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

## SYNTHESIS OF (−)-3-HYDROXY-N-METHYL-C-NOR-MORPHINAN DERIVATIVES

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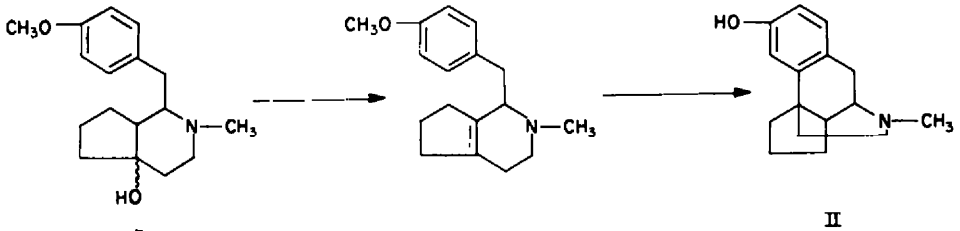
**Abstract**—Ketalization of 7-oxo-dihydrothebainone (the antipode of sinomeninone) gave 6,6; 7,7-diethylenedioxy and 6,7; 6,7-diethylenedioxy derivatives depending on the amount of toluene-*p*-sulphonic acid. Ullmann reaction of these ketal derivatives and sodium–liquid ammonia reduction followed by hydrolysis gave 4-desoxy-7-oxo-dihydrothebainone. Hydrogen peroxide oxidation of the foregoing compound and cyclization of the dibasic acid gave (−)-3-methoxy-6-oxo-N-methyl-C-nor-morphinan.

SUGASAWA *et al.*[1] synthesized racemic 3-hydroxy-N-methyl-C-nor-morphinan (II) from 1-(*p*-methoxybenzyl)-2-methyl-9-hydroxy-1,2,3,4,8,9-hexahydropentano-[C]-pyridine (I) by the action of 48% hydrobromic acid. An attempt has been made to synthesize an active form of this compound from natural products.

Among the compounds related to morphine and sinomenine, dihydrosinomenilan (IIIa) appeared to be the most suitable for this purpose, because it was anticipated that the Ullmann reaction of IIIa and subsequent sodium–liquid ammonia reduction of the phenyl ether (IVa) would give the active 3-methoxy-N-methyl-C-nor-morphinan (Va). Goto *et al.*[2] reported that the oxidation of methylsinomeninone (VI) with 30% hydrogen peroxide gave methylsinomeninic acid (VII) and that the treatment of the latter with acetic anhydride resulted in the preparation of methyldihydrosinomenilone (VIII) which could be reduced to methyldihydrosinomenilan (IX). Fortunately, the synthesis of 7-oxo-dihydrothebainone (the antipode of sinomeninone; XI) from thebaine (X) has been investigated.[3] Reexamination of the method according to Goto *et al.* showed that 7-oxo-dihydrothebainone (XI) was obtained from thebaine (X) in 67% over-all yield. The Ullmann reaction of XI failed yielding only resinous products and it was found necessary to protect the carbonyl groups in XI. In the ketalization of sinomeninone (XII) Goto *et al.*[4] reported only one product, m.p. 207°, $[\alpha]_D^{20}$ + 60·4°. Reexamination of this method revealed that ketalization of XI gave an oily new compound in addition to the product described by Goto.* In order to prevent confusion, the name of ketal-A is given for the known product (XIII) and the name of ketal-B for the new compound (XIV). The Ullmann reaction of XIII and XIV afforded a 66% yield of the corresponding phenyl ethers (XV and XVI) respectively. These compounds show dextro rotation though both were prepared from thebaine.

* The structure of these ketal derivatives will be reported in detail in a separate paper.

[1] S. Sugasawa and S. Saito, *Chem. pharm. Bull.* **4**, 237 (1956).
[2] K. Goto, K. Takubo and S. Mitsui, *Liebigs Ann.* **494**, 1 (1932).
[3] K. Goto and I. Yamamoto, *Proceeding of Japan Academy* **34**, 619 (1958).
[4] K. Goto, I. Yamamoto and T. Yamazaki, *Proceedings of Japan Academy* **37**, 282 (1960).



