# Synthesis of *N*-Substituted *C*-Normorphinans and Their Pharmacological Properties

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**Several *N*-substituted *C*-normorphinans (VIII and IX) were synthesized and tested for their analgetic and narcotic antagonist activities and physical dependence capacity. Treatment of *N*-formyl-octahydro-2-pyrindine (IIIc) with polyphosphoric acid readily gave *N*-formyl-*C*-normorphinan (IV). The *N*-nor bases (V and VII) obtained from IV were converted to VIII and IX. The *N*-methyl derivative (I), which was previously reported to be inactive by Haffner's method, exhibited potent analgetic activity by the hot plate method and the AcOH-induced writhing test. Compounds VIII and IX showed pharmacological properties similar to those of *N*-substituted morphinans and exhibited agonist (analgetic) and/or narcotic antagonist activities. The *C*-nor analogue (IXa) of cyclorphan (IIc) exhibited potent analgetic and antagonist activities with no physical dependence capacity in the single-dose suppression tests both in rats and monkeys.**

**Keywords** morphinan; *C*-normorphinan; cyclization; analgetic activity; narcotic antagonist activity; physical dependence capacity

In 1956, Sugasawa and Saito[3)] reported the synthesis of 3-hydroxy-*N*-methyl-*C*-normorphinan[4)] (I) in which the 6-membered *C*-ring of morphinan is replaced by a 5-membered ring. When tested by Haffner's method, I exhibited no appreciable analgetic activity.[5)] The appropriate *N*-substitution in the morphinan series produced levallorphan (IIb),[6,7)] a narcotic antagonist, and cyclorphan (IIc),[7,8)] a compound with mixed properties of agonist (analgetic) and antagonist actions. Therefore, it seemed of interest to explore *C*-normorphinan derivatives bearing various *N*-substituents. In this paper, we describe the synthesis and pharmacological properties of various *N*-substituted *C*-normorphinans (VIII and IX).

