Studies on Morphinan Derivatives. I. The Synthesis of Several New 3-Substituted Derivatives of N-Methylmorphinan having Antitussive Activities

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1,3-Dihydroxy-5,6,7,8-tetrahydroisoquinoline (VI) was synthesized from ethyl 2-ethoxycarbonyl-cyclohexylidene-cyanoacetate (IV) by treating it with concentrated sulfuric acid at 80–90° for five hours. 5,6,7,8-Tetrahydroisoquinoline (VIII) was synthesized from VI by first chlorinating it to form 1,3-dichloro-5,6,7,8-tetrahydroisoquinoline (VII) and then reducing VII with zinc dust in acetic acid. The synthesis of 3-hydroxy-N-methylmorphinan (II) starting from VIII was carried out according to the methods reported by Grewe and Schnider, *et al.* with some modifications. Several new 3-substituted derivatives of N-methylmorphinan were synthesized from II. In these derivatives, *d*-N,N'-dimethyl-3,3'-(carbonyldioxy)-dimorphinan (*d*-XVIII) synthesized from *d*-II and phosgene showed nearly the same antitussive activities as dextrometorphan (I) and a toxicity lower than the latter. Furthermore, *d*-XVIII did not form any physical dependence.

d-Morphinan derivatives are known as compounds having antitussive activities and, among them, *d*-3-methoxy-N-methylmorphinan (I) is the most important one which is now widely used as antitussive agent (dextrometorphan).²⁾

Since Grewe, *et al.* first succeeded in synthesizing morphinan derivatives in 1946,³⁻⁵⁾ many different methods or routes for the synthesis of them have been developed and reported.³⁻¹⁰⁾ A great number of N-substituted derivatives of 3-methoxymorphinan has been synthesized and the relationship between their N-substituents and pharmacological activities has been investigated.^{11,12)} As for 3-substituted derivatives of N-methylmorphinan, however, only four 3-alkoxy compounds in addition to several 3-acyloxy derivatives have been reported, *i.e.*, 3-ethoxy, propoxy, allyloxy and benzyloxy-N-methylmorphinans¹³⁾ have been synthesized by treating 3-hydroxy-N-methylmorphinan (II) with phenyl tri-alkyl, allyl, and benzyl ammonium halide respectively.

This report provides an improved method for the synthesis of new 3-substituted derivatives of N-methylmorphinan *via* 5,6,7,8-tetrahydroisoquinoline (VIII) and a brief discussion

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2) The abbreviations of *d*, *l*, and *dl* are noted only when it is necessary to differentiate the optical rotatory.

3) R. Grewe and A. Mondon, *Naturwissenschaften*, **33**, 333 (1946).

4) R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948).

5) R. Grewe, A. Mondon, and E. Nolte, *Ann. Chem.*, **564**, 161 (1949).

6) H. Henecka, *Ann. Chem.*, **583**, 110 (1953).

7) O. Schnider and A. Grüssner, *Helv. Chim. Acta.*, **32**, 821 (1949); O. Schnider and A. Grüssner, Brit. Patent 620258 (1949) [*C.A.*, **43**, 7517h (1949)]; O. Schnider and A. Grüssner, U.S. Patent 2524855 (1950) [*C.A.*, **45**, 1630a (1951)].

8) a) O. Schnider and J. Hellerbach, *Helv. Chim. Acta.*, **33**, 1437 (1950); b) O. Schnider and A. Grüssner, Brit. Patent 677595 (1952) [*C.A.*, **47**, 6447f (1953)].

9) E. Ochiai and M. Ikehara, *Pharm. Bull. (Japan)*, **2**, 109 (1954); E. Ochiai and M. Ikehara, *ibid.*, **2**, 111 (1954).

10) S. Bien, *J. Chem. Soc.*, **1963**, 2065.

11) J. Hellerbach, A. Grüssner, and O. Schnider, *Helv. Chim. Acta*, **39**, 429 (1956).

