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82. **Seiichi Saito** : Synthesis in the Morphinan Group. II.[1] The Structure of 3-Hydroxy-N-methyl-c-normorphinan.

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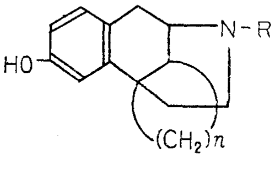
Sugasawa and the writer earlier reported[1] on the synthesis of the C-ring homologs (I) of 3-hydroxy-N-alkylmorphinan by the anticipation of powerful analgesic activity. The compounds so obtained were assumed to be the anticipated C-ring homologs from the similarity of their reactivity with the known 3-hydroxy-N-methylmorphinan (I : n=4, R=CH_3), qualitative reactions, and from their ultraviolet and infrared absorption spectra, but strict identity of their structures had been left to a later date. In the present series of experiments, the Hofmann degradation and synthesis of the degradation products were carried out and these enabled the establishment of their structures, which are described herein.

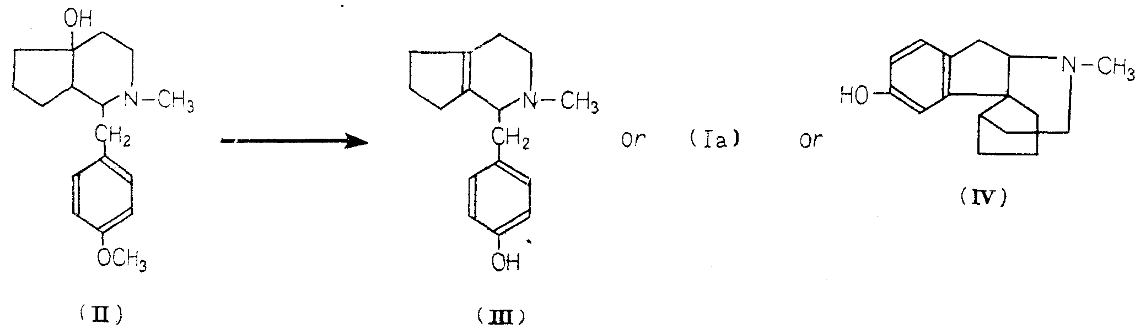
As described in the preceding report,[1] refluxing of 1-(*p*-methoxybenzyl)-2-methyl-9-hydroxy-1,2,3,4,8,9-hexahydrocyclopenta[*e*]pyridine (II) with concentrated hydrobromic acid affords the expected phenol base (A), m.p. 239.5~240° (decomp.), when refluxed over a long period of time, but when refluxed for 30 minutes, a phenol base (B) of m.p. 123~125° is obtained and this is assumed to be an intermediate (III) formed by dehydration and demethylation. The compounds anticipated from the reaction of (II) and concentrated hydrobromic acid are (III), (Ia), and (IV).

Chart 1.



(I)

(Ia) n=3, R=CH_3 : 3-Hydroxy-N-methyl-D-normorphinan.
(Ib) n=3, R=C_2H_5: 3-Hydroxy-N-ethyl-D-normorphinan.
(Ic) n=5, R=CH_3 : 3-Hydroxy-N-methyl-D-homomorphinan.



The properties of these two phenolic bases, (A) and (B), are compared with those of the structurally known (II) and 3-hydroxy-N-methylmorphinan (I : n=4, R=CH_3) in Table I.

TABLE I.

	(II)	(B)	(A)	(I) *n*=4, R=CH_3
Decolorization with 0.1% $KMnO_4$ in acetone	−	+	−	−
U.V. $\lambda_{max}^{2\%HCl}$ mμ	224 275	224 275	280	280
I.R. Absorption at ca. 865 cm^{-1}	−	−	+	+

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[1] Part I. S. Sugasawa, S. Saito : This Bulletin, **4**, 237(1956).

These properties indicate that (A) is a compound formed by the transition of the double bond in (B) to the benzene ring. It follows, therefore, that (B) would be the intermediate (III) and (A) the c-normorphinan (Ia) or a spirane-type compound (IVa) formed by the cyclization-condensation of the double bond in (III) with the benzene ring. The fact that (A) is formed when (B) is heated in 100% phosphoric acid at 140° endorses these assumptions. From the results of similar reactions, there is little possibility that (A) is a spirane-type compound (IV) but, in order to establish the structure of (A) more definitely, decomposition of (A) and synthesis of the decomposition product were carried out.

