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Azamorphinan and Related Compounds. II.[1] Synthesis of 3-Methoxy-9-azamorphinan Derivatives (Studies on the Syntheses of Heterocyclic Compounds. CCCXIX[2])

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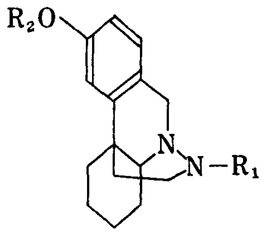
In order to examine an analgesic activity of azamorphinan derivatives, 3-methoxy-9-azamorphinan (XII) was synthesized as follows. Reduction of octahydrocinnoline derivatives (VIIIa and VIIIb), which were obtained by condensation of 2-(3-methoxyphenyl)-cyclohexanone-2-acetic acid (VI) with hydrazine or benzylhydrazine, with lithium aluminum hydride afforded the corresponding decahydrocinnoline derivatives (IXa and IXb). Pictet–Spengler reaction of IXb gave N-benzyl-3-methoxy-9-azamorphinan (XIV), but cyclization of IXa failed. Therefore, ring-closure of Xa, which was obtained by catalytic hydrogenation of VIIIa, with $HOCH_2SO_3Na$, followed by lithium aluminum hydride reduction of XI, afforded the compound (XII). This compound (XII) was also obtained by debenzylation of XIV. Furthermore, N-alkylation of XII at the N_{17}-position with methyl, acetyl, allyl, β-phenethyl and cyclopropylmethyl halides gave the corresponding compounds (I, XIII, XVI, XV, and XVII), respectively.

In the previous papers,[4] azabenzomorphan derivatives which contained an additional nitrogen atom in the benzomorphan ring were synthesized in order to examine an analgesic action. Furthermore, the syntheses of 3-methoxy- (I) and 3-hydroxy-N-methyl-9-azamorphinan (II) by Pictet-Spengler reaction was also reported.[1] The purpose of the present investigation was to study the modified synthesis of azamorphinan derivative (XII) and its N-alkyl–derivatives, which had an additional nitrogen atom in the morphinan ring system, by novel ring-closure.



I : $R_1 = R_2 = Me$
II : $R_1 = Me, R_2 = H$

Chart 1

2-(3-Methoxyphenyl)cyclohexanone (IV), which was obtained according to the procedures[5a–c] through five steps, was condensed with ethyl bromoacetate in the presence of sodium amide to give the cyclohexanone (V), whose hydrolysis with sodium hydroxide solution afforded 2-(3-methoxyphenyl)cyclohexanone-2-acetic acid (VI). Condensation of VI with hydrazine (VIIa) sulfate in the presence of potassium hydroxide aqueous solution under reuflx afforded the cinnoline derivative (VIIIa), whose infrared spectrum showed NH and carbonyl C=O at

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[1] Part I: T. Kametani, K. Kigasawa, M. Hiiragi, and N. Wagatsuma, *Chem. Pharm. Bull.* (Tokyo), **16**, 296 (1968).

[2] Part CCCXVIII: T. Kametani, I. Noguchi, and K. Saito, *J. Heterocyclic Chem.*, in press.

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[4] *a*) T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, and T. Iwate, *Yakugaku Zasshi*, **84**, 405 (1964); *b*) T. Kametani, K. Kigasawa, and M. Hiiragi, *ibid.*, **85**, 871 (1965); *c*) T. Kametani, K. Kigasawa, M. Hiiragi, and H. Ishimaru, *Chem. Pharm. Bull.* (Tokyo), **13**, 295 (1965); *d*) T. Kametani, K. Kigasawa, and T. Hayasaka, *ibid.*, **13**, 300 (1965); *e*) T. Kametani, K. Kigasawa, and M. Hiiragi, *ibid.*, **13**, 1220 (1965); *f*) T. Kametani, K. Kigasawa, and T. Hayasaka, *ibid.*, **13**, 1225 (1965).

[5] *a*) O. Schneider and A. Grüssner, *Helv. Chim. Acta*, **35**, 1328 (1952); *b*) W.C. Wildman and R.B. Wildman, *J. Org. Chem.*, **17**, 581 (1952); *c*) E.L. May and J.C. Murphy, *ibid.*, **20**, 1197 (1955).

3200 and 1670 cm^{-1}, respectively. In this case heating of V with hydrazine hydrate in ethanol also afforded the above compound (VIIIa) in poor yield.

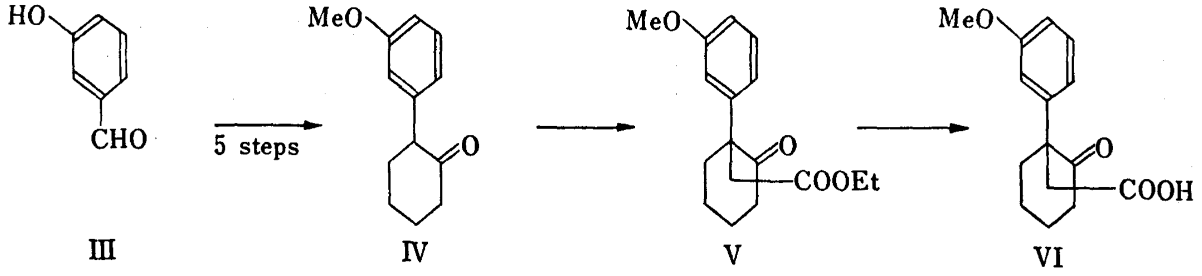

Chart 2

Secondly, ring-closure of decahydro-4a-(3-methoxyphenyl)cinnoline (IXa), which was obtained by reduction of VIIIa with lithium aluminum hydride, with formalin was attempted, but failed. In this case the compound (IXa) seems to have a tendency to be oxidized very easily to VIIIc as Shiotani, *et al.*[6] have reported in the other case. In fact, the free base (IXa) was changed easily to a brownish substance on exposure in the air. Therefore, the above compound (IXa) was characterized as its hydrochloride, mp 152—153°, in order to prevent from oxidation. In the infrared spectrum carbonyl absorption disappeared completely and nuclear magnetic resonance (NMR) spectrum showed the signal due to the methine at the C_{8a}-position as quartet with $J=7$ and 12 cps as was shown in Figure Ia and Ib. This fact showed the formation of IXa, but cyclization of IXa with formalin and hydrochloric acid

