crystals of sodium iodide was added to the aqueous solution. The precipitated azonia iodide (VII : X=I) was collected by filtration and was derived to azonia chloride (VII : X=Cl) by heating with silver chloride in water. This chloride was submitted to reduction in hydrogen stream with the Adams platinum oxide in which the absorption of hydrogen stopped when the yellow azonia chloride became colorless. The absorption curve of the infrared spectrum of 3-methoxy-10-methyl-9-azamorphinan (VIII)(Fig. 3) thereby obtained shows marked similarity with that of 3-methoxy-9-azamorphinan (II) (Fig. 2) that it may be assumed that the condensation-cyclization had occurred in the *para*-position of the methoxyl group as anticipated.

Demethylation of 3-methoxy-9-azamorphinan (II) was attempted by heating with hydrobromic acid from which 3-hydroxy-9-azamorphinan (IV) was obtained as colorless granular crystals, m.p. 242~245°.



Demethylation of (II) by heating with methylmagnesium iodide, followed by hydrolysis with aqueous solution of ammonium chloride gave colorless needles, m.p. 275° (from ethanol). The state of bonding in this compound is still unknown but a qualitative test revealed that it forms a double salt with magnesium chloride. The base (V) extracted with chloroform in ammoniac-alkaline solution came as a syrupy solid which formed a hydrochloride of m.p. 295°.

As shown in the foregoing, demethylation of (II) by hydrobromic acid and by methylmagnesium iodide gave different substances but the infrared absorption spectral analyses (Figs. 4 and 5) of (IV) and (V) showed that there was no great difference in their absorption and the elemental analytical values approximately agreed that it is concluded that (IV) and (V) are isomeric compounds. It is quite likely that stereoisomers had been formed by the conditions of demethylation in the configuration of the trimethylene at 15-, 16-, and 17-positions and the hydrogen attached to the carbon at 14-position. Attempt was therefore made for the isomerization of (V) into (IV) by heating with hydrobromic acid but resinification occurred with the heating and (IV) could not be isolated.

When 3-methoxy-10-methyl-9-azamorphinan (VIII) is heated with hydrobromic acid, the hydrobromide of (IX) separates out on cooling, and recrystallization from water gives the crystals of m.p. 160°.

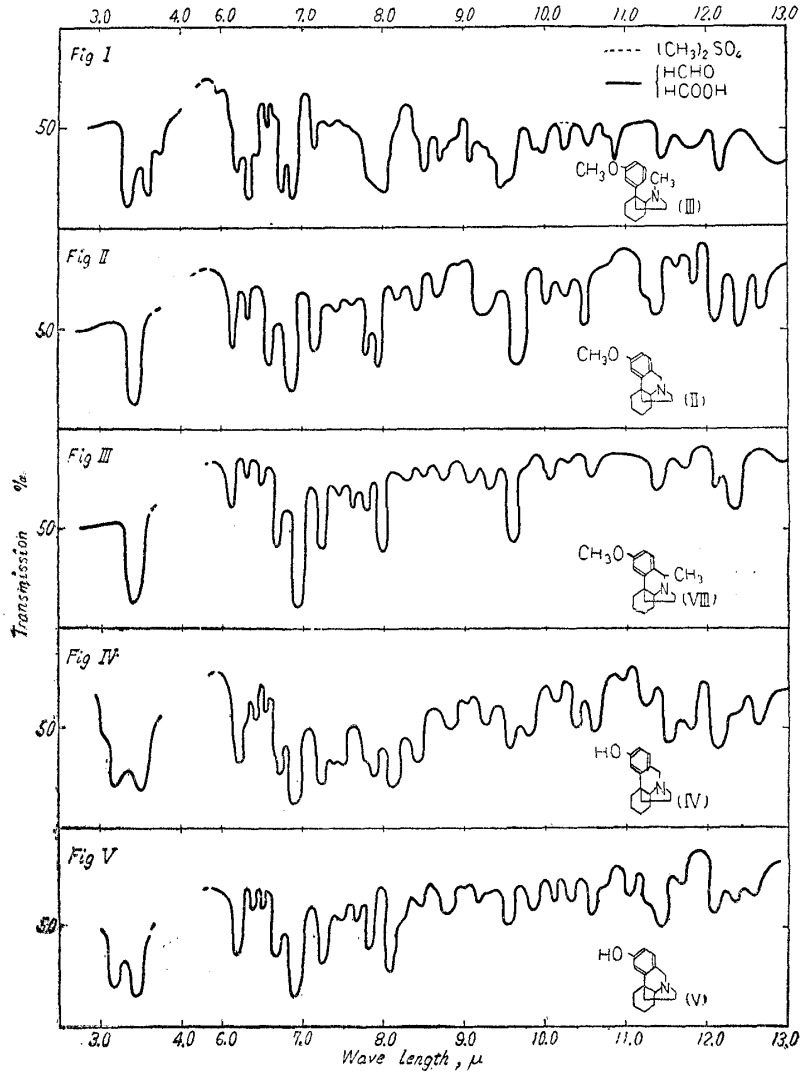


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Infrared Absorption Curves (in Nujol suspension)

The foregoing results have shown that the Bischler–Napieralski cyclization of the acyl compounds of phenethylamine, in which the carbon atoms at α- and β-postitions are bonded with several numbers of methylene groups and the carbon at β-position and the amino group are also bonded through several methylenes, was successfully concluded as anticipated.

