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

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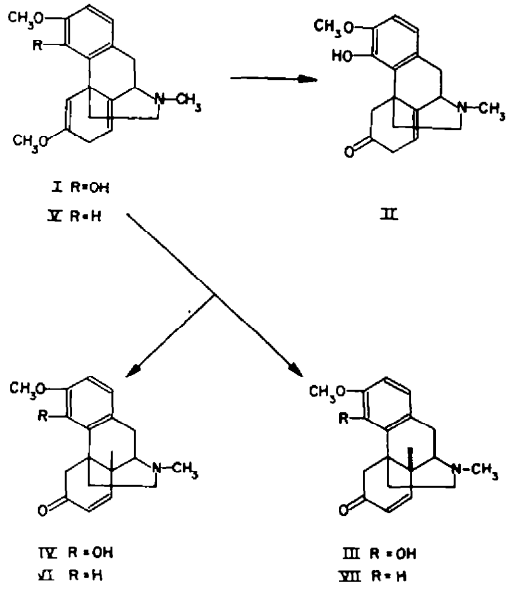
Abstract—Hydrolysis of desoxydihydrothebaine-ϕ gave desoxythebainone-A [(−)-3-methoxy-6 oxo-N-methyl-Δ^7-morphinan] and desoxy-β-thebainone-A [(−)-3-methoxy-6-oxo-N-methyl-Δ^7-isomorphinan].

Reductions of desoxythebainone-A to desoxydihydrothebainone and to 4-desoxythebainol derivatives were studied.

IN THE previous paper,[1] the elimination of the 4-hydroxyl group of sinomenine and thebaine derivatives was described. The present paper is concerned with the reduction of desoxythebainone-A and of desoxydihydrothebainone. It is well known that hydrolysis of dihydrothebaine-ϕ (I) with hydrobromic acid in alcohol at room temperature yields thebainone-B (II) and that hydrolysis with aqueous potassium bisulphate gives mainly β-thebainone-A (III) with an abnormal configuration at C_{14} together with a small amount of thebainone-A (IV). For the purpose of the preparation of some pharmacologically active compounds, hydrolysis of desoxydihydrothebaine-ϕ (V) was studied.

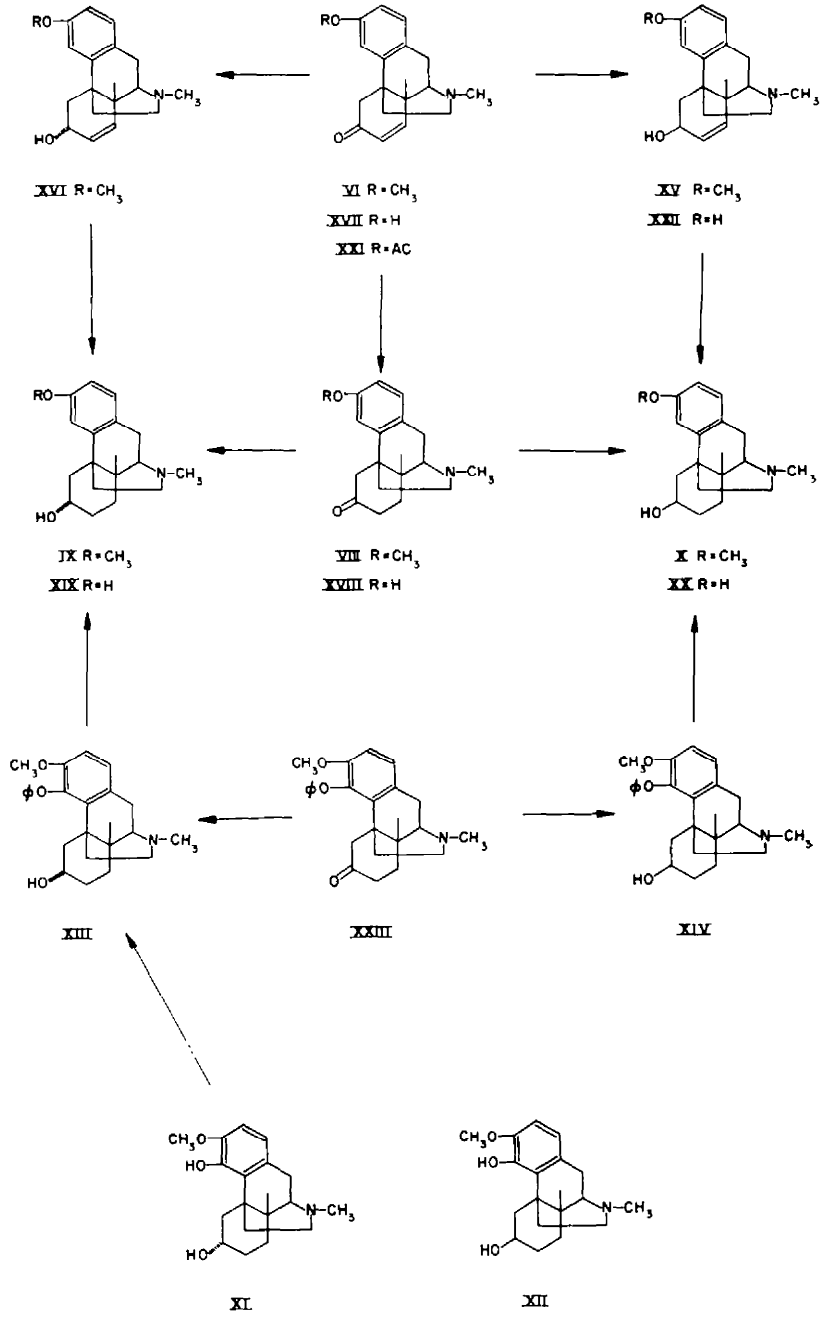
Treatment of V with 25% hydrochloric acid on a steam bath gives desoxythebainone-A [(−)-3-methoxy-6-oxo-N-methyl-Δ^7-morphinan] (VI) in a yield of 63%.