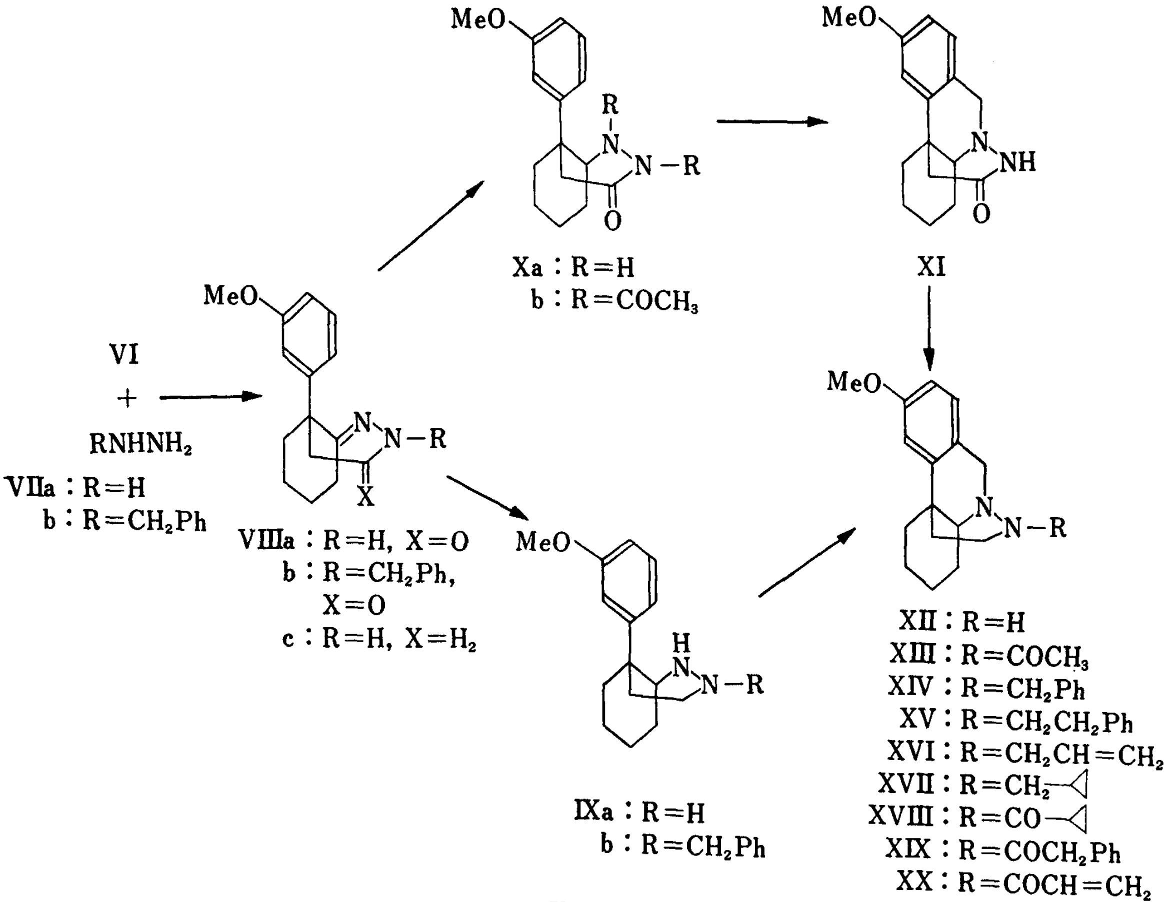

Chart 3

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[6] S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), 15, 761 (1967).

resulted in failure. Therefore, after the C=N double bond of VIIIa had been reduced, ring-closure of the resulting decahydro-4a-(3-methoxyphenyl)-3-cinnolinone (Xa) was investigated in order to obtain 3-methoxy-9-azamorphinan-16-one (XI). Namely, catalytic hydrogenation of VIIIa in methanol in the presence of Adams platinum and perchloric acid afforded the crystals, mp 219—220°, in good yield, which were characterized as N,N-diacetyl-derivative (Xb) by acetylation with acetic anhydride and sodium acetate as Mitsuhashi[7] has reported. Finally the cyclization of the above compound (Xa) with formalin was also examined, but failed. Accordingly, since it has been known that various amines were condensed with sodium hydroxymethanesulfonate to give N-methanesulfonate,[8] condensation of Xa with the above reagent, followed by heating with hydrochloric acid, was investigated to give an expected compound (XI) as colorless prisms, mp 202—203°, whose infrared spectrum showed NH and carbonyl absorption at 3150 and 1650 cm^{-1}, respectively. The NMR spectrum showed the signal due to the C_{10}-methylene at 3.79 and 4.29 ppm as AB type quartet with J=17 cps. Furthermore, the signal of aromatic protons of H_A, H_B and H_C, also revealed the direction of cyclization to be *para* to the methoxyl group as was shown in Fig. 2.

