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

SYNTHESIS OF (−)-3-METHOXY-N-METHYL-ISOMORPHINAN DERIVATIVES

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Abstract—The Ullmann reaction of β-tetrahydrodesoxycodeine and the successive sodium–liquid ammonia reduction gave (−)-3-methoxy-N-methylisomorphinan in excellent yield. Similar reduction of the ketal of β-dihydrothebainone phenyl ether followed by the hydrolysis gave the desired (−)-3-methoxy-6-oxo-N-methylisomorphinan, whereas a similar sequence of reactions with β-thebainone-A phenyl ether gave (−)-3-methoxy-6-oxo-N-methyl-Δ^7-morphinan and the corresponding Δ^7-isomorphinan derivative.

IN THE previous papers[1] the synthesis of the active 3-hydroxy-N-methylmorphinans (B/C *cis*) from the alkaloids related to morphine was described. In 1958 Gates *et al.*[2] synthesized 3-hydroxy-N-methylisomorphinan (B/C *trans*) from 6-benzoyloxy-1,2-naphthoquinone.

This marked success prompted the attempt to synthesize this compound from thebaine. Small *et al.*[3] stated that hydrolysis of dihydrothebaine-φ (I) with potassium bisulphate gave, in 38·5% yield, β-thebainone-A (II) possessing a *trans*-fusion of ring B and C. They also observed that hydrolysis of I with 1N HCl caused other changes giving a coloured, varnish-like substance.

In the hope of improving this yield, the hydrolysis was re-examined. Treatment of I with 5% hydrochloric acid gave, contrary to Small *et al.*, β-thebainone-A (II) in 53% yield. This compound was also obtained from thebainone-B hydrobromide (IV) by the action of 5% hydrochloric acid.

On the basis of these experiments it is clear that thebainone-B (IV) must be an intermediate in this hydrolysis as stated by Bentley *et al.*[4] Huang-Minlon reduction of β-dihydrothebainone (V) prepared from II by the catalytic hydrogenation gave, in a yield of 73%, β-tetrahydrodesoxycodeine (VI), m.p. 137–148°. This compound, together with β-dihydrothebainol, had been prepared by Gates[5] from β-thebainone-A perchlorate (II) by catalytic hydrogenation. The Ullmann reaction of β-tetrahydrodesoxycodeine (VI) with bromobenzene gave the desired phenyl ether (VII) in 95% yield. Sodium–liquid ammonia reduction* of VII gave (−)-3-methoxy-N-methylisomorphinan (VIII) as an oil in 94% yield. The picrate of VIII, m.p. 209–210° was

* M. Gates *et al.* recently reported the synthesis of this compound from β-tetrahydrodesoxycodeine via the 2',4'-dinitrophenyl ether derivative. (M. Gates and T. A. Montzka, *J. Medic. Chem.* 7, 127 (1964)). Our method was patented on Apr. 9, 1963 as U.S. Pat. 3,085,091.

[1] Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron* **15**, 144, 154 (1961).
[2] M. Gates and W. G. Webb, *J. Amer. Chem. Soc.* **80**, 1186 (1958).
[3] L. Small and G. L. Browning, Jr., *J. Org. Chem.* 3, 618 (1939).
[4] K. W. Bentley and A. E. Wain, *J. Chem. Soc.* 967 (1952).
[5] M. Gates and G. Tschudi, *J. Amer. Chem. Soc.* **78**, 1380 (1956).

undepressed on admixture with a sample[6] isolated on the ring closure of (—)-1-(p-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline according to Grewe's method. Demethylation of VIII with 48% hydrobromic acid gave (—)-3-hydroxy-N-methylisomorphinan (IX), m.p. 171–172°, which was undepressed on admixture with an authentic sample given through the courtesy of Prof. Gates.