(A) was methylated with diazomethane to the methoxyl compound (V) and its methiodide was refluxed with 16% potassium hydroxide, from which the methine base was easily obtained. The fact that the double bond in this base is conjugated with the benzene ring can be seen from the ultraviolet absorption spectral data. The methiodide of this methine base was treated with silver oxide, the decomposition product was distilled, and a nitrogen-free substance was obtained. Catalytic reduction of this substance, with palladium-carbon as the catalyst, resulted in absorption of 2 moles of hydrogen to afford a saturated, nitrogen-free substance (C). If (A) were the anticipated compound (Ia), then the foregoing reactions would proceed through the steps shown in Chart 1, and the final product (C) would be the compound (VIII).

In order to confirm this assumption, the compound (VIII) was synthesized by the route shown in Chart 3.

Chart 2.

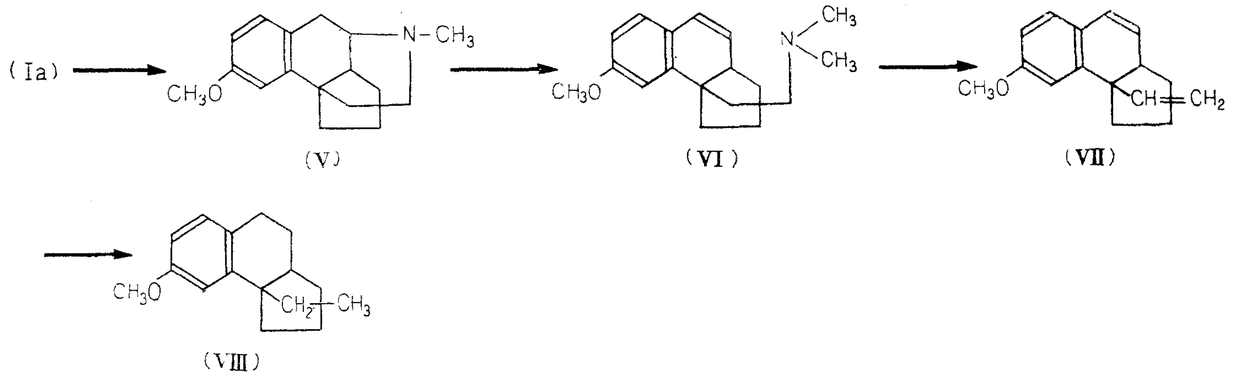
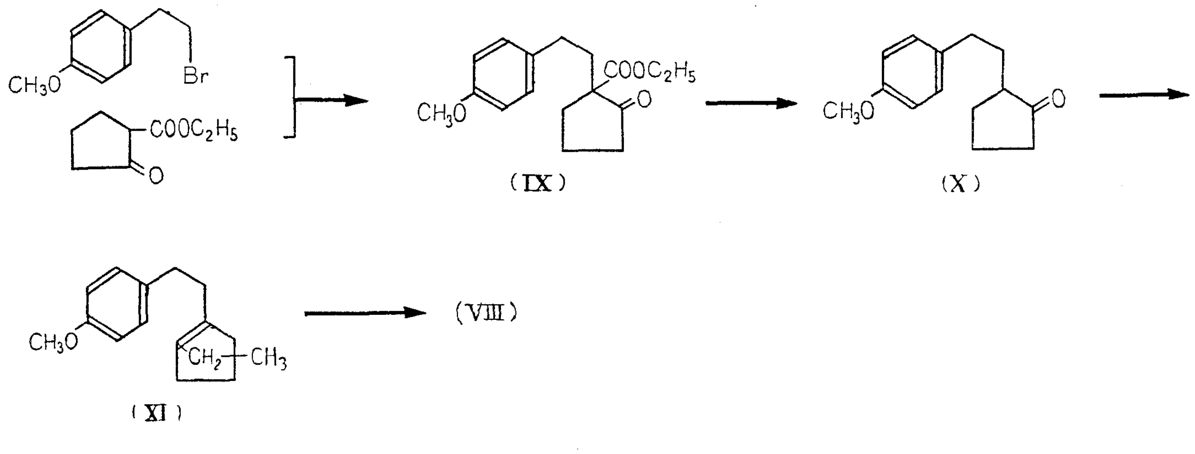
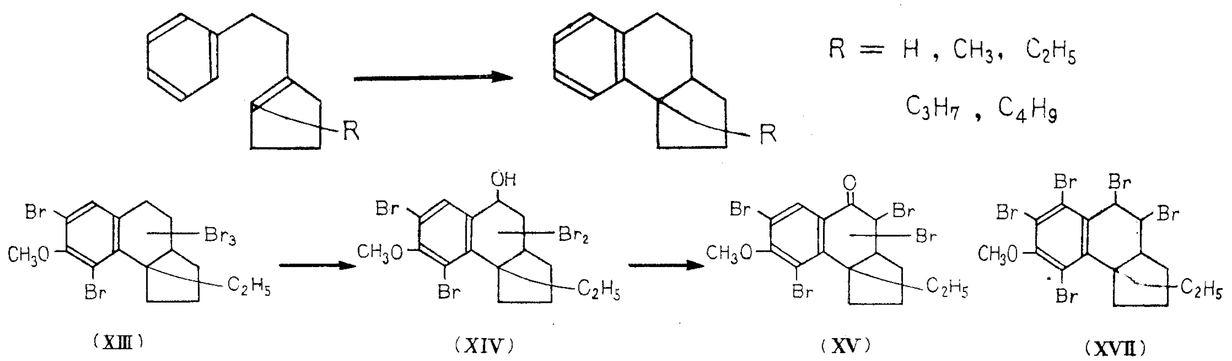