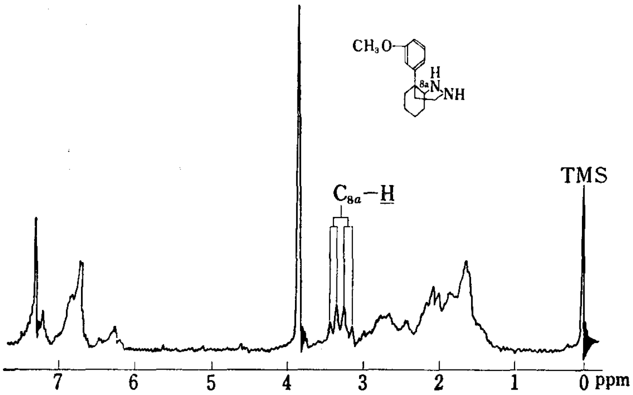

Fig. 1a. NMR Spectrum of IXa (in $CDCl_3$)

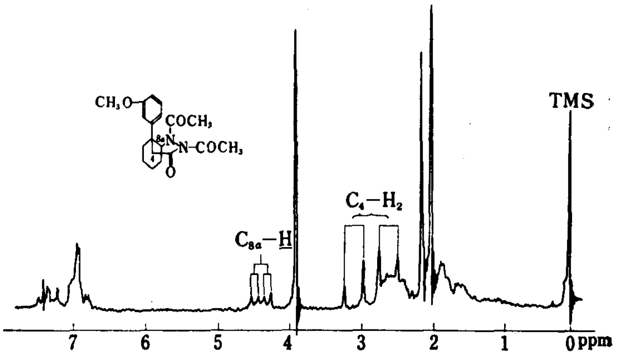

Fig. 1b. NMR Spectrum of Xb (in $CDCl_3$)

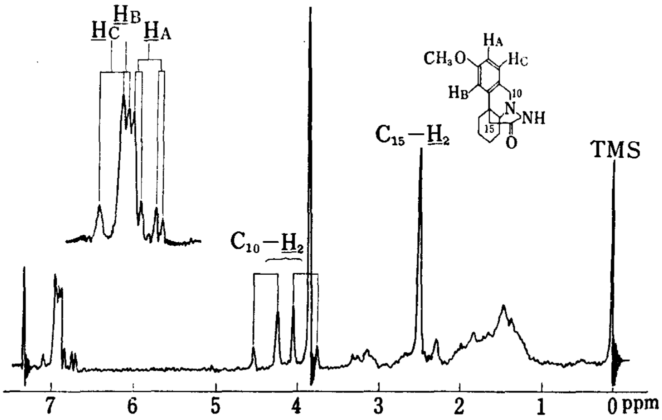

Fig. 2. NMR Spectrum of XI (in $CDCl_3$)

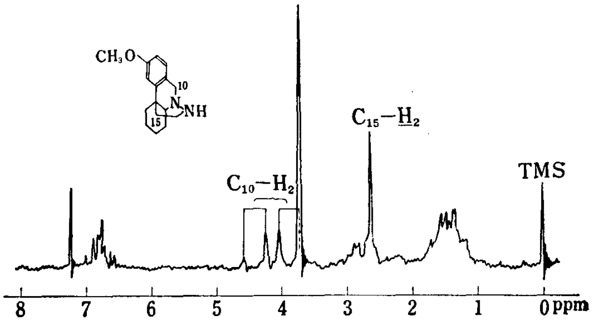

Fig. 3. NMR Spectrum of XII (in $CDCl_3$)

Perhaps the simplest mechanism to explain the formation of XI would initially involve attack of sodium methanesulfonyl group against more basic nitrogen and formation of the protonated intermediate in acidic media to yield XI.

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7) K. Mitsuhashi and S. Shiotani, *Yakugaku Zasshi*, **80**, 1348 (1960).

8) E. Maleac, *Roczniki Panstwowege Zakladu Hig*, **2**, 177 (1951) [*C.A.*, **46**, 7998 (1952)]; CIBA Ltd., Swiss Patent 270, 447—270, 449 and 270, 158—270, 159 (1950) [*C.A.*, **46**, 1044 (1952)]; T. Takahashi and K. Kanematsu, *Chem. Pharm. Bull.* (Tokyo), **6**, 98 (1958); M. Moriguchi, *Yakugaku Zasshi*, **82**, 50 (1962); S. One, R. Ohnishi, and K. Kawamura, *ibid.*, **86**, 11 (1966).

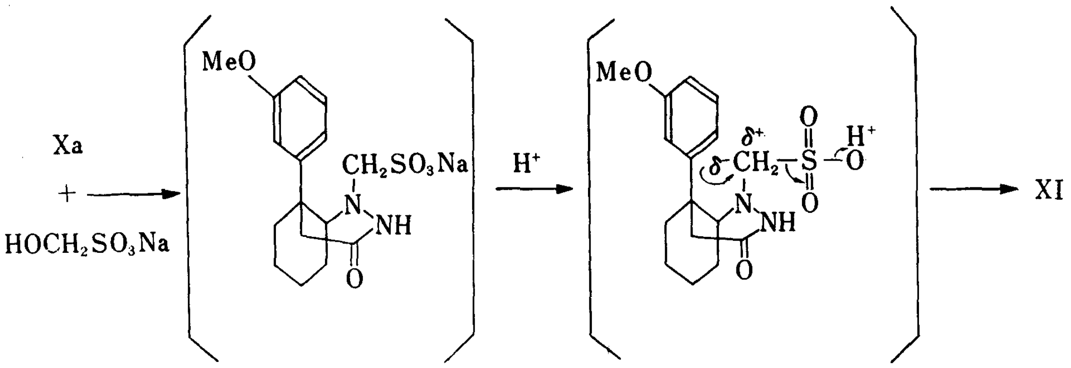

Chart 4

Lithium aluminum hydride reduction of XI in dry dioxane under reflux afforded the compound (XII) as colorless needles, mp 90—91°, after purification by alumina chromatography,[9] which lacked carbonyl absorption and showed the signals due to the methylene at the C_{10}-position at 3.92 and 4.43 ppm as AB type quartet with $J=18$ cps (Fig. 3). Acetylation of XII with acetic anhydride in the presence of sodium acetate afforded N-acetyl-derivative (XIII) and reductive methylation of XII with formalin and sodium borohydride yielded N-methyl-derivative (I) as its hydrochloride, mp 218—219°, which was identical with an authentic sample on mixed mp test and IR (KBr) spectral comparison.