On the other hand, hydrolysis with 10% hydrochloric acid under similar conditions decreases the yield of VI to 14% and gives desoxy-β-thebainone-A [(−)-3-methoxy-6-oxo-N-methyl-Δ^7-isomorphinan] (VII) in 43% yield.



[1] Yoshiro K. Sawa, Naoki Tsuji and Shin Maeda, *Tetrahedron* **15**, 144, 154 (1961).

Hydrogenation of desoxythebainone-A (VI) with Pd-C gives, in an excellent yield, desoxydihydrothebainone [(−)-3-methoxy-6-oxo-N-methylmorphinan] (VIII), which is identical in every respect to the sample described in the previous paper.[1] Compound VIII is hydrogenated in the presence of Adams' catalyst to give 4-desoxydihydrothebainol-B (IX), m.p. 133–134°, in high yield and is reduced with sodium borohydride to give, besides IX, 4-desoxydihydrothebainol-A (X), m.p. 208–209°.



These epimeric 6-hydroxyl compounds, (IX and X), are also obtained via the phenylethers, (XIII and XIV), from dihydrothebainol-B (XI) and dihydrothebainol-A (XII).

Recently the orientation of these hydroxyl groups at C_6 was determined by Okabe[2] of this laboratory.

According to his work, it is clear that the 6-hydroxyl group of dihydrothebainol-A (XII) orients β-equatorially and the 6-hydroxyl group of dihydrothebainol-B (XI) α-axially.

These facts show that the structure of 4-desoxydihydrothebainol-A (X) is represented as (—)-6β-hydroxy-3-methoxy-N-methylmorphinan and the structure of 4-desoxydihydrothebainol-B (IX) as (—)-6α-hydroxy-3-methoxy-N-methylmorphinan.

Furthermore the reduction of desoxythebainone-A (VI) was examined.

Reduction of the α,β-unsaturated ketone (VI) with $LiAlH_4$ and also with $NaBH_4$ gave a mixture of unsaturated alcohols and saturated alcohols, whose separation was quite difficult.

However the Ponndorf reduction of VI gives 4-desoxythebainol-A (XV), $[\alpha]_D$ −46·3° and 4-desoxythebainol-B (XVI), $[\alpha]_D$ +74·8°, in a ratio of about 1:1.

These unsaturated alcohols, (XV and XVI), may be related to 4-desoxydihydrothebainol-A (X) and 4-desoxydihydrothebainol-B (IX) respectively by catalytic hydrogenation.

The differences in $[\alpha]_D$ value between the epimeric unsaturated alcohols, (XV and XVI) is well in accordance with Mills' rule.