12) I. Seki, H. Takagi, and S. Kobayashi, *Yakugaku Zasshi*, **84**, 280 (1964).

13) O. Schnider and A. Grüssner, Japan Patent 3372 (1955).

Chart 1. An Improved Method for the Synthesis of 3-Hydroxy-N-methylmorphinan (II)

on their pharmacological activities. The synthetic scheme of the improved method is shown in Chart 1 and 3.

VIII is the most important intermediate for the preparation of morphinan derivatives. Among the several known methods to prepare VIII,^{4,5,8,14} the Grewe's method seems to be most useful one, in which 1,3-dihydroxy-5,6,7,8-tetrahydroisoquinoline (VI) was synthesized from ethyl 2-ethoxycarbonylcyclohexylidene cyanoacetate (IV) by first hydrolyzing it to 2-carboxycyclohexene-1-acetic acid (V) and then fusing V with ammonium carbonate. However, we have found that VI can be obtained directly from IV without *via* V, *i.e.*, VI is obtainable in a quantitative yield when IV is heated in concentrated sulfuric acid at 80–90° for five hours. VI was chlorinated with phosphorus oxychloride in pyridine to form 1,3-dichloro-5,6,7,8-tetrahydroisoquinoline (VII), and the latter was reduced with zinc dust in acetic acid under reflux to give VIII. The reduction with zinc dust in acetic acid is superior to the known catalytic one which is effected in the presence of palladium-carbon or Raney nickel catalyst.³⁻⁷ The product obtained by the catalytic reduction often contains 3-chloro-5,6,7,8-tetrahydroisoquinoline in a significant amount, even when a large amount of the catalyst were used. The above new procedures are considered useful and available for the production in an industrial scale of VIII.

The synthesis of 3-hydroxy-N-methylmorphinan(II) (*d,l*, and *dl*) starting from VIII was performed according to the methods reported by Grewe³⁻⁵) and Schnider, *et al.*⁷) with some modifications. Although Schnider, *et al.*⁷) reduced 1-(4-methoxybenzyl)-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline (X) to 1-(4-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octa-

14) E. Ochiai and M. Ikehara, *Pharm. Bull.* (Japan), **2**, 72 (1954); E. Ochiai and M. Ikehara, *ibid.*, **5**, 606 (1957); B. Witkop, *J. Am. Chem. Soc.*, **70**, 2617 (1948); U. Base and B. Banerje, *Ann. Chem.*, **516**, 243 (1935); E. Schlitter and R. Merian, *Helv. Chem. Acta*, **30**, 1339 (1947); R. Grewe, R. Hamann, G. Jacobsen, E. Nolte and K. Riecke, *Ann. Chem.*, **581**, 85 (1953).

hydroisoquinoline (XI) by catalytic reduction in the presence of a relatively large amount of palladium-carbon or Raney-nickel catalyst, the catalytic reduction of X is accompanied by such undesirable side reactions as producing 1-(4-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline, 2- β -(4-methoxyphenylethyl)-1- β -methylaminoethylcyclohexene-1 and 1-(4-methoxybenzyl)-2-methyldecahydroisoquinoline (Chart 2). Therefore, we have studied the chemical reduction of X in detail under various conditions. It has been consequently found that XI can easily be obtained in a satisfactory yield when X is reduced with sodium borohydride in a mixture of methanol and water.

Chart 2. Catalytic Reduction of 1-(4-Methoxybenzyl)-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline (X)

The resolution of *dl*-XI by means of L(+)-tartaric acid¹⁵⁾ and the cyclization reaction of XI (*d*, *l*, and *dl*) to II (*l*, *d*, and *dl*) by treating with 85% phosphoric acid^{3,5,16)} were carried out in the same methods as reported by Grewe and Schnider, *et al.* *d*-II gave dextrometorphan (I) in a satisfactory yield by treatment with phenyltrimethylammonium halide.

