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45. Shigehiko Sugasawa and Seiichi Saito : Synthesis in the Morphinan Group. I. Synthesis of "C"*-Nor and -Homo Derivatives of 3-Hydroxy-N-methylmorphinan.

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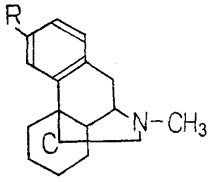
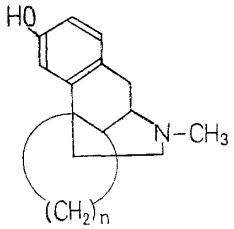
N-Methylmorphinan (I), which was first synthesized by Grewe and Mondon,[1] was found to possess a strong analgesic activity comparable to that of the natural base. A considerable increase in the activity was achieved by introducing a hydroxyl group in 3-position of (I), thus the *l*-form of 3-hydroxy-N-methylmorphinan (II), synthesized first by Schnider and Grüssner[2] and then by Henecka,[3] is claimed to be about three times as active as morphine. In view of the fact that some *D*-homosteroids possess the same order of, or rather enhanced, activity as the original compounds, it appeared worth while to synthesize and to test the pharmacological properties of "C"-homologous compounds, (III) and (IV), of (II).



I : R=H
II : R=OH



III : n=3
IV : n=5

Search of literature revealed that Goto *et al.*[4] obtained sinomenilone and dihydrosinomenilane from sinomenine, both of which can be regarded as derivatives of "C"-normorphinan. Our preliminary attempt to synthesize N-methyl-"C"-normorphinan (III, H instead of OH) failed,[5] which fact was also confirmed by the independent experiments by Protiva.[6] As for the "C"-homomorphinan nothing is yet known in the literature.

Three synthetic methods are known for the preparation of morphinans, except the one by Ochiai and Ikehara,[7] in which isoquinoline is one of the starting materials. Although Grewe and Mondon[1] were the first to synthesize morphinan, the second method by Schnider[2] and the third one by Henecka[3] seemed preferable for the present purpose, because of the simplicity in preparing the starting materials.

The cyclic ketones were Cope-condensed with cyanoacetic acid using ammonium acetate as the condensing agent and the products were decarboxylated, giving cyclopenten-1-yl-(Va) and cyclohepten-1-yl-acetonitrile (Vb), respectively. The cyclic nature of the double bond in these compounds was confirmed through their molecular refractive index, indicating that it is not conjugated with the cyano group, which fact is also

* "C" means the C-ring of morphinan throughout this paper.

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1) R. Grewe, A. Mondon : Chem. Ber., **81**, 279(1948).
2) O. Schnider, A. Grüssner : Helv. Chim. Acta, **32**, 821(1949).
3) H. Henecka : Ann., **583**, 110(1953).
4) K. Goto, K. Takubo : Ann., **495**, 122(1932); K. Goto, H. Shishido : *Ibid.*, **509**, 296(1933).
5) S. Sugasawa, S. Takano : Unpublished data.
6) M. Protiva : Chem. Listy, **1954**, 1045.
7) E. Ochiai, M. Ikehara : This Bulletin, **2**, 109(1954).

supported by the extensive work of Linstead.[8] On being reduced by lithium aluminum hydride both nitriles gave the corresponding unsaturated amines (VIa,b) in 26%[9] and 66% yield, respectively. The latter figure is comparable with that of 2-(cyclohexen-1-yl)ethylamine (74%), but the reason of the low yield of (VIa) is not explicable.

The reduction of these nitriles was also carried out catalytically over U-Co-B[10] and Raney cobalt both of which gave nearly the same results. Their catalytic activity was not quite selective and thus both amines (VIa,b) respectively contained about 40% and 30% of the saturated amines judged from the results of their hydrogenation over Adams' platinum catalyst. Their separation through distillation was impossible, but since the presence of the saturated amine was found not to interfere with the later reactions, the preparation of both these amines (VIa,b) in larger scale was resorted to by the catalytic method over Raney cobalt or U-Co-B.

