U.D.C. 547.831.3:547.833.3:615.783.19

8. **Hiroshi Kugita**: Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. VI.[1] Synthesis of 3-Hydroxy-N-methyl-4b,8a-ethanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene.

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

Sugimoto and his co-workers have reported[2] on the syntheses and pharmacological effects of hydrogenated quinoline and isoquinoline compounds in which morphinan skeleton has been incorporated and morphinan isomers.

N-Methyl-3-hydroxy-4b,8a-ethanoiminomethano-4b,5,6,7 8,8a,9,10-octahydrophenanthrene (B) synthesized in the present series of work may be regarded as an allied compound of N-methyl-3-hydroxymorphinan (A).

The morphan structure introduced into the skeleton of N-methyl-3-hydroxymorphinan (A) was first synthesized by Cronyn[3] in 1949 and by Ginsburg and others[4] in 1950, who reported that 3-oxomorphan possessed an analgesic action which is rapid but of short duration and that there was no analgesic action in morphan. In 1955, May and Murphy[5] synthesized 5-phenylmorphan and reported that its action was weaker than that of Dimerol but had less toxicity. Synthesis of 6,7-benzomorphan was reported by Barltrop[6] and Horning,[7] but May and others[5] synthesized N-methyl-5-methyl-6,7-benzomorphan and reported its pharmacological effect to be 1/3 of that of morphinan and its toxicity to be 1/2 to 1/4 of that of Dimerol, while the effect of its 8-hydroxyl compound was 1/2 of that of morphinan and a little weaker in toxicity and that there was no analgesic action in its 8-oxo compound.

In such a manner, the morphan and benzomorphan skeletons seem to play an important rôle in the analgesic action of N-methyl-3-hydroxymorphinan (A) and therefore, the synthesis of the compound (B) listed in the title was attempted for reasons given below, expecting a more powerful activity than that of (A).

1) Introduction of a decahydroisoquinoline ring in place of morphan in the morphinan skeleton to examine the effect on analgesic action and to find the rôle of morphan skeleton in the pharmacological action.

2) Morphinan itself possesses a decahydroisoquinoline ring (13, 5, 6, 7, 8, 14, 9, 17, 16, and 15 in (A) formula), so that it is not unnatural to introduce this ring system in a different position (cf. (B) formula) and this might give an important effect on its analgesic action.

3) The presence of a decahydroisoquinoline ring in place of the morphan ring still agrees with the generally accepted theory that analgesics should possess a tertiary amine attached to the carbon atom third from the quaternary carbon with the phenyl group.

Sugimoto and Kugita reported[1] on the synthesis of N-methyl-9-phenethyl-1,2,-3,4,6,7,8,9-octahydroisoquinoline (Ⅶ: $CH_3O=H$) and a modification of this method

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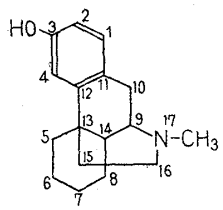
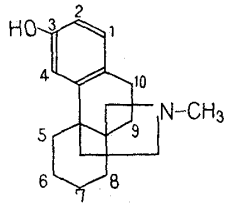
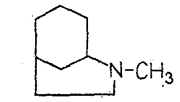
1) This constitutes a part of a series entitled "Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics" by Norio Sugimoto. Part V: J. Pharm. Soc. Japan, **76**, 169(1956).
2) N. Sugimoto, *et al.*: J. Pharm. Soc. Japan, **75**, 177(1955), *et seq.*
3) M. W. Cronyn: J. Org. Chem., **14**, 1013(1949).
4) D. Ginsburg: *Ibid.*, **15**, 1003(1950).
5) E. L. May, J. G. Murphy: *Ibid.*, **20**, 257(1955).
6) J. A. Barltrop: J. Chem. Soc., **1947**, 399.
7) E. C. Horning: *Ibid.*, **1949**, 1359.