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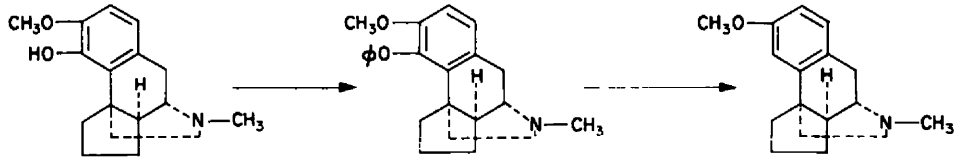

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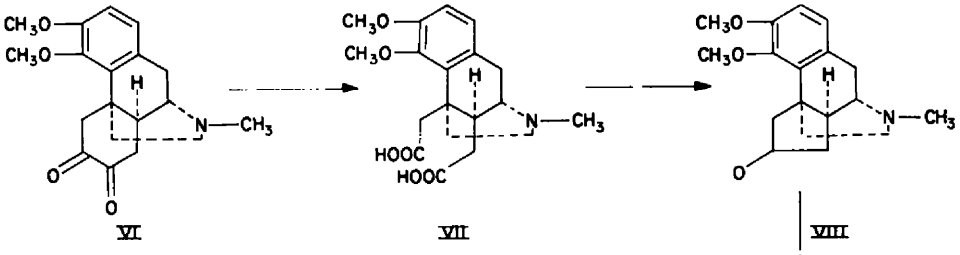

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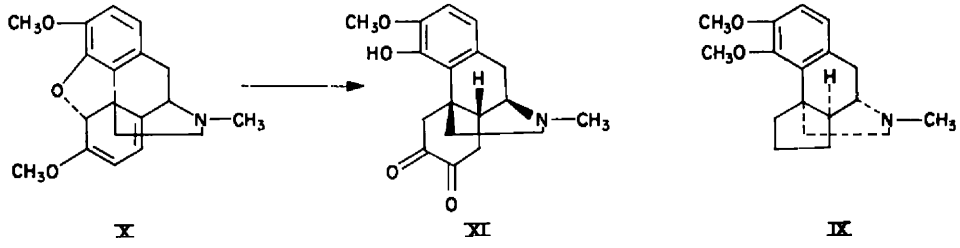
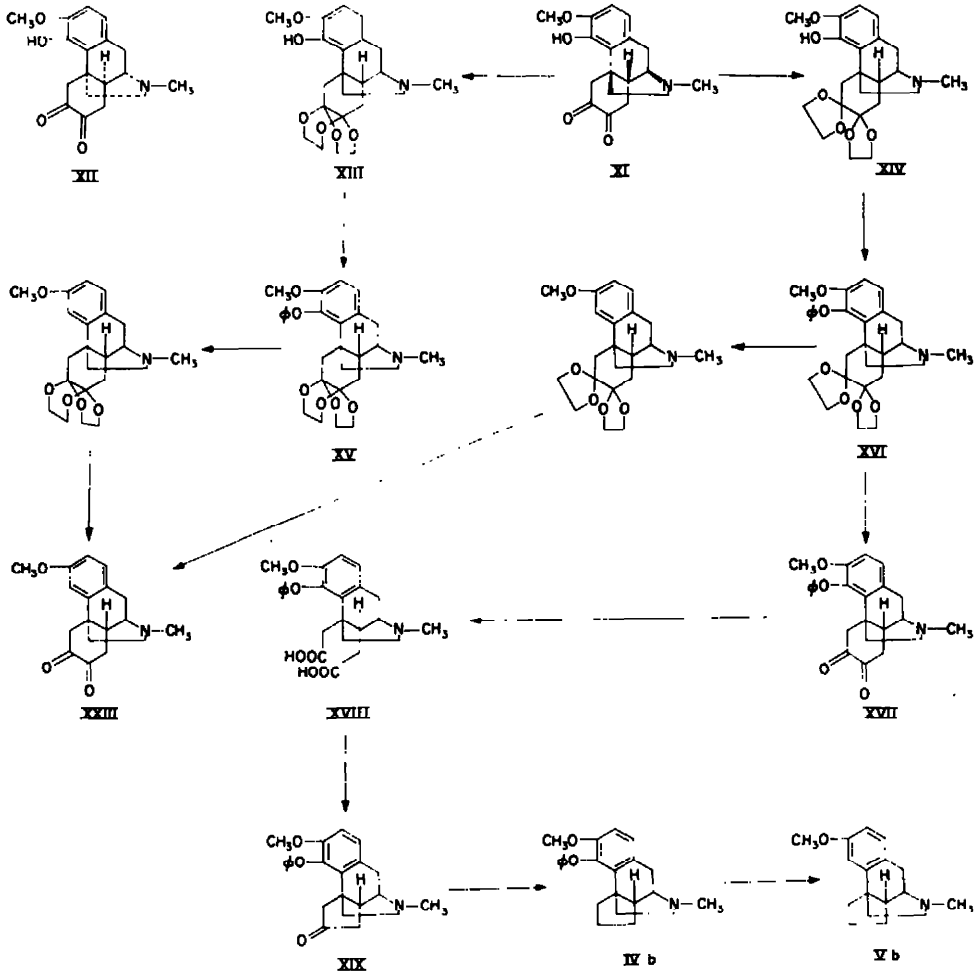