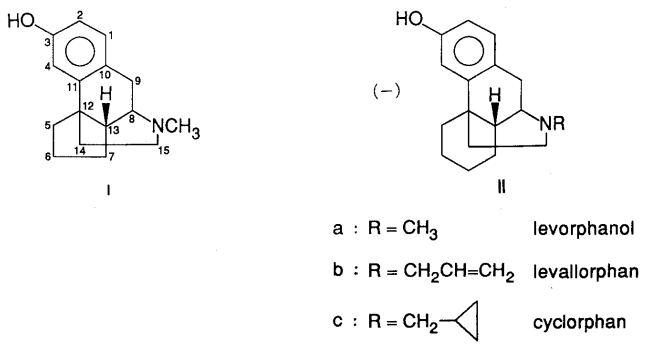



Chart 1

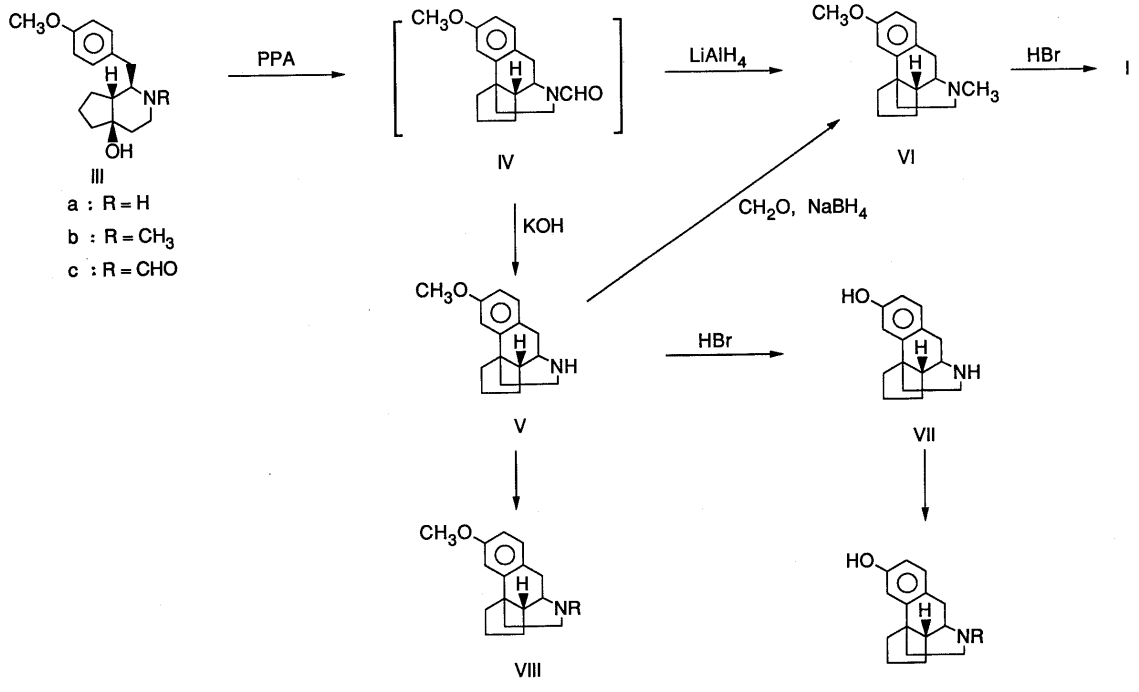



Chart 2

Dedicated to the memory of Prof. Shigehiko Sugasawa.

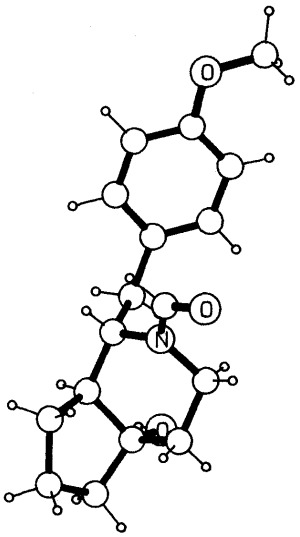


Fig. 1. Parallel View of IIIc

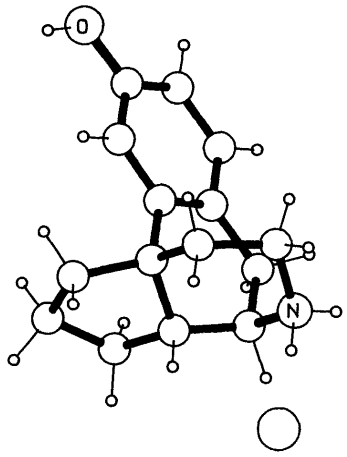


Fig. 2. Parallel View of VII·HCl

**Chemistry** Sugasawa and Saito[3] obtained I by the prolonged refluxing (24 h) of a *N*-methyl-octahydro-2-pyrindine derivative (IIIb) with 48% HBr through dehydration and cyclization in only a 25% yield. Protiva[9] reported the failure of cyclizing the demethoxy analogue of IIIb by heating in conc. $H_3PO_4$.

In recent years, Grewe type cyclization to morphinan has been reported to proceed much more easily by replacing the *N*-methyl group of the precursor with an *N*-acyl group.[10] Therefore, by treatment with formic acid and dicyclohexylcarbodiimide (DCC), IIIa[3] was converted to the *N*-formyl derivative (IIIc) in 98% yield. The relative stereochemistry of IIIc was determined by X-ray crystallographic analysis (Fig. 1). Treatment of IIIc with polyphosphoric acid (PPA) at 70—75 °C for 15 h, followed by alkaline hydrolysis of the resulting *N*-formyl derivative (IV), gave 3-methoxy-*C*-normorphinan (V) in 58.3% yield.

Treatment of V with formalin and $NaBH_4$ gave the *N*-methyl derivative (VI). Lithium aluminum hydride (LAH) reduction of the crude *N*-formyl derivative (IV) also gave VI. *O*-Demethylation of VI with 48% HBr gave I, which proved to be identical to an authentic specimen.[3] *O*-Demethylation of V with 48% HBr gave the 3-hydroxy-*N*-nor compound (VII), whose structure was unequivocally confirmed by X-ray crystallographic analysis of its hydrochloride (Fig. 2). The proton nuclear magnetic resonance ($^1$H-NMR) spectra of *C*-normorphinans (Experimental) were quite similar to those reported for morphinan derivatives.[11] The *C*-normorphinans with various *N*-substituents (VIII and IX) were synthesized from V and VII by *N*-alkylation (method A) or *N*-acylation followed by LAH reduction (method B) in the usual manner, and are listed in Table II.