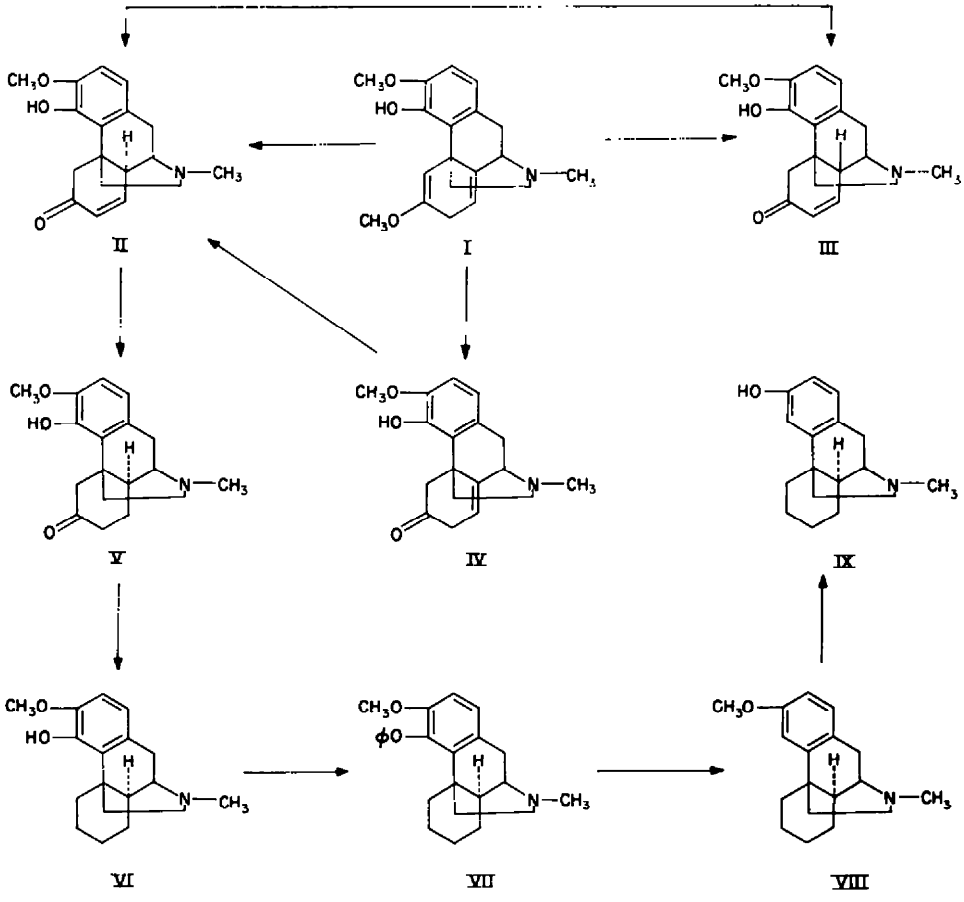
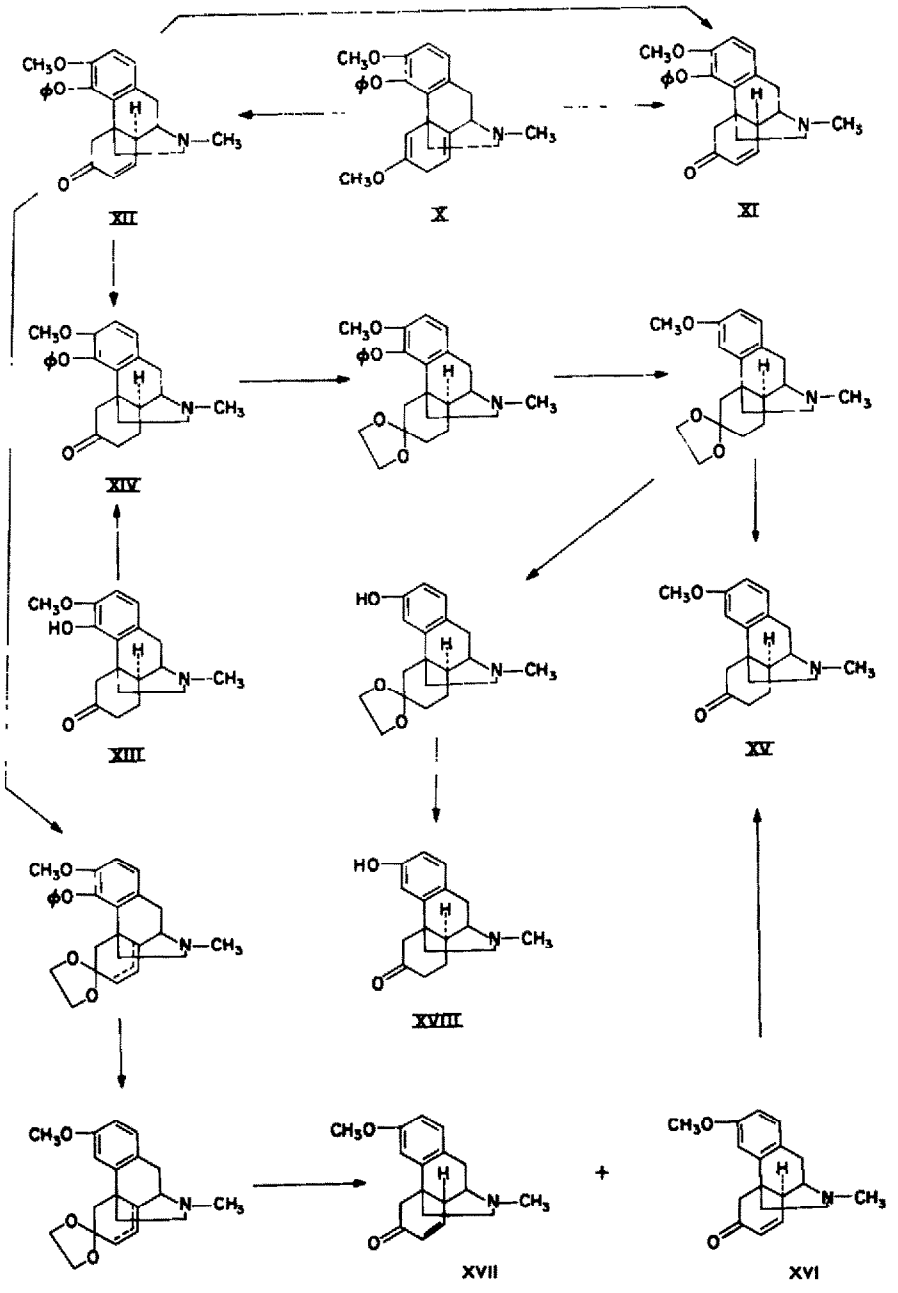


