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

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Abstract—(−)-3-methoxy-6-oxo-N-methylmorphinan and (−)-3-methoxy-6-oxo-N-methyl-Δ^7-morphinan were converted to the corresponding 6-hydroxyl-6-methyl derivatives by the action of methyllithium. Dehydration of these products was studied. Hydrogenation of the anhydro compounds yielded the saturated 6α- and 6β-methylmorphinan derivatives, from which 3-hydroxyl-6-methyl derivatives were obtained.

IN THE morphine series it is well known that elimination of the 6-hydroxyl group increases the analgesic activity and that introduction of a methyl group at C_6 gives similar results.

Accordingly, it was expected that it would be of interest to try these effects on (−)-3-methoxy-6-oxo-N-methylmorphinan (desoxydihydrothebainone; I). In the previous paper,[1] the synthesis of the foregoing compound from thebaine was described. The present report is concerned with the preparation of 3-methoxy-6,N-dimethylmorphinans and their derivatives.

(−)-3-Methoxy-6-oxo-N-methylmorphinan (I) was treated with methyllithium in benzene to yield (−)-6-hydroxy-3-methoxy-6,N-dimethylmorphinan (II) in 90% yield. The structure of this compound appears to be (−)-6α-hydroxy-3-methoxy-6β,N-dimethylmorphinan judging from the fact that the reagent usually attacks the molecule from the less hindered side.

Compound II is also obtained by the action of methylmagnesiumiodide in 52% yield based on unrecovered starting material. Dehydration of II was carried out with thionyl chloride in pyridine solution and also with 60% perchloric acid in glacial acetic acid to afford unsaturated compounds, m.p. 84–85° and m.p. 78–82° in yields of 83% and 96%, respectively. A gas chromatogram of each compound shows only one peak; but the former has $[\alpha]_D$ −30·3°, whereas the latter $[\alpha]_D$ −78°.

These facts suggest that the dehydration takes two courses. The crude products obtained by the action of thionyl chloride were recrystallized from acetone yielding pure (−)-3-methoxy-6,N-dimethyl-Δ^5-morphinan (III), m.p. 86–86·5°, $[\alpha]_D$ −10·5°, in 66% yield. In contrast, the separation of each compound from the crude bases obtained with perchloric acid was difficult.

Careful chromatographic separation of the bases and repeated recrystallization of the crude picrates from methanol yielded the pure picrate of the Δ^6-derivative (IV) in low yield. The liberated base melts at 105–106° and gives $[\alpha]_D$ −174°.

In the NMR spectra, the low melting product shows a proton signal at 4.20τ due to C_5-H, whereas the high melting product shows a proton signal at 4·83τ due to C_7-H. Thus the structure of these isomers was confirmed.

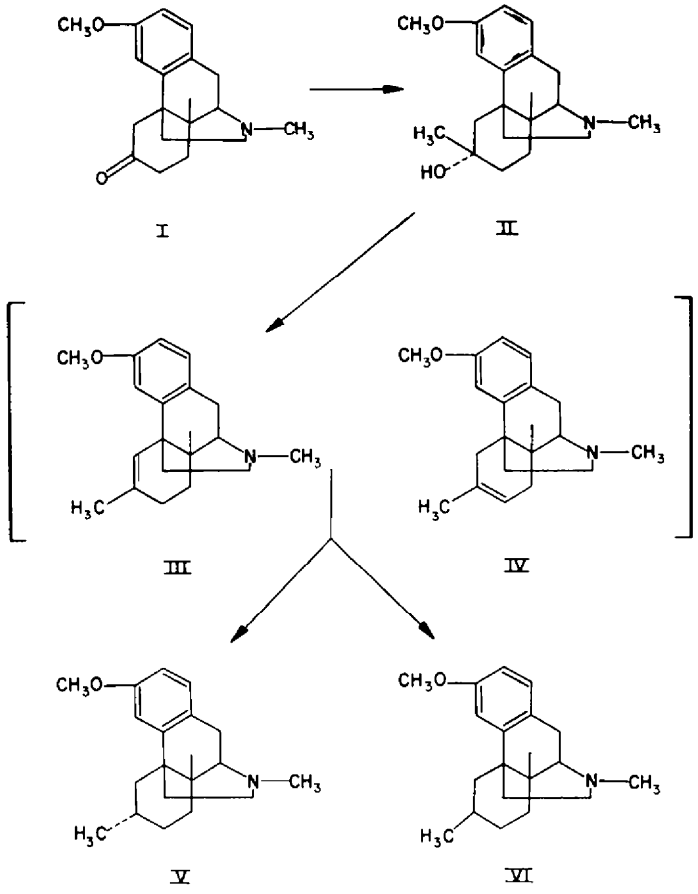
[1] Yoshiro K. Sawa, Naoki Tsuji and Shin Maeda, *Tetrahedron* **15**, 154 (1961).

