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**Studies on Morphinan Derivatives. II.<sup>1)</sup> The Synthesis of *d*-3-Methyl-N-methylmorphinan, a New Antitussive**MASUO MURAKAMI, SHIGEMI KAWAHARA, NORIYOSHI INUKAI, NORIAKI NAGANO,  
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N-Methyl-5,6,7,8-tetrahydroisoquinolinium bromide (IV) was reacted with *p*-methylbenzyl chloride by means of Grignard reaction to obtain 1-(4-methylbenzyl)-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline (V). V was immediately reduced to 1-(4-methylbenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI) with sodium borohydride. VI was resolved by means of L(+)-tartaric acid. *d*, *l* and *dl*-VI were cyclized to *d*, *l* and *dl*-3-methyl-N-methylmorphinan (II), respectively, by treating them with 85% phosphoric acid at 135—150°. Several 3-methyl-N-alkyl and alkenyl-morphinan derivatives were synthesized from 3-methylmorphinan (VIII), which was prepared by demethylation of II, by treating it with alkyl and alkenyl halides.

Antitussive activities of *d*-II were 1.5 times as strong as that of dextrometorphan (Ib), and a toxicity of *d*-II was lower than that of Ib. Furthermore, *d*-II did not form any physical dependence.

A great number of N-substituted derivatives of 3-methoxymorphinan and 3-substituted derivatives of N-methylmorphinan (Ib, Ic) have been synthesized<sup>4-9)</sup> and pharmacological activities of them have been studied.<sup>9-11)</sup> The authors also synthesized several new 3-substituted derivatives of N-methylmorphinan having powerful antitussive activities as described in the previous report.<sup>1)</sup> Substituents of 3-position of these derivatives reported so far were either acyloxy or alkyloxy group in connection with morphine and codeine. On the other hand, 3-alkyl-N-methylmorphinan derivatives have not been reported.<sup>12)</sup>

In this report, the authors describe the synthesis of 3-methyl-N-methylmorphinan (II) and 3-methyl-N-alkyl and alkenylmorphinan derivatives. In addition, their pharmacological activities are briefly discussed.

The synthetic scheme of II is shown in Chart 1. The synthesis of II starting from 5,6,7,8-tetrahydroisoquinoline (III) was carried out according to the method described in the previous report<sup>1)</sup> with some modifications.

N-Methyl-5,6,7,8-tetrahydroisoquinolinium bromide (IV) was allowed to react with *p*-methylbenzyl chloride by means of Grignard reaction and 1-(4-methylbenzyl)-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline (V) was obtained in a satisfactory yield. V, which is un-

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- 4) R. Grewe and A. Mondon, *Naturwissenschaften*, **33**, 333 (1964); R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948); R. Grewe, A. Mondon, and E. Nolte, *Ann. Chem.*, **564**, 161 (1949).
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- 11) O. Schnider and A. Grüssner, Japan Patent 3372 (1955).
- 12) O. Schnider and A. Grüssner, U.S. Patent 2524855 (1950) [*C.A.*, **45**, 1630a (1955)].