FIG. 1

Having completed the synthesis of (—)-3-methoxy-N-methylisomorphinan from thebaine, we turned to the synthesis of 6-oxo-isomorphinan derivatives. In the previous paper[7] hydrolysis of desoxydihydrothebaine-ϕ was studied. Dihydrothebaine-ϕ phenyl ether (X), upon hydrolysis with concentrated hydrochloric acid, gave thebainone-A phenyl ether (XI), m.p. 146–147°, in 44% yield. On the other hand, hydrolysis with 5% hydrochloric acid gave β-thebainone-A phenyl ether (XII), m.p. 157–158°, in 57% yield together with thebainone-A phenyl ether (XI) in 10·8% yield. β-Thebainone-A phenyl ether (XII) easily isomerized by the action of concentrated hydrochloric acid to XI, in 51% yield. Introduction of a phenyl group into the 4-hydroxyl group of β-thebainone-A was tried by the Ullmann reaction but failed.

[6] Y. K. Sawa, K. Kawasaki and S. Maeda, *Chem. Pharm. Bull.* **8**, 960 (1960).
[7] Y. K. Sawa and S. Maeda, *Tetrahedron* **20**, 2247 (1964).



However, a similar reaction with β-dihydrothebainone (XIII) gave β-dihydrothebainone phenyl ether (XIV; 72%), m.p. 156–157°, which was identical in every respect with the product prepared by catalytic hydrogenation from XII.

Sodium–liquid ammonia reduction of XIV caused not only the elimination of the 4-phenoxy grouping, but also the reduction of the 6-carbonyl grouping. Ketalization of XIV and the successive sodium–liquid ammonia reduction gave the ketal

of (−)-3-methoxy-6-oxo-N-methylisomorphinan, m.p. 126·5–128·5°, in an excellent yield. Hydrolysis of this compound was carried out with dil. hydrochloric acid to give (−)-3-methoxy-6-oxo-N-methylisomorphinan (XV), m.p. 93–94°, in 85% yield.