The amines (VIa,b) were then acylated with the chloride of *p*-methoxyphenylacetic acid and the cyclisation of the resultant amides was attempted according to the method of Schnider under a variety of conditions, but in none of the cases there was produced basic compound. Henecka's procedure was, however, found to be successful. Thus the amines (VIa,b) were treated with methyl *p*-methoxyphenylglycidate in aqueous solution at pH 3~4 for 48 hours. The yield of the products was 36% of (VIIa) and 5% of (VIIb), the latter of which was, however, raised to 15% by working under a revised reaction conditions (cf. experimental section). Formulae (VIIa,b) were assigned to the cyclized products, based on their analytical data and the absence of unsaturated bond in these compounds; Henecka's view was also taken into account. The corresponding N-methyl derivatives (VIIIa,b) were prepared by the usual method.

According to Henecka the 10-hydroxydecahydroisoquinoline derivative (VII : n=4) undergoes only demethylation and dehydration on refluxing with conc. hydrobromic acid for 30 minutes, giving a compound of m.p. 113° (IX, n=4), whereas a prolonged boiling for 6 hours results in the formation of 3-hydroxy-N-methylmorphinan (m.p. 250~251°). Our present bases behaved similarly, but a more prolonged heating was found necessary to effect the ultimate morphinan-type cyclization to give (Xa,b), as can be seen from Table I.

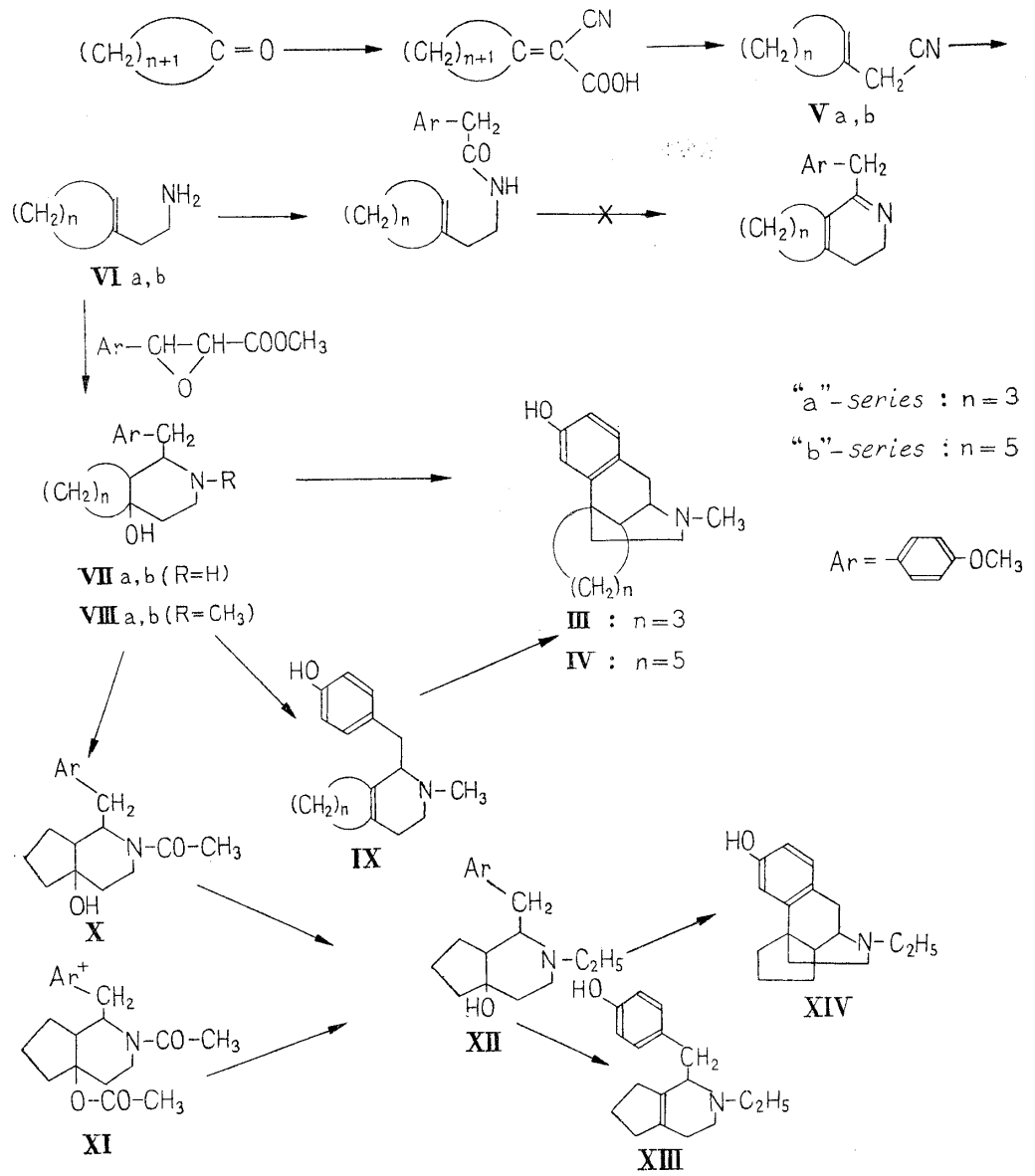
Table I.