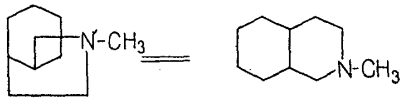
(A)



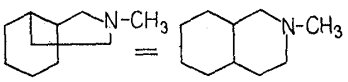
(B)

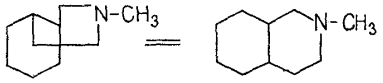


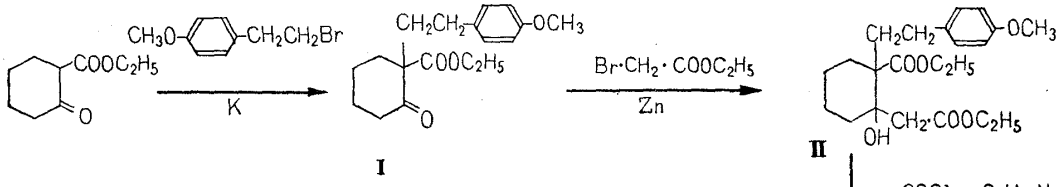
N-CH$_3$-*morphan*



N-CH$_3$-*decahydroisoquinoline*







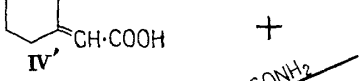
I

II

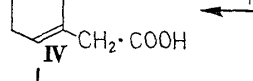
III

IV

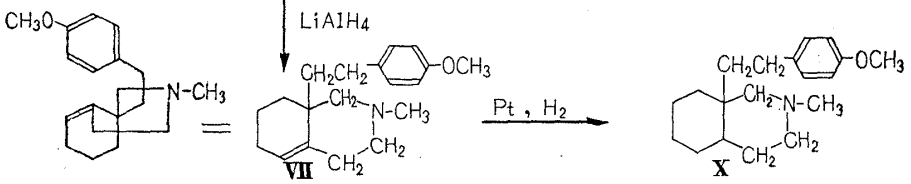
IV'



VI

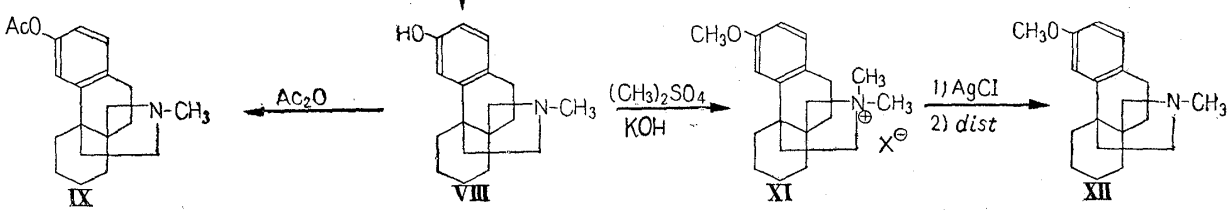


V



VII

X



IX

VIII

XI

XII

was used for the preparation of the intermediate used in the present work, N-methyl-9-(*p*-methoxyphenethyl)-1,2,3,4,6,7,8,9-octahydroisoquinoline (Ⅷ). Some new observations obtained during this work are also described in the present paper.