As described above, only four O-alkyl derivatives of II have been reported so far. It was considered that the difficulty in preparing such derivatives resided in the selective alkylation at 3-hydroxy group of II, and so the alkylation was performed not by using alkyl halide or alkyl sulfate but with phenyltrialkylammonium halide. We have investigated the alkylation and also the acylation of 3-hydroxy group of II, and succeeded in synthesizing several new derivatives of II according to the method as shown in Chart 3.

Chart 3. Synthesis of 3-Substituted Derivatives of N-methylmorphinan

15) W.D. Whitaker, Brit. Patent 725763 (1955) [C.A., **51**, 1310g (1957)].

16) Y. Sawa, K. Kawasaki, and S. Mayeda, *Chem. Pharm. Bull.* (Tokyo), **8**, 960 (1960).

3- β -Hydroxyethyloxy-N-methylmorphinan (XIII) was synthesized by treating with ethylene carbonate in the presence of potassium carbonate in a toluene solution under reflux. XIII was converted to 3- β -chloroethyloxy-N-methylmorphinan (XIV) by reaction with an equivalent amount of thionyl chloride in benzene at 60°. In this reaction, the use of excess thionyl chloride and of chloroform as solvent was undesirable, producing di- or tri-chlorosubstituted derivatives.

3- β -Methoxyethyloxy-N-methylmorphinan (XV) and 3- β -diethylaminoethyloxy-N-methylmorphinan (XVI) were synthesized by treating XIV in a sealed tube at 140° with sodium methylate and diethylamine, respectively.

3-Ethoxycarbonyloxy-N-methylmorphinan (XVII) was easily synthesized in a usual way using ethyl chloroformate.

N,N'-Dimethyl-3,3'-(carbonyldioxy)-dimorphinan (XVIII) was synthesized by treating II with dry phosgene. *d*-XVIII could be crystallized as hydrochloride containing chloroform of crystallization.

Pharmacological activities of these derivatives synthesized were investigated. It has consequently been found that *d*-XVIII is a compound useful as antitussive agent for the following reasons: When *d*-XVIII was compared with dextrometorphan (I) by an electrical stimulation method¹⁷⁾ using cat, *d*-XVIII showed nearly the same antitussive activities as I. On the other hand, the toxicity of *d*-XVIII was lower than that of I (Table I), as tested by a Kärber method.¹⁸⁾ Furthermore, *d*-XVIII did not form any physical dependence, when it was tested by Hosoya, *et al.* method¹⁹⁾ using rat. Details of pharmacological activities of *d*-XVIII will be reported soon, together with those obtained with other derivatives.

TABLE I. Pharmacological Activity of *d*-N,N'-Dimethyl-3,3'-(carbonyldioxy)-dimorphinan

Test sample	ED ₅₀ ^{a)} (mg/kg)	LD ₅₀ ^{b)} (mg/kg)	Safety margin (LD ₅₀ /ED ₅₀)
<i>d</i> -N,N'-Dimethyl-3,3'-(carbonyldioxy)-dimorphinan·hydrochloride	2.45	405	165
Dextrometorphan·hydrobromide	2.33	150	64
Codeine·phosphate	1.59	183	115

a) ED₅₀ (mg/kg) was calculated from the relation between the administered amount of the test sample and the percentage of inhibition.

b) LD₅₀ (mg/kg) was calculated from the relation of the test sample used and the mortality rate.

Experimental²⁰⁾

Ethyl 2-Ethoxycarbonylcyclohexylidene Cyanoacetate (IV)—This compound was synthesized by Grewe's method⁴⁾ using ethyl cyclohexanone-2-carboxylate (III)²¹⁾ and ethyl cyanoacetate; yield 76.5%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2210 (C≡N).