Material	Reaction time (hr.)	Products: Yield (%) l.m.b.[b]	Products: Yield (%) h.m.b.[c]	Products: m.p. (°C) l.m.b.	Products: m.p. (°C) h.m.b.
(VII) n=4[a]	0.5	27	—	113	250~251(decomp.)
	6	—	31		
(VIIa)	0.5	88	—	123~125	239.5~240(decomp.)
	7	31	trace		
	16	12	14		
	24	—	21		
(XIII)	0.5	81	—	116~118	228~229(decomp.)
	24	—	21		
	32	—	28		
(VIIb)	32	—	17		244~246(decomp.)
	40	—	25		

a) Data by Henecka b) Lower melting base c) Higher melting base

3-Hydroxy-N-ethyl-"C"-normorphinan was also prepared for the purpose of physiological testing.

8) A. Kandian, R. P. Linstead : J. Chem. Soc., **1929**, 2139.
9) Yield of 33% was claimed by Protiva (*loc. cit.*) in the same reduction.
10) S. Saito : J. Pharm. Soc. Japan, **76**, 351(1956).



By treating the more fusible base (IX) with 100% phosphoric acid at 140° for 72 hours, there also was produced the corresponding higher melting base (Xa), though in a low yield.

Ultraviolet spectra of the two series of the three lower melting and the three higher melting bases were measured. The former three have two maxima at 225 and 275 mμ, whereas the latter three have only one peak at 280 mμ, showing that another

Table II. Ultraviolet Spectra (2% HCl)

	λ_{max}(mμ)	log ε		λ_{max}(mμ)	log ε
(VIIa)	224	4.02	(IX)	224	4.01
	275	3.21		275	3.07
(VIIb)	224	4.03	(XIII)	224	4.03
	276	3.06		275	3.07
(VIIIa)	224	4.01	(III)	280	3.34
	275	3.14			
(VIIIb)	224	4.00	(XIV)	280	3.35
	276	3.13			
(XII)	224	4.00	(IV)	280	3.32
	275	3.17			

substitution had occured in the benzene ring. Further evidence for the structure of (Ⅲ) and (Ⅳ) was provided by their characteristic infrared absorption spectra around 865 cm^{-1}, indicating the presence of unsymmetrically substituted benzene ring, which spectral characteristic is also common with the authentic 3-hydroxy-N-methylmorphinan.

Structural proof on a pure chemical process is now also under progress and the result will be published in due course.

The pharmacological proporties of (Ⅲ), (Ⅳ), and (XIV) were examined by Dr. H. Fujimura of the University of Kyoto and the results will be published by him in detail. So they will be described briefly.

The nor compound (XIV) has no analgesic property, while (Ⅲ) is very slightly active and the corresponding homo derivative (Ⅳ) manifests about the same order of analgesic activity with morphine, but is about 3 times as toxic as the natural base. Therefore, the preparation of *l*-homo derivative appears desirable and the work along this line is now under progress.