TABLE I. Crystal Data of IIIc and VII·HCl

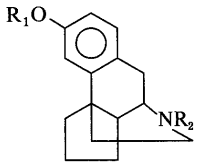
| | IIIc | VII·HCl |
|---|---|---|
| Crystal system | Monoclinic | Monoclinic |
| Space group | $P_c$ | $P2_1/a$ |
| $a$ (Å) | 6.420 (1) | 19.681 (2) |
| $b$ (Å) | 9.960 (1) | 7.004 (1) |
| $c$ (Å) | 12.926 (2) | 11.955 (1) |
| $\beta$ (°) | 106.81 (1) | 103.69 (1) |
| Volume (Å$^3$) | 791.2 (2) | 1601.3 (3) |
| $Z$ | 2 | 4 |
| $D_c$ (g/cm$^3$) | 1.214 | 1.293 |
| No. of unique reflections | 1184 | 2378 |
| No. of reliable reflections $\lvert F_O\rvert \geqq 2.67\sigma(\lvert F_O\rvert)$ | 1171 | 2213 |
| Final $R$ volume | 0.035 | 0.068 |

**Pharmacology** The *N*-substituted *C*-normorphinans prepared in the present study were tested[12] for their analgetic activity by the hot plate method, Haffner's method, and the AcOH-induced writhing test. These results and acute (24 h) toxicities are listed in Table III. Some selected compounds were tested for their narcotic antagonist activity by measuring the inhibition of morphine-induced analgesia in mice[12] and their physical dependence capacity (PDC) in rats.[13] PDC and antagonist potencies obtained from the Rhesus monkey[14] are also included in Table III.

In accordance with previous observations,[5] no appreciable analgetic activity of the *N*-methyl derivative (I) was detected by Haffner's method. However, when tested by the hot plate method, I was about three times as active as morphine in spite of its being a racemic modification. The potent activity of I was also shown in the AcOH-induced writhing test. In contrast to the high PDC observed[15] for levorphanol (IIa) and its racemate, the *C*-nor derivative (I) produced no PDC in the Rhesus monkey. In rats, however, I exhibited intermediate PDC.

In general, the structure–activity relationships of the *N*-substituted *C*-normorphinans were found to be quite similar to those reported for the morphinan series.[16] The 3-hydroxy derivatives invariably showed stronger analgetic activity than the corresponding 3-methoxy relatives. The changes in the alkyl substituent on nitrogen from Me to Et, Pr, and Bu greatly reduced the analgetic activity seen in I. A further lengthening of the chain ($C_5H_{11}$ and $C_6H_{13}$) again produced the active compounds (IXi and IXj). The short, straight-chain *N*-alkenyl and *N*-alkynyl compounds (IXc and IXd) showed no analgetic action, but produced strong narcotic antagonist activity comparable to nalorphine or levallorphan. Compound IXe, with a longer alkenyl chain, showed this action to a small extent while analgetic activity was again evident. The *N*-cyclopropyl-