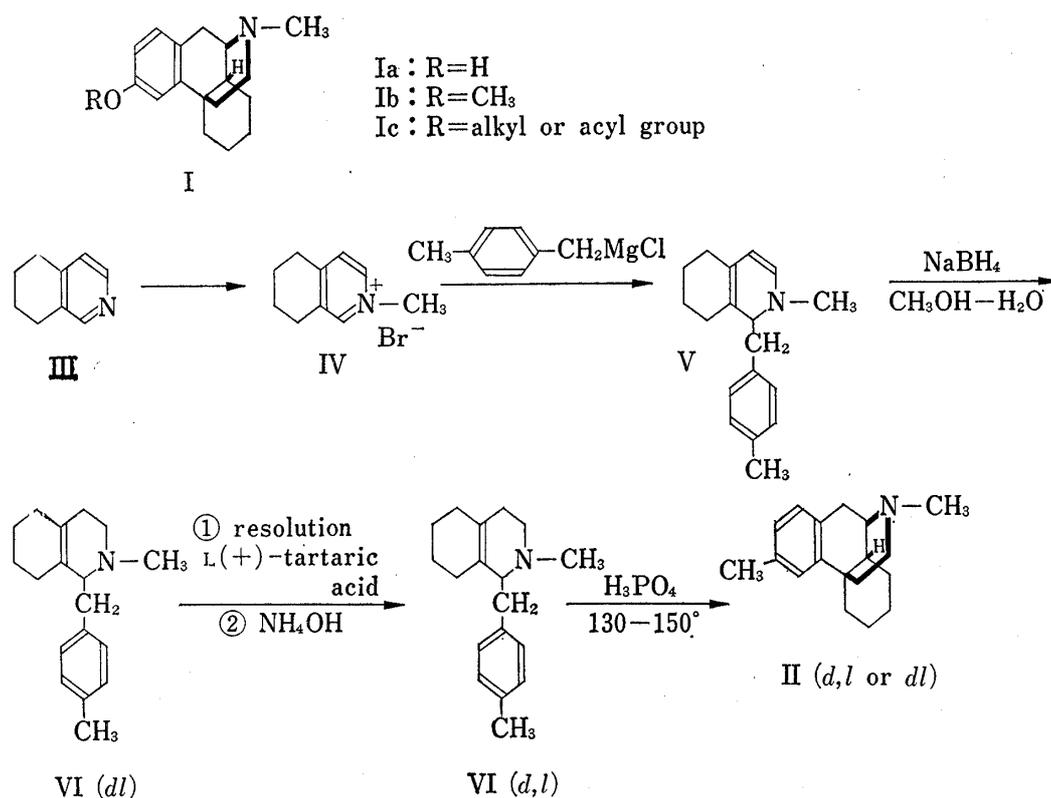


Chart 1. Synthesis of 3-Methyl-N-methylmorphinan

stable against air, was immediately reduced to *dl*-1-(4-methylbenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI) with sodium borohydride in a mixture of methanol and water. *dl*-VI was resolved by means of L(+)-tartaric acid in methanol: L(+)-tartaric acid salt of *d*-VI was precipitated as needle crystals in a 87% yield and *l*-VI was recovered from the mother liquor. *d*, *l*, and *dl*-VI were cyclized respectively to *d*, *l*, and *dl*-II by treating with 85% phosphoric acid solution at 135–150° for about seventy hours. This result is very interesting when compared with the cyclization of 1-(4-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline to 3-hydroxy-N-methylmorphinan (Ia), because in the latter case, *d*, *l*, and *dl*-form of the octahydroisoquinoline cyclized to *l*, *d*, and *dl*-form of Ia.<sup>1,6)</sup> II was obtained as white prism crystal in a 70% yield by treating the crude cyclization products with acetone and, from the acetone filtrate, 3-methyl-N-methylisomorphinan and 10-methyl-N-methylhexahydroaporphine were obtained as crystalline picrates respectively. The productive ratio of II, 3-methyl-N-methylisomorphinan and 10-methyl-N-methylhexahydroaporphine were about 83%:7%:9%, when it was detected by gas chromatography.<sup>13)</sup> II formed easily its crystalline salts with hydrogen bromide, sulfuric acid, phosphoric acid and L(+)-tartaric acid.

We synthesized also several N-alkyl and alkenyl-3-methylmorphinan derivatives as shown in Chart 2. 3-Methylmorphinan (VIII), demethylation derivative of II, was synthesized by first treating it with cyanogen bromide to obtain 3-methyl-N-cyanomorphinan (VII) and then hydrolyzing VII with aqueous hydrochloric acid. VIII was allowed to react with alkyl and alkenyl halides and 3-methyl-N-alkyl and alkenylmorphinan derivatives (IXa–d and X) were easily obtained in a satisfactory yield.

The pharmacological activities of these derivatives synthesized were investigated. It has consequently been found that the derivatives of *l*-series were powerful analgesic, whereas the derivatives of *d*-series, especially *d*-II, possessed a powerful antitussive activities. When

13) The analysis was performed using a 6ft × 0.125 in. column containing 10% silicone (UC W-98) at 230°.