On the other hand, since the above synthesis of XII is not suitable from the point of its yield and it needs many steps, introduction of benzyl group at the N_2-position of cinnoline derivative, followed by cyclization and debenzylation, was examined as follows.

First of all, though debenzylation[10] of 1,1-dibenzylhydrazine with palladium oxide has hitherto been known as a synthetic method of benzylhydrazine, its yield is not good and therefore a simple synthetic method was investigated. At first, reduction of benzylhydrazine with lithium aluminum hydride was examined to give benzylamine in 28% yield. Therefore, reduction of benzalhydrozine[11] with lithium aluminum hydride or sodium borohydride and catalytic hydrogenation in the presence of platinum oxide or palladium oxide were tried, by the result of which the latter method using palladium oxide was found to be available for the synthesis of VIIb. In case of lithium aluminum hydride reduction and catalytic hydrogenation with platinum oxide, benzylamine was also obtained in 43% and 50% yield, respectively. Secondly, the same treatment of γ-ketocarboxylic acid (VI) with VIIb afforded 2-benzyl-2,3,4,4a,5,6,7,8-octahydro-4a-(3-methoxyphenyl)-3-cinnolinone (VIIIb) as a yellow oil, bp 235° (0.08 mm), which was also obtained by heating a mixture of VIIIa and benzyl chloride in dimethylsulfoxide in the presence of sodium hydride. In this case the former method with benzylhydrazine was found to be better from the point of its yield. In the infrared spectrum carbonyl absorption was shown at 1658 cm^{-1} and NMR spectrum showed the signals due to the methylene of the C_4-position at 2.42 and 2.74 ppm as AB type quartet with $J=16.0$ cps and those of methylene of benzyl group at 4.62 and 5.09 ppm as AB type quartet with $J=15$ cps, the latter of which was exaplained by non-equivalency of two hydrogen atoms of the methylene group because it was fixed to the prefer conformation due to the influence of C_3-carbonyl group (Figure 4a). Reduction of VIIIb with lithium aluminum hydride in dry dioxane gave 2-benzyl-decahydro-4a-(3-methoxyphenyl)cinnoline (IXb), which was characterized as its hydrochloride, mp 216—217°. In this case the NMR spectrum showed a singlet at 4.47 ppm because of the lack of carbonyl group (Figure 4b).

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9) Wako's active alumina (300 mesh) was used.

10) L. Birkofer, *Chem. Ber.*, **75**, 429 (1942).

11) Th. Curtius, *J. Prakt. Chem.*, **44**, 537 (1913).

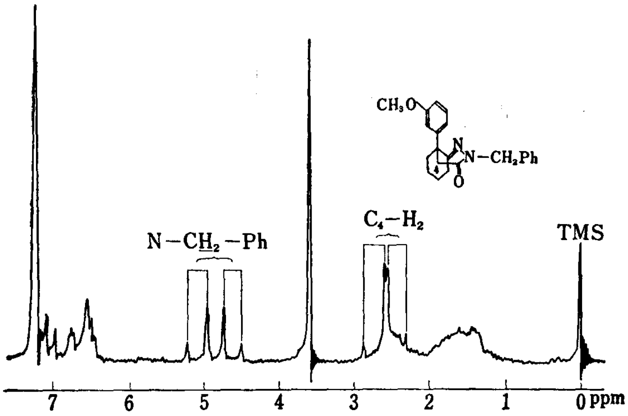


Fig. 4a. NMR Spectrum of VIIIb (in $CDCl_3$)

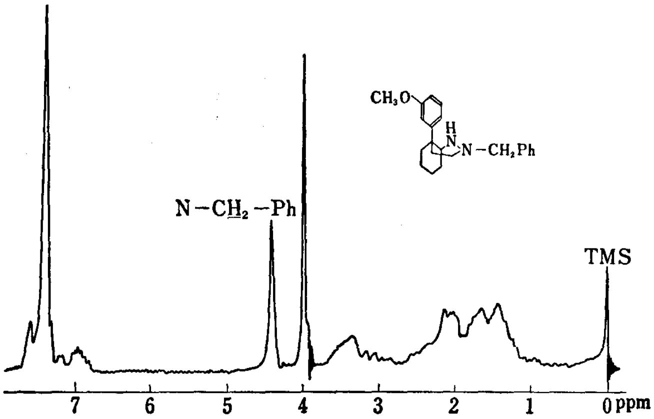


Fig. 4b. NMR Spectrum of IXb (in CF_3COOH)

Further cyclization of the above hydrochloride of IXb with formalin and hydrochloric acid afforded N-benzyl-3-methoxyazamorphinan (XIV) in 55.2% yield, which was also obtained in 22.3% yield by use of sodium hydroxymethanesulfonate. The NMR spectrum of XIV, which showed the signals due to the C_{10}-methylene at 3.99 and 4.57 ppm as AB type quartet with $J=17$ cps, also supports the structure of XIV (Figure 5). Further catalytic hydrogenation of XIV in ethanol in the presence of palladium charcoal afforded the same compound (XII) described above.