TABLE II. *N*-Substituted *C*-Normorphinans




| Compound No. | $R_1$ | $R_2$ | Yield[a] (%) (Method)[b] | Salt | mp (°C) (Recrystn solvent)[c] | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N |
| VIIIa | Me | $CH_2$-cyclopropyl | 80 (B) | HCl | 180—182 (A) | $C_{20}H_{28}ClNO$ | 71.94 (71.48) | 8.45 8.30 | 4.20 4.17) |
| VIIIb | Me | $CH_2CH=CMe_2$ | 65 (A) | Ox[d] | 181—183 (A–B–C) | $C_{23}H_{31}NO_5$ | 68.80 (68.91) | 7.78 7.87 | 3.49 3.51) |
| IXa | H | $CH_2$-cyclopropyl | 67 (B) | HBr | 190—192 (A) | $C_{19}H_{26}BrNO$ | 62.63 (62.48) | 7.19 7.13 | 3.85 3.70) |
| IXb | H | $CH_2$-cyclobutyl | 66 (B) | HCl | 135—143 (C–D) | $C_{20}H_{28}ClNO \cdot H_2O$ | 68.26 (67.79) | 8.59 8.47 | 3.98 3.80) |
| IXc | H | $CH_2CH=CH_2$ | 78 (A) | HCl | 223—225 (A–B–C) | $C_{18}H_{24}ClNO$ | 70.69 (70.40) | 7.91 7.78 | 4.58 4.50) |
| IXd | H | $CH_2C\equiv CH$ | 53 (A) | HCl | 209—211 (D) | $C_{18}H_{22}ClNO \cdot 0.5H_2O$ | 69.09 (69.10) | 7.14 7.41 | 4.39 4.48) |
| IXe | H | $CH_2CH=CMe_2$ | 69 (A) | HCl | 185—188 (A–C–D) | $C_{20}H_{28}ClNO$ | 71.94 (71.92) | 8.45 8.57 | 4.20 4.16) |
| IXf | H | Et | 70 (A) | HCl | 260—263[e] (A–B–C) | | | | |
| IXg | H | Pr | 92 (A) | HCl | 255—258 (A–B–C) | $C_{18}H_{26}ClNO$ | 70.22 (70.21) | 8.51 8.66 | 4.55 4.47) |
| IXh | H | Bu | 82 (A) | HCl | 125—156 (A–B–C) | $C_{19}H_{28}ClNO \cdot Me_2CO$ | 69.54 (69.81) | 9.02 9.20 | 3.68 3.84) |
| IXi | H | $C_5H_{11}$ | 80 (A) | HCl | 225—226 (A–B–C) | $C_{20}H_{30}ClNO$ | 71.51 (71.19) | 9.00 8.91 | 4.17 4.15) |
| IXj | H | $C_6H_{13}$ | 70 (A) | HBr | 177—180 (A–C) | $C_{21}H_{32}BrNO$ | 63.95 (64.13) | 8.18 8.07 | 3.55 3.53) |
| IXk | H | $CH_2$-2-t[f] | 63 (B) | HBr | 162–165 (A–C) | $C_{20}H_{24}BrNOS \cdot H_2O$ | 56.60 (56.91) | 6.18 6.01 | 3.30 3.36) |
| IXl | H | $CH_2$-2-f[g] | 77 (A) | HCl | 243—245 (B–C) | $C_{20}H_{24}ClNO_2$ | 69.45 (69.13) | 6.99 7.17 | 4.05 3.97) |
| IXm | H | $CH_2$-cyclopropyl(Me) | 78 (B) | HCl | 260—262 (A–C–E) | $C_{20}H_{28}ClNO$ | 71.94 (71.81) | 8.45 8.32 | 4.20 4.22) |
| IXn | H | $CH_2$-cyclopropyl(Ph) | 51 (B) | Pic[h] | 240—243 (B–F) | $C_{31}H_{32}N_4O_8$ | 63.25 (63.31) | 5.48 5.46 | 9.52 9.45) |

*a*) Not optimized. *b*) A=method A, B=method B. *c*) A=$Me_2CO$, B=EtOH, C=$Et_2O$, D=iso-PrOH, E=MeOH, F=DMF. *d*) Oxalate. *e*) Lit.,[3] mp 263—265 °C. *f*) t=thienyl. *g*) f=furyl. *h*) Picrate.

methyl derivative (IXa), the *C*-nor analogue of cyclorphan, showed potent analgetic and antagonist activities. No PDC was observed in either rats or monkeys. Similar profiles were seen in the analogous compounds (VIIIa and IXm). In contrast, the cyclobutyl analogue (IXb), the most potent analgetic compound in this series, was devoid of antagonist action with high PDC. The 2-thienylmethyl and 2-furylmethyl substitution[17] (IXk and IXl) conferred potent antagonist action with no appreciable agonist activity. The *N*-substituent of IXn may be regarded as a "hybrid" of phenethyl and cyclopropylmethyl groups, and was expected to display both agonist and antagonist actions. Compound IXn, however, showed only analgetic activity with high PDC.

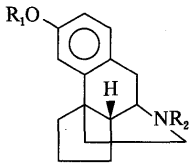
In view of the well-balanced analgetic and antagonist actions with no PDC in the signle-dose suppression tests, IXa was selected for further evaluation of its abuse potential. In the primary physical dependence study in the Rhesus monkey, however, IXa proved to produce low PDC after chronic administration for 44 d.[18]

## Experimental

All the melting points were uncorrected. Infrared (IR) spectra were taken with a Hitachi IR-215 or an Analect FX-6200 FT-IR spectrophotometer. NMR spectra were recorded with a Hitachi R-90H, a JEOL INM-FX-200 or a JEOL JNM-GSX-400 spectrometer. Chemical shifts are given as $\delta$ values from tetramethylsilane as an internal standard. The following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Electron impact-mass spectra (EI-MS) were recorded with a Hitachi RMU-6 or a JEOL JMS-HX 100 mass spectrometer. Microanalyses were performed on a Perkin-Elmer 240B C, H, N analyzer and Yokokawa IC-100 ion chromatographic analyzer. Organic extracts were dried over $Na_2SO_4$, and all evaporations were carried out *in vacuo*.