X XI IX

Hydrolysis of XVI was carried out by the action of 10% hydrochloric acid to give, in 93% yield, 7-oxo-dihydrothebainone phenyl ether (XVII), the antipode of which had been prepared from sinomenine phenyl ether.[5] This compound was treated with 30% hydrogen peroxide in glacial acetic acid to give a 72% yield of the dibasic acid (XVIII), the antipode of phenylsinomeninic acid. Upon refluxing with acetic anhydride, the dibasic acid cyclized to (−)-3-methoxy-4-phenoxy-6-oxo-N-methyl-C-nor-morphinan (XIX; 73%), the antipode of phenyldihydrosinomenilone. Clemmensen

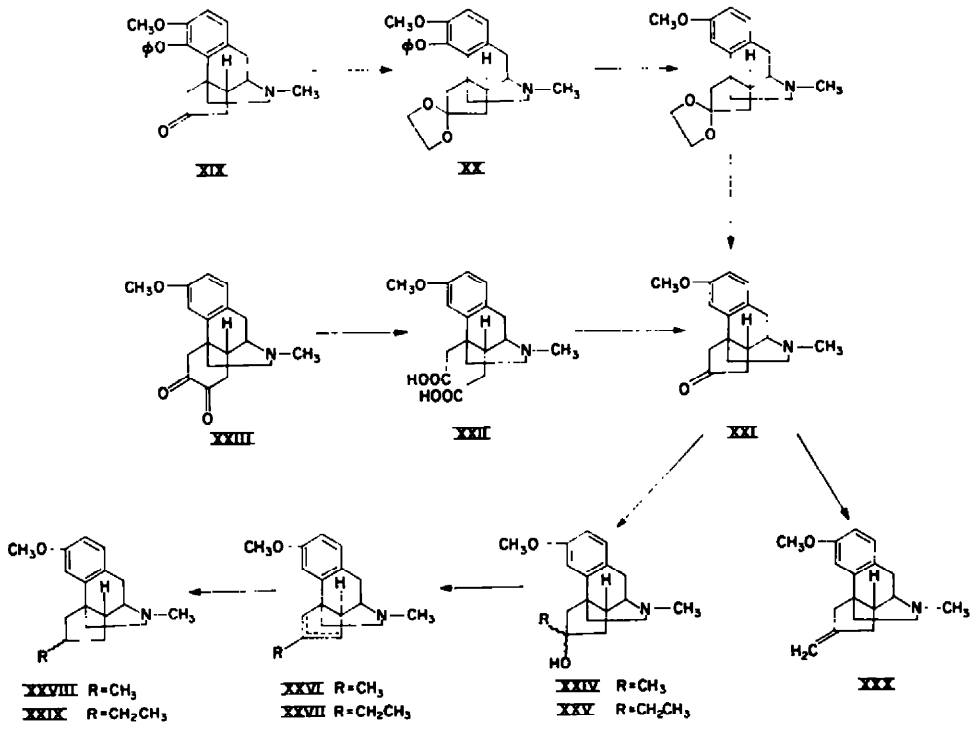


reduction of XIX gave 76% of (−)-3-methoxy-4-phenoxy-N-methyl-C-nor-morphinan (IVb), the antipode of phenyldihydrosinomenilan, from which (−)-3-methoxy-N-methyl-C-nor-morphinan (Vb) was obtained in an excellent yield by sodium–liquid ammonia reduction.

Furthermore, XIX was converted to (−)-3-methoxy-6-oxo-N-methyl-C-nor-morphinan (XXI) in high yield via the ketal derivative (XX). The compound XXI was

[5] Y. K. Sawa, N. Tsuji and S. Maeda, *Tetrahedron* **15**, 144 (1961).

also obtained by ring closure of XXII which was prepared by the oxidation of 4-desoxy-7-oxo-dihydrothebainone (XXIII). Alkylation of the 6-oxo group of XXI with reagents such as methyllithium and ethyllithium converted this compound to the corresponding 6-alkyl-6-hydroxyl derivatives (XXIV and XXV). Orientation of




these substituted groups was not confirmed. Dehydration with thionyl chloride–pyridine and hydrogenation of anhydro compounds XXVI and XXVII gave the corresponding 6-alkyl derivatives (XXVIII and XXIX).