Reduction of the crude dehydration products was achieved with Adams' catalyst and also with Pd-C yielding a mixture of (−)-3-methoxy-6α,N-dimethylmorphinan (V) and (−)-3-methoxy-6β,N-dimethylmorphinan (VI).

A gas chromatogram of the mixture shows two peaks at retention times of 6·8 and 7·8 minutes. An examination of the peak heights suggest that the hydrogenation with Adams' catalyst yields mainly 6-methyl compound showing a peak at the retention time of 7·8 minutes. Recrystallization of the crude product obtained with Adams' catalyst from ether gives pure 6-methyl compound, m.p. 118–119°. On the other hand, the isolation of the epimeric 6-methyl derivative was difficult. From the mother liquor after crystallization of the crude base obtained with Pd-C, the epimeric 6-methyl compound, m.p. 82–83°, was separated in low yield on chromatography over alumina followed by repeated crystallization of the picrates.

The high melting compound shows a methyl signal due to 6α axial orientation at 9·35τ and the low melting compound a methyl signal due to 6β equatorial orientation at 9·13τ in the NMR spectra.

Accordingly, the structure of the former is represented as (−)-3-methoxy-6α,N-dimethylmorphinan (V) and that of the latter as (−)-3-methoxy-6β,N-dimethylmorphinan (VI).

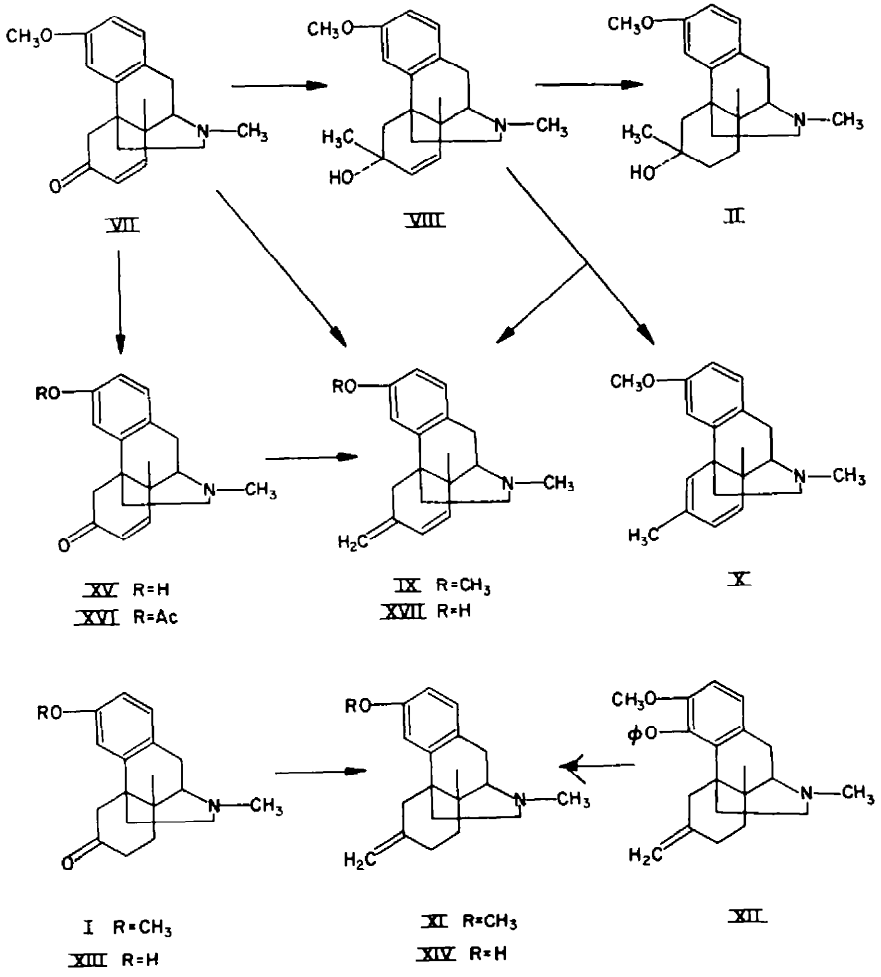


The methylation of (−)-3-methoxy-6-oxo-N-methyl-Δ^7-morphinan (VII) was studied. Treatment of the VII with methyllithium gives, in 86% yield, (+)-6α-hydroxy-3-methoxy-6β,N-dimethyl-Δ^7-morphinan (VIII), which is easily hydrogenated to II over Adams' catalyst.