2-Ethoxycarbonyl-2-(*p*-methoxyphenethyl)cyclohexanone (Ⅰ) was prepared by the condensation of the potassium salt of 2-ethoxycarbonylcyclohexanone and *p*-methoxyphenethyl bromide and its Reformatsky reaction with ethyl bromoacetate afforded 2-ethoxycarbonyl-2-(*p*-methoxyphenethyl)-1-ethoxycarbonylmethylcyclohexanol (Ⅱ), which was dehydrated to the unsaturated diester (Ⅲ), under the same conditions as those for the synthesis of (Ⅷ : $CH_3O=H$) described in the previous report.[1] Hydrolysis of the unsaturated diester (Ⅲ) with alkali gives two kinds of dicarboxylic acids. Recrystallization of the mixture of acids from diluted acetic acid first yields the lower-melting acid (Ⅳ) of m.p. 149~151°, in a larger amount, and its mother liquor gives the higher-melting dicarboxylic acid (Ⅳ′), m.p. 195~197°, in smaller amount. Infrared absorption spectrum of (Ⅳ′) showed the absorption of -CO- shifted to a longer wave length range, at 5.95 μ, and the absorption of a double bond conjugated to this carbonyl appeared markedly at 6.13 μ. Such phenomena were not observed in the spectra of (Ⅳ) and the dicarboxylic acid reported in the previous paper.[1] For these reasons, the structures as shown by (Ⅳ) and (Ⅳ′) were assigned respectively to the lower- and higher-melting dicarboxylic acids. Heating of the dicarboxylic acid (Ⅳ) with formamide at 180~190° for 9 hours, as previously described, gives the imide (Ⅵ). The dicarboxylic acid (Ⅳ′) was obtained only in a very small amount that the attempt for any further steps was given up.

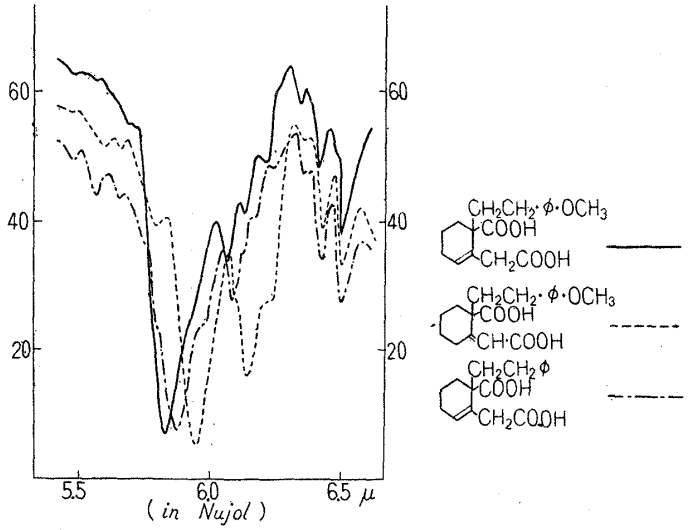


Fig. 1.
Infrared Absorption Spectra (in Nujol)

It is well known that the reduction of acid imide by lithium aluminum hydride does not generally give a good yield and that a better yield is obtained from the reduction of an N-alkylimide. For that reason, reduction after conversion of the acid imide to N-methylimide was adopted in the present series of work. The dicarboxylic acid (Ⅳ) was heated with methylformamide at 180° for 6~7 hours to N-methylimide (Ⅴ), m.p. 133~134.5°, and confirmed by admixture with the N-methylimide, m.p. 133~134.5°, obtained by the N-methylation of the sodium salt of the acid imide (Ⅵ) with dimethyl sulfate. Reduction of N-methylimide (Ⅴ) with lithium aluminum hydride afforded N-methyl-9-(*p*-methoxyphenethyl)-1,2,3,4,6,7,8,9-octahydroisoquinoline (Ⅷ) in 77% yield, a better yield than that from the reduction of the imide. Catalytic reduction of the octahydroisoquinoline (Ⅷ) with Adams' platinum oxide in hydrogen stream resulted in absorption of 1 mole of hydrogen to form the decahydroisoquinoline (Ⅹ).

Heating of the octahydroisoquinoline (VII) thereby obtained with 48% hydrobromic acid for 7 hours results in concurrent demethylation and rearrangement and N-methyl-3-hydroxy-4b,8a-ethanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenathrene (VIII) is obtained. Its acetyl compound (IX) is obtained by heating it with acetic anhydride.

Addition of potassium iodide crystals to the aqueous solution of the methoxy-methosulfate, obtained by the treatment of the hydroxy-phenanthrene compound (VIII) or its methiodide with alkali hydroxide and dimethyl sulfate, affords the methoxy-methiodide (XI : X = I). Its derivation to methochloride (XI : X = Cl) by its treatment with freshly prepared silver chloride and low-pressure distillation effected dechloromethylation to give N-methyl-3-methoxy-4b,8a-ethanoiminomethano-4b,5,6,7,8,8a,-9,10-octahydrophenanthrene (XII).