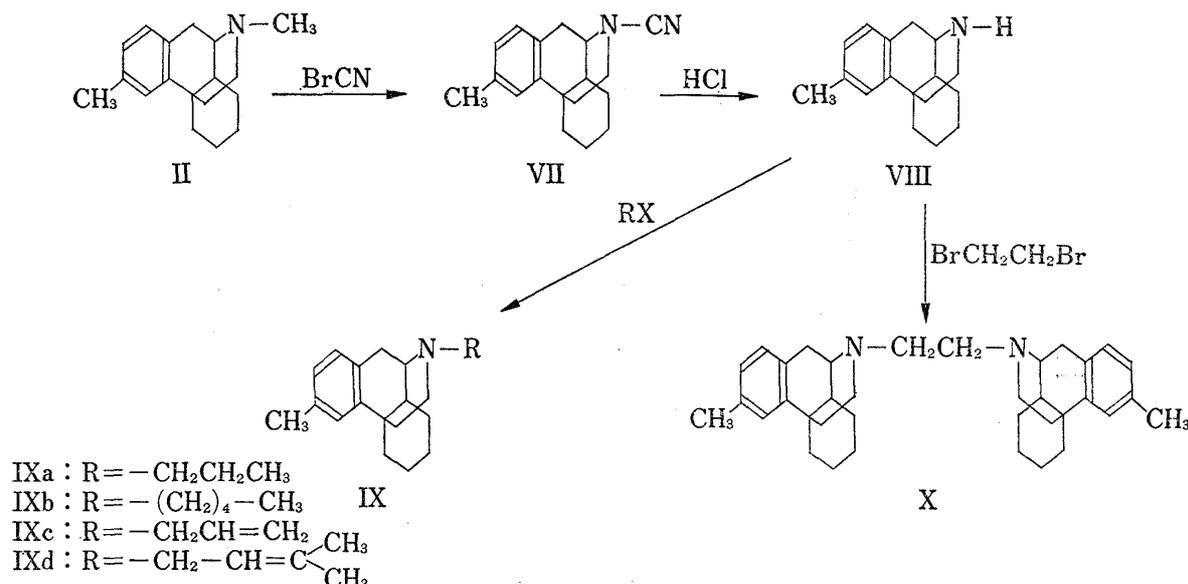


Chart 2. Synthesis of 3-Substituted Derivatives of N-Methylmorphinan

*d*-II was compared with dextrometorphan (Ib) by the method of Sanzari<sup>14)</sup> using 1,1-dimethyl-4-phenylpiperazinium iodide, antitussive activities of *d*-II were 1.5 times as strong as that of Ib. On the other hand, the toxicity of *d*-II was lower than that of Ib, as tested by a Kärber method.<sup>15)</sup> Furthermore, *d*-II did not form any physical dependence, when it was tested by a Hosoya, *et al.* method<sup>16)</sup> using rat. Details of the pharmacological activities of *d*-II will be reported soon, together with those obtained with other derivatives.

TABLE I. Pharmacological Activity of *d*-3-Methyl-N-methylmorphinan

Test sample	ED <sub>50</sub> <sup>a)</sup> (mg/kg)	LD <sub>50</sub> <sup>b)</sup> (mg/kg)	Safety margin (LD <sub>50</sub> /ED <sub>50</sub> )
<i>d</i> -3-Methyl-N-methylmorphinan·hydrochloride	1.0	185	185
Dextrometorphan·hydrobromide	1.6	150	94

a) ED<sub>50</sub> (mg/kg) was calculated from the relation between the administered amount of the test sample and the percentage of inhibition.

b) LD<sub>50</sub> (mg/kg) was calculated from the relation of the amount of the test sample used and the mortality rate.

From these results, we concluded that *d*-II (*d*-3-methyl-N-methylmorphinan) is more useful antitussive agent than Ib (*d*-3-methoxy-N-methylmorphinan: dextrometorphan).