Dehydration of VIII with perchloric acid affords the crude products in almost quantitative yield. A gas chromatogram of these products shows two peaks at retention times of 7·7 and 8·8 minutes.

Conversion to the picrates, recrystallization from methanol and successive liberation of each picrate gives two dienes, m.p. 66–67° and m.p. 110–110·5°, in 16% and 34% yields respectively.

In the IR spectrum the high melting diene shows absorption at 897 cm^{-1} and 1635 cm^{-1} due to an exo-cyclic methylene group. Furthermore, the m.p. of this diene is undepressed on admixture with a sample, m.p. 110–111°, obtained by the action of triphenylphosphinemethylene on (−)-3-methoxy-6-oxo-N-methyl-Δ^7-morphinan (VII).



It is clear that the structure of the high melting diene is represented as (−)-3-methoxy-6-methylene-N-methyl-Δ^7-morphinan (IX).

Accordingly the structure of the low melting compound must be (+)-3-methoxy-6,N-dimethyl-$\Delta^{5,7}$-morphinan (X).

In connection with this work the conversion of the 6-oxo group to an exo-methylene group was studied. (−)-3-Methoxy-6-oxo-N-methylmorphinan (I) was treated with triphenylphosphinemethylene to yield (+)-3-methoxy-6-methylene-N-methylmorphinan (XI) in 95% yield. This compound was also obtained from (+)-6-methylene-desoxodihydrothebainonephenylether (XII) by sodium–liquid ammonia reduction in 78% yield.

It is of interest that 3-methoxy-6-methylene derivatives show dextro rotation, whereas 3-methoxy-6-methylene-Δ^7-derivative shows laevo rotation though both these compounds have been obtained from thebaine.

Treatment of (−)-3-hydroxy-6-oxo-N-methylmorphinan (XIII) with triphenylphosphinemethylene gives the 6-methylene derivative (XIV) in 90% yield. On the other hand, similar treatment of the α,β-unsaturated ketone (XV) gives unknown complicated compounds.

For the purpose of the examination of analgesic activity, these 3-methoxy-6-methyl derivatives were treated with 48% hydrobromic acid.

The pharmacological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

(−)-6α-Hydroxy-3-methoxy-6β,N-dimethylmorphinan (II)

(a) *With methyllithium.* Methyllithium was prepared from 14·2 g methyl iodide and 1·53 g metallic Li in dry ether. To this solution, cooled to 0°, a solution of 14·3 g I in 600 cc benzene was added during 10 min and the mixture kept stirred at 10° in a N_2 atm. for 1 hr. Ice-water was added and the organic layer washed with dil. alkali and then with water. Distillation of the solvent gave 15·6 g crude material, from which 13·77 g pure II was obtained by crystallization from ether, (91·3%), m.p. 111–112°; $[\alpha]_D^{27}$ −44·7° ± 1° (*c*, 2·113, alc.). (Found: C, 75·32; H, 9·17; N, 4·48. $C_{19}H_{27}O_2N$ requires: C, 75·71; H, 9·03; N, 4·65%).

The methiodide was prepared in acetone and crystallized from ethanol, m.p. 242–243°(dec); $[\alpha]_D^{26}$ −18·4° ± 4° (*c*, 0·592, MeOH).

(b) *With methylmagnesium iodide.* To a solution of 8·55 g of the foregoing ketone in 290 cc dry tetrahydrofuran, a solution prepared from 4·68 g metallic Mg and 25·4 g methyl iodide in ether was added.

The ether was removed by distillation and the mixture refluxed for 3 hr under stirring. To the cold mixture ice-water was added to decompose excess reagent. The basic material was extracted into aqueous acid and back-extracted into chloroform after alkalization. The residue was treated with ether to remove 0·496 g starting material. The extracts were treated with hydroxylamine hydrochloride and sodium acetate in methanol to convert the remaining ketone to its oxime.