Confirmation of the structure of N-methyl-3-hydroxy-4b,8a-ethanoiminomethano-octahydrophenanthrene (VIII) was attempted through infrared absorption spectral measurements to see that the cyclization had been effected at the *meta*-position to the hydroxyl in the benzene ring. Gore and Colthup[8] have shown that the absorption of the 1,4-substituted benzene was present at 11.8~12.6 μ and those of the 1,3,4-substituted benzene at 11.4~12.0 μ and 11.9~12.7 μ. Whiffen and Thompson[9] and

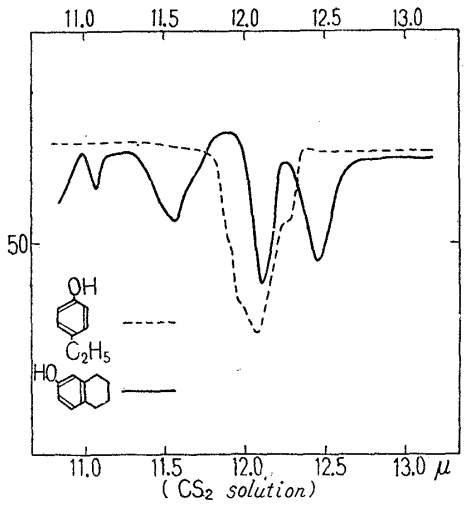


Fig. 2.
Infrared Absorption Spectra
(in CS_2 solution)

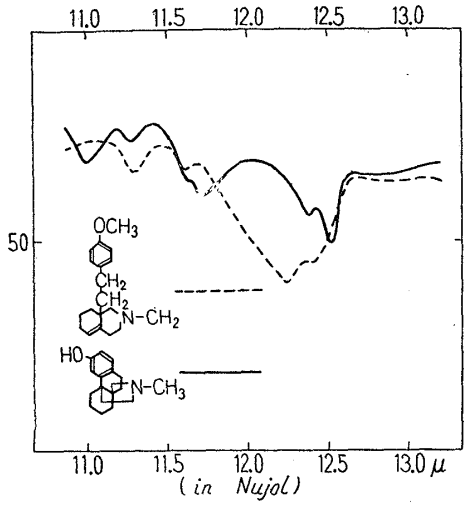


Fig. 3.
Infrared Absorption Spectra
(in Nujol)

Friedel[10] have given the absorptions for *p*-ethylphenol (12.1 and 12.3 μ) and for 6-hydroxytetraline (11.6, 12.15, and 12.45μ) (cf. Fig. 2). The infrared absorption spectra of the compounds synthesized in the present series of work (cf. Fig. 3) showed characteristic absorptions at 12.2 and 12.4 μ, in that of the octahydroisoquinoline compound (VII), at 11.7, 12.4, and 12.55 μ in that of the phenanthrene compound (VIII), and at 11.65, 12.35, and 12.6 μ in that of 3-hydroxy-9-azamorphinan.[11] These facts give rise to the assumption that the rearrangement to (VIII) occured at the position *meta* to the hydroxyl.

However, the foregoing explanations through the infrared spectra only indicate the *meta*-substitution to the hydroxyl. As for the rearranged bonding at 4a and 4b

8) R. C. Gore, N. B. Colthup : J. Optical Soc. Am., **40**, 397(1950).
9) D. H. Whiffen, H. W. Thompson : J. Chem. Soc., **1945**, 268.
10) R. A. Friedel : J. Am. Chem. Soc., **73**, 2881(1951).
11) N. Sugimoto, H. Kugita : This Bulletin, **3**, 11(1955).