1,3-Dihydroxy-5,6,7,8-tetrahydroisoquinoline (VI)—To 85% aqueous sulfuric acid solution (4 liters), compound IV (3.5 kg, 13.2 moles) was slowly added dropwise at 80–90° with stirring. The reaction mixture was further stirred for 5 hr at this temperature. After the reaction, the mixture was cooled to room temperature and the mixture was poured into ice water (30 liters). pH of the solution was carefully adjusted to 5 using ice-cold 28% aqueous ammonium hydroxide. After standing overnight at room temperature, the yellow crystals separated were collected by filtration and washed several times with water until ammonium sulfate was completely removed. The crystals were sufficiently pure to use to the following reaction without

17) R. Domenjoz, *Naunyn-Schmiedeberg's Arch. Exptl. Pathol. Pharmacol.*, **215**, 19 (1952).

18) G. Kärber, *Naunyn-Schmiedeberg's Arch. Exptl. Pathol. Pharmacol.*, **162**, 482 (1931).

19) E. Hosoya and M. Otsube, *Folia. Pharmacol. Japon.*, **54**, 120 (1958).

20) All melting points are not corrected.

21) H.R. Snyder, L.A. Brooks, and S.H. Shapiro, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1963, p. 531.

further purification procedures: Yield 1.9 kg (87.3%), mp 202—205° (lit.,⁴) mp 205°. The analytical sample was recrystallized from 70% acetic acid. *Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.28; H, 6.89; N, 8.30.

1,3-Dichloro-5,6,7,8-tetrahydroisoquinoline (VII)—A mixture of compound VI (30 g, 0.181 mole), phosphorus oxychloride (55 ml, 0.6 mole) and pyridine (10 g, 0.126 mole) was allowed to react for 2 hr at 200° in a sealed tube. After the reaction, the dark coloured solution was concentrated and the residue was poured into ice water (200 ml). The aqueous solution was neutralized with 28% aqueous ammonium hydroxide. The dark crystals precipitated were collected by filtration, washed with water and dried *in vacuo*. The dried crystals were purified by distillation at 145—147° at 0.5 mmHg. The distillate was crystallized as needle crystals: Yield 25.2 g (80.5%), mp 84—85° (lit.,⁴) mp 87°. *Anal.* Calcd. for $C_9H_9NCl_2$: C, 53.49; H, 4.49; N, 6.93. Found: C, 53.55; H, 4.67; N, 6.83.

5,6,7,8-Tetrahydroisoquinoline (VIII)—To a refluxed solution of compound VII (190 g, 0.941 mole) in acetic acid (2 liters), zinc dust (350 g) was added in a small portion over 30 hr with vigorous stirring (Each portion was about 50 g). The solution was cooled to room temperature and insoluble materials were filtered off. The filtrate was concentrated to small volume. The concentrated solution was strongly alkalized with 50% aqueous sodium hydroxide and the yellow oil separated was extracted with ether. The ethereal solution was dried over anhydrous sodium carbonate and the dried solution was concentrated to a syrup. The syrup was distilled under reduced pressure to collect a pale yellow oil; bp 77—81° (1 mmHg). (lit.,⁴) bp 102—104° (12 mmHg). Yield 101 g (80%).

2-Methyl-5,6,7,8-tetrahydroisoquinolinium Bromide (IX)—Compound VIII was treated with methylbromide according to the literature.⁴ The white needle crystals which are very hygroscopic were obtained in 91% yields.

1-(4-Methoxybenzyl)-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline (X)—To a suspension of powdered compound IX (60 g, 0.263 mole) in a mixture of dry tetrahydrofuran and dry ether (1:1) (150 ml), *p*-methoxybenzylmagnesium chloride prepared from magnesium (9.6 g, 0.395 atom) and *p*-methoxybenzyl chloride (63 g, 0.41 mole) in a mixture of dry tetrahydrofuran and dry ether (1:1) (200 ml) were added dropwise with stirring at 0—5° and the stirring was continued for 2 hr at this temperature. Ice water (140 ml) and cold 1.7*N* aqueous ammonium hydroxide saturated with ammonium chloride were 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 (100 ml). The ethereal layer collected was shaken twice with cold 1*N* aqueous hydrochloric acid saturated with ammonium chloride. The aqueous hydrochloric acid solution was alkalized with cold 1.7*N* aqueous ammonium hydroxide saturated with ammonium chloride. The oily product precipitated was extracted three times with cold ether (100 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 (49.6 g) used immediately to the following reaction without purification, because the oil was very unstable against air.