Demethylation of desoxythebainone-A [(—)-3-methoxy-6-oxo-N-methyl-Δ^7-morphinan] (VI) and desoxydihydrothebainone [(—)-3-methoxy-6-oxo-N-methylmorphinan] (VIII) is achieved by the action of $AlBr_3$ in a benzene solution to yield the corresponding 3-hydroxyl compounds, (XVII and XVIII) in good yields.

(—)-3-Hydroxy-6-oxo-N-methylmorphinan (XVIII) is catalytically reduced to (—)-3,6α-dihydroxy-N-methylmorphinan (XIX) in 78% yield and to the (—)-3,6β-dihydroxy-N-methylmorphinan (XX) with sodium amalgam in 66% yield.

These 3,6-dihydroxyl compounds, (XIX and XX), are also obtained from the corresponding 6-hydroxyl-3-methoxy derivatives by the action of dried pyridine hydrochloride at 210°. Thus the configuration of the 6-hydroxyl groups of 3-hydroxyl compounds, (XIX and XX), was confirmed.

On the other hand, the reduction of (—)-3-hydroxy-6-oxo-N-methyl-Δ^7-morphinan (XVII) failed, because it gave a complicated mixture, separation of which was quite difficult. However the Ponndorf reduction of (—)-3-acetoxy-6-oxo-N-methyl-Δ^7-morphinan (XXI) gives (—)-3,6β-dihydroxy-N-methyl-Δ^7-morphinan (XXII) in 24% yield along with another unknown product.

The structure of XXII was confirmed by hydrogenation to (—)-3,6β-dihydroxy-N-methylmorphinan (XX).

The pharmacological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

Hydrolysis of desoxydihydrothebaine-ϕ (V)

(a) *With 25% hydrochloric acid.* A solution of 20 g desoxydihydrothebaine-ϕ in 100 cc 25% HCl aq. was kept on a steam bath for 1 hr. After cooling, the mixture was diluted, made basic with NH_4OH and extracted with benzene.

[2] Kei Okabe, *Yakugakuzasshi* **82**, 1503 (1962).

The crude product was crystallized from ether to yield 12·1 g VI (63%), m.p. 154–155°; $[\alpha]_D^{28}$ −92° ± 1° (*c*, 2·025, alc.). (Found: C, 76·40; H, 7·71; N, 4·68. $C_{18}H_{21}O_3N$ requires: C, 76·29; H, 7·47; N, 4·94%).

The picrate, crystallized from ethanol, m.p. 184–185°. (Found: C, 56·34; H, 5·02; N, 10·82. $C_{18}H_{21}O_3N{\cdot}C_6H_3O_7N_3$ requires: C, 56·25; H, 4·72; N, 10·93%).

(b) *With* 50% *acetic acid.* Hydrolysis with 50% acetic acid, as in the case of 25% HCl aq. gave the same product, m.p. 153·5–154·5°(53·5%).

(c) *With* 10% *hydrochloric acid.* A solution of 5 g desoxydihydrothebaine-ϕ in 25 cc 10% HCl aq. was heated on a steam bath for 1 hr. The solution was made basic with NH_4OH and extracted with benzene. The crude product was chromatographed on 100 g alumina and developed with benzene. The first eluate obtained with 300 cc benzene weighed 1·949 g. This was crystallized from isopropanol giving 1·325 g VII.

Although the thin layer chromatogram showed only one spot, no sharp m.p. was observed after several recrystallization; m.p. 116–124°; $[\alpha]_D^{28}$ +51·7° ± 1° (*c*, 2·055, alc.). (Found: C, 76·66; H, 7·69; N, 5·17. $C_{18}H_{21}O_3N$ requires: C, 76·26; H, 7·47; N, 4·94%).

The second eluate obtained with 900 cc benzene (wt 0·954 g) was rechromatographed later. The third eluate obtained with 1800 cc benzene and the fourth eluate obtained with 800 cc chloroform were combined (wt 1·014 g). This was crystallized from ether yielding 0·577 g VI, m.p. and mixed m.p. 153–154°.

The crude bases recovered from the isopropanol and ether solutions were combined with the foregoing second eluate. The mixture was again chromatographed and similar treatments as above gave 0·76 g VII and 0·22 g VI.

*Reduction of desoxythebainone-*A (VI) *to desoxydihydrothebainone* (VIII)

A solution of 0·3 g VI in 10 cc methanol was hydrogenated in the presence of Pd-C. The crude product was crystallized from ethanol giving 0·228 g VIII, m.p. 188–189°. This compound was undepressed on admixture with the sample prepared from XXIII.