In connection with these studies, (−)-3-methoxy-6-oxo-N-methyl-C-nor-morphinan (XXI) was treated with triphenylphosphinemethylene to give 73% of the 6-exo-methylene derivative (XXX). These new C-nor-morphinan 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,N-dimethyl-C-nor-morphinan is about 19 times as active as morphine in the former test and about 6·9 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.

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

*Dihydrothebaine*

Catalytic hydrogenation of thebaine hydrochloride over Pd–C gave dihydrothebaine, m.p. 162–162·5° (63·2%), dihydrothebainone, m.p. 141–148° (3%) and tetrahydrothebaine, m.p. 81–82° (12·2%).

*7-Oxo-dihydrothebainone* (XI) (*the antipode of sinomeninone*)

According to the method of Goto *et al.*,[3] dihydrothebaine was treated with N-bromosuccinimide in MeOH. The residue, after evaporation of the solvent, was dissolved in $CHCl_3$ and washed with dil. $Na_2CO_3$ aq and then water. A solution of the extracts in EtOH was adjusted to pH 6.0 with 10% HCl aq and the hydrochloride of 7-bromodihydrothebainone dimethylketal separated in 80% yield, m.p. 180–181° (dec.). The product was hydrolysed by heating with 5% HCl aq at 75° for 1 hr. The solution was made basic with dil. alkali and extracted with benzene to remove non-phenolic compounds. The water layer was made acidic and then made basic with dil. $Na_2CO_3$ aq.

Extraction with $CHCl_3$ gave the crude product, which was crystallized from MeOH to give the solvate of XI, m.p. 140–141° (67% based on dihydrothebaine).

*Ketalization of 7-oxo-dihydrothebainone* (XI)

A solution of 10·42 g of the methanol adduct of XI and 10 ml ethylene glycol in benzene was azeotropically refluxed with 7·1 g toluene-*p*-sulphonic acid. The reaction mixture was treated with water and made basic with 20% $NH_4OH$ aq at −10°.

The crystalline product was filtered off, dissolved in $CHCl_3$ and washed with 5% $NH_4OH$ aq. The residue after evaporation of the $CHCl_3$ was treated with benzene to separate 4·17 g the crude product, from which 3·87 g diketal-A (XIII) was obtained by crystallization from MeOH, m.p. 205–207°, 32%; $[\alpha]_D^{24.5}$ −59·9° ± 2° (*c*, 1·061, alc.). (Found: C, 65·23; H, 7·33; N, 3·10. $C_{22}H_{29}O_6N$ requires: C, 65·49; H, 7·25; N, 3·47%.) The benzene solution was chromatographed over alumina and elution with benzene gave 8·27 g of an oily diketal-B (XIV; 68%) which on standing did not crystallize. The methiodide was prepared in and crystallized from EtOH, m.p. 266–267° (dec). (Found: C, 49·39; H, 6·18; N, 2·88; I, 22·80. $C_{22}H_{29}O_6N{\cdot}CH_3I{\cdot}\frac{1}{2}H_2O$ requires: C, 49·82; H, 6·00; N, 2·53; I, 22·89%.)

*The Ullmann reaction of diketal-*A (XIII) *and diketal-*B (XIV)

A solution of 10·47 g diketal-A, m.p. 205–207°, and 10 g bromobenzene in 35 ml pyridine was refluxed under stirring with 0·96 g metallic Cu and 6·9 g finely powdered $K_2CO_3$ for 6 hr and the mixture filtered while hot. The residue after evaporation of the pyridine was dissolved in $CHCl_3$, washed with water and dried. Chromatography over alumina and elution with benzene followed by crystallization from MeOH gave 8·28 g XV, m.p. 248–249°, 66·5%; $[\alpha]_D^{25}$ +13·2° + 2° (*c*, 1·112, $CHCl_3$). (Found: C, 70·16; H, 7·12; N, 3·18. $C_{32}H_{33}O_6N$ requires: C, 70·12; H, 6·94; N, 2·92%.)