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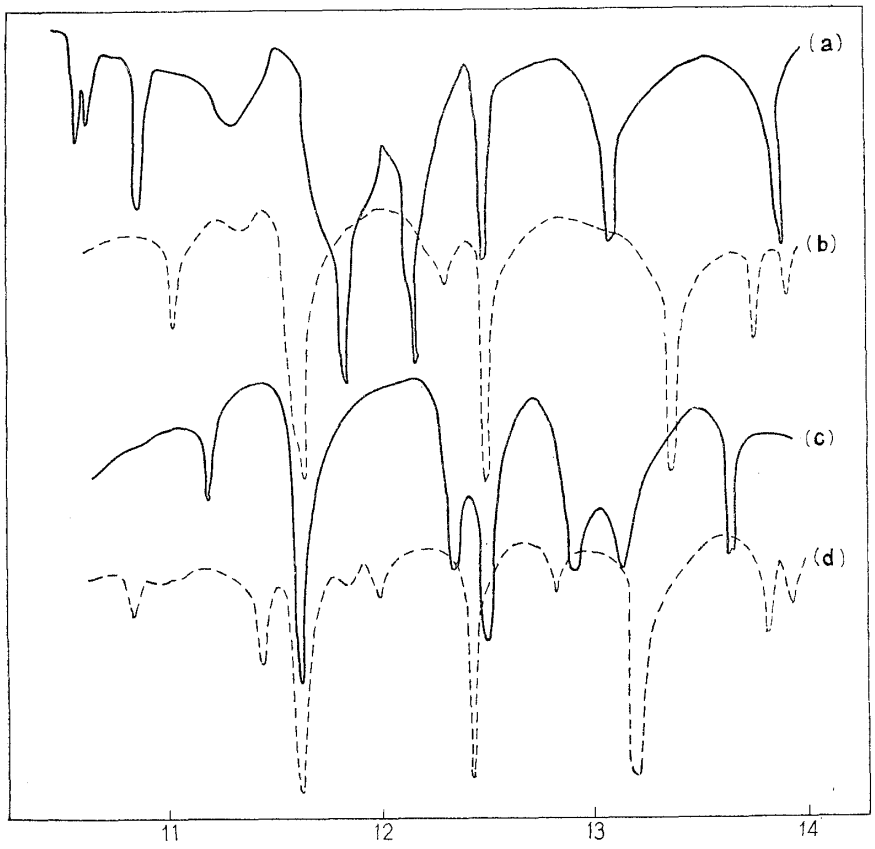
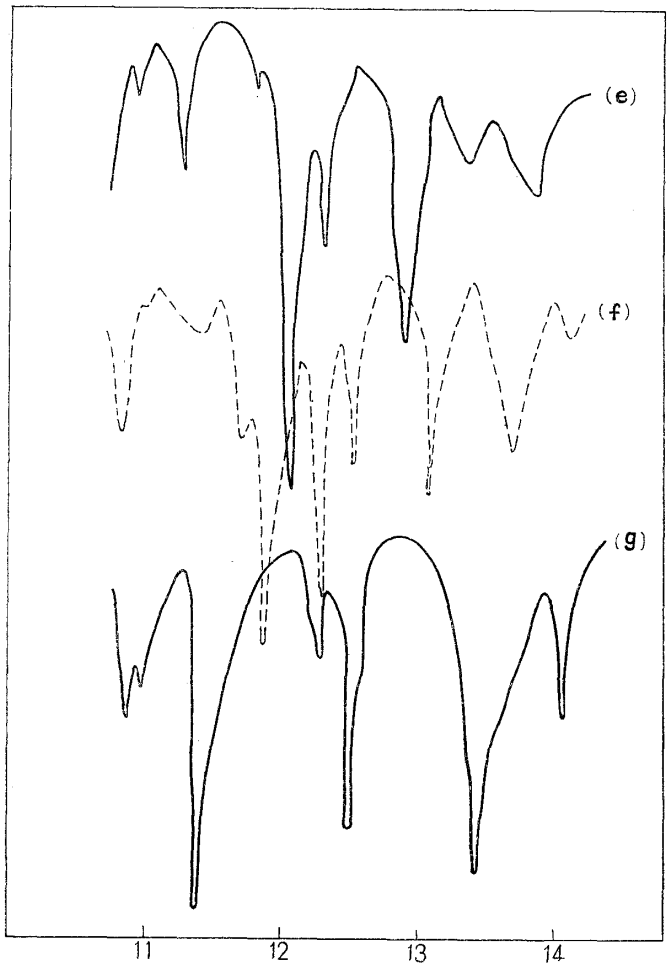


(a) : (Ⅷa) , (b) : (Ⅲ) , (c) : (Ⅳ) , (d) : (Ⅱ)

Infrared Spectra in Nujol Perkin-Elmer Model 12-C



(e) : (XII), (f) : (XIII), (g) : (XIV)

Experimental

Cyclopenten-1-ylacetonitrile (Va)—Cyclopentanone (100 g.), cyanoacetic acid(100 g.), and ammonium acetate (7 g.) were mixed with 90 cc. of pure benzene and the whole was refluxed. Water was distilled off azeotropically with benzene as it was formed and thus the theoretical amount of water separated in ca. 20 hrs. Benzene was now removed and the residue was distilled at 160~180°(oil-bath temp.) in aspirator vacuum with simultaneous evolution of CO_2. The distillate was dissolved in ether, washed successively with soda solution and water, and was dried over K_2CO_3. (Va) was obtained as a colorless liquid of $b.p_{17}$ 79~82°, with cinnamon-like odor. Yield, 110 g. or 80%.