Reduction of desoxydihydrothebainone (VIII)

(a) *Catalytic hydrogenation to desoxydihydrothebainol-*B [(−)-6α-*hydroxy*-3-*methoxy*-N-*methyl-morphinan*] (IX). A solution of 5 g VIII in 20 cc glacial acetic acid was hydrogenated in the presence of 0·5 g Adams' catalyst at room temp.

The crude base was chromatographed on alumina and the ether eluate (4·936 g), which on standing solidified, was crystallized from ethyl acetate, m.p. 133·5–134°. $[\alpha]_D^{30}$ −34·2° ± 1° (*c*, 2·045, alc.). (Found: C, 75·22; H, 8·73; N, 4·95. $C_{18}H_{23}O_3N$ requires: C, 75·22; H, 8·77; N, 4·87%).

The picrate, crystallized from ethanol, m.p. 213–214°(dec). (Found: C, 55·84; H, 5·50; N, 11·05. $C_{18}H_{25}O_3N{\cdot}C_6H_3O_7N_3$ requires: C, 55·83; H, 5·46; N, 10·85%).

(b) *Sodium borohydride reduction.* To a solution of 10 g VIII in 250 cc ethanol was added 1·32 g $NaBH_4$ under stirring and the mixture was kept at room temp overnight. Treatment as usual gave 10·5 g of crude bases which on standing solidified. The mixture was treated with 50 cc benzene and insoluble material was filtered to give 3·34 g high melting substance. The benzene solution was chromatographed on alumina and eluted in turn with benzene, chloroform and 2% ethanol–chloroform.

The benzene eluate (4·656 g) and the chloroform eluate (1·11 g) were combined and crystallization from ethyl acetate yielded 4·358 g low melting substance, (43·4%), m.p. 134–135° and identified as IX (described below).

The high melting substance and the 2% ethanol–chloroform eluate were crystallized from ethyl acetate to give 3·248 g of X, (32·3%), m.p. 208–209°; $[\alpha]_D^{30}$ −74·0° ± 2° (*c*, 1·044, alc.). (Found: C, 75·05; H, 8·80; N, 4·69. $C_{18}H_{25}O_3N$ requires: C, 75·22; H, 8·77; N, 4·87%).

The picrate, crystallized from ethanol, m.p. 216–217°. (Found: C, 55·62; H, 5·55; N, 10·84. $C_{18}H_{25}O_3N{\cdot}C_6H_3O_7N_3$ requires: C, 55·81; H, 5·46; N, 10·85%).

Reduction of dihydrothebainone-phenylether (XXIII)

To a solution of 7·55 g XXIII in 200 cc dried isopropanol, 8·2 g aluminium isopropylate was added and the stirred solution distilled slowly until the distillate was free from acetone, during which time isopropanol was occasionally added. The excess of isopropanol was removed by distillation,

the residue was diluted with 30 cc water and basified with 10% NaOH aq. The crude bases were chromatographed on alumina to give an oily product and a solid.

The former eluted with benzene–chloroform (1:1) was treated with 10% HCl aq to afford 4·107 g crude hydrochloride. Crystallization from hot water gave 3·483 g pure salt, (40%), m.p. 253–254° (dec); $[\alpha]_D^{23}$ +34·3° ± 1° (*c*, 2·069, H_2O). (Found: C, 66·34; H, 7·44; N, 3·27; Cl, 8·44; H_2O, 4·40. $C_{24}H_{29}O_3N \cdot HCl \cdot H_2O$ requires: C, 66·42; H, 7·43; N, 3·23; Cl, 8·17; H_2O, 4·13%).

The free base was crystallized from ether, m.p. 106–107°, $[\alpha]_D^{23.5}$ +26·8° ± 1° (*c*, 2·005, alc.). (Found: C, 75·83; H, 8·07; N, 3·83. $C_{24}H_{29}O_3N$ requires: C, 75·96; H, 7·70; N, 3·69%).

This compound was identified as XIII (described below).

The crystalline eluates, developed with chloroform and with 1% ethanol–chloroform, were crystallized from ether yielding 2·891 g pure product, (38%), m.p. 137–138°, $[\alpha]_D^{23}$ −7·0° ± 1° (*c*, 2·116, alc.). (Found: C, 72·64; H, 8·04; N, 3·69; H_2O, 4·36. $C_{24}H_{29}O_3N \cdot H_2O$ requires: C, 72·51; H, 7·86; N, 3·52; H_2O, 4·53%). This product was identified as XIV (described below).