Furthermore, ketalization of the α,β-unsaturated ketone (XII) in the presence of toluene-*p*-sulphonic acid and the successive sodium–liquid ammonia reduction gave, in high yield, the desired desoxy compounds, which were treated with 5% hydrochloric acid to afford (−)-3-methoxy-6-oxo-N-methyl-Δ^7-isomorphinan (XVI) and (−)-3-methoxy-6-oxo-N-methyl-Δ^7-morphinan (XVII) in 45% and 19% yields respectively.* The sequence of these reactions shows that double bond migration occurred during the ketalization of the α,β-unsaturated ketone system. For the purpose of preparing (−)-3-hydroxy-6-oxo-N-methylisomorphinan, the ketal of (−)-3-methoxy-6-oxo-N-methylisomorphinan was heated at 240–250° (bath temp) in the presence of potassium hydroxide in triethylene glycol.

Hydrolysis of the protecting group gave a high yield of the desired (−)-3-hydroxy-6-oxo-N-methylisomorphinan (XVIII), m.p. 212–212·5°. Some of these isomorphinan derivatives have been screened for analgesic activity in rats by the D'amour-Smith method and in mice by the Haffner method. (−)-3-Hydroxy-6-oxo-N-methylisomorphinan is about 12 times as active as morphine in the former test and about 2·7 times as active as morphine in the latter test.†

EXPERIMENTAL

All m.ps are uncorrected. Microanalyses were carried out by Messrs. K. Miyahara and T. Ieki of this laboratory. The IR spectra were determined on a Nippon-Bunko DS-201 IR spectrophotometer.

β-Thebainone-A (II)

(a) *From dihydrothebaine-φ* (I). A solution of 31·3 g dihydrothebaine-φ in 500 ml 5% HClaq was heated on a steam bath for 45 min. The cold solution was made basic with 30% NH_4OHaq and extracted with benzene. The extracts were chromatographed on alumina and elution with benzene gave 23 g of an oily material. The bases were acidified with 60% perchloric acid.

The product formed was collected, washed with water and dried. Recrystallization from 50% alcohol gave a total of 23·2 g perchlorate in two crops, m.p. 121–122° (dec); 53·4%. $[\alpha]_D^{28.5}$ +65·6° ± 3° (*c*, 0·698, alc.). (Found: C, 50·12, H, 6·20; N, 3·02; H_2O, 7·96. Calc. for $C_{18}H_{21}O_3N \cdot HClO_4 \cdot 2H_2O$: C, 49·58; H, 6·02; N, 3·47; H_2O, 8·27%.)

A suspension of 30 g of the perchlorate in water was made basic with dil. NH_4OHaq and extracted with $CHCl_3$. The solution was chromatographed on alumina to remove a small amount of coloured material. The residue after evaporation of the solvent was treated with 30 cc 50% acetone and the remaining $CHCl_3$ was removed by distillation under red. press. The crystalline product was collected, washed with 50% acetone and dried, yielding 19·3 g (88·5%), m.p. 121–123°. A small sample was recrystallized from 50% acetone, m.p. 122–123°; $[\alpha]_D^{28.6}$ +107·5° ± 1° (*c*, 2·039, alc.). (Found: C, 67·97; H, 7·39; N, 4·04; H_2O, 5·82. Calc. for $C_{18}H_{21}O_3N \cdot H_2O$: C, 68·11; H, 7·30; N, 4·41; H_2O, 5·67%.)

(b) *From thebainone-B hydrobromide* (IV). A solution of 3·13 g thebainone-B hydrobromide, prepared by the method of Bentley *et al.*,[4] in 45 ml 5% HClaq. was heated on a steam bath for 10 min. Similar treatment as above gave 2·302 g crude perchlorate, m.p. 112–118° (64%). Recrystallization from 50% EtOH gave 1·647 g β-thebainone-A perchlorate, m.p. 120–121°.

Isomerization of β-thebainone-A (II) *to thebainone-A* (III)

A solution of 3·17 g β-thebainone-A in 15 ml conc. HCl was heated on a steam bath for ½ hr. The solution was diluted with water and made basic with NH_4OHaq. The crude products in

* These products were already reported in the previous paper.[7]

† The pharmacological activity of these compounds will be reported in detail by Dr. R. Kido of this laboratory.