***dl*-1-(4-Methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (XI)**—To a chilled solution of compound X (49.6 g, 0.185 mole) in a mixture of methanol (700 ml) and water (60 ml), sodium borohydride (9 g, 0.238 mole) was added portionwise with stirring and the reaction mixture was left overnight at room temperature. The solvent was evaporated off under reduced pressure. Water (50 ml) was added to the residue and the oily product precipitated was extracted with ether (200 ml). 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 140—153° (0.4 mmHg). Yield 36.9 g (73.5%). (lit.,^{8a}) bp 117—119° (0.008 mmHg). *Anal.* Calcd. for $C_{18}H_{25}ON$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.14; H, 9.02; N, 5.29.

If X was reduced by catalytic reduction, 1-(4-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline, 1-(4-methoxybenzyl)-2-methyldecahydroisoquinoline and 2-β-(4-methoxyphenylethyl)-1-β-methylaminoethylcyclohexene-1 were produced as by-products. The former two compounds were oily substances. The latter was needle crystal: mp 100—102° (from methanol). *Anal.* Calcd. for $C_{18}H_{27}ON$: C, 79.09; H, 9.95; N, 5.12. Found: C, 79.02; H, 9.93; N, 5.42.

The Resolution of *dl*-XI—The resolution of *dl*-XI was carried out according to the literature.¹⁵ *l*-XI·*l*(+)-tartaric acid salt was obtained in 70% yield; mp 174—175°, $[\alpha]_D^{20} + 42$ —43.5° (*c*=1, methanol). (lit.,¹⁵) mp 173—174°, $[\alpha]_D^{20} + 48.8$ ° (*c*=2, methanol).

***d*-3-Hydroxy-N-methylmorphinan (*d*-II)**—*l*-XI was converted to *d*-II by cyclization reaction using 85% aqueous phosphoric acid according to Sawa's method.¹⁶ *l*-Amyl alcohol adduct of *d*-II; mp 193—196°, $[\alpha]_D^{20} + 40.3$ ° (*c*=1.7, methanol). (lit.,¹⁶) mp 197—198°, $[\alpha]_D^{20} + 42 \pm 2$ °. *Anal.* Calcd. for $C_{21}H_{35}O_2N$: C, 76.48; H, 10.21; N, 4.05. Found: C, 76.19; H, 9.92; N, 4.07. *d*-II (pale yellow crystals); mp 193—195°, $[\alpha]_D^{20} + 49.5$ ° (*c*=1, methanol). (lit.,¹⁵) mp 197—198°, $[\alpha]_D^{20} + 56$ ° (*c*=1, methanol).

***d*-N,N'-Dimethyl-3,3'-(carbonyldioxy)dimorphinan (*d*-XVIII)**—To a solution of compound *d*-II (68.7 g, 0.267 mole) dissolved in a mixture of dry tetrahydrofuran and dry chloroform (2:1) (1.5 liters), dry phosgene gas was introduced for 1 hr. The temperature of the solution raised gradually to 40—50° with the reaction. After the reaction, the excess phosgene gas was removed by passing nitrogen through the solution. The solution was concentrated and the residue was dissolved in water. pH of the aqueous solu-

tion was adjusted to 10 with 2N aqueous sodium carbonate and the precipitated oil was extracted with cold chloroform. When the chloroform solution was shaken with cold N aqueous hydrochloric acid solution, white needle crystals were precipitated. The crystals, hydrochloric acid salt of *d*-XVIII, were collected by filtration and washed with cold water and dried over phosphorus pentoxide; wt. 52.7 g (27.5%), mp 240° (decomp.), $[\alpha]_D^{25} + 21.7^\circ$ ($c=1$, methanol). *Anal.* Calcd. for $C_{35}H_{44}O_3N_2 \cdot 2HCl \cdot 1/3CHCl_3 \cdot 3H_2O$: C, 59.98; H, 7.46; N, 3.96; Cl, 15.05. Found: C, 59.83; H, 6.77; N, 4.39; Cl, 14.82. IR ν_{max}^{KBr} cm⁻¹: 1770 (C=O), 1240 (C-O).