Chart 3.



The problem in this process is the final cyclization reaction of (XI) into (VIII), in which there is also a fear that a spirane-type compound might be formed. However,

Chart 4.



there are a number of reports on similar reactions,[2~5] but none of them indicate that a spirane-type compound had been formed. There are no examples with *p*-methoxy group in the benzene ring but it seems impossible that a spirane type would be formed by change in the direction of cyclization due to the presence of the methoxyl group. Therefore, it may be concluded that the cyclization of (VI) affords (VIII).

Condensation of *p*-methoxyphenethyl bromide and 2-ethoxycarbonyl-cyclopentanone, as its potassium salt, to (IX) and its hydrolysis and decarboxylation afforded 2-(*p*-methoxyphenethyl)cyclopentanone (X). Application of ethylmagnesium bromide to (X), low-pressure distillation of its product to isolate (XI), and its cyclization-condensation in 85% sulfuric acid finally afforded the compound (VIII).

The ultraviolet and infrared absorption spectra of this synthesized (VIII) and the product (C) obtained from the Hofmann degradation agreed well, as shown in Figs. 1 and 2. Both these compounds form crystalline bromide on bromination in glacial acetic acid on a boiling water bath. These two bromides showed no depression of the

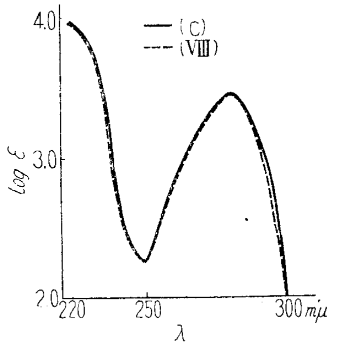


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

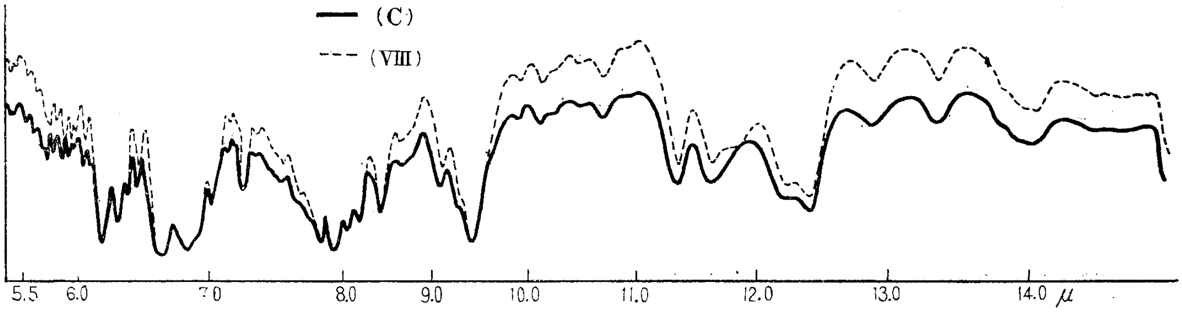


Fig. 2. Infrared absorption Spectra

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2) H. Adkins, G. F. Hager : J. Am. Chem. Soc., **71**, 2965(1949).
3) C. A. R. Kon : J. Chem. Soc., **1933**, 1081.
4) F. J. McQuillin, R. Robinson : J. Chem. Soc., **1938**, 1097.
5) Y. I. Densenko : C. A., **32**, 4160(1938).

melting point on admixture and gave well-agreeing elementary analytical data and infrared absorption spectral data. However, the analytical values of the bromide corresponded to those of a pentabromide. As for the position of the bromine atoms, details will be given later.

