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ELIMINATION OF THE 4-HYDROXYL GROUP OF THE ALKALOIDS RELATED TO MORPHINE—IX

SYNTHESIS OF 3-METHOXY-N-METHYLISOMORPHINAN DERIVATIVES

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Abstract—Reduction of 3-methoxy-6-oxo-N-methylisomorphinan has been investigated. Methylation of the foregoing 6-oxo compound and 3-methoxy-6-oxo-N-methyl-Δ^7-isomorphinan gave the respective 6-methyl-6-hydroxyl compounds. Dehydration of the methylol derivative and the Wittig reaction of 6-oxo compound also has been investigated.

IN THE preceding paper[1] the synthesis of (−)-3-methoxy-6-oxo-N-methylisomorphinan (I) and (−)-3-methoxy-6-oxo-N-methyl-Δ^7-isomorphinan (II) from thebaine was described. The reduction of the 6-oxo group and the synthesis of 6-methyl derivatives in the isomeric morphinan series (B/C *cis*) have been reported.[2]

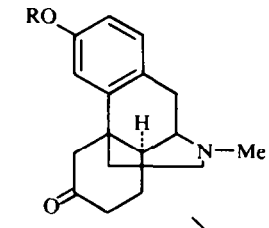
This report is concerned with similar reactions of the isomorphinan series (B/C *trans*). Catalytic hydrogenation of the compound I in acidic medium gave a 6-hydroxyl compound (III), m.p. 116–117°, together with a small amount of an epimeric alcohol (IV), m.p. 124–125° and sodium-alcohol reduction afforded the high melting alcohol IV in a yield of 50%.

The acetylation rate of these hydroxyl compounds and the NMR of the acetates showed that the structure of the low melting alcohol could be represented as 6β(*axial*)-hydroxy-3-methoxy-N-methylisomorphinan and that of the high melting alcohol as 6α(*equatorial*)-hydroxy-3-methoxy-N-methylisomorphinan. Contrary to these reductions, sodium borohydride reduction afforded a mixture of both compounds increasing the yield of IV. In connection with this work the reduction of (−)-3-hydroxy-6-oxo-N-methylisomorphinan (V) also has been investigated.

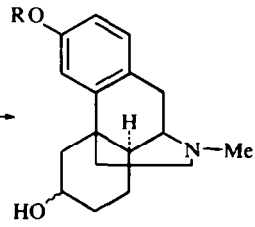
Catalytic hydrogenation of this compound in neutral medium gave, in a yield of 50%, (−)-3,6-dihydroxy-N-methylisomorphinan (VI), m.p. 228–230°, which was easily methylated to the 6β-hydroxy-3-methoxy derivative III with Rodinov's reagent.

Similarly the reduction of the α,β-unsaturated ketone II to unsaturated alcohols was tried, but failed. Sodium borohydride reduction gave a mixture of the saturated and unsaturated alcohols. Ponndorf reduction gave the desired unsaturated alcohols, the separation of which was quite difficult.

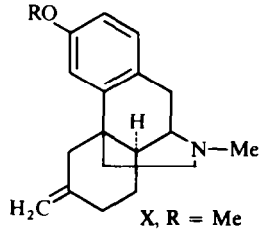
Methyllithium reagent converted I and II to the corresponding 6-hydroxy-6-methyl derivatives (VII and XII) in high yields. Although the orientation of the introducing group was not confirmed, it is expected that the orientation of these substituents is 6α-*equatorial* as the reagent usually attacks the molecule from the less hindered side, i.e. α-side.



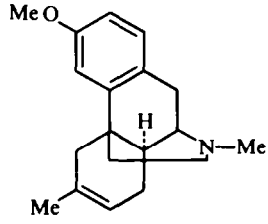
I. R = Me
V R = H



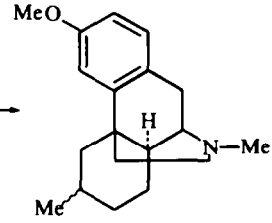
III. R = Me, 6β-OH
IV. R = Me, 6α-OH
VI. R = H, 6β-OH