(10a,4a,4b,8a,9,10=6-membered ring) and that at 4a and 5 (10a,4a,5,4b,8a,9,10=7-membered ring), it seems more rational to assume the 4a-4b bond, i.e. the ethano-iminomethano-phenanthrene structure (VIII), from the consideration of the tension between carbon atoms in the ring compounds.

Pharmacological tests were carried out by Dr. Hajime Fujiwara of the University of Kyoto by the Haffner method with mice. The toxicity of (VIII) was about twice that of morphine. The analgesic action, at 0.5 mg./10 g. dose, was 25% but showed a strong tail-raising reaction (at morphine at 0.5 mg./10 g. dose as 100%).

The antitussive action of (VIII), tested by the Kasé method[12] with a dog by Dr. Yoshitoshi Kasé of the University of Kumamoto, was about 1/5 that of morphine, about the same as that of codeine.

Deep gratitude is expressed for the kind guidance and encouragement of Prof. S. Sugasawa of the University of Tokyo and of Dr. M. Fujisawa, the Director of this Laboratory. The author is grateful to Miss F. Hisamichi and Mr. T. Yoda for carrying out the microanalyses and to Mr. K. Kodera of this Laboratory for the infrared spectral measurements.

Experimental

2-Ethoxycarbonyl-2-(*p*-methoxyphenethyl)cyclohexanone (I)—*p*-Methoxyphenethyl bromide (76 g.) was added to the solution of K 2-ethoxycarbonylcyclohexanone prepared from 2-ethoxycarbonylcyclohexanone (60 g.), K (13 g.), and anhyd. toluene (450 cc.), and heated in an oil bath for about 65 hrs. Reaction mixture was worked up in the usual manner, and distilled. $b.p_{0.15\sim0.2}$ 172~176°. Yield, 76.0 g. 2,4-Dinitrophenylhydrazone: Yellow needles (EtOH), m.p. 132~135°. *Anal.* Calcd. for $C_{24}H_{28}O_7N_4$: C, 59.5; H, 5.85; N, 11.55. Found: C, 59.2; H, 6.0; N, 11.75.

1-Ethoxycarbonylmethyl-2-ethoxycarbonyl-2-(*p*-methoxyphenethyl)cyclohexanol (II)—A mixture of the ketonic compound (I) (10.0 g.), Zn (4,5 g.), ethyl bromoacetate (7.5 g.), and anhyd. benzene (25 cc.) was heated to the boiling. After the violent reaction subsided (about 10 mins.), ethyl bromoacetate (2.5 g.) and Zn (1.0 g.) were added, heated for further 2.5 hrs., cooled, and decomposed with dil. AcOH. Organic layer was separated, dried, and benzene was removed. The residue was distilled *in vacuo* at 192~204°/0.3 mm. Yield, 9.0 g. of almost colorless oil. Analytical sample, $b.p_{0.3}$ 202°. *Anal.* Calcd. for $C_{22}H_{32}O_6$: C, 67.3; H, 8.2. Found: C, 67.0; H, 8.2.

1-Ethoxycarbonylmethyl-2-ethoxycarbonyl-2-(*p*-methoxyphenethyl)cyclohex-6-ene (III)—A mixture of the hydroxy-ester (II) (9.0 g.), pyridine (5.5 cc.), and anhyd. benzene (20 cc.) was cooled to 0°, and $SOCl_2$ (3.4 g.) was added in drops with stirring. After standing over night at room temperature, the mixture was decomposed with ice water, treated in the usual way, and distilled. $b.p_{0.06\sim0.01}$ 182~188°. Yield, 8.0 g. of almost colorless oil. Analytical sample, $b.p_{0.06}$ 185°. *Anal.* Calcd. for $C_{22}H_{30}O_5$: C, 70.55; H, 8.0. Found: C, 70.0; H, 8.05.