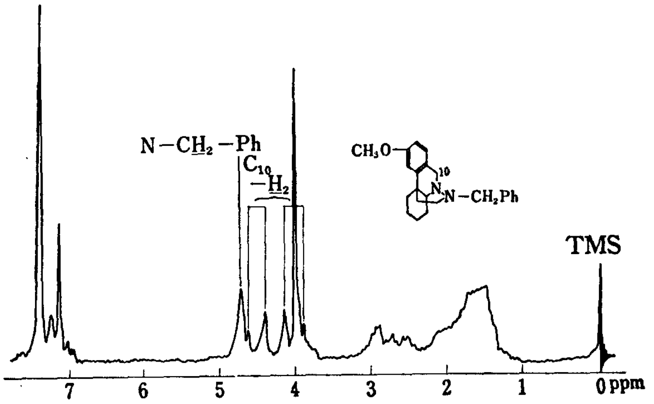


Fig. 5. NMR Spectrum of XIV (in CF_3COOH)

Finally, N-alkylation of XII in toluene with phenethyl, allyl, and cyclopropylmethyl bromides in the presence of potassium carbonate afforded the corresponding N-alkyl-derivatives (XV, XVI, and XVII), respectively. Furthermore, Schotten-Baumann reaction of XII with phenacetyl, cyclopropylcarbonyl, and acrylyl chlorides in the presence of 5% sodium hydroxide afforded N-acyl-derivatives (XIX, XVIII, and XX), respectively, whose reduction with lithium aluminum hydride afforded the objective compounds, (XV) and (XVII). In this case reduction of XX with lithium aluminum hydride failed.

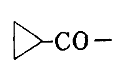
Experimental

The NMR spectra were measured on Hitachi H-60 using deuteriochloroform and trifluoroacetic acid as solvents and tetramethylsilane as internal reference.

2,3,4,4a,5,6,7,8-Octahydro-4a-(3-methoxyphenyl)-3-cinnolinone (VIIIa)——(a) The Reaction of γ-Ketocarboxylic Acid (VI) with $NH_2NH_2 \cdot H_2SO_4$: A mixture of 5.2 g of γ-ketocarboxylic acid, 3.1 g of $NH_2NH_2 \cdot H_2SO_4$ and 77 ml of H_2O was heated on a water-bath for 1 hr. The crystals which separated were collected by filtration and recrystallization from MeOH gave 2.5 g of the compound (VIIIa) as colorless needles, mp 218°. After neutralization of the above filtrate with 10% H_2SO_4 at pH 7.3, the resultant solution was heated on a water-bath for 2 hr and the same treatment as above afforded 0.3 g of VIIIa. Total yield, 2.8 g (54.7%). IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1670 (C=O). *Anal.* Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.66; H, 7.10; N, 10.87.

(b) The Reaction of γ-Ketoester (V) with $NH_2NH_2 \cdot H_2O$: A mixture of 3 g of V, 1 g of $NH_2NH_2 \cdot H_2O$ and 30 ml of EtOH was refluxed on a water-bath for 6 hr and, after the reaction, the solvent was distilled off to give an oily substance, which was triturated with ether. Collection of the crystals which separated and recrystallization from MeOH afforded 60 mg (2.2%) of the compound (VIIIa) as colorless needles, mp 218°, which were identical with the above compound prepared by method (a) on mixed mp test and infrared spectral (in KBr) comparison.

Table I. Physical Properties of N-Alkyl- or Acyl-3-methoxy-9-azamorphinan

No.	R	Free base (recryst. solvent)	Yield (%)	mp, °C of HCl salt (recryst. solvent)	Formula
XVI	$CH_2=CHCH_2$–	pale yellow oil	24.2 as free base	177—178 (AcOEt) colorless prisms	$C_{19}H_{26}ON_2 \cdot HCl$
XVII		pale yellow oil	54 as HCl salt	179—180 (iso-PrOH–ether)	$C_{20}H_{28}ON_2 \cdot HCl$
XVIII		colorless needles (hexane) mp 136°	61.7 as free base	——	$C_{20}H_{26}O_2N_2$
XX	$CH_2=CHCO$–	colorless prisms (hexane) mp 110—112°	65 as free base	——	$C_{19}H_{24}O_2N_2$

No.	% Calcd			% Found			Procedure	Spectral data
	C	H	N	C	H	N		
XVI	68.14	8.13	8.37	68.31	8.14	8.40	A	NMR (ppm) (in $CDCl_3$): 3.80 (3H, singlet, OCH_3), 4.45 (2H, singlet, C_{10}–H_2), 5.05–6.30 (3H, multiplet, allyl protons), 6.73—7.23 (3H, multiplet, aromatic protons)
XVII	68.85	8.38	8.03	68.81	8.53	8.18	A,B	NMR (ppm) (in CF_3COOH): 0.23—0.93 (5H, multiplet, protons of cyclopropane ring), 3.99 (3H, singlet, OCH_3), 4.54 (2H, singlet, C_{10}–H_2)
XVIII	73.59	8.03	8.58	73.74	7.99	8.80	C	The following spectra were measured as its free base; IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1645 (C=O); NMR (ppm) (in $CDCl_3$): 3.77 (3H, singlet, OCH_3), 3.79 and 4.47 (2H, AB type quartet, $J=18.5$ cps, C_{10}–H_2), 6.61—7.03 (3H, multiplet, $J_{ortho}=8$ cps, $J_{meta}=2.5$ cps, aromatic protons)
XX	73.04	7.74	8.97	72.56	8.07	9.53	C	Free base; IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1645 (C=O); NMR (ppm) (in $CDCl_3$): 3.71 (3H, singlet, OCH_3), 3.85 and 4.43 (2H, AB type quartet, $J=18.3$ cps, C_{10}–H_2), 5.61 $\left(1H, \text{quartet}, J=10.5 \text{ cps and } 3.0 \text{ cps}, {}^{CO}{>}C{=}C{<}^{H}_{H_A}\right)$, 6.30 $\left(1H, \text{quartet}, J=17.2 \text{ cps and } 3.0 \text{ cps}, {}^{CO}{>}C{=}C{<}^{H_B}_{H}\right)$, 7.24 $\left(1H, \text{quartet}, J=17.2 \text{ cps and } 10.5 \text{ cps}, {}^{CO}_{H_X}{>}C{=}C{<}\right)$, 6.64—7.01 (3H, multiplet, $J_{ortho}=8.0$ cps, $J_{meta}=2.5$ cps, aromatic protons)