The ether solution was chromatographed on alumina after treatment with dil. alkali. The ether eluate gave 5·61 g crude base, from which 4·5 g pure II was obtained, (52·7% based on unrecovered starting material).

(c) *Reduction of (+)-6α-hydroxy-3-methoxy-6β,N-dimethyl-Δ^7-morphinan* (VIII). A solution of 0·2 g VIII in 10 cc methanol was hydrogenated over 0·04 g Adams' catalyst. Crystallization of the residue from n-hexane yielded 0·16 g saturated compound, m.p. and the mixed m.p. 110–111°.

Dehydration of (−)-6α-hydroxy-3-methoxy-6β,N-dimethylmorphinan (II)

To a solution of 12·06 g II in pyridine, cooled to −10°, 11·44 g thionyl chloride was added dropwise and the mixture kept under stirring at that temp for ½ hr. Ice-water (300 cc) was added to the

reaction mixture and the aqueous solution evaporated to ½ the original volume under red. press. The solution was made basic with Na_2CO_3 aq. and then extracted with ether. The crude product (9·42 g) was crystallized from acetone to yield 7·49 g pure III, (66%), m.p. 86–86·5°, $[\alpha]_D^{25.5}$ −10·5° ± 1° (*c*, 2·040, alc.), NMR 4·20τ(C_5—H), 8·30τ(C_6—CH_3). (Found: C, 80·70; H, 9·05; N, 4·91. $C_{19}H_{25}ON$ requires: C, 80·52; H, 8·89; N, 4·96%).

The picrate was prepared in and crystallized from ethanol, m.p. 156–157°. (Found: C, 58·89; H, 5·26; N, 10·69. $C_{19}H_{25}ON{\cdot}C_6H_3O_7N_3$ requires: C, 58·58; H, 5·51; N, 10·93%).

To a solution of 9 g II in 180 cc glacial acetic acid, 5·5 g 60% $HClO_4$ aq. was added and the mixture heated on a steam bath for 10 min. The solution was evaporated to about 50 cc under red. press., diluted with water, made alkaline with NH_4OH and extracted with benzene. The crude base was chromatographed on 246 g alumina. Elution with 1·5 l. n-hexane gave 1·618 g, m.p. 80–85°. Crystallization of the crude base from acetone, conversion to picrate and crystallization from acetone gave 1·011 g pure picrate, m.p. 156–158°.

Liberation of the picrate and two crystallizations of the base from acetone gave the pure Δ^8-compound, m.p. 85–86°. Further elution with 16 l. n-hexane gave 3·877 g of the mixture which was not purified. Further elution with 6 l. benzene gave 2·648 g crude Δ^6-base. Conversion to the picrate and two crystallization from methanol gave relatively pure picrate.

Liberation of the picrate and two crystallizations of the base from acetone yielded 0·42 g IV, m.p. 105–106°; $[\alpha]_D^{24}$ −171·7° ± 2° (*c*, 1·03, alc.); NMR 4·83τ(C_7—H) 8·35τ(C_6—CH_3). (Found: C, 80·73; H, 8·99; N, 5·04. $C_{19}H_{25}ON$ requires: C, 80·52; H, 8·89; N, 4·94%).

The picrate was prepared in and crystallized from ethanol, m.p. 180·5–181°. (Found: C, 58·71; H, 5·65; N, 11·19. $C_{19}H_{25}ON{\cdot}C_6H_3O_7N_3$ requires: C, 58·58; H, 5·51; N, 10·93%).

(+)-6α-*Hydroxy*-3-*methoxy*-6β,N-*dimethyl*-Δ^7-*morphinan* (VIII)

To a cold solution of MeLi prepared from 0·833 g metallic Li and 8·52 g methyl iodide in ether, a solution of 5·66 g VII in 300 cc benzene was added dropwise during 10 min and the mixture kept at 10° under N_2 for ½ hr. The reaction mixture was treated as in the foregoing saturated compound. The crude base was chromatographed over alumina and the crystallization of the eluate from benzene gave 5·125 g pure VIII (85·6%), m.p. 131–132°. $[\alpha]_D^{24}$ +30·5° ± 1° (*c*, 2·151, alc.). (Found: C, 76·23; H, 8·47; N, 4·69. $C_{19}H_{25}O_2N$ requires: C, 76·22; H, 8·42; N, 4·68%).