**(1α,4aα,7aα)-2-Formyl-(2,3,4,4a,5,6,7,7a)-octahydro-4a-hydroxy-1-(4-methoxybenzyl)-1*H*-2-pyrindine (IIIc)** Formic acid (5.28 g, 0.115 mol) was added dropwise to a stirred solution of IIIa[3] (20 g, 0.0766 mol) and DCC (23.5 g, 0.115 mol) in $CH_2Cl_2$ (500 ml) under ice-cooling. Stirring was continued for 1.5 h and the precipitated solid was filtered off. The filtrate was evaporated and the residue was recrystallized from AcOEt to give 21.6 g (97.6%) of IIIc, mp 157—159 °C as pillars. MS *m/z*: 289 ($M^+$),

TABLE III. Pharmacological Properties of *C*-Normorphinans




| Compound No. | $R_1$ | $R_2$ | Analgetic activity $ED_{50}$ (mg/kg, s.c.) (Confidence interval (95%)) H.P.[a] | Haf.[b] | Wri.[c] | Antagonist activity Mouse[d] ($AD_{50}$, mg/kg, s.c.) | Monkey[e] | $LD_{50}$[f] (mg/kg, s.c.) | PDC[g] (Single dose suppression test) Rat[h] | Monkey[e] (mg/kg) |
|---|---|---|---|---|---|---|---|---|---|---|
| I[i] | H | Me | 1.6 (1.1—2.4) | >15 | 0.59 (0.41—0.83) | — | No | 104.8 | Intermediate | None (0.5—2.0) |
| V[i] | Me | H | >22.5 | >22.5 | | | | >100 | | |
| VI[i] | Me | Me | 4.9 (3.2—7.6) | >10 | 3.0 (1.6—5.4) | — | No | 81.6 | Low | None (1.0—4.0) |
| VII[i] | H | H | >22.5 | | >22.5 | | | | >100 | |
| VIIIa[i] | Me | $CH_2$-cyclopropyl | 3.7 (1.6—8.6) | >22.5 | 1.0 (0.6—1.7) | +++ | | 123.1 | None | |
| VIIIb[j] | Me | $CH_2CH=CMe_2$ | >22.5 | | *ca.* 22.5 | + | | >100 | High | |
| IXa[k] | H | $CH_2$-cyclopropyl | 2.0 (1.1—3.4) | >22.5 | 0.12 (0.065—0.2) | +++ | Yes[n] | 122.4 | None | None (0.2) |
| IXb[i] | H | $CH_2$-cyclobutyl | 0.51 (0.3—0.88) | 0.39 (0.16—0.97) | 0.08 (0.004—0.133) | — | No | 132.7 | Intermediate | High (0.1—0.4) |
| IXc[i] | H | $CH_2CH=CH_2$ | >4.5 | | >4.5 | +++ (0.086) | Yes[o] | 123.1 | | None (0.5) |
| IXd[i] | H | $CH_2C\equiv CH$ | >22.5 | | >22.5 | +++ (0.062) | Yes[p] | 234.3 | | None (1.0) |
| IXe[i] | H | $CH_2CH=CMe_2$ | 4.5 (3.4—6.0) | >22.5 | 1.4 (0.7—2.5) | + | No | 144.8 | Intermediate | None (0.5—0.8) |
| IXf[i] | H | Et | >10 | | >10 | | | | >30 | |
| IXg[i] | H | Pr | 17.2 (10.0—29.5) | >22.5 | >22.5 | +++ (0.22) | | 123.1 | | |
| IXh[i] | H | Bu | *ca.* 22.5 | | 7.7 (4.4—13.6) | | | 123.1 | | |
| IXi[i] | H | $C_5H_{11}$ | 2.9 (2.0—4.3) | 2.6 (1.8—4.0) | 0.7 (0.6—0.9) | — | | 97.2 | High | |
| IXj[k] | H | $C_6H_{13}$ | 2.7 (1.9—3.8) | 4.0 (2.7—6.0) | 1.1 (0.82—1.52) | — | | 156.2 | Intermediate | |
| IXk[k] | H | $CH_2$-2-t[q] | >22.5 | | >22.5 | +++ (0.2) | | >225 | | |
| IXl[i] | H | $CH_2$-2-f[r] | >22.5 | | >22.5 | +++ (0.094) | | 234.3 | | |
| IXm[i] | H | $CH_2$-cyclopropyl-Me | 1.4 (0.9—2.0) | >10 | 0.12 (0.07—0.21) | +++ | | 125.6 | None | |
| IXn[l] | H | $CH_2$-cyclopropyl-Ph | 16.6 (11.1—24.9) | >22.5 | 6.8 (1.1—41.4) | — | | 169.4 | High | |
| Morphine[i] | | | 4.5 (3.8—5.3) | 6.5 (4.2—9.1) | 0.8 (0.6—1.1) | — | | 407.0 | High | |
| Codeine[m] | | | 24.3 (19.1—31.0) | 25.4 (14.7—41.8) | 9.5 (7.4—12.1) | — | | 231.2 | Intermediate | |
| Nalorphine[i] | | | >100 | >100 | 4.5 (1.8—11.1) | +++ (0.078) | | *ca.* 670 | None | |
| Levallorphan[i] | | | >22.5 | >22.5 | >22.5 | +++ (0.04) | | | | |
| Pentazocine[i] | | | 14.5 (8.3—23.6) | >100 | 4.5 (3.2—6.4) | ++ (6.0) | | 190.1 | Low | |