Decahydro-4a-(3-methoxyphenyl)cinnoline (IXa) Hydrochloride——To a suspension of 1 g of $LiAlH_4$ in 20 ml of dry dioxane was added dropwise with stirring a solution of 1 g of the compound (VIIIa) in 60 ml of dry dioxane at room temperature within 10 min and the mixture was refluxed mildly for 5 hr. After the reaction, the excess of $LiAlH_4$ was decomposed with a small amount of H_2O under cooling in a current of N_2, and the solvent layer was separated and dried over K_2CO_3. Into the above solution was introduced dry HCl gas. Removal of the solvent *in vacuo* gave 0.8 g of a pale yellowish oil, which was triturated with ether to give a solid. Recrystallization from MeOH–ether afforded the HCl salt of IXa as a colorless powder, mp 152—153°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}, 2700—2200 ($N^{+}H$). NMR (in $CDCl_3$) ppm: 3.24 (1H, quartet, $J=7$ and 12 cps, C_{8a}–H), 6.19 (3H, singlet, OCH_3). *Anal.* Calcd. for $C_{15}H_{22}ON_2 \cdot HCl$: C, 63.71; H, 8.20; N, 9.90. Found: C, 64.10; H, 7.84; N, 9.88.

Decahydro-4a-(3-methoxyphenyl)-3-cinnolinone (Xa)——A solution of 3 g of octahydrocinnoline (VIIIa) in 600 ml of MeOH was hydrogenated catalytically in the presence of 1 ml of 60% $HClO_4$ and 0.7 g of PtO_2 at 40—50°, one molar equivalent of H_2 being absorbed. After removal of the catalyst, MeOH was distilled to give crystals, whose recrystallization from MeOH gave 2.8 g of the compound (Xa) as colorless scales, mp 219—220°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3200—2950 (NH), 1635 (C=O). *Anal.* Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.10; H, 7.58; N, 10.73.

1,2-Diacetyl Decahydro-4a-(3-methoxyphenyl)-3-cinnolinone (Xb)——A mixture of 0.2 g of Xa, 2 ml of Ac_2O, and 0.1 g of AcONa was heated on a water-bath for 1 hr. After the reaction, the mixture was poured into cold water and allowed to stand overnight. Collection of the crystals and recrystallization from EtOH gave Xb as colorless cubes, mp 198—199°. IR ν_{max}^{KBr} cm^{-1}: 1750 and 1725 (acetyl C=O), 1670 (lactam C=O). NMR (in $CDCl_3$) ppm: 1.86 and 1.98 (each 3H, 2 singlets, 2 N-$COC\underline{H}_3$), 2.46 and 2.93 (2H, AB type quartet, $J=15.5$ cps, C_4-$\underline{H}_2$), 3.77 (3H, singlet, $OC\underline{H}_3$), 4.25 (1H, quartet, $J=4.5$ and 10.5 cps, C_{8a}-$\underline{H}$). *Anal.* Calcd. for $C_{19}H_{24}O_4N_2$: C, 66.26; H, 7.02; N, 8.13. Found: C, 65.84; H, 6.75; N, 8.38.

3-Methoxy-9-azamorphinan-16-one (XI)——A mixture of 0.95 g of Xa, 0.9 g of $HOCH_2SO_3Na$ and 30 ml of MeOH was refluxed mildly on a water-bath for 1 hr. After the reaction the solvent was removed by distillation and a mixture of the resultant residue, 20 ml of H_2O and 3 ml of conc. HCl was heated on a water-bath for 3 hr. The reaction mixture was cooled and made basic with 10% NaOH aq. solution to separate the crystals. Collection and recrystallization from MeOH gave 0.48 g (48.5%) of the compound (XI) as colorless prisms, mp 202—203°. IR ν_{max}^{KBr} cm^{-1}: 3150 (NH), 1650 (C=O). NMR (in $CDCl_3$) ppm: 2.38 (2H, singlet, -$C\underline{H}_2CO$-), 3.75 (3H, singlet, $OC\underline{H}_3$), 3.79 and 4.29 (2H, AB type quartet, $J=17$ cps, C_{10}-$\underline{H}_2$), 2.80—3.27 (1H, multiplet, $\rangle C\underline{H}N\langle$), 6.61—7.02 (3H, multiplet, $J_{ortho}=8$ cps, $J_{meta}=2.5$ cps, aromatic protons). *Anal.* Calcd. for $C_{16}H_{20}O_2N_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.22; H, 7.27; N, 10.48.

Benzylhydrazine——A solution of 7 g of benzalhydrazine in 100 ml of EtOH was hydrogenated catalytically in the presence of 0.5 g of PdO, 1450 ml of H_2 being absorbed. After the reaction, the catalyst was removed by filtration and the filtrate was evaporated to give an oil, which was distilled *in vacuo* to give 4.2 g (58.8%) of a colorless oil, bp 113° (8 mmHg). Recrystallization of the HCl salt from EtOH afforded colorless needles, mp 110—111° (lit,[10] mp 111°).