$CHCl_3$ and after distillation of the solvent gave 3·62 g oily material which on standing overnight did not crystallize.

Addition of a small amount of water to a solution of the material in ethyl acetate caused the separation of thebainone-A hemihydrate (1·735 g; 56·4%), m.p. 145–147° (sintering at 138°); $[\alpha]_D^{24}$ −44·7° ± 2° (*c*, 1·053, alc.).

β-Dihydrothebainone (V)

Hydrogenation of β-thebainone-A (II) on Pd–C gave β-dihydrothebainone, m.p. 129–130° (L[5]. m.p. 119–120°), $[\alpha]_D^{26.5}$ −53·5° ± 2° (*c*, 1·059, alc.).

β-Tetrahydrodesoxycodeine (VI)

β-Dihydrothebainone (0·894 g) was added to a solution of 2 g KOH pellets in 10 ml triethylene glycol and 2 ml 80% hydrazine hydrate and maintained at 150° (bath). The mixture was heated at 170° for 3 hr and then at 190–200° for 3 hr. The solution was diluted with water and extracted repeatedly with $CHCl_3$. The residue after distillation of the $CHCl_3$ was recrystallized from EtOH to give 0·624 g β-tetrahydrodesoxycodeine, m.p. 137–148° (sintering at 130°), 73%, $[\alpha]_D^{27.5}$ −20·8° ± 1° (*c*, 2·051, alc.). (Found: C, 72·80; H, 8·90; N, 4·71. Calc. for $C_{18}H_{25}O_2N \cdot \frac{1}{2}H_2O$: C, 72·93; H, 9·18; N, 4·73%.) (L[5]. hemihydrate, m.p. 140–152°, sintering at 126°.)

β-Tetrahydrodesoxycodeine phenyl ether (VII)

A solution of 6·5 g β-tetrahydrodesoxycodeine and 7·1 g bromobenzene in 40 ml pyridine was heated under reflux with stirring for 15 hr in the presence of 4·7 g finely powdered K_2CO_3 and 0·65 g metallic Cu. The reaction mixture was treated in the usual manner and the crude products chromatographed on alumina. The benzene eluate (7·795 g; 94·7%) did not crystallize.

The methiodide, crystallized from EtOH, m.p. 243–244° (dec), $[\alpha]_D^{24}$ −4·9° ± 2° (*c*, 1·054, alc.). (Found: C, 59·53; H, 6·43; N, 3·11; I, 25·31. $C_{24}H_{29}O_3N \cdot CH_3I$ requires: C, 59·41; H, 6·38; N, 2·77; I, 25·18%.)

(−)-3-*Methoxy*-N-*methylisomorphinan* (VIII)

A solution of 4·64 g VII in 200 ml abs. ether was added dropwise to 200 ml liquid ammonia at −55° and the mixture treated with 0·6 g metallic Na. The crude products were chromatographed on alumina and development with ether gave 3·25 g (94%) of an oily (−)-3-methoxy-N-methylisomorphinan.

The picrate, crystallized from acetone, m.p. 212–213°, was undepressed on admixture with the sample obtained as a by-product on the ring closure of (−)-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline.

Demethylation of the 3-methoxy grouping with 48% HBraq yielded IX, m.p. 171–172, which was undepressed on admixture with the authentic sample.

Hydrolysis of dihydrothebaine-φ-phenyl ether (X)

(a) *With concentrated hydrochloric acid.* A solution of 7·79 g dihydrothebaine-φ phenyl ether in 40 ml 30% HClaq was heated on a steam bath for ½ hr. The solution was diluted with water, made alkaline with NH_4OHaq and extracted with $CHCl_3$.

The extracts were chromatographed on alumina and the eluates dissolved in 50 ml ether.