*a*) Hot plate method. *b*) Haffner's method. *c*) AcOH-induced writhing test. Six male mice were used in each test (a—c). For methodology, see reference 12. *d*) Antagonism of morphine-induced analgesia. Six male mice were used. For methodology, see reference 12. *e*) See reference 14. *f*) Tested in six male mice. *g*) Physical dependence capacity obtained by single-dose suppression tests. *h*) Ten rats were used. See reference 13. *i*) Hydrochloride. *j*) Oxalate. *k*) Hydrobromide. *l*) Free base dissolved in diluted HCl. *m*) Phosphate. *n*) From 0.025 to 0.2 mg/kg. Somewhat more potent and longer acting than nalorphine. *o*) From 0.03 to 0.5 mg/kg, with a shorter duration of action than nalorphine. *p*) From 0.008 to 1 mg/kg. More potent than nalorphine. *q*) t=thienyl. *r*) f=furyl.

271, 226, 168, 150, 121, 95. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1640 (C=O), 3380 (OH). $^1$H-NMR ($CDCl_3$) $\delta$: 1.20—1.90 (9H, m, C–$CH_2$–C and OH), 2.04 (1H, m, C–CH–C), 2.82—3.48 (4H, m, $PhCH_2$ and $NCH_2$), 3.77 (3H, s, $OCH_3$), 4.20 (1H, m, NCH), 6.82 (2H, d, $J$=8.8 Hz, aromatic protons *ortho* to $OCH_3$), 7.02 (2H, d, $J$=8.8 Hz, aromatic protons *meta* to $OCH_3$), 7.53 and 8.07 (1H, s, CHO). *Anal.* Calcd for $C_{17}H_{23}NO$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.19; H, 8.07; N, 4.94.