Catalytic hydrogenation of XXIII in acetic acid also gave the low melting alcohol in high yield and sodium–ethanol reduction gave the high melting alcohol in a yield of 49%.

The Ullmann reaction of dihydrothebainol-B (XI)

A solution of 2 g XI prepared according to Skita[3] in 20 cc freshly distilled dry pyridine was refluxed under stirring with 3·1 g bromobenzene, 1·8 g finely powdered K_2CO_3 and 0·2 g Cu for 8 hr. The mixture was filtered while still hot and washed with hot pyridine. The pyridine solution was treated as described in the previous papers.[1]

The crude base (1·72 g) was purified as the hydroiodide, m.p. 237–238°(dec), and treatment of the salt with alkali gave the oily base, which on standing solidified. After crystallization from ether, XIII, m.p. 106–107°, was undepressed on admixture with the sample prepared by the catalytic reduction of XXIII.

Sodium-liquid ammonia reduction of dihydrothebainol-phenylethers, (XIV *and* XIII)

A solution of 1·06 g XIV in 15 cc toluene was added to 100 cc liquid ammonia at −50 to −55°. Metallic Na (0·41 g) was added gradually to this stirred solution and, after it had disappeared, the solution was kept for 30 min.

Ammonium chloride was added until the blue colour was discharged, NH_3 was evaporated and water added. The crystalline product was filtered and dried (0·323 g, m.p. 203–206°). From the toluene solution the solvent was removed under red. press. and the residue treated with ether to separate 0·362 g crude base, m.p. 192–199°. Recrystallization of these two crops from ethyl acetate gave 0·512 g pure X (63·7%), m.p. 207–209°. The IR spectrum of this base was identical with that of the sample prepared from VIII.

Similarly 0·95 g XIII in toluene–liquid ammonia was treated with 0·41 g metallic Na.

Treatment as above gave 0·568 g crude base, (78·9%), m.p. 132–134°. Recrystallization from ether raised its m.p. to 134–135°. This compound was undepressed on admixture with the sample obtained from VIII by the catalytic hydrogenation.

Ponndorf reduction of desoxythebainone-A (VI)

To a solution of 8·5 g VI in 60 cc dried isopropanol, 6·15 g aluminium isopropylate was added under stirring and the mixture distilled slowly until the distillate was free from acetone. Working as described in the case of the reduction of XXIII gave 8·93 g crude bases. The mixture was chromatographed on alumina. The eluate with benzene was crystallized from ethyl acetate to give 2·246 g XVI, (26·3%), m.p. 153–154°. $[\alpha]_D^{23}$ +83·3° ± 1° (*c*, 2·020, alc.). (Found: C, 75·81; H, 8·40; N, 5·10. $C_{18}H_{23}O_3N$ requires: C, 75·66; H, 8·11; N, 4·90%).

The picrate, crystallized from ethanol, m.p. 185°. (Found: C, 55·99; H, 5·12; N, 11·11. $C_{18}H_{23}O_3N \cdot C_6H_3O_7N_3$ requires: C, 56·03; H, 5·09; N, 10·89%). 4-Desoxythebainol-B was easily hydrogenated in the presence of Adams' catalyst to yield 4-desoxydihydrothebainol-B, m.p. 133–134°.

The eluate with 3% methanol–benzene was crystallized from ethyl acetate to give 2·601 g XV, (30·4%), m.p. 146–148°. Recrystallization from isopropanol raised its m.p. to 149·5–150·5°, $[\alpha]_D^{26}$ −47·6° ± 2° (*c*, 1·039, alc.). (Found: C, 75·95; H, 8·29; N, 4·93. $C_{18}H_{23}O_3N$ requires: C, 75·75; H, 8·12; N, 4·91%).

[3] A. Skita, F. F. Nord, J. Reichert and P. Stukart, *Ber. Dtsch. Chem. Ges.* **54**, 1560 (1921).

The picrate, crystallized from ethanol, m.p. 197–198°. (Found: C, 56·38; H, 5·26; N, 11·07. $C_{18}H_{23}O_3N \cdot C_6H_3O_7N_3$ requires: C, 56·03; H, 5·09; N, 10·89%).

Hydrogenation of 4-desoxythebainol-A in the presence of Pd-$SrCO_3$ gave 4-desoxydihydrothebainol-A, m.p. 206–208°, in almost quantitative yield.