Addition of 5 ml water to the ether solution caused the separation of 3·571 g (43·9%) XI, m.p. 143–144°. A small sample crystallized from ether saturated with water had m.p. 146–147°; the free base had $[\alpha]_D^{22.5}$ +30·1° ± 2° (*c*, 1·054, alc.). (Found: C, 76·72; H, 6·79; N, 3·69. $C_{24}H_{25}O_3N$ requires: C, 76·77; H, 6·71; N, 3·73%.) The hydrate, (Found: C, 73·19; H, 7·05; N, 3·81; H_2O, 4·23. $C_{24}H_{25}O_3N \cdot H_2O$ requires: C, 73·26; H, 6·92; N, 3·56; H_2O, 4·56%.) The picrate, crystallized from MeOH, m.p. 214–215°.

(b) *With 5% hydrochloric acid.* A solution of 38·95 g dihydrothebaine-φ phenyl ether in 200 ml 5% HClaq was heated on a water bath for 1 hr. The solution was made basic with NH_4OHaq, extracted with benzene, chromatographed on alumina and developed with benzene.

The eluates were treated with 50 ml ether to separate 19·168 g β-thebainone-A phenyl ether, m.p. 157–158°. A second crop, 2·25 g, m.p. 157·5–158·5°, was obtained from the filtrate, total yield 21·418 g (57%). Analytically pure XII melts at 157·5–158·5° after crystallization from EtOH, $[\alpha]_D^{23}$

+91·1° ± 3° (*c*, 0·684, alc.). (Found: C, 76·77; H, 6·77; N, 3·85. $C_{26}H_{25}O_3N$ requires: C, 76·77; H, 6·71; N, 3·73%.) The hydrochloride, crystallized from hot water, m.p. 214–215° (dec; colouring at 180°), $[\alpha]_D^{28}$ +55·4° ± 2° (*c*, 1·004, H_2O). (Found: C, 62·02; H, 6·87; N, 3·02; Cl, 7·72; H_2O, 11·09. $C_{24}H_{25}O_3NCl·3H_2O$. requires: C, 61·86; H, 6·92; N, 3·01; Cl. 7·61; H_2O, 11·59%.) The residue after evaporation of the filtrate of the second crop was dissolved in benzene and chromatographed on alumina. To a solution of the eluate in ether, 3 ml water was added to afford 4·04 g (10·78%) thebainone-A phenyl ether hydrate, m.p. 145–146°.

Isomerization of β-thebainone-A phenyl ether (XII) *to thebainone-A phenyl ether* (XI)

A solution of 3·75 g β-thebainone-A phenyl ether in 18 ml conc. HClaq was heated on a steam bath for ½ hr. The crude bases were dissolved into 20 ml ether and addition of a small amount of water separated 2·004 g (51%) crystalline product, m.p. 142–143°, whose IR spectrum in $CHCl_3$ was identical with that of thebainone-A phenyl ether.

β-Dihydrothebainone phenyl ether (XIV)

(a) *Ullman reaction of β-dihydrothebainone* (XIII). A solution of 3·8 g β-dihydrothebainone and 3·97 g bromobenzene in 11 ml pyridine was heated under reflux with stirring in the presence of 3·48 g finely powdered K_2CO_3 and 0·4 g metallic Cu for 9 hr. The reaction mixture was filtered while hot and the residue, after evaporation of the pyridine, was dissolved in benzene and washed with water. The benzene solution was chromatographed on 30 g alumina and development with benzene gave 4·026 g crude phenyl ether, which was crystallized from EtOH to yield 3·492 g (72·2%) XIV, m.p. 156–157°, $[\alpha]_D^{23}$ −40·3° ± 3° (*c*, 0·667, alc.). (Found: C, 76·36; H, 7·39; N, 3·92. $C_{24}H_{27}O_3N$ requires: C, 76·36; H, 7·21; N, 3·71%.)

The methiodide, crystallized from acetone, m.p. 235–236° (dec). $[\alpha]_D^{23.5}$ −16·3° ± 2° (*c*, 0·974, alc.).

(b) *Reduction of β-thebainone-A phenyl ether* (XII). A solution of 5 g β-thebainone-A phenyl ether in 150 ml EtOH was hydrogenated over Pd-C. The solution was concentrated under red. press., after removal of the catalyst, to give 4·052 g β-dihydrothebainone phenyl ether, m.p. 155–156°, which was undepressed on admixture with the phenyl ether described above.