The pharmacological action of these compounds was tested by Dr. Hajime Fujimura of the Department of Pharmacology, Medical Faculty, University of Kyoto. When tested by the Haffner method using mice, the compound (IV) showed analgesic action about equal to that of morphine but with much stronger toxicity, while (II), (V), and (IX) showed no analgesic action even at a toxic dose, with stronger toxicity than that of (IV). The interesting fact revealed by this test was that (IV) worked synergetically with morphine in its analgesic action.

The writers take this opportunity to extend their gratitude to Prof. Shigehiko Sugasawa of the University of Tokyo and to Dr. Masao Fujisawa, Director of this Laboratory, for their unfailing guidance and encouragement. They are also indebted to Miss T. Hisamichi and Mr. T. Yoda for the microanalytical data.

Experimental

3-Methoxy-9-azamorphinan (II)—a) A mixture of 10-(*m*-anisyl)decahydroquinoline (I) (1.0 g.), 36% HCHO solution (0.4 g.), $NaHCO_3$ (0.2 g.), and water (3 cc.) was heated for 40 min. on a water bath. The resinous substance that separated was cooled, washed several times with water, and 20% HCl (5 cc.) was added to it. The acid solution was heated for 30 min. on a boiling water bath and the solvent was distilled off *in vacuo*. Repetition of this procedure gave the crude hydrochloride of 3-methoxy-9-azamorphinan as colorless needles (AcOEt+EtOH), m.p. 249~250°. *Anal.* Calcd. for $C_{17}H_{23}ON \cdot HCl$: C, 69.5; H, 8.2; N, 4.8. Found: C, 69.7; H, 8.2; N, 5.05.

Picrate: Yellow prisms (EtOH), m.p. 160~162°. *Anal.* Calcd. for $C_{23}H_{26}O_8N_4$: C, 56.8; H, 5.4; N, 11.5. Found: C, 57.0; H, 5.7; N, 11.35.

Methiodide: Yellow needles (AcOEt+MeOH), m.p. 235~236°. *Anal.* Calcd. for $C_{18}H_{26}ONI$: C, 54.2; H, 6.5; N, 3.5. Found: C, 53.8; H, 6.6; N, 3.6.

Free base from the hydrochloride purified by distillation *in vacuo*, gave colorless oil, b.$p_{3.5}$ 160~162°; yield, 0.3 g.

b) A mixture of 10-(*m*-anisyl)decahydroquinoline (I) (2.5 g.), 36% HCHO (1.5 g.), 78% formic acid (5 cc.), and water (5 cc.) was heated in a sealed tube at 130~140° for 7 hrs. Reaction mixture was concentrated, basified with an excess of K_2CO_3, extracted with ether, dried, and the solvent was removed. Residue came over at 167~171°(3.5 mm.), as colorless oil; yield, 2.3 g. This base was converted to the hydrochloride (II-b) and proved to be identical with the hydrochloride obtained in method (a) by a mixed melting determination and analysis of infrared absorption spectrum.

On evaporation of acetone from the mother liquor of the hydrochloride, non-crystalline hydrochloride was obtained. Distillation of this free base *in vacuo* gave 0.5 g. of colorless oil, b.p_4 157~160°, which did not give crystalline derivatives and was characterized through its infrared absorption spectrum as 10-(*m*-anisyl)-N-methyldecahydroquinoline (III) (methylated by dimethyl sulfate).

N-Acetyl-10-(*m*-anisyl)decahydroquinoline (VI)—A mixture of 10-(*m*-anisyl)decahydroquinoline (2.0 g.) and Ac_2O (8 cc.) was refluxed in an oil bath (150°) for 1 hr. Reaction mixture was decomposed with ice water, neutralized with $NaHCO_3$, and extracted with ether. Ether extracts were dried and evaporated to dryness. The residue soon solidified. Yield, 2.3 g. of white needles (from ligroine), m.p. 108~109°. *Anal.* Calcd. for $C_{18}H_{25}O_2N$: C, 75.2; H, 8.8; N, 4.85. Found: C, 74.8; H, 8.9; N, 4.9.

3-Methoxy-10-methyl-9-azoniamorphinan Chloride (VII: X=Cl)—A mixture of the crude acetyl compound (VI) (2.3 g.), $POCl_3$ (5 cc.), and abs. toluene (10 cc.) was refluxed in an oil bath (120°) for 1.5 hrs. Excess of the solvents were distilled off *in vacuo*, the residue was dissolved in water, treated with charcoal, and the filtrate was added with NaI, separating azonia iodide (VII: X=I) as a yellow powder. Azonia iodide crystallized in yellow prism, m.p. 228~229°. *Anal.* Calcd. for $C_{18}H_{24}ONI$: C, 54.4; H, 6.05; N, 3.5. Found: C, 54.25; H, 6.5; N, 3.5.