#### Experimental<sup>17)</sup>

**1-(4-Methylbenzyl)-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline (V)**—To a suspension of powdered compound IV<sup>1)</sup> (420 g, 1.842 moles) in a mixture of dry tetrahydrofuran and dry ether (1:1) (150 ml), *p*-methylbenzylmagnesium chloride prepared from magnesium (54 g, 2.22 moles) and *p*-methylbenzyl chloride (325 g, 2.313 moles) in a mixture of dry tetrahydrofuran and dry ether (1:1) (800 ml) was added dropwise with stirring at 0–5° and the stirring was continued for 2 hr at this temperature. Ice water (840 ml) and 1.7 N aqueous ammonium hydroxide saturated with ammonium chloride was added to the reaction mixture and the mixture was shaken well. The upper ethereal layer was separated and the aqueous layer was further shaken twice with cold ether (600 ml). The ethereal layer collected was shaken twice with cold 1 N aqueous hydrochloric acid saturated with ammonium chloride. The aqueous solution was alkalinized with cold 1.7 N aqueous ammonium hydroxide saturated with ammonium chloride. The oily product precipitated

14) N.P. Sanzari, F.B. Fainman, and J.F. Emele, *J. Pharmacol. Exptl. Therap.*, **162**, 190 (1968).

15) G. Kärber, *Naunyn-Schmiedebergs Arch. Exptl. Pathol. Pharmacol.*, **162**, 482 (1931).

16) E. Hosoya and M. Otsube, *Folia Pharmacol. Japan.*, **54**, 120 (1958).

17) All melting points are not corrected.

was extracted three times with cold ether (600 ml). The ethereal extract was washed with water and dried over anhydrous sodium carbonate. The dried solution was concentrated under reduced pressure below room temperature. The orange coloured oily residue (343 g) used immediately to the following reaction without purification, because the oil was very unstable against air.

***dl*-(4-Methylbenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI)**—To a chilled solution of compound V (343 g, 1.35 moles) in a mixture of methanol (8 liters) and water (400 ml), sodium borohydride (45 g, 1.187 moles) was added portionwise with stirring and the reaction mixture was left overnight at room temperature. The solvent was evaporated off under reduced pressure. Water (3 liters) was added to the residue and the oily product precipitated was extracted with ether (4 liters). The ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated off and the residue was distilled under reduced pressure to collect a pale yellow oil; bp 133—136° (0.35 mmHg), wt. 258 g (75.2%). Mass Spectrum *m/e*: 255 (M<sup>+</sup>). NMR<sup>18)</sup> (CCl<sub>4</sub>)  $\tau$ : 7.33 (2H, singlet, -CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>-CH<sub>3</sub>), 7.73 (6H, N-CH<sub>3</sub>, Ar-CH<sub>3</sub>). *Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>N: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.21; H, 9.56; N, 6.02.

**The resolution of *dl*-VI**—A mixture of *dl*-VI (48.5 g, 0.19 mole) and L(+)-tartaric acid (28.5 g, 0.19 mole) was dissolved in methanol (280 ml) at room temperature. After a few minutes, white needle crystals began to precipitate and the mixture was left alone overnight. The crystals were collected by filtration and washed with cold methanol. The crystals were recrystallized once or twice from methanol until the optical rotation became constant. *d*-VI·L(+)-tartaric acid salt was obtained in 87% yield; mp 190—192°,  $[\alpha]_D^{20} +47.5 \pm 1^\circ$  (*c*=1, methanol). *Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>N·C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>: C, 65.17; H, 7.71; N, 3.45. Found: C, 64.92; H, 7.85; N, 3.39.

From the mother liquor, *l*-VI·L(+)-tartaric acid salt was obtained; mp 80—90°,  $[\alpha]_D^{20} -13.2^\circ$  (*c*=1, methanol).

*d*-VI·L(+)-tartaric acid salt was dissolved in water and alkalinized with 28% aqueous ammonium hydroxide. The precipitated oil was extracted with ether and washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated off and the oily product, *d*-VI, was obtained quantitatively;  $[\alpha]_D^{20} +33.3^\circ$  (*c*=0.9, methanol). *l*-VI was obtained in the same method;  $[\alpha]_D^{20} -27.3^\circ$  (*c*=1, methanol).