Demethylation of desoxydihydrothebainone (VIII)

(a) *With 48% hydrobromic acid.* A solution of 3 g VIII in 15 cc 48% HBr aq was refluxed for 7 min. The mixture was cooled rapidly and the excess HBr was removed by distillation under red. press. at 50°. The residue was diluted with water, made alkaline with NH_4OH aq and extracted with chloroform. The phenolic substance was extracted with 5% NaOH aq and carbonation of the water layer separated the crude phenol.

The crude product from the chloroform was crystallized from amylene hydrate to give 2·142 g of the solvate (64·7%). Treatment of the chloroform solution containing non-phenolic substance gave 0·375 g the starting material.

The amylene hydrate adduct, m.p. 227–228°, $[\alpha]_D^{29}$ −101·5° ± 1° (*c*, 2·054, alc.). (Found: C, 73·57; H, 9·32; N, 3·89. $C_{17}H_{21}O_3N \cdot C_5H_{12}O$ requires: C, 73·50; H, 9·25; N, 3·90%).

The acetone adduct, prepared in acetone, m.p. 226–227°, $[\alpha]_D^{30}$ −109·1° ± 2° (*c*, 1·087, alc.).

The D-tartrate, crystallized from 60% alcohol, m.p. 265–266°, $[\alpha]_D^{30}$ −55·9° ± 2° (*c*, 1·007, H_2O). Prolonged treatment with 48% HBr aq under refluxing decreased the yield, for example, after 30 min to 37% and after 1 hr to 17·3%.

(b) *With aluminium tribromide.* To a solution of 28·6 g VIII in 570 cc benzene, a solution of 80 g $AlBr_3$ in 180 cc benzene was added over 10 min. The mixture was kept for 10 min at 40° and refluxed for 30 min. After cooling, the precipitate was decanted and decomposed with water. The solution was made alkaline with 10% Na_2CO_3 aq and extracted with chloroform. Similar treatments as in the foregoing experiment gave 0·78 g pure starting material and 2·297 g pure XVIII. The IR spectrum was identical with that of the product obtained by the action of 48% HBr.

Demethylation of desoxythebainone-A (VI)

To a solution of 7·5 g VI in 110 cc benzene, a solution of 21·2 g $AlBr_3$ in 110 cc benzene was added dropwise under stirring. The mixture was refluxed for 30 min. Similar treatment as above gave 0·209 g pure starting material and 6·895 g crude phenolic base. This was crystallized from tetrahydrofuran to yield the solvate, which weighed 5·65 g after drying at 100° for 2 hr (79·2%), m.p. 203–204°. $[\alpha]_D^{24.5}$ −101·5° ± 2° (*c*, 1·012. alc.). (Found: C, 75·50; H, 7·20; N, 5·20. $C_{17}H_{19}O_3N$ requires: C, 75·81; H, 7·11; N, 5·20%). This compound (XVII) was easily hydrogenated in the presence of Pd-C to XVIII, m.p. 227–228°.

Catalytic hydrogenation of (−)-3-*hydroxy*-6-*oxo*-N-*methylmorphinan* (XVIII)

A solution of 2·5 g of the amylene hydrate adduct of the 6-oxo compound in 50 cc glacial acetic acid was hydrogenated on Adams' catalyst and the excess acetic acid removed by distillation under red. press. Treatment of the residue with ethanol separated 1·675 g acetate, m.p. 206–208°. Crystallization from ethanol did not change the m.p., $[\alpha]_D^{30}$ −26·8° ± 1° (*c*, 2·117, alc.). (Found: C, 68·37; H, 8·40; N, 4·24. $C_{17}H_{23}O_3N \cdot C_2H_4O_2$ requires: C, 68·44; H, 8·16; N, 4·20%).

Ethanol was removed by distillation from the mother solution and the residue was made basic with NH_4OH. The solution was extracted with benzene and then chloroform. The benzene extract (66 mg), m.p. 221–228° was depressed on admixture with the starting material, m.p. 227–228°. Recrystallization from ethyl acetate raised its m.p. to 244–246° and this compound was later assigned as (−)-6α-acetoxy-3-hydroxy-N-methylmorphinan.