Cyclohepten-1-ylacetonitrile (Vb)—Prepared as above. Colorless liquid of $b.p_{19}$ 111~112.5°, with cinnamon-like odor. Yield, 70%. d_4^{27} 0.9336, n_D^{27} 1.4799.

2-(Cyclopenten-1-yl)ethylamine (VIa)—The foregoing nitrile (17 g.) in 150 cc. of pure ether was added dropwise into the solution of $LiAlH_4$(6.5 g.) in 400 cc. of pure ether at 0° with stirring. Then the whole was stirred for additional 1.5 hrs. at room temp. and then worked up as usual. The base (VIa) forms colorless liquid of characteristic basic odor boiling at 67~84°/24 mm.; yield, 4.5 g. or 26%.

Picrate : Yellow rhombic pillars of m.p. 150~152° from EtOH-ether. *Anal.* Calcd. for $C_7H_{13}N \cdot C_6H_3O_7N$: C, 45.9; H, 4.7; N, 16.5. Found : C, 45.9; H, 5.0; N, 16.8.

2-(Cyclohepten-1-yl)ethylamine (VIb)—Prepared from (Vb) in a like manner. Colorless liquid of $b.p_{18}$ 93.5~94.5°; yield 66%.

Picrate : Yellow pillars of m.p. 169~170° from MeOH-ether. *Anal.* Calcd. for $C_9H_{17}N \cdot C_6H_3O_7N_3$: C, 48.9; H, 5.5; N, 15.2. Found : C, 49.2; H, 5.6; N, 14.8.

1-(*p*-Methoxybenzyl)-9-hydroxy-1, 2, 3, 4, 8, 9-hexahydrocyclopentano[c]pyridine (VIIa) —The amine (VIa, 3 g.) in 130 cc. of water was adjusted to pH 3 by adding conc. HCl. To this solution was now added methyl β-(*p*-methoxyphenyl)-α,β-epoxypropionate (5.3 g.) and the mixture was heated on a boiling water bath for 48 hrs. with stirring. The filtrate from the dark resinous

substance was shaken with ether, the aq. layer was treated with charcoal and basified with conc. NaOH soultion. The base separated was taken up in AcOEt, dried over K_2CO_3, and evaporated. The residual solid was triturated with ether,furnishing colorless needles of m.p. 130~135°, which formed the crude (VIIa); yield 2.5 g. or 36%. Purified repeatedly from hydrous MeOH, forming colorless needles of m.p. 140~141°. *Anal.* Calcd. for $C_{16}H_{23}O_2N$: C, 73.6; H, 8.9; N, 5.3. Found: C, 73.2; H, 9.2; N, 5.6. Hydrochloride : Colorless long needles (from acetone-MeOH), m.p. 201~203°.

1-(*p*-Methoxybenzyl)-11-hydroxy-1,2,3,4,10,11-hexahydrocycloheptano[c]pyridine (VIIb)—The amine (VIb, 64 g.) in 2500 cc. of water was acidified with conc. HCl to pH 3 and to this mixture was added methyl β-(*p*-methoxyphenyl)-α,β-epoxypropionate (30 g.) and the whole was heated on a steam bath with stirring. In every 10 hrs., a 30-g. portion of the same ester was added until the total reaction time reached 120 hrs. The stirring was continued for additional 20 hrs. after the last addition of the ester. The product was now isolated as above, yielding 18 g. of the crude (VIIb) as colorless needles of m.p. 122~125°. Purified from hydrous MeOH, forming colorless needles of m.p. 130~133°. *Anal.* Calcd. for $C_{18}H_{27}O_2N$: C, 74.7; H, 9.4; N, 4.8. Found: C, 75.0; H, 9.2; N, 4.9.

Hydrogen oxalate : Colorless needles of m.p. 194~195° from EtOH. *Anal.* Calcd. for $C_{18}H_{27}O_2N \cdot C_2H_2O_4$: C, 63.3; H, 7.7; N, 3.7. Found : C, 63.2; H, 7.9; N, 3.7.