2-Benzyl-2,3,4,4a,5,6,7,8-octahydro-4a-(3-methoxyphenyl)-3-cinnolinone (VIIIb)——(a) The Reaction of VI with Benzylhydrazine: A mixture of 8 g of the above carboxylic acid (VI), 4.1 g of VIIb, and 30 ml of EtOH was refluxed on a water-bath for 20 hr. After the reaction the mixture was evaporated to give a syrup, which was extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and water, dried over K_2CO_3 and evaporated to give a yellow oil, which was distilled *in vacuo* to give 5.5 g (51.9%) of VIIIb as a pale yellowish oil, bp 235° (0.08 mmHg). IR ν_{max}^{liquid} cm^{-1}: 1658 (C=O). NMR (in $CDCl_3$) ppm: 2.45 and 2.73 (2H, AB type quartet, $J=16$ cps, -$C\underline{H}_2CO$-), 3.52 (3H, singlet, $OC\underline{H}_3$), 4.62 and 5.09 (2H, AB type quartet, $J=15$ cps, $NC\underline{H}_2Ph$), 7.26 (5H, singlet, aromatic protons of benzyl group). *Anal.* Calcd. for $C_{22}H_{24}O_2N_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.95; H, 6.95; N, 8.01.

b) The Reaction of VIIIa with Benzyl Chloride: A mixture of 0.7 g of VIIIa, 20 ml of N,N-dimethylformamide, 0.3 g of 55% NaH (oil suspension) and 0.7 g of benzyl chloride was refluxed in an oil-bath for 4 hr and the solvent was removed by distillation. The residue was decomposed with H_2O and extracted with ether. The extract was treated as the method (a) to give 0.3 g (31.6%) of a pale yellowish oil, which was identical with the above sample prepared by method (a).

2-Benzyl-decahydro-4a-(3-methoxyphenyl)cinnoline (IXb) Hydrochloride——To a stirred suspension of 4 g of $LiAlH_4$ in 150 ml of dry dioxane was added dropwise under reflux a solution of 4 g of VIIIb in 20 ml of dry dioxane. After addition, the stirring was continued for 5 hr under reflux. The reaction mixture was decomposed with 20 ml of H_2O under cooling in a current of N_2. After removal of an inorganic substance, the filtrate was dried over K_2CO_3, and then dry HCl gas was introduced into the solvent layer under cooling. Removal of the solvent *in vacuo* gave a syrup, which was triturated with iso-PrOH to give a solid. Recrystallization from iso-PrOH gave 1.5 g (35%) of the HCl salt of IXb as colorless needles, mp 216—217°. IR ν_{max}^{KBr} cm^{-1}: 2600—2300 (N^+H). NMR (in CF_3COOH) ppm: 4.01 (3H, singlet, $OC\underline{H}_3$), 4.47 (2H, singlet, $NC\underline{H}_2Ph$). *Anal.* Calcd. for $C_{22}H_{28}ON_2 \cdot HCl$: C, 70.85; H, 7.83; N, 7.51. Found: C, 71.28; H, 7.85; N, 7.47.

N-Benzyl-3-methoxy-9-azamorphinan (XIV) Hydrochloride——(a) The Reaction with CH_2O and HCl: A mixture of 1 g of HCl salt of IXb, 20 ml of H_2O, 5 g of 37% CH_2O and 1 ml of conc. HCl was heated on a water-bath for 3 hr. The reaction mixture was condensed to a volume of 5 ml, which was made basic with 10% NaOH aq. solution and extracted with ether. The extract was washed with water, dried over K_2CO_3. and treated with dry HCl gas. Removal of the solvent afforded to give a colorless oil, whose recrystallization from iso-PrOH gave 0.57 g (55.2%) of the HCl salt of XIV as colorless prisms, mp 226—228° (decomp.), IR ν_{max}^{KBr} cm^{-1}: 2300—1980 (N^+H). NMR (in CF_3COOH) ppm: 3.98 (3H, siglet, $OC\underline{H}_3$), 3.99 and 4.57 (2H, AB type quartet, $J=17$ cps, C_{10}-$\underline{H}_2$), 4.76 (2H, singlet, $NC\underline{H}_2Ph$). *Anal.* Calcd. for $C_{23}H_{28}ON_2 \cdot HCl$: C, 71.76; H, 7.59; N, 7.28. Found: C, 71.78; H, 7.43; N, 7.68.

(b) The Recaction with $HOCH_2SO_3Na$ and HCl: A mixture of 1 g of IXb, 0.54 g of $HOCH_2SO_3Na$, and 30 ml of MeOH was refluxed on a water-bath for 2 hr and the mixture was then condensed to a volume of 10 ml, to which was added 3 ml of conc. HCl and 30 ml of H_2O. The resultant mixture was heated on a water-bath for 5 hr. After removal of the solvent, the residue was made basic with 10% NaOH and extracted with ether. The extract was washed with water, dried over K_2CO_3 and evaporated to give an oil, whose HCl salt was recrystallized from iso-PrOH to yield 0.23 g (22.3%) of the HCl salt of XIV as colorless prisms, mp 226—228° (decomp.), identical with the sample prepared by the method (a).

3-Methoxy-9-azamorphinan (XII)——(a) $LiAlH_4$ Reduction of XI: To a stirred suspension of 1 g of $LiAlH_4$ in 30 ml of dry dioxane was added drop by drop with stirring a solution of 1 g of XI in 50 ml of dry dioxane at room temperature within 10 min, and the mixture was then stirred under reflux for 6 hr. After the reaction, the excess of $LiAlH_4$ was decomposed carefully with a small amount of H_2O and an inorganic substance was filtered off. The filtrate was dried over K_2CO_3 and evaporated to give a pale yellow oil, which was chromatographed on Al_2O_3 using benzene, benzene–$CHCl_3$ (2:1), benzene–$CHCl_3$ (1:1) and $CHCl_3$ as eluent. Removal of the second and third benzene–$CHCl_3$ fraction afforded a pale yellow oil, which was triturated with ether to give a solid. Recrystallization from ether gave 0.25 g (26.3%) of XII as colorless needles, mp 90—91°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3350—3200 (NH). NMR (in $CDCl_3$) ppm: 3.80 (3H, singlet, $OC\underline{H}_3$), 3.92 and 4.43 (2H, AB type quartet, $J=18$ cps, C_{10}-$\underline{H}_2$), 6.60—7.02 (3H, multiplet, $J_{ortho}=7.5$ cps, $J_{meta}=2.5$ cps, aromatic protons). *Anal.* Calcd. for $C_{16}H_{22}ON_2$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.72; H, 8.83; N, 10.48.