***d*-3-Methyl-N-methylmorphinan (*d*-II)**—A solution of compound *d*-VI (26.5 g, 0.103 mole) in 85% aqueous phosphoric acid (130 ml) was heated at 140—145° for 70 hr in an oil bath. After the reaction was complete, the reaction mixture was poured into ice water (300 ml) and the aqueous solution was alkalinized with 28% aqueous ammonium hydroxide and the oil precipitated was extracted with benzene. The benzene solution was washed with water, dried over anhydrous magnesium sulfate and then the solvent was evaporated off. The yellow oily residue was distilled under reduced pressure to collect a pale yellow oil which contained by-products; bp 130—136° (0.3 mmHg), yield 24.7 g (93.4%). Acetone (25 ml) was added to the oily product and the white prism crystals precipitated were collected by filtration; mp 90—93°, yield 18.8 g (71%). Mass Spectrum *m/e*: 255 (M<sup>+</sup>),  $[\alpha]_D^{20} +52.0 \pm 0.5^\circ$  (*c*=1, methanol). *Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>N: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.88; H, 9.78; N, 5.69. NMR<sup>18)</sup> (CCl<sub>4</sub>)  $\tau$ : 7.71 (6H, -N-CH<sub>3</sub>, Ar-CH<sub>3</sub>).

From the acetone filtrate, 3-methyl-N-methylisomorphinan and 10-methyl-N-methylhexahydroaporphine were obtained as picrates respectively. The former: Picrate, mp 206—207°; Free base, bp 138—140° (0.3 mmHg),  $[\alpha]_D^{20} +54.7^\circ$  (*c*=1, methanol). The latter: Picrate, mp 123—125°; free base, mp 65—66° (white crystal from acetone),  $[\alpha]_D^{20} +118.7^\circ$  (*c*=1, methanol).

Compound *l*-II and *dl*-II were also prepared in a same manner as *d*-II. *l*-II; bp 130—134° (0.65 mmHg),  $[\alpha]_D^{20} -49.7^\circ$  (*c*=0.9, methanol), mp 92—93° (from acetone). *dl*-II; bp 130—134° (0.65 mmHg), mp 53—56°.

Following crystalline acid-salts of *d*-II were easily obtained in quantitative yields. Hydrobromide: mp 213—216°,  $[\alpha]_D^{20} +26.8^\circ$  (*c*=1.13, methanol). *Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>N·HBr: C, 64.28; H, 7.79; N, 4.16; Br, 23.76. Found: C, 64.06; H, 7.83; N, 3.82; Br, 24.01. Phosphate: mp 267—269°,  $[\alpha]_D^{20} +25.7^\circ$  (*c*=0.5, methanol). *Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>N·H<sub>3</sub>PO<sub>4</sub>: C, 61.18; H, 7.99; N, 3.96. Found: C, 61.01; H, 7.76; N, 4.03. Sulfate: mp 209—211°,  $[\alpha]_D^{20} +26.9^\circ$  (*c*=0.4, methanol). *Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>N·H<sub>2</sub>SO<sub>4</sub>: C, 61.16; H, 7.70; N, 3.96. Found: C, 61.93; H, 7.78; N, 4.06. *d*-Tartarate: mp 125—126°,  $[\alpha]_D^{20} +35.1^\circ$  (*c*=0.4, methanol). *Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>N·C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>·½H<sub>2</sub>O: C, 63.75; H, 7.78; N, 3.38. Found: C, 63.71; H, 7.67; N, 3.33.

***d*-3-Methyl-N-cyanomorphinan (*d*-VII)**—A mixture of *d*-II (3.7 g, 0.0145 mole) and cyanogen bromide (2 g, 0.0189 mole) in chloroform (60 ml) was refluxed for 2 hr, cooled, and the solvent was evaporated off. The solid residue was extracted with ether and the ether solution was washed successively with water, 1N aqueous hydrochloric acid and water, and then dried over anhydrous sodium sulfate. The dried solution was concentrated. The white crystalline residue was triturated with petroleum ether and collected by filtration; mp 126—128°, yield 2.7 g (70%). IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 2200 (C≡N),  $[\alpha]_D^{20} +129.7^\circ$  (*c*=1, chloroform). *Anal.* Calcd. for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>: C, 81.16; H, 8.32; N, 10.52. Found: C, 80.83; H, 8.33; N, 10.91.

*l*-VII and *dl*-VII were also obtained as crystals in the same manner.