1-Carboxymethyl-2-carboxy-2-(*p*-methoxyphenethyl)cyclohex-6-ene (IV) and 2-Carboxy-2-(*p*-methoxyphenethyl)cyclohexylideneacetic Acid (IV')—The diester (III) (8.0 g.) was heated to boiling with 20% NaOH solution (NaOH 15 g. and H_2O 65 cc.) and a homogeneous solution was obtained after about 4 hrs. Additional heating was continued for 4 hrs. The solution was acidified with conc. HCl, extracted with ether after acidification of $NaHCO_3$ solution, ethereal layer was dried, evaporated, and the residue was recrystallized from dil. AcOH. Yield, 4.4 g. of colorless pillars (IV), m.p. 149~151°. *Anal.* Calcd. for $C_{18}H_{22}O_5$: C, 67.9; H, 6.95. Found: C, 67.7; H, 7.2.

After standing over night, 0.05 g. of (IV') separated from the mother liquor. Colorless prisms (from dil. AcOH), m.p. 195~197°. *Anal.* Calcd. for $C_{18}H_{22}O_5$: C, 67.9; H, 6.95. Found: C, 68.1; H, 7.3.

N-Methyl-9-(*p*-mothoxyphenethyl)-1,3-dioxo-1, 2, 3, 4, 6, 7, 8, 9-octahydroisoquinoline (V)—1) The diacid (IV) (12.5 g.) was heated with N-methylformamide (25 g.) in an oil bath (180°) for 8 hrs. The reaction mixture was poured into water and separated crystals were filtered, washed with $NaHCO_3$ solution, and then with water. 8.0 g. of N-methyl-imide (V) was obtained as colorless plates (from EtOH), m.p. 133~134.5°. *Anal.* Calcd. for $C_{19}H_{23}O_3N$: C, 72.85; H, 7.5; N, 4.45. Found: C, 73.15; H, 7.4; N, 4.45.

2) The diacid (IV) (3.6 g.) was heated with formamide (18 g.) in an oil bath (180~190°) for 9 hrs., poured into water, and the separated crystals were filtered. Two g. of the imide (VI) was obtained as colorless prisms (from EtOH), m.p. 183~184.5°. *Anal.* Cacld. for $C_{18}H_{21}O_3N$: C, 72.2; H, 7.0; N, 4.7. Found: C, 72.5; H, 7.0; N, 4.6.

12) Y. Kasé: This Bulletin, **2**, 298(1954); Japan. J. Pharmacol., **4**, 130(1955).

To the above imide (VI) (1.75 g.) suspended in EtOH (20 cc.) was added EtONa solution (0.4 g. Na in 10 cc. abs. EtOH). Clear solution resulted. Me_2SO_4 (0.8 g.) was added and the mixture was refluxed in a water bath for 3 hrs. After cooling, separated crystals were filtered and recrystallized from EtOH. Yield, 1.0 g. of N-methyl-imide (V), m.p. 133~134.5°. A mixed melting point with the sample from (1) was not depressed.

N-Methyl-9-(*p*-methoxyphenethyl)-1,2,3,4,6,7,8,9-octahydroisoquinoline (VII)—A solution of the N-methyl-imide (V) (13 g.) in dioxane (150 cc.) was added with stirring to a solution of $LiAlH_4$ (4.8 g.) in abs. ether (380 cc.) during 1.5 hrs. The reaction mixture was refluxed for a further 3 hrs. After standing over night, the mixture was decomposed with a small quantity of water, freed from inorganic material, and the solvents were evaporated. The residue was dissolved in ether, ethereal layer extracted with dil. HCl, and the extract was basified with an excess of K_2CO_3. This was extracted with ether, dried, distilled, and 9.1 g. of octahydroisoquinoline (VII) was obtained as colorless viscous oil, $b.p_3$ 184~187°. Picrate: Yellow granules (from EtOH), m.p. 143~145°. *Anal.* Calcd. for $C_{25}H_{30}O_8N_4$: C, 58.35; H, 5.9; N, 10.9. Found: C, 58.3; H, 5.9; N, 10.9. Oxalate: White granules (from AcOEt-EtOH), m.p. 161°. *Anal.* Calcd. for $C_{21}H_{29}O_5N$: N, 3.75. Found: N, 3.90.