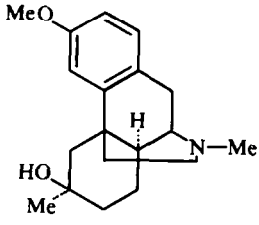


X, R = Me
XI, R = H

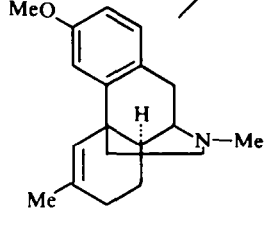


VIII

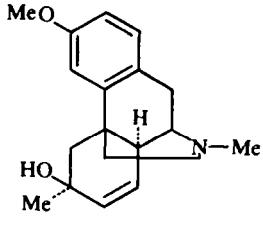




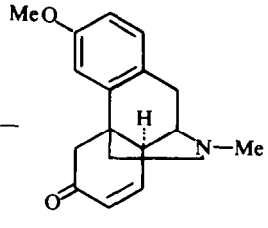
VII



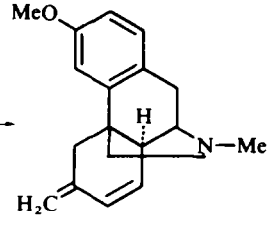
IX



XII



II



XIII

Dehydration of the methylol derivative VII was achieved by the action of perchloric acid in glacial acetic acid. A gas chromatogram of the crude product showed two peaks at retention times 10·25 and 11·0 min in a ratio of 67·7:32·3. Alumina chromatography and crystallization of the eluate obtained with n-hexane gave, in 49% yield, anhydro compound VIII, m.p. 73–74°, $[\alpha]_D$ + 26·2°. Further elution with benzene gave another anhydro compound IX, m.p. 60–62°, $[\alpha]_D$ − 40·8°, in 16% yield. In the NMR spectra the low melting substance shows a vinyl proton due to C_5-H at 4·01 τ and the high melting substance a vinyl proton due to C_7-H at 4·53 τ.

These facts suggest that the structure of the low melting substance is represented as 3-methoxy-6,N-dimethyl-Δ^5-isomorphinan and that the structure of the high melting substance as 3-methoxy-6,N-dimethyl-Δ^6-isomorphinan.

Dehydration with thionyl chloride was also studied. Similar separation of the products gave the Δ^5- and Δ^6-compounds in 29% and 34% yields, respectively.

The Wittig reaction of I, V and II affords the corresponding exo-methylene derivatives X, XI and XIII in good yields. The catalytic hydrogenation of VIII, IX and X gave a mixture of 6α- and 6β-methylisomorphinan derivatives, separation of which was quite difficult.

The pharmacological activity of these compounds will be reported elsewhere by R. Kido of this laboratory.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were obtained with the Nihon Bunko DS-201 recording spectrometer. NMR spectra were recorded in $CDCl_3$ unless otherwise stated and peaks were measured using TMS as an internal reference.

Reduction of (−)-3-*methoxy*-6-*oxo*-N-*methylisomorphinan* (I)

(*a*) *Catalytic hydrogenation.* A soln of 1 g (−)-3-methoxy-6-oxo-N-methylisomorphinan in 35 cc glacial AcOH was hydrogenated on 0·2 g Adams' catalyst. The residue from distillation of the solvent was dissolved into water, made basic with NH_4OH aq and extracted with ether. The crude base was converted to the picrate, m.p. 175–176° (dec). Repeated crystallization from MeOH gave 0·11 g (6·1%) the less soluble picrate, m.p. 209–210° (dec; sinterring at 200°) and 1·215 g (62%) the relatively soluble picrate, m.p. 174–176°. Liberation of the more soluble picrate and crystallization from ether gave 6β-hydroxyl compound III, m.p. 116–117°, $[\alpha]_D^{26}$ −47·7° ± 1° (*c*, 2·022, alc.). (Found: C, 75·87; H, 8·89; N, 4·81. $C_{18}H_{25}O_2N$ requires: C, 75·22; H, 8·77; N, 4·87%). The picrate, prepared from the above pure compound and crystallized from MeOH, m.p. 187–188° and sinterring at 184°. (Found: C, 55·95; H, 5·82; N, 10·82. $C_{18}H_{25}O_2N \cdot C_6H_3O_7N_3$ requires: C, 55·81; H, 5·46; N, 10·85%).