This complete identity of the decomposition product (C) and the synthesized compound (VIII) proves that the phenolic base (A) in question is the anticipated 3-hydroxy-N-methyl-c-normorphinan (Ia). Since the structures of (Ia) and 3-hydroxy-N-methylmorphinan (I, n=4, $R=CH_3$) have been clarified, chemical examination of 3-hydroxy-N-methyl-c-homomorphinan (Ic), obtained by the similar reaction, was not made but its structure seems reliable.

Next, some examinations were made on the structure of the crystalline pentabromide (XII) of (VIII). As was exemplified by Grewe,⁶⁾ it seems certain that the two *ortho* positions of the methoxyl group in (VIII), 7- and 9-positions, would be preferably brominated. This leaves three bromine atoms in unknown positions. Reaction of the pentabromo compound (XII) with magnesium carbonate results in the conversion of one bromine atom to a hydroxyl and the position of this hydroxyl seems to be a benzyl alcohol type, i.e. in 5-position. Oxidation of this carbinol (XIV) with chromium trioxide affords a ketone compound, whose ultraviolet absorption spectrum, as shown in Fig. 3, indicates the presence of a carbonyl conjugated to the benzene ring, viz. the 5-oxo compound. The absorption at 1720 cm^{-1}($\nu_{c=o}$) in the infrared spectrum (Fig. 4) can only be interpreted without inconsistency as that of aromatic α-haloketone. It seems almost certain, therefore, that the ketone compound would be represented by formula (XV). Its immediate reaction with dimethylamine in benzene solution to precipitate dimethylamine hydrobromide endorses the appropriateness of this formula.

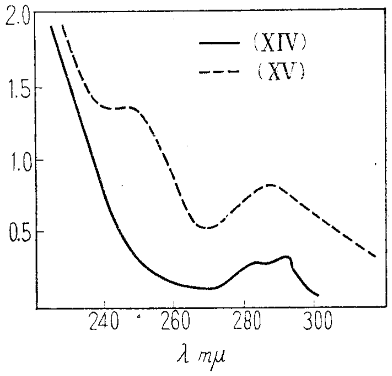

Fig. 3.
Ultraviolt Absorption Spectra (in EtOH)

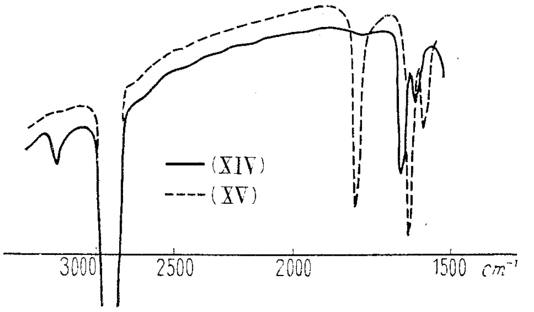

Fig. 4.
Infrared Absoption Spectra

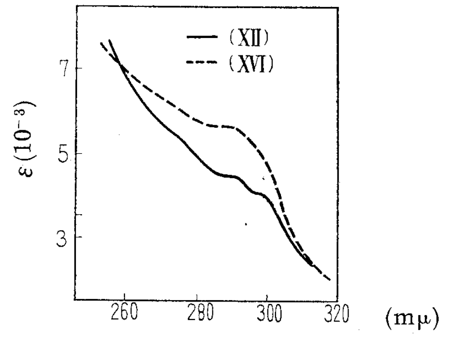

Fig. 5.
Ultraviolet Absorption Spectra (in CCl_4)