The Ullmann reaction of diketal-B was carried out under similar conditions. To a solution of 68·2 g XIV and 65 g bromobenzene in 210 ml pyridine, 6·47 g metallic Cu and 44·7 g finely powdered $K_2CO_3$ was added and the mixture refluxed for 6 hr. Treatment as above gave 53·3 g XVI, m.p. 196–197°, after crystallization from MeOH, 66%; $[\alpha]_D^{24.5}$ +36·3° ± 2° (*c*, 1·036, alc.). (Found: C, 70·13; H, 7·07; N, 3·11. $C_{32}H_{33}O_6N$ requires: C, 70·12; H, 6·94; N, 2·92%.)

*7-Oxo-dihydrothebainone phenyl ether* (XVII) (*the antipode of phenylsinomeninone*)

A solution of 11·3 g XVI in 56·5 ml 10% HCl aq was heated on a steam bath for 3 hr. The solution was diluted with water, made alkaline with $Na_2CO_3$ and extracted with $CHCl_3$. The residue after evaporation of the solvent, m.p. 202–208°, crystallized from MeOH to yield the solvate of XVII, m.p. 211–212°, 93·5%; $[\alpha]_D^{24.5}$ +65·7° ± 2° (*c*, 1·040, $CHCl_3$). (Found: C, 72·60; H, 6·76; N, 3·57. $C_{24}H_{23}O_4N{\cdot}\frac{1}{2}CH_3OH$ requires: C, 72·21; H, 6·68; N, 3·44%.)

*The antipode of phenylsinomeninic acid* (XVIII)

To a solution of 15 g of the methanol adduct of 7-oxo-dihydrothebainone phenyl ether in 75 ml glacial acetic acid, 5·3 cc 30% $H_2O_2$ was added and the mixture heated on a steam bath for 6 hr. The excess $H_2O_2$ and the acetic acid were removed by distillation under red. press. and the residue treated with 40 ml MeOH to separate 12·24 g (72%) crude acid, m.p. 262–263°.

This product was used for the next step without further purification.

(−)-3-*Methoxy*-4-*phenoxy*-6-*oxo*-N-*methyl*-C-*nor*-*morphinan* (XIX)
(*the antipode of phenylsinomenilone*)

A suspension of 11·4 g of XVIII in 46 ml acetic anhydride was refluxed for 2 hr and the excess reagent removed by distillation under red. press. The residue was again refluxed with 46 ml acetic anhydride for 2 hr. The residue was dissolved in water, made basic with $Na_2CO_3$ aq and extracted with benzene. The crude base was converted to the hydrochloride, m.p. 269·5–270° (dec), 7·52 g, 72·8%.

A small sample was recrystallized from EtOH, m.p. 273–273·5° (dec); $[\alpha]_D^{24}$ −110·1° ± 2° (*c*, 1·054 $H_2O$). (Found: C, 68·51; H, 6·61; N, 3·51; Cl, 8·67. $C_{23}H_{25}O_3N$·HCl requires: C, 69·08; H, 6·55; N, 3·50; Cl, 8·87%.) The free base melted at 149–149·5° after recrystallization from EtOH, $[\alpha]_D^{25.5}$ −128·6° ± 2° (*c*, 1·060, alc.). (Found: C, 76·07; H, 7·05; N, 3·83. $C_{23}H_{25}O_3N$ requires: C, 76·00; H, 6·93; N, 3·85%.)

(−)-3-*Methoxy*-4-*phenoxy*-N-*methyl*-C-*nor*-*morphinan* (IV-b)
(*the antipode of phenyldihydrosinomenilan*)

To a solution of 6·6 g of the hydrochloride of the foregoing compound in 58 ml 36% HCl aq, amalgamated Zn (prepared from 45 g mossy Zn and 4·5 g $HgCl_2$) was added and the mixture heated on a steam bath for 7 hr, during which time 75 ml 36% HCl aq was added dropwise. The solution was diluted with water, made basic with dil. NaOH aq and extracted with benzene. Distillation of the benzene gave 5·8 g crude product, which still showed the absorption band due to the carbonyl group in the IR spectrum.

Conversion of the remaining starting material to oxime, separation with dil. NaOH aq and chromatography on alumina gave 4·42 g the desired product (76·7%.)

(−)-3-Methoxy-4-phenoxy-N-methyl-C-nor-morphinan melted at 84·5–85·5° after crystallization from ether; $[\alpha]_D^{23.5}$ −39·1° ± 2° (*c*, 1·029, alc.). (Found: C, 78·90; H, 7·72; N, 4·17. $C_{23}H_{27}O_3N$ requires: C, 79·05; H, 7·79; N, 4·01%.) The hydrobromide, crystallized from hot water, m.p. 129–131°, $[\alpha]_D^{23}$ −30·4° ± 2° (*c*, 1·096, alc.). (Found: C, 60·74; H, 6·86; N, 3·17; Br, 17·45; $H_2O$, 6·15. $C_{23}H_{27}O_3N$·HBr·1½$H_2O$ requires: C, 60·39; H, 6·83; N, 3·06; Br, 17·47; $H_2O$, 5·91%.)