The picrate was prepared in and crystallized from methanol, m.p. 176°(dec.). (Found: C, 56·69; H, 5·44; N, 10·46. $C_{19}H_{25}O_2N{\cdot}C_6H_3O_7N_3$ requires: C, 56·81; H, 5·34; N, 10·60%).

Dehydration of (+)-6α-*hydroxy*-3-*methoxy*-6β,N-*dimethyl*-Δ^7-*morphinan* (VIII)

To a solution of 8·982 g VIII in 180 cc glacial acetic acid, 5·5 g 60% perchloric acid was added and the mixture heated on a steam bath for 10 min. The reaction mixture was cooled, diluted with 180 cc water and evaporated to about 150 cc under red. press. The liberated base (8·21 g) was chromatographed over alumina and the benzene eluate (7·421 g) converted to the picrate. Crystallization from methanol gave 6·02 g of less soluble picrate, m.p. 212–213°. Liberation of the picrate gave 3·47 g of the base, m.p. 107–108°, from which pure IX (2·887 g) was obtained by crystallization from isopropanol, m.p. 110–111°. $[\alpha]_D^{25.5}$ −39·7° ± 1° (*c*, 2·188, alc.). This compound was undepressed on admixture with a sample obtained from VII by the Wittig reaction.

Concentration of the filtrate gave 7·34 g of more soluble picrate, m.p. 201–204°. Liberation of the picrate and chromatography of the crude product over alumina gave low melting material. The hexane eluate was crystallized from pet. ether yielding 1·351 g pure X, m.p. 66–67°, $[\alpha]_D^{22}$ +77·4° + 2° (*c*, 1·055, alc.). (Found: C, 80·63; H, 8·29; N, 5·14. $C_{19}H_{23}ON$ requires: C, 81·10; H, 8·24; N, 4·98%). This compound is rather unstable.

The picrate was prepared in and crystallized from methanol, m.p. 210–211°. (Found: C, 58·75; H, 5·25; N, 11·19. $C_{19}H_{23}ON{\cdot}C_6H_3O_7N_3$ requires: C, 58·82; H, 5·13; N, 10·98%).

(−)-3-*Methoxy*-6-*methylene*-N-*methyl*-Δ^7-*morphinan* (IX)

To a solution of phenyllithium prepared from 3·06 g bromobenzene and 0·27 g metallic Li in ether, 6·97 g triphenylmethylphosphoniumbromide was added and the mixture kept at room temp for 3 hr. Purified tetrahydrofuran (90 cc) was added to this reagent and the ether removed by fractional distillation. To the solution, cooled to −5°, a solution of 4·25 g of VII in 90 cc tetrahydrofuran was

added during 30 min and the mixture kept at room temp for 1 hr. Then the reaction mixture was refluxed for 40 hr under stirring in a N_2 atm.

The residue after evaporation of the tetrahydrofuran was dissolved in chloroform and the solution, after being washed with alkali, extracted thoroughly with 1% H_3PO_4 aq. Concentrated NH_4OH liberated the free base from the combined acidic extracts. The chloroform extract was chromatographed on alumina and the benzene eluate (3·134 g) was crystallized from isopropanol giving 2·489 g pure IX, m.p. 110–111°; $[\alpha]_D^{25}$ −40·0° ± 1° (*c*, 2·067, alc.). (Found: C, 81·21; H, 8·35; N, 5·11. $C_{19}H_{23}ON$ requires: C, 81·10; H, 8·24; N, 4·98%); IR 1635 cm^{-1}, 897 cm^{-1} (exo-methylene).

The picrate was prepared in and crystallized from ethanol, m.p. 213–214°. (Found: C, 58·33; H, 5·42; N, 10·82. $C_{19}H_{23}ON{\cdot}C_6H_3O_7N_3$ requires: C, 58·82; H, 5·13; N, 10·98%).