The perchlorate, crystallized from MeOH, m.p. 125–127°. (Found: C, 58·13; H, 6·23; N, 3·00; Cl, 7·43; H_2O, 4·24. $C_{24}H_{27}O_3N·HClO_4·H_2O$ requires: C, 58·12; H, 6·10; N, 2·83; Cl, 7·15; H_2O, 3·63%.)

The ketalization of β-dihydrothebainone phenyl ether (XIV)

A solution of 3·77 g β-dihydrothebainone phenyl ether and 12·4 g ethylene glycol in benzene was heated azeotropically under reflux with 2·85 g toluene-*p*-sulphonic acid for 6 hr. The reaction mixture was washed with dil. NaOHaq and crystallization of the crude ketal (4·996 g) from ether gave the pure product, m.p. 121–122°, 83%, $[\alpha]_D^{22.5}$ −34·1° ± 3° (*c*, 0·675, alc.). (Found: C, 74·37; H, 7·61; N, 3·37. $C_{26}H_{31}O_4N$ requires: C, 74·08; H, 7·41; N, 3·32%.)

(−)-3-*Methoxy*-6-*oxo*-N-*methylisomorphinan* (XV)

A solution of 40·25 g of the foregoing compound in 300 ml toluene was added to 600 ml liquid ammonia at −50° to −55° and the mixture treated with 4·95 g metallic Na. The usual work up followed by crystallization from alcohol gave 28·98 g (92%) of the ketal of (−)-3-methoxy-6-oxo-N-methyliso-morphinan, m.p. 126·5–128·5°. A small sample was purified from alcohol for analysis, m.p. 128–129°, $[\alpha]_D^{26}$ −74·6° ± 1°(*c*, 2·175, alc.). (Found: C, 72·92; H, 8·26; N, 4·25. $C_{20}H_{27}O_3N$ requires: C, 72·99; H, 8·41; N, 4·47%.)

A solution of 12·041 g of the ketal derivative in 50 ml 5% HClaq was heated on a water bath for 1 hr and extraction with ether after being made alkaline with NH_4OHaq gave 9·488 g crude product, which was crystallized from ether to give 8·872 g (85·3%) pure product, m.p. 93–94°; $[\alpha]_D^{26}$ −81·4° ± 2° (*c*, 1·040, alc.). (Found: C, 75·75; H, 8·12; N, 4·91. $C_{18}H_{23}O_3N$ requires: C, 75·89; H, 7·77; N, 5·03%.)

Sodium–liquid ammonia reduction of β-dihydrothebainone phenyl ether (XIV)

A solution of 3 g β-dihydrothebainone phenyl ether in 25 ml toluene was added dropwise to 200 ml liquid ammonia at −55° and the solution treated with 0·81 g metallic Na until the blue colour persisted for ½ hr. The toluene solution was washed with dil. NaOHaq and then with water.

The residue (0·963 g) after distillation of the toluene was chromatographed on 15 g alumina and

developed with ether. The first eluate (0·262 g) obtained with 20 ml ether partly crystallized and crystallization from ether gave (−)-3-methoxy-6-oxo-N-methylisomorphinan, m.p. and the mixed m.p. 94–95°.

The successive crystalline eluates (0·439 g) obtained with ether were crystallized from ether to give (−)-6-hydroxy-3-methoxy-N-methylisomorphinan, m.p. 125–127°, $[\alpha]_D^{22}$ −51·9° ± 3° (*c*, 0·722, alc.). (Found: C, 75·22; H, 8·94; N, 4·81. $C_{18}H_{25}O_3N$ requires: C, 75·22; H, 8·77; N, 4·87%.)

The $CHCl_3$ eluate (83 mg) was converted to the picrate, m.p. 217–219° (dec), which was identified as (−)-6-hydroxy-3-methoxy-N-methylisomorphinan picrate.

Demethylation of (−)-3-*methoxy*-6-*oxo*-N-*methylisomorphinan* (XV)

A solution of 9·87 g of the ketal of (−)-3-methoxy-6-oxo-N-methylisomorphinan, 11 ml 80% hydrazine hydrate and 20 g KOH in 200 ml triethylene glycol was heated under N_2 at 240–250°(bath temp) for 3 hr. The reaction mixture was diluted with water, carbonated with dry ice and extracted with $CHCl_3$. The crude products were treated with dil. NaOHaq to remove the non-phenolic compound (2·178 g). The phenolic compound was crystallized from alcohol to yield 7·612 g (85%) of the desired ketal derivative, m.p. 211–214° (sintering at 208°), $[\alpha]_D^{23.5}$ −75·9° ± 2° (*c*, 1·050, alc.). (Found: C, 72·62; H, 8·08; N, 4·35. $C_{19}H_{25}O_5N$ requires: C, 72·35; H, 7·99; N, 4·44%.)