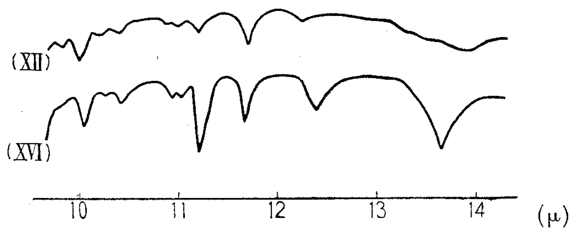

Fig. 6.
Infrared Absorption Spectra (in Nujol)

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6) R. Grewe, *et al.*: Ann., **564**, 161(1949)

It was later found that the bromination of (VIII) in chloroform affords a tetrabromo compound (XVI). Comparison of the ultraviolet and infrared spectra (Figs. 5 and 6) of the tetrabromo compound (XVI) and pentabromo compound (XII) indicates that the difference between these two is that due to the difference of substituents in the benzene ring. As was shown earlier, it seems certain that the 7- and 9-positions are first brominated and a different position of a substituent can only occur in the 6-position. Further examination of the infrared absorption spectra indicates that the spectrum of the tetrabromo compouds exhibits absorptions of strong intensity in the regions below 900 cm^{-1} characteristic of out-of-plane vibration of a benzene ring, such as that at 895 cm^{-1}, while that of the pentabromo compound lacks such intense absorption and suggests a hexa-substituted benzene. From the foregoing facts, it may be assumed that the pentabromide (XII) is a 4, 5, 6, 7, 9-pentabromo compound (XVII).

The writer expresses his deep gratitude to Prof. S. Sugasawa for his kind encouragement throughout the course of this study, and to Dr. Masao Fujisawa, Director of the Osaka Research Laboratory, and Dr. Norio Sugimoto, Vice-Director of the same, of Gohei Tanabe & Co., Ltd. for their interest in this work. The writer is indebted to Mrs. F. Hisamichi and Mr. T. Yoda of the Tokyo Research Laboratory of the said firm for elemental analyses and to Mr. K. Kodera for infrared spectral measurement.

Experimental

3-Methoxy-N-methyl-c-normorphinan (V)—Excess of ethereal diazomethane was added to a suspension of 3-hydroxy-N-methyl-c-normorphinan (I) (2.5 g.) in MeOH (25 cc.) and the mixture was allowed to stand for 5 days at room temp. After evaporating the solvents, the residue was distilled *in vacuo*, giving (V) (2.3 g. or 89%) as a viscous colorless liquid, b.p$_{0.15}$ 152~153°.

Picrate: Brilliant yellow prisms (from glacial AcOH), m.p. 167~169°. *Anal.* Calcd. for $C_{20}H_{26}O_8N_7$: C, 56.8; H, 5.3, N, 11.5. Found: C, 56.55; H, 5.4; N, 11.5.

8-Methoxy-9b-(β-dimethylaminoethyl)-2, 3, 3a, 9b-tetrahydro-1*H*-benz[*e*]indene (VI)—A mixture of (V) methiodide (2.8 g.) and 16% KOH (30 cc.) was refluxed for 40 mins., separating a clear brown oil which was taken up in benzene, washed with water, and dried. After evaporating the benzene, the residue was distilled *in vacuo*, giving (VI) (1.6 g. or 83%) as a viscous colorless liquid, b.p$_{0.06}$ 160° (oil bath temp.).

Hydrochloride: Colorless needles (from MeOH and ether), m.p. 181~183°. *Anal.* Calcd. for $C_{19}H_{26}ONCl$: C, 70.2; H, 8.3; N, 4.55. Found: C, 69.8; H, 8.3; N, 4.7.