(+)-3-*Methoxy*-6-*methylene*-N-*methylmorphinan* (XI)

(a) To a Wittig reagent prepared from 0·5 g metallic Li, 5·65 g bromobenzene and 12·8 g triphenylmethylphosphoniumbromide in ether, a solution of 8·22 g I in 300 cc tetrahydrofuran was added and the mixture refluxed in a N_2 atm. for 40 hr. Similar treatments as in the foregoing compound gave 8·34 g the crude base, m.p. 113–114°. Chromatography over alumina and crystallization of the benzene eluate from ether gave 7·73 g pure XI, (94·5%), m.p. 117–118°; $[\alpha]_D^{23.5}$ +4·0° ± 1° (*c*, 2·063, alc.). (Found: C, 80·51; H, 9·05; N, 4·93. $C_{19}H_{25}ON$ requires: C, 80·52; H, 8·89; N, 4·94%).

The picrate was prepared in and crystallized from ethanol, m.p. 193–194°. (Found: C, 58·81; H, 5·60; N, 10·99. $C_{19}H_{25}ON{\cdot}C_6H_3O_7N_3$ requires: C, 58·58; H, 5·51; N, 10·93%).

(b) *From dihydrothebainonephenylether via 6-methylene derivative.* To a solution of triphenylphosphinemethylene prepared from 0·724 g metallic Li, 8·16 g bromobenzene and 18·6 g triphenylmethylphosphoniumbromide in ether, a solution of 7·54 g dihydrothebainonephenylether in 150 cc tetrahydrofuran was added and the mixture refluxed in a N_2 atm for 40 hr. Similar treatments as above gave the crude base, which on treating with D-tartaric acid yielded 8·53 g D-tartrate, m.p. 123–125°(dec) after crystallization from hot water (8·27 g, 76%). Aqueous ammonia liberated the free base from the D-tartrate and crystallization of the base from pet. ether gave pure XII, m.p. 99–100°; $[\alpha]_D^{26}$ +98·1° ± 1° (*c*, 2·117, alc.). (Found: C, 79·85; H, 7·91; N, 3·90. $C_{25}H_{29}O_2N$ requires: C, 79·96; H, 7·79; N, 3·73%).

A solution of 0·7 g 6-methylene-phenylether derivative in 13 cc toluene was added to 50 cc liquid ammonia at −50–−55°. To this stirred solution 0·397 g metallic Na was added gradually and, after it had disappeared, the solution was kept for 30 min. Treatment as usual gave 0·64 g crude product, which on chromatography over alumina followed by crystallization from n-hexane gave 0·414 g of the desired 6-methylenedesoxodesoxydihydrothebainone, m.p. and the mixed m.p. with XI 117–117·5°.

Syntheses of 6α- and 6β-methyl-3-methoxy-N-methylmorphinan

(a) *From the dehydration product of* (−)-6α-*hydroxy*-3-*methoxy*-6β,N-*dimethylmorphinan* (II) *with perchloric acid.* Dehydration product prepared with $HClO_4$ was used as a starting material. It gave $[\alpha]_D^{25}$ −78·4°. A solution of 0·5 g of the product in 25 cc 50% acetic acid was hydrogenated over Adams' catalyst.

Treatment as usual gave 0·495 g saturated compound, m.p. 114–118° (sintering at 109°); $[\alpha]_D^{24}$ −27·4° ± 1° (*c*, 2·038, alc.). The gas chromatogram showed two peaks at retention times 6·8 and 7·8 mins in a ratio of 4·4:95·6. On the other hand, catalytic hydrogenation of the same anhydro compound over Pd-C afforded the saturated compound, m.p. 55–110°, $[\alpha]_D^{24}$ −43·6° ± 1° (*c*, 2·193, alc.). The gas chromatogram showed two peaks at the same retention times as above in a ratio of 46·1:53·9.

(b) *From the dehydration product of* (−)-6α-*hydroxy*-3-*methoxy*-6β,N-*dimethylmorphinan* (II) *with thionyl chloride.* Dehydration product showed $[\alpha]_D^{23}$ −30·3° ± 1° (*c*, 2·035, alc.). Catalytic hydrogenation of the anhydro compound over Adams' catalyst in 50% acetic acid gave the saturated mixture, m.p. 117–119° (sintering at 113°); $[\alpha]_D^{23}$ −27·5° ± 1° (*c*, 2·002, alc.). The gas chromatogram showed two peaks in a ratio of 2·8:97·2. On the other hand, the similar reduction over Pd-C gave the mixture showing $[\alpha]_D^{23}$ −44·4° ± 1° (*c*, 2·120, alc.). The gas chromatogram showed two peaks in a ratio of 43:57.