Picrate: Yellow plates (from EtOH+dioxane). *Anal.* Calcd. for $C_{24}H_{26}O_8N_4$: C, 57.8; H, 5.2; N, 11.25. Found: C, 57.7; H, 4.8; N, 11.0.

The crude azonia iodide was converted to azonia chloride by the usual method and subjected to the following process as an aqueous solution.

3-Methoxy-10-methyl-9-azamorphinan (VIII)—The azonia chloride (VII : X=Cl) was reduced at atmospheric pressure in the presence of the Adams' Pt catalyst, about 1 mole of H_2 being smoothly absorbed. The filtrate from the catalyst was evaporated *in vacuo* and a crystalline hydrochloride was obtained. Yield, about 2.0 g.

Hydrochloride : Colorless needles (from EtOH+ether), m.p. >285°. *Anal.* Calcd. for $C_{18}H_{26}ONCl$: C, 75.2; H, 8.8; N, 4.85. Found : C, 74.8; H, 8.9; N, 4.9.

Picrate : Yellow plates (from EtOH+dioxane), m.p. 217~219°. *Anal.* Calcd. for $C_{24}H_{28}O_8N_4$: C, 57.6; H, 5.6; N, 11.2. Found : C, 57.55; H, 5.9; N, 10.9.

3-Hydroxy-9-azamorphinan (IV)—A solution of 3-methoxy-9-azamorphinan (II) (1.0 g.) in 48% HBr (5.0 cc.) was refluxed for about 4 hrs. After cooling, the reaction mixture was diluted with water, neutralized with $NaHCO_3$, and the separated crystals were filtered and recrystallized from EtOH. Colorless prisms, m.p. 242~245°. It was soluble in NaOH solution, insoluble in $NaHCO_3$ solution, and $FeCl_3$ caused yellow green coloration. *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 79.0; H, 8.7; N, 5.75. Found : C, 78.8; H, 8.7; N, 5.45.

Hydrochloride : Colorless hygroscopic, amorphous substance.

3-Hydroxy-9-azamorphinan (Isomer) (V)—3-Methoxy-9-azamorphinan hydrochloride (II) (2.2 g.) was added to the Grignard reagent prepared from Mg (0.85 g.), CH_3I (5.0 g.), and abs. ether (10 cc.). Ether was evaporated and this mixture was slowly heated to 190°(bath temp.). Gas evolution was observed at about 140°. After 1 hr., the reaction mixture was decomposed with ice water containing NH_4Cl and separated crystals were filtered and recrystallized from EtOH. These crystals (m.p. 275~276°) were determined as a complex salt of magnesium chloride by assay. Converted to the hydrochloride by EtOH-HCl solution. Yield, 1.4 g.

Hydrochloride : Colorless needles, m.p. 295°(decomp.). It was soluble in NaOH solution, insoluble in $NaHCO_3$; $FeCl_3$ reaction was green yellow. *Anal.* Calcd. for $C_{16}H_{22}ONCl \cdot H_2O$: C, 64.5; H, 8.05; N, 4.7. Found : C, 64.85; H, 7.65; N, 4.8.

The hydrochloride was neutralized with NH_4OH, extracted with $CHCl_3$, dried, and evaporated. This base came as a light yellow resinous substance.

3-Hydroxy-10-methyl-9-azamorphinan (IX)—A solution of 3-methoxy-10-methyl-9-azamorphinan (VIII) (2.0 g.) was heated with 48% HBr (15 cc.) in an oil bath at 130° for about 4 hrs. The reaction mixture was filtered in warm and cooled. The separated hydrobromide was collected by filtration. Yield, 1.3 g.

Hydrobromide : White needles (from water), m.p. 160°(decomp.). *Anal.* Calcd. for $C_{17}H_{24}ONBr$: C, 60.35; H, 7.1; N, 4.15. Found : C, 60.0; H, 7.3; N, 4.15.

Summary

1) Isoquinoline cyclization by the Bischler-Napieralski reaction proved to be successful in the acyl derivatives of phenethylamines in which the carbon at α- and β-positions are bonded by a few number of methylene groups, or the amino and the carbon in α-position or those in which the carbon at α- and β-positions and the amino and the carbon in the β-position are both bonded by a few number of methylene groups, but unsuccessful in those in which the carbon at β-position and the amine are bonded by some methylene groups.

2) 3-Hydroxy-9-azamorphinan and its allied compounds were synthesized by such means.

3) Animal tests showed that 3-hydroxy-9-azamorphinan possesses analgesic action equal to that of morphine but its toxicity is far stronger.

4) The isomers and allied compounds of 3-hydroxy-9-azamorphinan does not possess any analgesic action.

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