8-Methoxy-9b-vinyl-2, 3, 3a, 9b-tetrahydro-1*H*-benz[*e*]indene (VII)—Fresh Ag_2O, prepared from $AgNO_3$ (2.4 g.) and 3*N* NaOH (10 cc.), was added to a solution of (VI) methiodide (1.4 g.) in warm water (30 cc.) and the mixture was shaken for 4 hrs. at room temp. After removing the inorganic materials, the filtrate was evaporated below 50° to dryness, giving a semisolid. When this semisolid was heated *in vacuo* (2~3 mm. Hg), the evolution of trimethylamine began at about 90° (oil bath temp.) and then 0.6 g. of a pale brown liquid distilled out until 140° (oil bath temp.). The distillate was dissolved in ether, washed with 10% HCl, and dried. After evaporating ether, the residual liquid was redistilled *in vacuo*, giving (VII) (0.5 g. or 65%) as a pale yellow liquid, b.p$_{1.5}$ 130° (oil bath temp.).

8-Methoxy-9b-ethyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-benz[*e*]indene (VIII)—A solution of (VII) (0.3 g.) in EtOH (20 cc.) was reduced at atmospheric pressure in the presence of 10% Pd-C catalyst (0.1 g.), about 2 moles of H_2 being smoothly absorbed during 3 hrs. The reaction mixture was worked up as usual and (VIII) was obtained as a colorless liquid of b.p$_{1.0}$ 100~120° (oil bath temp.). Yield, 0.3 g.

The mixture of (VIII) (0.15 g.), glacial AcOH (10 cc.), and bromine (0.3 cc.) was allowed to stand for 1 hr. at room temp. and then heated on steam bath for 45 mins. The colorless crystals that separated from the reaction mixture was washed with EtOH and recrystallized from EtOH and benzene, giving (VIII)-pentabromide as colorless plates; m.p. 168~170° (decomp.) (yield, 30%). *Anal.* Calcd. for $C_{16}H_{17}OBr_5$: 30.75; H, 2.75; Br, 63.95; CH_3O, 4.95. Found: C, 31.15; H, 3.0; Br, 63.7; CH_3O, 4.8. U.V. $\lambda_{max}^{CCl_4}$ 288, 298 mμ.

2-Ethoxycarbonyl-2-(*p*-methoxyphenethyl)cyclopentanone (IX)—To a suspension of powdered K (5.6 g.) in abs. toluene (220 cc.), 2-ethoxycarbonylcyclopentanone (23.5 g.) was added slowly below 5° and then was continued to stir for 1 hr. at room temp. separating yellow crystals of K-salt. *p*-Methoxyphenethyl bromide (23.5 g.) was added dropwise in it and the mixture was gently heated and refluxed for 10 hrs. After cooling, water was added, separated organic layer was washed with water, and worked up as usual. (IX) was obtained as pale yellow liquid of b.p$_{1.5}$ 168~170°. Yield, 20 g.

or 63%.

2-(*p*-Methoxyphenethyl) cyclopentanone (X)—A solution of (IX) (20 g.), AcOH(95 cc.), conc HCl (45 cc.), and water (150 cc.) was refluxed for 3 hrs. when evolution of CO_2 ceased and then the reaction mixture was concentrated to ca. 1/4 volume *in vacuo*. The seperated oil was taken up in benzene, washed with 5% $NaHCO_3$ and sat. NaCl, and then worked up as usual. (X) was obtained as colorless liquid of b.$p_{1.5}$ 130∼137°. Yield, 12 g. or 79%.

Semicarbazone: Colorless needles (from EtOH), m.p. 205∼207° (decomp.). *Anal.* Calcd. for $C_{15}H_{21}O_2N_3$: C, 65.45; H, 7.7; N, 15.25. Found: C, 65.4; H, 7.8; N, 15.3.

1-Ethyl-2-(*p*-methoxyphenethyl)cyclopent-1-ene (XI)—A solution of (X) (12 g.) in toluene (50 cc.) was added to the Grignard reagent prepared from Mg(6 g.), ethyl bromide (26.4 g.), and dehyd. ether (30 cc.). Ether was distilled off until the temperatur of reaction mixture reached 85°, heating was continued for 5 hrs., and decomposed with ice-water containing conc. HCl. The brown organic layer was washed with sat. NaCl and worked up as usual. (XI) was obtained as pale brown liquid of b.p_2 138∼143°. Yield, 11 g. or 87%. This substance gave negative tests with carbonyl reagent and decolorized the solution of 0.1% $KMnO_4$ in acetone.