Free base of *d*-XVIII: $[\alpha]_D^{20} + 42.5^\circ$ ($c=2$, methanol). *Anal.* Calcd. for $C_{35}H_{44}O_3N_2 \cdot 2H_2O$: C, 72.88; H, 8.39; N, 4.86. Found: C, 72.71; H, 8.33; N, 4.51. This sample was dried at 80° for 6 hr *in vacuo*. *Anal.* Calcd. for $C_{35}H_{44}O_3N_2 \cdot H_2O$: C, 75.23; H, 8.30; N, 5.01. Found: C, 75.97; H 8.35; N 4.95. Mass Spectrum m/e : 540 (M^+).

l-XVIII and *dl*-XVIII were obtained in a similar manner. Infrared (IR), nuclear magnetic resonance (NMR) and mass spectra of these compounds were completely the same as those of *d*-XVIII.

***dl*-3- β -Hydroxyethyloxy-N-methylmorphinan (*dl*-XIII)**—A mixture of *dl*-II (4 g, 0.015 mole), ethylene carbonate (25 g, 0.284 mole) and anhydrous potassium carbonate (1.3 g, 0.0094 mole) in toluene (200 ml) was refluxed for 8 hr with stirring. Ethylene carbonate (10 g, 0.113 mole) was further added and the reflux was continued for another 10 hr with stirring. The reaction mixture was cooled to room temperature and washed well with water. The solution was shaken with 1N aqueous hydrochloric acid (50 ml) and the aqueous layer was separated and washed with ether. The aqueous solution was alkalized with potassium carbonate and the oily product precipitated was extracted with ether. The ethereal solution was washed well with water and dried over anhydrous sodium sulfate. The solvent was evaporated off to obtain an oily product which was purified by column chromatography on silica gel; wt. 2.1 g (46.7%). *Anal.* Calcd. for $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.38; H, 8.97; N, 5.02. NMR²²⁾ ($CDCl_3$) τ : 5.98 (4H, m, -O-CH₂-CH₂-O-), 6.55 (1H, OH). Mass Spectrum m/e : 301 (M^+).

l-XIII and *d*-XIII were obtained in a similar manner.

***dl*-3- β -Chloroethyloxy-N-methylmorphinan (*dl*-XIV)**—To a solution of compound *dl*-XIII (2.24 g, 0.0074 mole) dissolved in dry benzene (100 ml), a solution of thionyl chloride (1 g, 0.0084 mole) in dry benzene (10 ml) was slowly added. The mixture was allowed to react for 40 min at 60–70° with stirring followed by refluxing for 20 min. Water (40 ml) was added to the solution and shaken well. The aqueous layer separated was alkalized with potassium carbonate and the precipitated oil was extracted with ether. The extracted solution was washed with water and dried over anhydrous sodium carbonate. The solvent was evaporated off and the residue was crystallized from a small amount of ether. 1.6 g (65%) of the yellow needle crystal was obtained; mp 105–108°. *Anal.* Calcd. for $C_{19}H_{26}ONCl$: C, 71.34; H, 8.19; N, 4.38; Cl, 11.08. Found: C, 70.76; H, 8.14; N, 4.44; Cl, 10.56. Mass Spectrum m/e : 319 (M^+). NMR²²⁾ ($CDCl_3$) τ : 5.80 (2H, t, $J=5.5$ cps, -O-CH₂-), 6.21 (2H, t, $J=5.5$ cps, -CH₂Cl).

d-XIV and *l*-XIV were obtained in the same method as a pale yellow oil respectively: *d*-XIV; $[\alpha]_D^{15} + 40.2^\circ$ ($c=1$, methanol).