(b) Debenzylation of XIV: A solution of 0.38 g of HCl salt of XIV in 50 ml of EtOH was hydrogenated catalytically in the presence of dil. HCl and 0.3 g of 30% Pd–C, one molar equivalent of H_2 (33 ml) being absorbed. After removal of the caralyst by filtration, the filtrate was evaporated to give an oil which was made basic with 10 % NaOH aq. solution and exrtacted with $CHCl_3$. The extract was washed with H_2O, dried over K_2CO_3 and evaporated to give an oil, whose recrysatllization from ether afforded 0.2 g (78%) of XII as colorless needles, mp 90—91°. This was identical with the above sample, obtained by the method (a), on mixed mp test and infrared spectral data (in KBr).

N-Acetyl-3-methoxy-9-azamorphinan (XIII)——A mixture of 0.12 g of XII, 1 ml of Ac_2O, and 0.1 g of AcONa was heated on a water-bath for 3 hr, and the reaction mixture was allowed to stand with saturated $NaHCO_3$ aq. solution to separate a yellow oil, which was extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. The resultant residue was triturated with ether–hexane to give 105 mg (75.2%) of a colorless powder, which was recrystallized from hexane to give XIII as colorless prisms, mp 173—174°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1650 (C=O). NMR (in $CDCl_3$) ppm: 2.17 (3H, singlet, $NCOC\underline{H}_3$), 3.77 (3H, singlet, $OC\underline{H}_3$), 3.71 and 4.43 (2H, AB type quartet, $J=19$ cps, C_{10}-$\underline{H}_2$), 6.62-7.03 (3H, multiplet, $J_{ortho}=7.5$ cps, $J_{meta}=2.5$ cps, aromatic protons). *Anal.* Calcd. for $C_{18}H_{24}O_2N_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.33; H, 8.52; N, 9.48.

3-Methoxy-N-methyl-9-azamorphinan(I) Hydrochloride——A mixture of 0.12 g of XII, 1 ml of 37% CH_2O, and 50 ml of MeOH was refluxed on a water-bath for 30 min. After cooling, 1 g of $NaBH_4$ was added in portions with stirring to the above mixture within 20 min. After removal of the solvent by distillation, the resultant residue was extracted with ether. The extract was washed with H_2O, dried over K_2CO_3 and evaporated to give 93 mg (74%) of a pale yellow oil. Recrystallization of the HCl salt of I from EtOH afforded colorless prisms, mp 218—219°, which were identical with an authentic sample (lit.,[1]) mp 219—220°) on mixed melting test and spectral data.

3-Methoxy-N-phenethyl-9-azamorphinan(XV) Hydrochloride——(a) N-Alkylation with Phenethyl Bromide (Procedure A): A mixture of 10 g of XII, 7.2 g of phenethyl bromide, 3 g of K_2CO_3 and 50 ml of toluene was heated in an oil-bath for 5 hr. After the reaction the mixture was cooled, acidified with 10 % HCl aq. solution and filtered. The resultant acidic solution was made basic with 10% NaOH aq. solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried over K_2CO_3, and evaporated to give a pale brown oil, which was triturated with ether to give an oily solid. After removal of the solid,[12]) the filtrate was evaporated to give an oil, which was chromatographed on silica gel (Wakogel Q-22) using benzene–$CHCl_3$–EtOH (5:5:1) as an eluent. Removal of the solvent afforded 5.8 g (41.3%) of a colorless oil (XV). Recrystallization of the HCl salt from AcOEt gave colorless prisms, mp 179—180.5°, NMR (in $CDCl_3$) ppm: 3.77 (3H, singlet, $OC\underline{H}_3$), 4.36 (2H, singlet, C_{10}-$\underline{H}_2$), 6.70—7.35 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{24}H_{30}ON_2 \cdot HCl \cdot 1/2H_2O$: C, 70.66; H, 7.91; N, 7.44. Found: C, 71.02; N, 7.69; H, 7.27.

(b) $LiAlH_4$ Reduction of XIX (Procedure B): To a stirred suspension of 3 g of $LiAlH_4$ in 140 ml of dry dioxane was added dropwise under reflux a solution of 0.5 g of XIX in 40 ml of dry dioxane and the mixture was stirred under reflux for 5 hr. After the rection the excess of $LiAlH_4$ was decomposed carefully with 10% NaOH. After filtration, the dioxane layer was dried over K_2CO_3 and distilled to give an oil, whose HCl salt was recrystallized from iso-PrOH–ether to afford 0.47 g (90%) of colorless prisms, mp 179—180.5°, identical with the above sample.

3-Methoxy-N-phenacetyl-9-azamorphinan (XIX) (Procedure C)——To a stirred mixture of 1 g of XII, 200 ml of ether, and 7.8 ml of 5% NaOH was added dropwise under cooling with ice and water a solution of 0.4 g of phenylacetyl chloride in 50 ml of ether within 15 min, and the stirring was continued at room temperature for an additional 30 min. The organic layer was separated, washed with water, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was chromatographed on silica gel using ether as an eluent. Removal of the eluate and distillation of the residue *in vacuo* gave 0.56 g (38.4%) of XIX as a pale yellow oil, bp 250° (0.08 mmHg). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 1640 (C=O). NMR (in $CDCl_3$) ppm: 3.72 (3H, singlet, $OC\underline{H}_3$), 3.83 (2H, AB type quartet, C_{10}-$\underline{H}_2$), 3.82 (2H, singlet, $NC\underline{H}_2Ph$), 6.65—6.85 (3H, multiplet, aromatic protons), 7.28 (5H, singlet, aromatic protons). *Anal.* Calcd. for $C_{24}H_{28}O_2N_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.56; H, 7.38; N, 7.04.

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