1-(*p*-Methoxybenzyl)-2-methyl-9-hydroxy-1, 2, 3, 4, 8, 9-hexahydrocyclopentano[c]pyridine (VIIIa)—The foregoing base (VIIa, 13 g.) was mixed with formic acid (130 cc. of 85%) and aq. formaldehyde (11 g. of 25%). The mixture was left standing for 2 hrs. and then heated on a steam bath for 12 hrs. Formic acid was now removed, the residue was dissolved in a small amount of water, and basified with NaOH solution. The base was extracted with ether, which was dried and evaporated. The oily residue distilled at 169~172°/0.03~0.04 mm. as a faint yellow syrup; 12 g.

Hydrochloride: Colorless pillars of m.p. 210~212° from MeOH-ether. *Anal.* Calcd. for $C_{17}H_{25}O_2N \cdot HCl$: C, 64.5; H, 8.5; N, 4.5. Found : C, 64.6; H, 8.4; N, 4.6.

1-(*p*-Methoxybenzyl)-2-methyl-11-hydroxy-1, 2, 3, 4, 10, 11-hexahydrocycloheptano[c]pyridine (VIIIb)—(VIIb) was N-methylated as above. Yield 86% of a faint yellow viscous oil of $b.p_{0.04}$ 177~181°.

Hydrobromide : Colorless plates of m.p. 104~105° from MeOH-ether. *Anal.* Calcd. for $C_{19}H_{20}O_2N \cdot HBr$: C, 59.4; H, 7.9; N, 3.6. Found : C, 59.4; H, 7.8; N, 3.6.

3-Hydroxy-N-methyl-"C"-normorphinan (III)—The hydrochloride (12 g.) of the afore-said base (VIIIa) was refluxed with HBr (120 cc. of 48%) for 24 hrs., giving clear, faint red solution, from which HBr was evaporated *in vacuo*. A reddish purple syrupy residue was dissolved in MeOH(25 cc.), which solution was poured onto crashed ice (ca. 50 cc.), basified with ammonia, and the base liberated was collected in AcOEt, dried, and evaporated. The reddish residue obtained was triturated with a little acetone, separating crystalline solid, which was filtered, washed with EtOH, furnishing faint yellow thin pillars of m.p. 235~240°(decomp.); yield, 2.35 g. or 25%. Purified from MeOH (decolorizing charcoal), forming colorless pillars of m.p. 239.5~240°(decomp.). *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 79.0; H, 8.7; N, 5.8. Found : C, 78.6; H, 8.6; N, 5.4.

3-Hydroxy-N-methyl-"C"-homomorphinan (IV)—The base (VIIIb, 5 g.) was refluxed with HBr (50 cc. of 48%) for 40 hrs. and then worked up as above. (IV) forms colorless pillars of m p. 244~246°(decomp.); yield 1.1 g. or 25%. *Anal.* Calcd. for $C_{18}H_{24}ON$: C, 79.7; H, 9.3; N, 5.2. Found: C, 79.7; H, 9.2; N, 5.2.

Picrate : Yellow needles, m.p. 118~120°, from EtOH. *Anal.* Calcd. for $C_{18}H_{24}ON \cdot C_6H_3O_7N_3$: C, 57.6; H, 5.6; N, 11.2 : Found : C, 57.1; H, 6.0; N, 11.1.

1-(*p*-Hydroxybenzyl)-2-methyl-1, 2, 3, 4-tetrahydrocyclopentano[c]pyridine (IX)—The hydrochloride (1.2 g) of the compound (VIIIa) was mixed with HBr (12 cc. of 48%) and the whole was refluxed for 30 mins. The reaction product was then added to ca. 20 g. of crushed ice, basified with ammonia, the base separated was extracted with AcOEt, dried, and evaporated. The reddish syrupy residue was triturated with a little acetone, separating crystalline solid which was purified from hydrous EtOH, forming colorless pillars of m.p. 222~224° from MeOH-ether.

Hydrobromide : Colorless plates from MeOH-ether, m.p. 201~202°. *Anal.* Calcd. for $C_{16}H_{21}ON \cdot HBr$: C, 59.3; H, 6.9; N, 4.3. Found : C, 59.6; H, 6.6; N, 4.5.