8-Methoxy-9b-ethyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-benz[*e*]indene (VIII)—(XI) (11 g.) was added to 85% H_2SO_4(35 cc.) with stirring at 0° to 5°, then stirred for further 30 mins. at 15∼20°. The reaction mixture was extracted with benzene and the extract was washed with 5% $NaHCO_3$, dried, and evaporated. The residue was distilled *in vacuo*, giving (VIII) (8.5 g. or 77%) as colorless liquid, b.$p_{1.5}$ 116∼118°.

Pentabromide: Colorless plates (from EtOH and benzene), m.p. 168∼170° (decomp.). *Anal.* Calcd. for $C_{16}H_{17}OBr_5$: C, 30.75; H, 2.75; Br, 63.95. Found: C, 31.2; H, 2.85; Br, 63.60.

A mixed melting point with (VIII)-pentabromide prepared by the degradation of 3-hyroxy-N-methyl-c-normorphinan was not depressed.

8-Methoxy-9b-ethyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-benz[*e*]indene Tetrabromide (XVI)—A mixture of (VIII) (0.5 g), $CHCl_3$(20 cc.), and Br_2(0.4 cc.) was allowed to stand for 1 hr. at room temp. and then refluxed for 30 mins. After evaporating $CHCl_3$, glacial AcOH(15 cc.) and Br_2(0.01 cc.) were added to the syrupy residue and heated on a steam bath for 10 mins. The colorless crystals that separated from the reaction mixture was washed with EtOH and recrystallized from EtOH and benzene, giving (VIII)-tetrabromide (XVI) as colorless plates, m.p. 172∼174° (decomp.) (yield, 9%). *Anal.* Calcd. for $C_{16}H_{18}OBr_4$: C, 35.2; H, 3.3; Br, 58.55. Found: C, 35.1; H, 3.35; Br, 58.9. U.V.: $\lambda_{max}^{CCl_4}$ 287 mμ (log ε 3.74).

5-Hydroxy-8-methoxy-4, 6, 7, 9-tetrabromo-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-benz[*e*]indene (XIV)—A mixture of the pentabromide (XII) (0.7 g.), $MgCO_3$(0.7 g.), dioxane (15 cc.), and H_2O (15 cc.) was refluxed for 5 hrs., poured into H_2O (30 cc.), and extracted with benzene. The crystals which had been obtained by evaporating benzene were recrystallized from ligroine, giving (XIV) (0.35 g. or 55%) as colorless prisms, m.p. 168∼170°. *Anal.* Calcd. for $C_{16}H_{18}O_2Br_4$: C, 34.2; H, 3.25. Br, 56.9. Found: C, 34.05; H, 3.65; Br, 56.75. U.V. λ_{max}^{EtOH}: 282 mμ (log ε 3.46), 291 mμ (log ε 3.53).

5-Oxo-8-methoxy-4, 6, 7, 9-tetrabromo-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-benz[*e*]indene (XV)—A mixture of carbinol (XIV) (0.3 g.), CrO_3(0.15 g.), and AcOH(10 cc.) was heated at 70° for 3 hrs. AcOH was evaporated, H_2O was added, and resulting crystals were taken up in benzene. The benzene solution was washed with 3% $NaHCO_3$ and dried. The crude product which had been obtained by evaporating benzene was recrystallized from EtOH and benzene, giving (XV) (0.2 g. or 65%) as colorless plates, m.p. 186∼188°. *Anal.* Calcd. for $C_{16}H_{16}O_2Br_4$: C, 34.3; H, 2.9; Br, 57.1. Found: C, 34.25; H, 2.95; ; Br, 56.55. U.V. λ_{max}^{EtOH}: 245 mμ (log ε 4.11), 287 mμ (log ε 3.89).

Summary

3-Hydroxy-N-methyl-c-normorphinan, synthesized earlier, was submitted to the Hofmann degradation and by the synthesis of its degradation products, its structure was confirmed.

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