9-(*p*-Methoxyphenethyl)-N-methyldecahydroisoquinoline (X)—A solution of octahydroisoquinoline (VII) (0.4 g.) in EtOH (15 cc.) was reduced at atmospheric pressure in the presence of the Adams' PtO_2 catalyst, about 1 mole of H_2 being absorbed. The filtrate from the catalyst was evaporated, the residue was converted to the picrate, and recrystallized from aceton-EtOH to yellow pillars, m.p. 160—175°. *Anal.* Calcd. for $C_{25}H_{32}O_8N_4$; C, 58.1; H, 6.25; N, 10.85. Found: C, 57.65; H, 6.2; N, 10.95.

3-Hydroxy-N-methyl-4b,8a-ethanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene (VIII)—Octahydroisoquinoline (VII) oxalate (11.5 g.) was heated with 48% HBr (90 cc.) in an oil bath (140~145°) for 7 hrs. HBr was removed under reduced pressure, the residue was dissolved in water, basified with NH_4OH, and extracted with ether. Ethereal solution was dried and evaporated. The residue was washed with AcOEt. Yield, 4.6 g. of (VIII) as white needles (from EtOH), m.p. 181~183°. *Anal.* Calcd. for $C_{18}H_{25}ON$: 79.65; H, 9.2; N, 5.15. Found: C, 79.7; H, 9.15; N, 5.05. Methiodide: White pillars (from MeOH), m.p. 259°. *Anal.* Calcd. for $C_{19}H_{28}ONI$: N, 3.4. Found: N, 3.35. Hydrochloride: Colorless needles (from AcOH-EtOH), m.p. 298°.

N-Methyl-3-acetoxy-4b,8a-ethanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene (IX)—A mixture of (VIII) (0.2 g.) and Ac_2O (2 cc.) was refluxed in an oil bath for 3 hrs. Reaction mixture was decomposed with ice water, neutralized with K_2CO_3, and extracted with ether. Ether extract was dried and evaporated to dryness. The residue solidified to 0.22 g. of (IX) as colorless granules (from hyd. EtOH). m.p. 103°. *Anal.* Calcd. for $C_{20}H_{27}O_2N$: C, 76.65; H, 8.7; N, 4.45. Found: C, 76.3; H, 8.4; N, 4.5.

N-Methyl-3-methoxy-4b,8a-ethanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene (XII)—A mixture of (VIII) methiodide (prepared from the hydroxy-compound (VIII) (0.6 g.)), KOH solution (2 g. KOH in 5 cc. H_2O), and Me_2SO_4 (2.0 g.) was shaken vigorously for about 10 mins., neutralized with HCl, and KI added. Yellow crystalline solid formed was filtered to 0.78 g. of methiodide (XI) of 3-methoxy compound as white needles (from EtOH), m.p. 263~264°. *Anal.* Calcd. for $C_{20}H_{30}ONI$: C, 56.2; H, 7.0; N, 3.25. Found: C, 56.5; H, 7.1; N, 3.5.

A mixture of the methoxy-methiodide (XI) (0.9 g.) and water (20 cc.) was treated with fresh AgCl at 95° and converted to the methochloride. AgI was filtered off and the filtrate was concentrated to dryness. The residue was distilled *in vacuo* to colorless, very viscous oil, $b.p_2$ 240~250° (bath temp.). Yield, 0.35 g. of the methoxy compound (XII). Picrate: Yellow needles (from AcOH), m.p. 211~213°. *Anal.* Calcd. for $C_{25}H_{30}O_8N_4$: N, 10.9. Found: N, 10.95.

Summary

The compound listed in the title, in which the morphan structure in the N-methyl-3-hydroxymorphinan skeleton had been substituted with a decahydroisoquinoline, was synthesized and its analgesic and antitussive actions were examind but the compound did not show as powerful an action as was anticipated.

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