(−)-3-*Methoxy*-N-*methyl*-C-*nor*-*morphinan* (V-b)

A solution of 4·01 g IV-b in 80 ml toluene was added dropwise to 500 ml liquid ammonia at −60° to −65° and the mixture treated with 1·06 g metallic Na under stirring. The reaction mixture was worked up as described[5] yielding crude base, 2·77 g (94%). (−)-3-Methoxy-N-methyl-C-nor-morphinan melted at 64–65° after crystallization from ether; $[\alpha]_D^{23}$ −36·7° ± 2° (*c*, 1·067, alc.). (Found: C, 79·37; H, 9·14; N, 5·37. $C_{17}H_{23}ON$ requires: C, 79·33; H, 9·01; N, 5·44%.) D-tartrate, crystallized from hot water, m.p. 87–88°. $[\alpha]_D^{25.5}$ + 3·9° ± 2° (*c*, 1·022, alc.).

(−)-3-*Hydroxy*-N-*methyl*-C-*nor*-*morphinan*

A solution of 1·05 g Vb in 10 ml 48% HBr aq was refluxed for 15 min and the excess reagent removed by distillation. The residue was dissolved in dil. NaOH aq and extracted with benzene. The water layer was treated with excess $NH_4Cl$ to separate 0·725 g phenolic compound (75·7%), m.p. 214–216° after crystallization from EtOH; $[\alpha]_D^{26.5}$ −45·2° ± 2° (*c*, 1·028, alc.). (Found: C, 78·63; H, 8·99; N, 5·68. $C_{16}H_{21}ON$ requires: C, 78·97; H, 8·70; N, 5·76%.)

(−)-3-*Methoxy*-6-*oxo*-N-*methyl*-C-*nor*-*morphinan* (XXI)

(a) *From* (−)-3-*methoxy*-4-*phenoxy*-6-*oxo*-N-*methyl*-C-*nor*-*morphinan* (XIX) (*the antipode of phenylsinomenilone*). A solution of 17·7 g XIX and 49·4 g ethylene glycol in 490 ml benzene was azeotropically refluxed with 1·41 g toluene-*p*-sulphonic acid for 7·5 hr. The mixture was worked up as described for the ketalization of XI and yielded 20·6 g of an oily crude ketal. A solution of the above compound in 115 ml toluene was added dropwise to 300 ml liquid ammonia at −55° and the mixture reduced with 2·35 g metallic Na. The mixture was worked up as described for the sodium–liquid ammonia reduction of IVb and yielded 15·8 g crude product, which was hydrolysed with 5% HCl aq to yield 11·3 g XXI, m.p. 96·5–97°, or 85·5% based on (−)-3-methoxy-4-phenoxy-6-oxo N-methyl-C-nor-morphinan. Recrystallization from ether did not change the m.p.; $[\alpha]_D^{26.5}$ −221·0° ± 2° (*c*, 1·039, alc.). (Found: C, 75·54; H, 7·96; N, 5·19. $C_{17}H_{21}O_2N$ requires: C, 75·24; H, 7·80; N, 5·16%.)

(b) *From dibasic acid* (XXII). The basic acid XXII (13·17 g) was refluxed with 53 ml acetic anhydride for 2 hr. The reaction mixture was worked up as described for the cyclization of XVIII.

The basic product was chromatographed on alumina and elution with benzene gave 6·53 g of the desired ketonic substance, which was purified as its hydrochloride (52%) which crystallized from EtOH, m.p. 259–260° (dec); $[\alpha]_D^{26.5}$ −148·0° ± 2° (*c*, 1·042, $H_2O$). (Found: C, 59·81; H, 7·59; N, 4·29; Cl, 10·97. $C_{17}H_{21}O_2N \cdot HCl \cdot 2H_2O$ requires: C, 59·37; H, 7·62; N, 4·07; Cl, 10·31%.) The liberated base, m.p. 96–97°, was not depressed on admixture with the sample obtained from (−)-3-methoxy-4-phenoxy-6-oxo-N-methyl-C-nor-morphinan.