Two crystallization of the mixture obtained by the catalytic hydrogenation over Adams' catalyst from acetone gave pure V, m.p. 118–119°; $[\alpha]_D^{23.5}$ −26·3° ± 2° (*c*, 1·072, alc.); NMR 9·35τ(6α-CH_3). (Found: C, 79·60; H, 9·53; N, 4·96. $C_{19}H_{27}ON$ requires: C, 79·95; H, 9·54; N, 4·91%).

The picrate was prepared in and crystallized from ethanol, m.p. 156–157°. (Found: C, 58·56; H, 6·10; N, 10·81. $C_{19}H_{27}ON{\cdot}C_6H_3O_7N_3$ requires: C, 58·36; H, 5·88; N, 10·89%). The crude mixture obtained by the hydrogenation over Pd-C was crystallized from ether to separate the crude 6α-methyl compound. After removing as much of the 6α-methyl compound as possible, the remaining bases were chromatographed over alumina with ether.

Each fraction was converted to picrate. Three crystallization of each picrate gave the pure picrate of VI, m.p. 163–163·5°. (Found: C, 58·45; H, 5·91; N, 10·69. $C_{19}H_{27}ON{\cdot}C_6H_3O_7N_3$ requires: C, 58·36; H, 5·88; N, 10·89%).

The liberated base, m.p. 82–83°, crystallized from n-hexane; $[\alpha]_D^{24.5}$ −69·4° ± 1° (*c*, 2·021, alc.), NMR 9·13τ(6β-CH_3). (Found: C, 80·09; H, 9·54; N, 5·03. $C_{19}H_{27}ON$ requires: C, 79·95; H, 9·54; N, 4·91%). The gas chromatogram of each base showed only one peak: (−)-3-methoxy-6α,N-dimethylmorphinan at a retention time of 7·8 min and (−)-3-methoxy-6β,N-dimethylmorphinan at a retention time of 6·8 min.

(c) *Reduction of* (+)-3-*methoxy*-6-*methylene*-N-*methyl-morphinan* (XI). A solution of 1 g 6-methylene derivative in 50% acetic acid was hydrogenated over 0·2 g Adams' catalyst. The gas chromatogram showed two peaks due to 6α- and 6β-methyl derivatives in a ratio of 91·7:8·3. Crystallization of the crude bases from acetone gave 0·83 g pure V, m.p. and the mixed m.p. 117–117·5°.

(d) *Reduction of* (−)-3-*methoxy*-6-*methylene*-N-*methyl*-Δ^7-*morphinan* (IX). A solution of 0·3 g 6-methylene derivative in 15 cc 50% acetic acid was hydrogenated in the presence of 0·06 g Adams' catalyst. Treatment as above gave 0·294 g crude 6α-methyl base, m.p. 117–118°. Crystallization from n-hexane didn't raise its melting point.

(e) *Reduction of* (+)-3-*methoxy*-6,N-*dimethyl*-$\Delta^{6,7}$-*morphinan* (X). A solution of 0·05 g $\Delta^{6,7}$ diene in 50% acetic acid was catalytically reduced over Adams' catalyst. The crude product, m.p. 117–118° was undepressed on admixture with the sample of V.

(−)-3-*hydroxy*-6-*methylene*-N-*methylmorphinan* (XIV)

To a solution of triphenylphosphinemethylene prepared from 0·6 g metallic Li, 7·85 g bromobenzene and 17·8 g triphenylmethylphosphoniumbromide in ether, 200 cc tetrahydrofuran was added and the ether removed by fractional distillation. A solution of 5·43 g XIII in 200 cc tetrahydrofuran was added dropwise to the reagent at −5° and the mixture refluxed for 40 hr in a N_2 atm. after removal of the ether.

The residue after evaporation of the solvent was dissolved in chloroform and washed with water. The precipitate was filtered to give 0·523 g crude phenolic compound, m.p. 218–219°. The chloroform solution was extracted with 3% H_3PO_4 aq. and the water layer made basic with NH_4OH.

The precipitate (5·2 g, m.p. 218–219°) and the foregoing phenolic compound were combined. Crystallization of the crude base from isopropanol gave 4·847 g XIV (88·9%), m.p. 219·5–221°.

Sublimation at 150°(3 mm) gave a pure sample, m.p. 220–221°; $[\alpha]_D^{24.5}$ −5·0° ± 1° (*c*, 2·080, alc.). (Found: C, 80·18; H, 8·69; N, 5·19. $C_{18}H_{23}ON$ requires: C, 80·25; H, 8·61; N, 5·20%).