(*b*) *Na-alcohol reduction.* To a soln of 3·8 g (−)-3-methoxy-6-oxo-N-methylisomorphinan in 76 cc 99% alcohol 3·8 g metallic Na was added in thin slices and the mixture heated until the metallic Na had dissolved. The soln was diluted with water and the solvent removed by distillation under red. press. The crude product was several times extracted with ether, washed with water and dried. Crystallization of the crude product from ether gave 1·917 g 6α-hydroxyl compound IV, m.p. 124–126°, 50·2%. A small sample was recrystallized from the same solvent for analysis, m.p. 125–126°, $[\alpha]_D^{26}$ −54·3° ± 1° (*c*, 2·101, alc.). (Found: C, 75·22; H, 8·94; N, 4·81. $C_{18}H_{25}O_2N$ requires: C, 75·22; H, 8·77; N, 4·87%). The picrate, prepared in ether and crystallized from MeOH, m.p. 215–216° (dec, sinterring at 204°). (Found: C, 55·83; H, 5·76; N, 10·43. $C_{18}H_{25}O_2N \cdot C_6H_3O_7N_3$ requires: C, 55·81; H, 5·46; N, 10·85%).

(*c*) *Sodium borohydride reduction.* To a soln of 0·57 g (−)-3-methoxy-6-oxo-N-methylisomorphinan in 30 cc EtOH 0·15 g $NaBH_4$ was added at room temp and the soln allowed to stand for 3 hr under stirring. The residue from distillation of the solvent under red. press. was treated with water, made acidic with dil. HCl to decompose the excess reagent. The soln was made basic with dil. NH_4OH aq and extracted with benzene. The crude base was converted to the picrate, which was repeatedly crystallized from MeOH

to give 0·267 g (26·0%) the less soluble picrate, m.p. 213–214° (dec; sinterring at 205°) and 0·603 g (60%) the relatively soluble picrate, m.p. 177–178° (sinterring at 170°).

Acetylation of 6-hydroxy-3-methoxy-N-methylisomorphinan derivatives

(*a*) Compound IV (0·5 g) was heated with 5 cc Ac_2O on a water bath for 2 hr. The residue from distillation of the reagent was dissolved in water, made basic with dil NH_4OH aq and extracted with ether. The crude acetate was recrystallized from ether to give 0·526 g (72·0%) 6α-acetoxy-3-methoxy-N-methylisomorphinan, m.p. 141–142°, $[\alpha]_D^{21.5}$ −117·1° ± 2° (*c*, 0·996, 1% alc–chloroform); NMR 4·95 τ (C_6-H, multiplet) 7·95 τ (C_6-acetoxy). (Found: C, 72·60; H, 8·34; N, 4·36. $C_{20}H_{27}O_3N$ requires: C, 72·92; H, 8·26; N, 4·25%).

(*b*) Compound III (0·503 g) was acetylated (Ac_2O–pyridine). The crude acetate was recrystallized from ether to give 0·499 g (86·5%) 6β-acetoxy-3-methoxy-N-methylisomorphinan, m.p. 142–144°, $[\alpha]_D^{22}$ −48·4° ± 2° (*c*, 0·972, 1% alc–chloroform); NMR 4·78 τ (C_6-H, triplet) 7·95 τ (C_6-acetoxy). (Found: C, 72·93; H, 8·37; N, 4·26. $C_{20}H_{27}O_3N$ requires: C, 72·92; H, 8·26; N, 4·25%). The IR spectrum of this compound was not identical with that of the foregoing 6α-acetate, and the mixed m. p. with the epimeric acetate showed a depression.

Ponndorf reduction of the unsaturated ketone (II)

A soln of 6·562 g purified aluminium isopropoxide and 3·02 g (−)-3-methoxy-6-oxo-N-methyl-Δ^7-isomorphinan in 100 cc dry isopropanol was heated under stirring until the distillate no longer gave positive test for acetone. Most of the remaining isopropanol was removed by distillation under red. press. The residue was treated with excess 5% NaOH aq and extracted with ether. Distillation of the solvent gave 2·773 g a mixture of the crude unsaturated alcohols. Careful chromatography on alumina didn't give the desired compounds, and the mixture was reduced to the saturated alcohols without further purification. Conversion to the picrates followed by repeated recrystallization gave 2·239 g the picrate of 6α-alcohol IV and 1·113 g that of 6β-alcohol III.

Reduction of (−)-3-hydroxy-6-oxo-N-methylisomorphinan (V)

A soln of 1 g (−)-3-hydroxy-6-oxo-N-methylisomorphinan in 20 cc MeOH was catalytically reduced on 0·1 g Adams' catalyst. The crude base was treated with a small amount of EtOH to separate 0·504 g (50·2%) of the solvate of 3,6β-dihydroxy-N-methylisomorphinan, m.p. 228–230°. A small sample was recrystallized from EtOH for analysis, m.p. 228–230°, $[\alpha]_D^{23.5}$ −44·3° ± 2° (*c*, 1·031, alc.). (Found: C, 71·29; H, 9·04; N, 4·42. $C_{17}H_{23}O_2N \cdot C_2H_5OH$ requires: C, 71·44; H, 9·15; N, 4·39%).