(−)-3-*Hydroxy*-6-*oxo*-N-*methyl*-C-*nor-morphinan*

A solution of 1·01 g XXI in 10 ml 48% HBr aq was refluxed for 15 min and the excess reagent removed by distillation under red. press. The residue, treated as described for the preparation of (−)-3-hydroxy-N-methyl-C-nor-morphinan, crystallized from EtOH yielding 0·612 g phenolic compound, m.p. 212–213°, 63·9%; $[\alpha]_D^{26}$ −233·0° ± 2° (*c*, 1·063, alc.). (Found: C, 74·30; H, 7·50; N, 5·27. $C_{16}H_{19}O_2N$ requires: C, 74·68; H, 7·44; N, 5·44%.)

4-*Desoxy*-7-*oxo*-*dihydrothebainone* (XXIII)

A solution of 3 g XV in 220 ml toluene was added to 500 ml liquid ammonia at −55° and the mixture treated with 1·2 g metallic Na. The residue after evaporation of the liquid ammonia and the usual treatment crystallized from MeOH yielding 2·498 g of the solvate of the desired product, m.p. 78° (dec) and m.p. 141–142° after the solvate had been dried under red. press. at 50° for 3 hr; $[\alpha]_D^{25.5}$ −72·3° ± 2° (*c*, 1·007, alc.). (Found: C, 68·02; H, 7·69; N, 3·72. $C_{22}H_{29}O_5N$ requires: C, 68·12; H, 7·54; N, 3·62%.) The above diketal (0·67 g) was hydrolysed with 10% HClaq to yield the crude diketone, from which 0·499 g 4-desoxy-7-oxo-dihydrothebainone, m.p. 190–192°, was obtained after crystallization from benzene; $[\alpha]_D^{24}$ −52·7° ± 2° (*c*, 1·046, alc.). (Found: C, 71·76; H, 7·16; N, 4·83. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; N, 4·68%.)

Sodium–liquid ammonia reduction of XVI and crystallization from benzene gave the desired ketal derivative, m.p. 202–202·5° (90%); $[\alpha]_D^{24}$ −48·8° ± 2° (*c*, 1·041, alc.). (Found: C, 68·45; H, 7·68; N, 3·80. $C_{22}H_{29}O_5N$ requires: C, 68·19; H, 7·54; N, 3·62%.)

Hydrolysis of this compound by the action of 20% HCl aq yielded a sample, m.p. and the mixed m.p. with that obtained from, XV 190–191°.

*Dibasic acid* (XXII)

A solution of 19·16 g XXIII in 96 ml galcial acetic acid was heated with 6·7 ml 30% $H_2O_2$ and the reaction mixture treated as described for the oxidation of 7-oxo-dihydrothebainone yielded a product, (13·17 g; 61·7%), m.p. 275–277° (dec). A small sample recrystallized from hot water had m.p. >285°; $[\alpha]_D^{26.5}$ −8·4° ± 2° (*c*, 1·068, 1 N-HCl). (Found: C, 64·81; H, 7·08; N, 4·26. $C_{18}H_{23}O_5N$ requires: C, 64·85; H, 6·95; N, 4·20%.)

(−)-6-*Hydroxy*-3-*methoxy*-6,N-*dimethyl*-C-*nor-morphinan* (XXIV)

To a methyllithium reagent prepared from 0·52 g metallic Li and 5·2 g MeI in ether was added dropwise a solution of 3·32 g XXI in ether–tetrahydrofuran at −5° to −10° and the mixture kept under stirring in a $N_2$ atm. for 1 hr. Ice–water was added and the organic layer washed with water. The residue after evaporation of the solvent crystallized from ether to yield 3·38 g methylol derivative (96·0%), m.p. 132–133°; $[\alpha]_D^{23.5}$ −26·6° ± 2° (*c*, 1·096, alc.). (Found: C, 75·17; H, 8·76; N, 5·07. $C_{18}H_{25}O_3N$ requires: C, 75·22; H, 8·77; N, 4·87%.)

(−)-3-*Methoxy*-6,N-*dimethyl*-C-*nor-morphinan* (XXVIII)

To a solution of 3·20 g of the foregoing compound in 32 ml pyridine was added dropwise 3·2 ml thionyl chloride at −10° and the mixture kept under stirring for ½ hr. The reaction mixture was poured into 100 ml ice–water, made basic with $Na_2CO_3$ and the excess pyridine removed by distillation. The crude product extracted with ether was chromatographed over alumina to give 2·30 g an oily anhydro compound XXVI (76·7%) which was hydrogenated over Adams' catalyst to give XXVIII (2·22 g), m.p. 66–68°.