**3-Methoxy-*C*-normorphinan (V) Hydrochloride** A mixture of IIIc

(21.3 g, 0.0737 mol) and PPA (250 g) was stirred and heated at 70—75 °C under $N_2$ atmosphere for 15 h. The mixture was decomposed by the addition of ice–$H_2O$, extracted with $CHCl_3$, and washed with $H_2O$ and saturated aqueous $NaHCO_3$. Evaporation of the dried extracts left 25 g of a brown oil. A small portion of this oil was purified by $SiO_2$ chromatography ($CHCl_3$) to give *N*-formyl-3-methoxy-*C*-normorphinan (IV) as an oil. MS *m/z*: 271 ($M^+$), 199, 85, 83. IR $\nu_{max}^{film}$ $cm^{-1}$: 1660 (C=O). A solution of the crude oil (24 g) described above in MeOH (575 ml) and 10% aqueous NaOH (238 ml) was refluxed for 16 h and evaporated. The residue was diluted with $H_2O$ and extracted with $Et_2O$. The organic layer was extracted with 10% aqueous HCl, and the acidic layer was basified with 20% aqueous NaOH. The liberated oil was taken in $Et_2O$, dried, and evaporated. Distillation of the residue gave 12 g of a colorless oil, bp 135—140 °C (0.3 mmHg). Conversion to the HCl salt and recrystallization from $Me_2CO$–EtOH–$Et_2O$ gave 11.6 g (58.3% from IIIc) of V·HCl, mp 196—199 °C, as needles. MS *m/z*: 243 ($M^+$), 215, 198, 171, 122, 45. $^1$H-NMR ($D_2O$) $\delta$: 1.15—2.03 (8H, m, C–$CH_2$–C), 2.46—2.70 (2H, m, $C_{15}$–H), 3.03 (1H, d, $J$=19.54 Hz, $C_9\beta$-H), 3.38 (1H, dd, $J$=19.54, 5.86 Hz, $C_9$ $\alpha$-H), 3.17 (1H, m, $C_{13}$-H), 3.84 (3H, s, $OCH_3$), 4.18 (1H, m, $C_8$-H), 6.92 (1H, dd, $J$=2.93, 8.3 Hz, $C_2$-H), 7.08 (1H, d, $J$=2.93 Hz, $C_4$-H), 7.20 (1H, d, $J$=8.3 Hz, $C_1$-H). *Anal.* Calcd for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.68; H, 7.94; N, 5.02.

**3-Hydroxy-*C*-normorphinan (VII)** A mixture of V·HCl (6.8 g, 0.0243 mol) and 48% HBr (50 ml) was refluxed for 40 min and evaporated. The residue was dissolved in $H_2O$, made basic with conc. $NH_4OH$, and filtered to give 4.96 g (88.5%) of VII, mp 208—210 °C. Recrystallization from AcOEt gave prisms, mp 212—215 °C. MS *m/z*: 229 ($M^+$), 201, 184, 157, 45. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3290, 3280 (OH). $^1$H-NMR ($CDCl_3$–DMSO-$d_6$) $\delta$: 1.08—1.80 (8H, m, C–$CH_2$–C), 2.30—2.73 (3H, m, $C_{15}$–$H_2$ and $C_{13}$-H), 2.74 (1H, d, $J$=18.06 Hz, $C_9\beta$-H), 3.12 (1H, dd, $J$=18.06, 5.86 Hz, $C_9\alpha$-H), 3.43 (1H, m, $C_8$-H), 6.60 (1H, dd, $J$=8.30, 2.44 Hz, $C_2$-H), 6.78 (1H, d, $J$=2.44 Hz, $C_4$-H), 6.88 (1H, d, $J$=8.30 Hz, $C_1$-H). *Anal.* Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.29; H, 8.38; N, 6.01. The hydrochloride was recrystallized from EtOH–$Et_2O$ as needles, mp 259—262 °C. *Anal.* Calcd for $C_{15}H_{20}ClNO$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.43; H, 7.64; N, 5.08.

**3-Methoxy-*N*-methyl-*C*-normorphinan (VI) Hydrochloride** $NaBH_4$ (0.6 g, 0.016 mol) was added to a mixture of V (regenerated from 0.5 g (0.0018 mol) of the HCl salt), 37% formalin (0.8 ml), and MeOH (10 ml) under ice-cooling. The mixture was stirred at room temperature for 30 min, diluted with $H_2O$, and extracted with $Et_2O$. Evaporation of the dried extracts and conversion of the residue to the HCl salt gave, after recrystallization from $Me_2CO$–EtOH–$Et_2O$, 0.43 g (82%) of VI·HCl, mp 190—192 °C, as needles. MS *m/z*: 257 ($M^+$), 242, 229, 214, 199, 171, 136, 59. $^1$H-NMR ($D_2O$) $\delta$: 1.24—2.20 (m, 8H, C–$CH_2$–C), 2.58 (2H, m, $C_{15}$–$H_2$), 2.93 (3H, s, $NCH_3$), 3.18 (1H, m, $C_{13}$-H), 3.25 (2H, m, $C_9$–$H_2$), 3.84 (3H, s, $OCH_3$), 4.04 (1H, m, $C_8$-H), 6.92 (1H, dd, $J$=2.93, 8.30 Hz, $C_2$-H), 7.07 (1H, d, $J$=2.93 Hz, $C_4$-H), 7.22 (1H, d, $J$=8.3 Hz, $C_1$-H). *Anal.* Calcd for $C_{17}H_{24}ClNO\cdot0.5H_2O$: C, 67.42; H, 8.32; N, 4.63. Found: C, 67.08; H, 8.22; N, 4.40.