The Wittig reaction of (−)-3-acetoxy-6-oxo-N-methylmorphinan also gave the foregoing compound in 24% yield. Methylation of XIV with Rodinov's reagent gave (+)-3-methoxy-6-methylene-N-methylmorphinan in 79·7% yield.

Attempted Wittig reaction of (−)-3-*hydroxy*-6-*oxo*-N-*methyl*-Δ^7-*morphinan*

(a) To a Wittig reagent prepared from 0·52 g metallic Li, 5·9 g bromobenzene and 13·4 g triphenylmethylphosphoniumbromide in ether, a solution of 4·04 g XV in 300 cc dry tetrahydrofuran was added and the mixture refluxed in a N_2 atm. for 40 hr after removal of the ether. No desired product was obtained on treatment of the reaction mixture.

(b) To a Wittig reagent prepared from 0·52 g metallic Li, 5·9 g bromobenzene and 13·4 g triphenylmethylphosphoniumbromide in ether, a solution of 3·11 g XVI in 100 cc dry tetrahydrofuran was added. The mixture was refluxed for 27 hr after removal of the ether.

The residue from evaporation of the solvent was dissolved in chloroform, washed with water and then extracted with 5% H_3PO_4 aq. The water layer was made basic and extracted with chloroform.

The crude bases were chromatographed over alumina and developed with chloroform. The chloroform eluates were combined and the mixture crystallized from ethanol to give 0·236 g pure XVII, m.p. 253–255°, $[\alpha]_D^{24.5}$ −53·0° ± 10° (*c*, 0·1033, alc.). (Found: C, 80·86; H, 7·95; N, 5·29. $C_{18}H_{21}ON$ requires: C, 80·86; H, 7·92; N, 5·24%).

This diene was converted to IX by the action of phenyltrimethylammoniummethoxide, m.p. and the mixed m.p. 110–111°.

(−)-3-*Hydroxy*-6α,N-*dimethylmorphinan*

(a) A solution of 1·427 g V in 14 cc 48% HBr aq. was refluxed for 15 min and the excess HBr removed by distillation under red. press.

The residue was dissolved in water, made basic with NH_4OH and extracted with chloroform. The crude base (1·348 g) was crystallized from isopropanol to give 1·146 g (−)-3-hydroxy-6α,N-dimethylmorphinan, 84·5%, m.p. 232–233°; $[\alpha]_D^{25}$ −29·2° ± 4° (*c*, 0·524, alc.). (Found: C, 79·65; H, 9·30; N, 5·13. $C_{18}H_{25}ON$ requires: C, 79·66; H, 9·29; N, 5·16%).

(b) A mixture of 1 g of (−)-3-methoxy-6α,N-dimethylmorphinan, 10 cc triethylene glycol, 2 g KOH and 1 g 85% hydrazine hydrate was heated under N_2 for 3 hr at 235–245° (bath). The mixture was cooled, diluted with water and extracted with ether.

To the water layer, excess NH_4Cl was added and the solution extracted with chloroform. The crude extracts were recrystallized from isopropanol to yield the desired phenolic compound, m.p. 230–232°, undepressed on admixture with the foregoing compound.

(−)-3-*hydroxy*-6β,N-*dimethylmorphinan*

A solution of 0·94 g VI in 10 cc 48% HBr aq. was refluxed for 15 min.

The residue after evaporation of excess HBr was treated with 30 cc water to separate the crude salt.

The hydrobromide recrystallized from hot water, m.p. 107–108° (0·529 g); $[\alpha]_D^{22.5}$ −44·9° ± 2° (*c*, 1·032, H_2O). (Found: C, 57·64; H, 7·76; N, 3·90. $C_{19}H_{25}ON \cdot HBr \cdot 1\frac{1}{2}H_2O$ requires: C, 56·99; H, 7·71; N, 3·70%).

Concentrated NH_4OH liberated the free base from the mother liquor of the hydrobromide (0·472 g), m.p. 230–231° after crystallization from ethanol; $[\alpha]_D^{23.5}$ −75·5° ± 2° (*c*, 1·001, alc.). (Found: C, 79·38; H, 9·37; N, 4·83. $C_{18}H_{25}ON$ requires: C, 79·66; H, 9·29; N, 5·16%).

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