***l*-3-Methylmorphinan (*l*-VIII)**—A mixture of *l*-VII (1 g, 0.0036 mole) in 6N aqueous hydrochloric acid (25 ml) was refluxed for 16 hr. After the aqueous solution was cooled to room temperature, the solution

18) The standard sample is trimethylsilane.

was washed with ether (15 ml). The aqueous solution was alkalinized with 28% aqueous ammonium hydroxide and the precipitated oily product was extracted with ether. The ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The dried solution was concentrated. The residual oil was purified by column chromatography on silica gel, followed by distillation; bp 148—155° (0.15 mmHg), yield 0.42 g (46.3%). *Anal.* Calcd. for  $C_{17}H_{23}N$ : C, 84.59; H, 9.60; N, 5.80. Found: C, 84.22; H, 8.90; N, 5.88. NMR<sup>18)</sup> ( $CCl_4$ )  $\tau$ : 7.56 (1H, singlet, NH).  $[\alpha]_D^{25} - 32.8^\circ$  ( $c=1$ , methanol).

*d*-VIII and *dl*-VIII were also prepared in the same manner. *d*-VIII: bp 130—132° (0.5 mmHg),  $[\alpha]_D^{20} + 34.5^\circ$  ( $c=1.1$ , methanol).

***l*-3-Methyl-N-propylmorphinan (*l*-IXa)**—A mixture of *l*-VIII (506.6 mg, 0.0021 mole), propyl bromide (258 mg, 0.0021 mole) and sodium bicarbonate (176 mg, 0.0021 mole) in *N,N*-dimethylformamide (12 ml) was refluxed for 5 hr. After the reaction, the solvent was evaporated off under reduced pressure. The residue thus obtained was dissolved in ether (10 ml) and the ethereal solution was shaken well with 2*N* aqueous hydrochloric acid (4 ml). The white crystals precipitated were collected by filtration and the crystals were dissolved in chloroform and insoluble materials were filtered off. The solution was concentrated to give white needle crystals and the crystals were collected by filtration and washed well with dry ether; wt. 200 mg (28.6%), mp >265°,  $[\alpha]_D^{25} - 41.9^\circ$  ( $c=0.9$ , methanol). *Anal.* Calcd. for  $C_{20}H_{30}NCl \cdot 1\frac{1}{2}H_2O$ : C, 69.24; H, 9.59; N, 4.04; Cl, 10.22. Found: C, 68.84; H, 9.20; N, 4.20; Cl, 10.53.

This compound was also prepared by cyclization reaction of *l*-1-(4-methylbenzyl)-2-propyl-1,2,3,4,5,6,7,8-octahydroisoquinoline.

***l*-3-Methyl-N-*n*-amylmorphinan (*l*-IXb)**—A mixture of *l*-VIII (315.5 mg, 0.0013 mole), *n*-amyl bromide (190 mg, 0.0013 mole) and sodium bicarbonate (110 mg, 0.0013 mole) in *N,N*-dimethylformamide (7.5 ml) was refluxed for 4 hr. After the reaction, the reaction mixture was treated as described above; wt 195 mg (52%), mp 224—227°,  $[\alpha]_D^{25} - 47.5^\circ$  ( $c=0.8$ , methanol). *Anal.* Calcd. for  $C_{22}H_{34}NCl \cdot 2H_2O$ : C, 68.81; H, 9.98; N, 3.65; Cl, 9.23. Found: C, 69.04; H, 9.55; N, 3.90; Cl, 9.51.

This compound was also prepared by cyclization reaction of *l*-1-(4-methylbenzyl)-2-amyl-1,2,3,4,5,6,7,8-octahydroisoquinoline.