The methylation of this compound with Rodinov's reagent gave (−)-6β-hydroxy-3-methoxy-N-methylisomorphinan, m.p. 112–114°.

The residue (0·335 g) from distillation of the EtOH did not crystallize on standing and was methylated with Rodinov's reagent. Conversion of the crude product to the picrate and repeated crystallization from MeOH gave the less soluble picrate, m.p. 217–218° (dec; sinterring at 213°) besides a small amount of the more soluble 6β-hydroxy-3-methoxy-N-methylisomorphinan picrate.

(−)-6-*Hydroxy*-3-*methoxy*-6,N-*dimethylisomorphinan* (VII)

A soln of 11·4 g (−)-3-methoxy-6-oxo-N-methylisomorphinan in 600 cc benzene was added dropwise to the MeLi reagent (prepared from 1·66 g metallic Li and 17 g MeI in ether) at 0– −5° and the soln was kept for 1 hr at 0–10° under stirring. Water (200 cc) was added to the soln. The benzene soln was washed with 1N NaOH and dried. The residue from distillation of the solvent was crystallized from benzene to give 10·97 g (91%) the 6-hydroxy-6-methyl compound, m.p. 144–145°, $[\alpha]_D^{25.5}$ −49·2° ± 1° (*c*, 2·066, alc). (Found: C, 75·52; H, 9·14; N, 4·61. $C_{19}H_{27}O_2N$ requires: C, 75·51; H, 9·03; N, 4·65%). The picrate, crystallized from alcohol, m.p. 214–215° (dec). (Found: C, 56·59; H, 6·01; N, 10·43. $C_{19}H_{27}O_2N \cdot C_6H_3O_7N_3$ requires: C, 56·60; H, 5·70; N, 10·56%).

(−)-6-*Hydroxy*-3-*methoxy*-6,N-*dimethyl*-Δ^7-*isomorphinan* (XII)

A soln of 2·854 g (−)-3-methoxy-6-oxo-N-methyl-Δ^7-isomorphinan in 160 cc benzene was added dropwise to the MeLi reagent (prepared from 0·453 g metallic Li and 4·35 g MeI in ether) and worked up as above. The oily product was crystallized from ether to give 2·3 g (77%) the desired Me compound, m.p. 122–124°, $[\alpha]_D^{23.5}$ −28·6° ± 2° (*c*, 1·078, alc). (Found: C, 76·64; H, 8·59; N, 4·66. $C_{19}H_{25}O_2N$ requires:

C, 76·22; H, 8·42; N, 4·68%). The picrate, crystallized from alcohol, m.p. 180–181° (dec). (Found: C, 56·67; H, 5·67; N, 10·35. $C_{19}H_{25}O_2N \cdot C_6H_3O_7N_3$ requires: C, 56·81; H, 5·34; N, 10·60%).

Dehydration of (−)-6-*hydroxy*-3-*methoxy*-6,N-*dimethylisomorphinan* (VII)