***d*-3- β -Methoxyethyloxy-N-methylmorphinan (*d*-XV)**—To a solution of sodium methylate prepared from sodium (0.3 g, 0.13 atom) in methanol (10 ml), *d*-XIV (0.6 g, 0.00188 mole) was added and the mixture was heated at 140° for 11 hr in a sealed tube. After the reaction the mixture was poured into water (50 ml). The precipitated oil was extracted with ether (80 ml) and washed with water and then dried over anhydrous magnesium sulfate. The solvent was evaporated off to obtain a pale yellow oil; yield 0.5 g (86%). $[\alpha]_D^{15} + 47.3^\circ$ ($c=1$, methanol). *Anal.* Calcd. for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.47; H 9.34; N, 4.53. Mass Spectrum m/e : 315 (M^+). NMR²²⁾ ($CDCl_3$) τ : 6.55 (3H, s, CH₃O-).

l-XV and *dl*-XV were also prepared in the same method and IR, NMR, and mass spectral data of these compounds were completely the same as those of *d*-XV.

***d*-3- β -Diethylaminoethyloxy-N-methylmorphinan (*d*-XVI)**—A mixture of *d*-XIV (0.6 g, 0.00188 mole) and diethylamine (4 ml, 0.039 mole) was allowed to react at 140° for 11 hr in a sealed tube. After the reaction, the excess diethylamine was evaporated off under reduced pressure and the residue was poured into water (50 ml). The precipitated oil was extracted with ether and washed with water and then dried over anhydrous sodium sulfate. The solvent was evaporated off and the yellow coloured oil was obtained: wt. 0.45 g (67.2%). $[\alpha]_D^{15} + 47.3^\circ$ ($c=0.73$, methanol). NMR²²⁾ ($CDCl_3$) τ : 5.98 (2H, t, $J=6$ cps, C-CH₂-O-) 7.16 (2H, t, $J=6$ cps, C-CH₂-N), 7.37 (4H, q, $J=7$ cps, -N-CH₂-CH₃), 8.93 (6H, t, $J=7$ cps, CH₃-CH₂-N-). Mass Spectrum m/e : 315 (M^+). *Anal.* Calcd. for $C_{23}H_{36}ON_2$: C, 75.57; H, 10.20; N, 7.66. Found: C, 76.07; H, 10.04; N, 7.25.

dl-XVI and *l*-XVI were also prepared by the same method and the spectral data of these compounds were completely the same as those of compound *d*-XVI.

***d*-3-Ethoxycarbonyloxy-N-methylmorphinan (XVII)**—To a mixture of *d*-II (2 g, 0.0077 mole) and anhydrous potassium carbonate (1.3 g, 0.0094 mole) in dry tetrahydrofuran (30 ml), a solution of ethyl chloroformate (1.2 g, 0.105 mole) in tetrahydrofuran (5 ml) was slowly added with stirring and allowed to

22) The standard sample is trimethylsilane.

react overnight at room temperature. After the reaction, the solvent was evaporated off under reduced pressure. Water (20 ml) was added to the residue and the insoluble material was extracted with ether. The ethereal solution was shaken well with aqueous 1N hydrochloric acid solution (30 ml). The aqueous layer was separated and alkalized with potassium carbonate. The precipitated oily product was extracted with ether. The ethereal solution was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated off and the residue was purified by column chromatography on silica gel. 0.9 g (35.5%) of the oily product was obtained. $[\alpha]_D^{15} + 51.5^\circ$ ($c=0.75$, methanol). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1755 (C=O), 1240 (C-O). NMR²²⁾ (CDCl_3) τ : 5.71 (2H, q, $J=7$ cps, $-\text{CH}_2-\text{CH}_3$). Mass Spectrum m/e : 329 (M^+). Anal. Calcd. for $\text{C}_{20}\text{H}_{27}\text{O}_3\text{N}$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.39; H, 8.25; N, 4.21.

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