VI·HCl was also obtained by LAH reduction of the crude *N*-formyl derivative (IV) described above in 62% yield.

**3-Hydroxy-*N*-methyl-*C*-normorphinan (I) Hydrochloride** A mixture of VI·HCl (0.4 g, 0.0013 mol) and 48% HBr (8 ml) was refluxed for 30 min and evaporated. The residue was made basic with conc. $NH_4OH$ and extracted with $CHCl_3$. The dried extracts were evaporated, and the residue was digested with AcOEt and filtered to give 0.265 g (80%) of I, mp 236—238 °C. The recrystallized sample from MeOH had mp 238—239 °C. Lit.,[3] mp 239—240 °C. This proved to be identical with an authentic specimen[3] in every respect. The HCl salt was recrystallized from $Me_2CO$–EtOH–$Et_2O$ as needles, mp 192—194 °C. *Anal.* Calcd for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.92; N, 5.01. Found: C, 68.47; H, 7.96; N, 5.11.

**3-Hydroxy-*N*-cyclopropylmethyl-*C*-normorphinan (IXa) Hydrobromide (Method B)** Cyclopropancarbonyl chloride (1.35 g, 0.013 mol) was added dropwise to a stirred solution of VII (1 g, 0.00437 mol) and $Et_3N$ (8 ml) in *N*,*N*-dimethylformamide (DMF, 12 ml) under ice-cooling. The mixture was stirred at 25 °C for 3 h, diluted with $H_2O$ (30 ml), and extracted with $Et_2O$. The extracts were washed with $H_2O$, 10% aqueous HCl, and saturated $NaHCO_3$, successively. Evaporation of the dried extracts left 1.45 g of an oil. A mixture of this oil, LAH (1 g, 0.0263 mol), and tetrahydrofuran (THF, 30 ml) was refluxed for 3 h. The mixture was diluted with $Et_2O$, decomposed by the addition of $H_2O$ (1 ml), and filtered. Evaporation of the filtrate and conversion of the residue to the HBr salt gave, after recrystallization from $Me_2CO$, 1.06 g (67%) of IXa·HBr, mp 190—192 °C, as needles. Analytical data is given in Table II.

**3-Hydroxy-*N*-(3-methyl-2-butenyl)-*C*-normorphinan (IXe) Hydrochloride (Method A)** A mixture of VII (0.343 g, 0.0015 mol), 1-bromo-3-methyl-2-butene (0.24 g, 0.0016 mol), $NaHCO_3$ (0.25 g, 0.003 mol), and DMF (5 ml) was heated at 80—90 °C for 2 h and evaporated. The residue was diluted with $H_2O$ and extracted with $Et_2O$. Evaporation of the dried extracts and conversion of the residue to the HCl salt gave, after recrystallization from $Me_2CO$–iso-PrOH–$Et_2O$, 0.345 g (69%) of IXe·HCl, mp 185—188 °C. Analytical data is given in Table II.

The *N*-substituted *C*-normorphinans (VIII and IX) were similarly prepared from V and VII by method A or B and are listed in Table II.

**X-Ray Crystallographic Analysis** All data collection processing was carried out by AFC-5R (Rigaku) with Cu$K_\alpha$ radiation ($\lambda$=1.54184 Å). The scan range of the $2\theta$ volume was within 120° and the scan mode was the $\omega$–$2\theta$ scan technique. The structures were solved by a direct method using MULTAN and refined by the full matrix least-squares method. The calculation for the structure determinations was performed by a NEWS-3860 (Sony) computer. The crystal data is summarized in Table I.

**Pharmacological Tests** The *C*-normorphinans (VIII and IX) were tested for their analgetic activity after s.c. administration in mice by the hot plate method, Haffner's method, and the AcOH-induced writhing test using the reported procedures.[12] The narcotic antagonist activity was tested by measuring the inhibition of morphine-induced analgesia after s.c. administration in mice by the reported procedure.[12] The physical dependence capacity was assessed by the single-dose suppression test after s.c. administration in rat by the method reported previously.[13] The results are summarized in Table III.

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**References and Notes**

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