(*a*) *With* 60% *perchloric acid.* To a soln of 3·01 g the methylol derivative VII in 60 cc glacial AcOH 1·83 g 60% perchloric acid was added and the soln was heated on a water bath for 10 min under N_2. The soln was diluted with 60 cc ice-water, and made basic with NH_4OH aq. Extraction with benzene gave 3·004 g the crude anhydro compounds, whose gas chromatogram showed two peaks due to Δ^6- and Δ^5-compounds at retention times 10·25 and 11·0 min in a ratio of 67·7:32·3. The crude products were chromatographed on 85 g alumina. Elution with 0·8 l. n-hexane gave 1·365 g the crude Δ^6-compound, m.p. 69–73°, which was recrystallized from MeOH to give 1·030 g (+)-3-methoxy-6,N-dimethyl-Δ^6-isomorphinan, m.p. 73–74°, $[\alpha]_D^{27.5}$ + 26·2° ± 1° (*c*, 2·080, alc). (Found: C, 80·42; H, 9·01; N, 5·05. $C_{19}H_{25}ON$ requires: C, 80·52; H, 8·89; N, 4·95%). The gas chromatogram of this compound showed only one peak at retention time 10·25 min. In the NMR spectrum this compound showed a signal due to C_7-H at 4·53 τ. The picrate, crystallized from alcohol, m.p. 213–214° (dec). Elution with further 4 l. n-hexane gave 0·576 g the anhydro compounds which partly crystallized. These products were re-chromatographed later. Elution with 1·3 l. benzene gave 0·448 g oily product. Conversion to the picrate and recrystallization from MeOH gave 0·386 g the relatively pure picrate, m.p. 191·5–193°. Liberation of the picrate followed by distillation under red. press. (0·06 mm, 165–170° bath temp (gave 0·123 g Δ^5-isomorphinan derivative, m.p. 60–62° (sinterring at 57°), $[\alpha]_D^{27}$ −40·8° ± 1° (*c*, 2·145, alc). The gas chromatogram showed only one peak at retention time 11·0 min; NMR 4·02 τ (C_5-H). (Found: C, 80·62; H, 9·05; N, 5·32. $C_{19}H_{25}ON$ requires: C, 80·52; H, 8·89; N, 4·95%). The picrate, prepared from the pure base and crystallized from MeOH, m.p. 195–196°. (Found: C, 58·44; H, 5·62; N, 10·78. $C_{19}H_{25}ON \cdot C_6H_3O_7N_3$ requires: C, 58·58; H, 5·51; N, 10·93%). The residue from the filtrate of the Δ^6-compound and the second eluate were combined and re-chromatographed. Similar treatments as above gave further Δ^5- and Δ^6-compounds; total yield: 1·383 g (48·8%) (+)-3-methoxy-6,N-dimethyl-Δ^6-isomorphinan picrate and 0·809 g (15·8%) (−)-3-methoxy-6,N-dimethyl-Δ^5-isomorphinan picrate. Further elution with 0·6 l. 3% alc-benzene gave 0·358 g the crystalline product, which was recrystallized from n-hexane yielding 0·228 g the starting material, m.p. 142–143°.

(*b*) *Dehydration with thionyl chloride.* Thionyl chloride (4·76 g) was added dropwise under stirring to a soln of 6·028 g the methylol derivative in 120 cc pyridine and the soln was kept at 0– −5° for 20 min. The reaction mixture was diluted with 300 g ice-water and the excess pyridine was removed by distillation under red. press. Treatment as above gave 5·43 g the crude anhydro compounds. Similar treatments as above gave 1·664 g (29%) (−)-3-methoxy-6,N-dimethyl-Δ^5-isomorphinan and 1·957 g (34%) (+)-3-methoxy-6,N-dimethyl-Δ^6-isomorphinan.

(−)-3-*Methoxy*-6-*methylene*-N-*methylisomorphinan* (X)

A soln of 8·55 g (−)-3-methoxy-6-oxo-N-methylisomorphinan in 160 cc THF was added dropwise at −5–−2° to the Wittig reagent (prepared from 6·58 g bromobenzene, 0·54 metallic Li and 13·9 g triphenylmethylphosphoniumbromide in ether–THF). The ether was removed by the fractional distillation and the remaining soln was refluxed for 40 hr. The residue from distillation of the solvent was dissolved in chloroform, washed with 5% NaOH and then with water. Extraction with 10% phosphoric acid gave 9·05 g the basic substance which didn't crystallize on standing. The picrate, crystallized from EtOH, m.p. 182–183°. (Found: C, 58·59; H, 5·68; N, 10·65. $C_{19}H_{25}ON$ requires: C, 58·58; H, 5·51; N, 10·93%). The D-tartrate, crystallized from hot water, m.p. 86–88°, $[\alpha]_D^{23}$ −64·0° ± 1° (*c*, 2·045, alc). (Found: C, 58·83; H, 7·59; N, 3·05; H_2O, 8·27; $C_{19}H_{25}ON \cdot C_4H_6O_6 \cdot 2H_2O$ requires: C, 58·83; H, 7·51; N, 2·98; H_2O, 7·67%). The salicylate, crystallized from EtOH, m.p. 126–128° (sinterring at 117°), $[\alpha]_D^{24.5}$ −77·1° ± 2° (*c*, 1·018, alc). (Found: C, 72·61; H, 7·88; N, 3·25. $C_{19}H_{25}ON \cdot C_7H_6O_3 \cdot \frac{1}{2}C_2H_5OH$ requires: C, 72·94; H, 7·71; N, 3·15%).