The chloroform extract (0·58 g) was crystallized from acetone to yield XIX, m.p. 211–212° (foaming at 162–163° and then solidifying); $[\alpha]_D^{23.5}$ −33·1° ± 1° (*c*, 1·997, alc.). (Found: C, 72·71; H, 8·76; N, 4·61; H_2O, 4·00%. $C_{17}H_{23}O_3N \cdot \frac{1}{2}H_2O$ requires: C, 72·31; H, 8·57; N, 4·96; H_2O, 3·04%). This compound was also obtained from IX by the action of dry pyridine hydrochloride at 230–240° for 10 min.

The mixture was diluted with water, made basic with dil. alkali and extracted with benzene. Distillation of the benzene gave the starting material in a yield of 82·5%. To the water layer, excess NH_4Cl was added and the phenolic substance, extracted with chloroform, melted at 207–209° and was undepressed on admixture with the sample obtained from XVIII.

Sodium amalgam reduction of (−)-3-*hydroxy*-6-*oxo*-N-*methylmorphinan* (XVIII)

To a suspension of 5·39 g amylene hydrate adduct of the 6-oxo compound in 45 cc water, 34·5 g 5% NaHg was added over 1 hr. The solution was kept under stirring at room temp for 3 hr and heated on a steam bath for ½ hr. The solution was then made acidic with HCl aq, concentrated to about 40 cc, made basic with Na_2CO_3 aq and extracted repeatedly with chloroform. Concentration of the chloroform solution gave 4·244 g of the desired 6-alcohol as its solvate. The crude base was crystallized from acetone to yield 2·924 g the solvate (64·5%), $[\alpha]_D^{23.5}$ −73·4° ± 2° (*c*, 1·077, alc.). The acetone adduct of XX melted at 241–243°. The IR spectrum shows an absorption band due to carbonyl group. (Found: C, 72·68; H, 8·63; N, 4·72. $C_{17}H_{23}O_2N \cdot \frac{1}{2}CH_3COCH_3$ requires: C, 73·47; H, 8·67; N, 4·63%).

This compound was also obtained from X by treatment with dried pyridine hydrochloride at 230–240° for 10 min. Separation of the mixture with NaOH aq gave the starting material in 84% yield and the 3,6β-dihydroxyl compound in 5·5% yield.

Acetylation of (−)-3-*hydroxy*-6-*oxo*-N-*methyl*-Δ^7-*morphinan* (XVII)

A suspension of 11·5 g XVII in 57·5 cc acetic anhydride containing 1·1 cc pyridine was kept at 20° for 50 hr. It became a clear solution after 40 hr.

The mixture was poured onto cold water to decompose the excess acetic anhydride. To the solution, Na_2CO_3 aq was added until only slightly acidic and the solution was extracted with benzene to remove resinous substances. The water layer was made basic with Na_2CO_3 and again extracted with benzene. The benzene solution was chromatographed on 25 g alumina to remove a small amount of resinous product.

The benzene eluate weighed 12·27 g, (92·2%). It didn't solidify on standing. In this reaction the excess of pyridine caused the formation of brown black resins. The methiodide, crystallized from methanol, m.p. 206–207°. $[\alpha]_D^{23}$ −22·8° ± 4° (*c*, 0·139, MeOH). (Found: C, 53·00; H, 5·44; N, 3·19; I, 28·21. $C_{19}H_{21}O_2N \cdot CH_3I$ requires: C, 52·99; H, 5·34; N, 3·09; I, 28·00%).

The Ponndorf reduction of (−)-3-*acetoxy*-6-*oxo*-N-*methyl*-Δ^7-*morphinan* (XXI)

To a solution of 9·34 g 6-oxo compound in 60 cc isopropanol, 12·24 g aluminium isopropylate was added. The excess isopropanol was removed by distillation after the reduction was complete. To the residue, 150 cc chloroform and 20 cc water was added.

The crude product was extracted with chloroform, washed with water and dried. The solution was concentrated to about 100 cc and after keeping at room temp overnight, the crude base, m.p. 241–243° separated. Recrystallization from acetone raised the m.p. to 246–247° yielding 1·954 g XXII (24%), $[\alpha]_D^{23}$ −44·9° ± 2° (*c*, 1·026, alc.). (Found: C, 75·12; H, 7·86; N, 5·13. $C_{17}H_{21}O_2N$ requires: C, 75·24; H, 7·86; N, 5·16%).

The foregoing unsaturated 3,6β diol was reduced to (−)-3,6β-dihydroxy-N-methylmorphinan in the presence of Adams' catalyst.

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