Hydrolysis of the foregoing compound (12·44 g) with 5% HClaq and crystallization from $CHCl_3$ gave 9·953 g (95·5%) XVIII, m.p. 212–212·5° (sintering at 208°). The IR spectrum was decidedly different from that of the ketal of the phenolic compound. A small sample was crystallized from alcohol for analysis, m.p. 211–212° (sintering at 208°), $[\alpha]_D^{22}$ −85·5° ± 2° (*c*, 1·021, alc.). (Found: C, 75·22; H, 7·87; N, 5·55. $C_{17}H_{21}O_2N$ requires: C, 75·24; H, 7·80; N, 5·16%). Demethylation by the action of 48% HBraq was carried out, but the phenolic compounds showed 2 spots on the thin layer chromatogram and gave a positive Beilstein reaction.

The IR spectrum was similar to, but not identical with that of the product prepared via the ketal derivative.

The ketalization of β-thebainone-A phenyl ether (XII)

A solution of 11·28 g β-thebainone-A phenyl ether and 37·7 g ethylene glycol in benzene was heated azeotropically under reflux with 8·55 g toluene-*p*-sulphonic acid for 6 hr. The crude product (13·68 g) was used for the next step without further purification.

Sodium–liquid ammonia reduction of the ketal of β-thebainone-A phenyl ether

A solution of 13·68 g of the foregoing compound in 125 ml toluene was added dropwise to 300 ml liquid ammonia at −55° and the mixture treated with 2·1 g metallic Na. Distillation of the solvent after having been washed with dil. alkali gave 9·7 g of an oily product, which did not crystallize on standing. The crude product was hydrolysed with 40 ml 5% HClaq. The solution was made basic with dil. NH_4OHaq and extracted with benzene. The crude product was chromatographed over 200 g alumina and developed with benzene and then $CHCl_3$.

The eluate (4·092 g) obtained with 2 l. benzene was crystallized from ether to give 2·376 g (−)-3-methoxy-6-oxo-N-methyl-Δ⁷-isomorphinan, m.p. and the mixed m.p. 115–116°. A second crop, 0·667 g, m.p. 122–124° (sintering at 114°) was obtained from the filtrate.

The second eluate (0·665 g) obtained with a further 1 l. benzene was used later. The eluate (2·176 g) obtained with 1·3 l. $CHCl_3$ was crystallized from ether to give 1·471 g (−)-3-methoxy-6-oxo-N-methyl-Δ⁷-morphinan, m.p. and the mixed m.p. 154–154·5° (sintering at 149°).

The ether filtrate and the second eluate were combined and rechromatographed on alumina to yield 0·805 g (−)-3-methoxy-6-oxo-N-methyl-Δ⁷-isomorphinan and 0·163 g (−)-3-methoxy-6-oxo-N-methyl-Δ⁷-morphinan, total yields 3·848 g (−)-3-methoxy-6-oxo-N-methyl-Δ⁷-isomorphinan (45·2% based on XII) and 1·634 g (−)-3-methoxy-6-oxo-N-methyl-Δ⁷-morphinan (19·2% based on XII).

(−)-3-*Methoxy*-6-*oxo*-N-*methylisomorphinan* (XV)

A solution of 10 g (−)-3-methoxy-6-oxo-N-methyl-Δ⁷-isomorphinan in 150 ml alcohol was hydrogenated over Pd-C catalyst. Crystallization of the crude product from ether gave 9·423 g (−)-3-methoxy-6-oxo-N-methylisomorphinan, m.p. and the mixed m.p. 94·5–95·5° (94%).

Acknowledgement—We thank Prof. emeritus E. Ochiai of Tokyo University and Dr. K. Takeda, director of this laboratory for valuable discussions.