1-(*p*-Methoxybenzyl)-2-acetyl-9-hydroxy-1,2, 3, 4, 8, 9-hexahydrocyclopentano[c]pyridine (X)—A mixture of the hydroxy-base (VIIIa, 5 g.), Ac_2O (30 cc.), and pyridine (2 cc.) was heated on a steam bath for 5 hrs. Excess Ac_2O was removed *in vacuo*, the residue, mixed with water, was allowed to stand overnight to decompose the remaining Ac_2O, and was then extracted with AcOEt, which was washed successively with dil. HCl, $KHCO_3$ solution, and, water, dried, and evaporated. The residue (5.6 g.), when mixed with 10 cc. of ether, gave colorless crystalline solid of m.p. 125~130°, the crude (X); yield, 2 g. or 34%. Purified from ligroine-benzene, this formed colorless needles of m.p. 132~134°. *Anal.* Calcd. for $C_{18}H_{25}O_3N$: C, 71.3; H, 8.3; N, 4.6. Found : C, 70.9; H, 8.4; N, 4.6.

From the ethereal mother liquor of (X), the solvent was removed, furnishing a liquid, which is probably O-acetate (XI) of (X), judging from the result of its reduction by means of $LiAlH_4$; yield 3 g. or 45%.

1-(*p*-Methyoxybenzyl)-2-ethyl-9-hydroxy-1,2,3,4,8,9-hexahydrocyclopentano[c]pyridine (XII)—The foregoing compound (X, 1.7 g.) in tetrahydrofurane (10 cc.) was added slowly to a solution of $LiAlH_4$(0,8 g.) in ether (50 cc.) with cooling and the whole was then refluxed for 6 hrs. The required amount of water was now added and boiled for 30 mins. The filtrate from inorganic salts was dried over NaOH, and then mixed with the theoretical amount of 30% EtOH-HCl, separating syrupy (XIV)·HCl on the bottom. The supernatant layer was discarded and the residue was triturated with acetone, giving a solid substance, which was now purified from EtOH-ether, forming colorless needles of m.p. 181~183°; yield, 1.5 g. or 82% of (XII)·HCl. *Anal.* Calcd. for $C_{18}H_{27}O_2N$·HCl : C, 66.3; H, 8.7; N, 4.4. Found : C, 65.9; H, 8.7; N, 4.7.

The same compound (XII)·HCl was obtained from (XI) in a like manner; yield, 85%.

1-(*p*-Hydroxybenzyl)-2-ethyl-1,2,3,4-tetrahydrocyclopentano[c]pyridine (XIII)—The hydrochloride (3 g.) of the base (XII) was refluxed with HBr (30 cc. of 48%) for 30 mins. On working up the reaction product properly as in the homologous case, (XIII) was obtained as colorless needles of m.p. 116~117°; yield, 1.9 g. of 81%. *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.4; H, 9.0; N, 5.5. Found: C, 79.4; H, 9.0; N, 5.4.

Hydrobromide : Colorless pillars from EtOH, m.p. 197~199°. *Anal.* Calcd. for $C_{17}H_{23}ON$·HBr: C, 60.3; H, 7·2; N, 4.1. Found : C, 60.2; H, 7.5; N, 4.3.

3-Hydroxy-N-ethyl-"C"-normorphinan (XIV)—The hydrochloride (18 g.) of the base (XII) was refluxed with HBr (180 cc. of 48%) for 32 hrs. and was worked up as in the homologous case. The crude (XIV) was obtained as colorless pillars of m.p. 215~220°(decomp.); yield, 5 g.or 35%. Purified from MeOH, forming colorless pillars of m.p. 228~229°(decomp.); yield, 4 g. or 28%. *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.4; H, 9.0; N, 5.5. Found : C, 79.1; H, 8.9; N, 5.3.

Hydrochloride : Colorless pillars of m.p. 263~265° from MeOH-ether. *Anal.* Calcd. for $C_{17}H_{23}ON$·HCl : C, 69.5; H, 8.3; N, 4.8. Found : C, 69.5; H, 8.2; N, 4.5.

Summary

For pharmacological evaluation, 3-hydroxy-N-methyl-"C"-normorphinan, 3-hydroxy-N-ethyl-"C"-normorphinan, and 3-hydroxy-N-methyl-"C"-homomorphinan were prepared after the Henecka's method. The former two compounds are devoid of analgesic activity, whereas the latter manifests a strong physiological activity comparable with morphine, but was found to be about three times as toxic as the natural base.

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