(−)-3-*Hydroxy*-6-*methylene*-N-*methylisomorphinan* (XI)

A soln of 2·71 g (−)-3-hydroxy-6-oxo-N-methylisomorphinan in 120 cc THF was added dropwise to a soln of the Wittig reagent (prepared from 3·9 g bromobenzene, 0·35 g metallic Li and 8·93 g triphenylmethylphosphoniumbromide in ether–THF). The ether was removed by fractional distillation and the remaining soln was refluxed for 40 hr. Extraction with 5% phosphoric acid gave the crude 6-methylene phenol, which was converted to the salicylate, m.p. 194–208°. Recrystallization from EtOH gave 2·901 g

the pure salt, m.p. 271–218°, $[\alpha]_D^{25.5}$ −81·8° ± 2° (*c*, 1·068, alc). (Found: C, 72·43; H, 7·47; N, 3·23. $C_{18}H_{23}ON \cdot C_7H_6O_3 \cdot \frac{1}{2}C_2H_5OH$ requires: C, 72·53; H, 7·49; N, 3·25%). Liberation of the salt and crystallization from isopropanol gave the solvate of (−)-3-hydroxy-6-methylene-N-methylisomorphinan, m.p. 146·5–147·5°, $[\alpha]_D^{25.5}$ −131·8° ± 2° (*c*, 1·002, alc). (Found: C, 76·49; H, 9·42; N, 4·29. $C_{18}H_{23}ON \cdot C_3H_7OH$ requires: C, 76·55; H, 9·48; N, 4·25%). A small sample of the solvate was sublimed at 165° (4 mm) to give the free base, m.p. 146·5–147°, $[\alpha]_D^{23}$ −150·2° ± 1° (*c*, 2·151, alc). (Found: C, 79·82; H, 8·67; N, 5·09. $C_{18}H_{23}ON$ requires: C, 80·25; H, 8·61; N, 5·20%).

(−)-3-*Methoxy*-6-*methylene*-N-*methyl*-Δ^7-*isomorphinan* (XIII)

A soln of 8·50 g the unsaturated ketone II in 180 cc THF was added dropwise to the Wittig reagent (prepared from 6·12 g bromobenzene, 0·54 g metallic Li, and 13·95 g triphenylmethylphosphonium-bromide in THF) and the mixture worked up as above. The crude products were chromatographed on alumina and developed with benzene. Distillation of the solvent from the eluate followed by the crystallization from alcohol gave 5·136 g (56·5%) the desired conjugated methylene derivative, m.p. 128–129°, $[\alpha]_D^{27.5}$ −61·6° ± 2° (*c*, 1·057, alc). (Found: C, 81·27; H, 8·38; N, 5·02. $C_{19}H_{23}ON$ requires: C, 81·10; H, 8·21; N, 4·98%). The picrate, prepared in and crystallized from alcohol, m.p. 220–221°. (Found: C, 58·78; H, 5·22; N, 10·73: $C_{19}H_{23}ON \cdot C_6H_3O_7N_3$ requires: C, 58·82; H, 5·13; N, 10·98%).

3-*Methoxy*-6,N-*dimethylisomorphinan*

(*a*) *From* (−)-3-*methoxy*-6-*methylene*-N-*methylisomorphinan* (X). A soln of 4·25 g the 6-methylene compound in 210 cc 50% AcOH was hydrogenated on 0·425 g Adams' catalyst. The residue from distillation of the solvent was dissolved in water, made basic with NH_4OH aq and extracted with benzene. The crude bases were chromatographed on alumina and developed with benzene. The gas chromatogram of the eluate showed two peaks at retention times 7·8 and 9·0 min in a ratio of 44:56.

(*b*) *From* (−)-3-*methoxy*-6,N-*dimethyl*-Δ^5-*isomorphinan* (IX). Hydrogenation of the Δ^5-isomorphinan derivative in 50% AcOH gave a mixture of two Me derivatives, whose gas chromatogram showed two peaks at the same retention times as above in a ratio of 51:49.

(*c*) *From* (+)-3-*methoxy*-6,N-*dimethyl*-Δ^6-*isomorphinan* (VIII). Hydrogenation of the Δ^6-isomorphinan derivative was carried out on Adams' catalyst in 50% AcOH acid. The gas chromatogram of the crude products showed two peaks in a ratio of 30:70 at the same retention times as above.

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