***l*-3-Methyl-N-allylmorphinan (*l*-IXc)**—A mixture of *l*-VIII (2.41 g, 0.01 mole) allyl bromide (1.2 g, 0.01 mole) and sodium bicarbonate (0.9 g, 0.0107 mole) in *N,N*-dimethylformamide (10 ml) was refluxed for 5 hr, cooled to room temperature and an insoluble material was filtered off. The solvent was evaporated off under reduced pressure and the residue was dissolved in 1*N* aqueous hydrochloric acid (50 ml). The aqueous solution was washed with ether and alkalinized with 28% aqueous ammonium hydroxide. The oil precipitated was extracted with ether and the ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The dried solution was shaken with 1*N* aqueous hydrochloric acid and the aqueous layer was concentrated under reduced pressure to give an oily product (300 mg). The oil was crystallized from ethyl acetate and recrystallization from acetone gave white prism crystals which have 1/3 mole acetone of crystallization; mp 236—239° (in a sealed tube),  $[\alpha]_D^{25} - 53.6^\circ$  ( $c=1$ , methanol). *Anal.* Calcd. for  $C_{20}H_{27}N \cdot HCl \cdot \frac{1}{3}CH_3COCH_3$ : C, 74.80; H, 8.92; N, 4.16; Cl, 10.52. Found: C, 74.05; H, 8.93; N, 4.31; Cl, 10.77. IR  $\nu_{max}^{KBr}$   $cm^{-1}$ : 1720 (acetone). NMR<sup>18)</sup> ( $CDCl_3$ )  $\tau$ : 3.68 (1H, multiplet, -CH=C-), 4.42, 4.66 (2H, C=CH<sub>2</sub>), 7.82 (2H, 1/3CH<sub>3</sub>COCH<sub>3</sub>). Mass Spectrum *m/e*: 281 ( $M^+$ ).

*d*-IXc and *dl*-IXc were also prepared in the same method.

***l*-3-Methyl-N-(3,3-dimethylallyl)morphinan (*l*-IXd)**—A mixture of *l*-VIII (2.41 g, 0.01 mole), 1-bromo-3-methyl-2-butene (1.57 g, 0.0105 mole) and sodium bicarbonate (0.88 g, 0.0104 mole) in *N,N*-dimethylformamide (60 ml) was refluxed for 5 hr. After the reaction, insoluble materials were filtered off. The *N,N*-dimethylformamide was evaporated off under reduced pressure and the residue was dissolved in ether. The ether solution was shaken with 1*N* aqueous hydrochloric acid and the aqueous layer separated was alkalinized with 28% aqueous ammonium hydroxide. The oil precipitated was extracted with ether and washed with water and dried over anhydrous magnesium sulfate. The dried solution was concentrated to a syrup (2.5 g). The syrup was dissolved in methanol (10 ml) and hydrogen chloride gas was bubbled through the solution. The solvent was evaporated off and the oily residue was crystallized from ethyl acetate. The crude crystals were collected by filtration and recrystallized from acetone in needles; mp 227—228° (in a sealed tube), yield 0.84 g (24.3%).  $[\alpha]_D^{25} - 65.6^\circ$  ( $c=1$ , methanol). *Anal.* Calcd. for  $C_{22}H_{31}N \cdot HCl$ : C, 76.38; H, 9.32; N, 4.05; Cl, 10.25. Found: C, 76.38; H, 9.38; N, 3.96; Cl, 10.41. NMR<sup>18)</sup> ( $CDCl_3$ )  $\tau$ : 4.30 (1H, triplet,  $J=7$  cps, -CH=C(CH<sub>3</sub>)<sub>2</sub>), 6.35 (2H, -N-CH<sub>2</sub>-C), 8.14, 8.19 (6H, C=C(CH<sub>3</sub>)<sub>2</sub>). Mass Spectrum *m/e*: 309 ( $M^+$ ).

*d*-IXd and *dl*-IXd were also prepared in the same manner and infrared (IR), nuclear magnetic resonance (NMR) and mass spectral data of these compounds were completely the same as those of *l*-IXd.

***l*-N,N'-Ethylene-bis(3-methylmorphinan) (*l*-X)**—A mixture of *l*-VIII (380.6 mg, 0.00158 mole), 1,2-dibromoethane (149 mg, 0.00079 mole) and sodium bicarbonate (133 mg, 0.00158 mole) in *N,N*-dimethylformamide (8 ml) was refluxed for 4 hr. After the reaction, the mixture was treated as described above; wt 350 mg (34%), mp 203—204°,  $[\alpha]_D^{25} - 60.8^\circ$  ( $c=0.8$ , methanol). *Anal.* Calcd. for  $C_{36}H_{48}N_2 \cdot 2HCl \cdot 4H_2O$ : C, 66.14; H, 8.94; N, 4.28. Found: C, 65.88; H, 8.50; N, 4.69. Mass Spectrum (free base) *m/e*: 508 ( $M^+$ ).

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