The hydroiodide, crystallized from hot water, m.p. 103–107° (with foaming). (Found: C, 51·86; H, 6·82; N, 3·46; I, 30·25. $C_{16}H_{23}ON \cdot HJ \cdot H_2O$ requires: C, 51·80; H, 6·76; N, 3·36; I, 30·41%.) Liberation of the hydroiodide with dil. $Na_2CO_3$aq gave the free base, m.p. 71–73°; $[\alpha]_D^{24}$ −12·3° ± 2° (*c*, 1·087, alc.). (Found: C, 79·72; H, 9·27; N, 5·16. $C_{16}H_{23}ON$ requires: C, 79·66; H, 9·29; N, 5·16%.)

(−)-3-*Hydroxy*-6,N-*dimethyl*-C-*nor-morphinan*

A solution of 1·14 g XVIII in 12 ml 48% HBr aq was refluxed for 15 min and then treated as described for the preparation of (−)-3-hydroxy-N-methyl-C-normorphinan. Crystallization of the crude phenolic substance from acetone gave 0·929 g (−)-3-hydroxy-6,N-dimethyl-C-normorphinan, m.p. 203–204° (86%); $[\alpha]_D^{23}$ −20·9° ± 2° (*c*, 1·038, alc.). (Found: C, 79·29; H, 9·07; N, 5·39. $C_{17}H_{23}ON$ requires: C, 79·33; H, 9·01; N, 5·44%.)

6-*Ethyl*-3-*methoxy*-N-*methyl*-C-*nor-morphinan* (XXIX)

To an ethyllithium reagent prepared from 0·26 g metallic Li and 3·27 g EtBr in ether was added a solution of 2·71 g XXI in ether–tetrahydrofuran and the mixture stirred under $N_2$ for 1 hr. The reaction mixture was treated as described for XXIV to give 2·45 g of an oily product, which on standing did not crystallize (81·4%.)

A solution of 2·40 g XXV in 24 ml pyridine was treated with 2·4 ml thionyl chloride to yield 1·866 g an oily anhydro compound XXVII (82·4%.) The crude product was catalytically reduced to give 1·85 g of the saturated compound XXIX. The methiodide, crystallized from EtOH, m.p. 213–215°; $[\alpha]_D^{24}$ 0° ± 2° (*c*, 1·099, MeOH). (Found: C, 56·05; H, 7·33; N, 3·23; I, 26·97. $C_{19}H_{27}ON$. $CH_3I \cdot C_2H_5OH$ requires: C, 55·81; H, 7·66; N, 2·96; I, 26·81%.)

(−)-3-*Methoxy*-6-*methylene*-N-*methyl*-C-*nor-morphinan* (XXX)

To a Wittig reagent prepared from 0·17 g metallic Li, 2·07 g bromobenzene and 5·37 g triphenylmethylphosphonium bromide in ether was added a solution of 2·71 g XXI in 100 ml tetrahydrofuran under $N_2$ at −5°. The ether was removed by fractional distillation and the mixture refluxed for 40 hr. The residue after evaporation of the solvent was dissolved in $CHCl_3$, washed with dil. alkali and extracted with 5% $H_3PO_4$aq. The acidic water layer was made basic with dil. $NH_4OH$aq and extracted with benzene. The crude product was chromatographed on alumina and elution with benzene gave 2·23 g 6-methylene compound, from which 1·98 g (−)-3-methoxy-6-methylene-N-methyl-C-nor-morphinan, m.p. 84–85°, was obtained after crystallization from n-hexane; $[\alpha]_D^{27.5}$ −108·4° ± 2° (*c*, 1·045, alc.). (Found: C, 80·15; H, 8·68; N, 5·40. $C_{18}H_{23}ON$ requires: C, 80·25; H, 8·61; N, 5·20%.)

(−)-3-*Hydroxy*-6-*methylene*-N-*methyl*-C-*nor-morphinan*

A solution of 2·57 g (−)-3-hydroxy-6-oxo-N-methyl-C-nor-morphinan in 100 ml tetrahydrofuran was added to the Wittig reagent prepared from 0·347 g metallic Li, 4·32 g bromobenzene and 8·95 g triphenylmethylphosphonium bromide in ether. After similar treatment, 2·36 g crude methylene derivative, m.p. 181–185°, was obtained. A small sample crystallized from EtOH had m.p. 200–200·5°; $[\alpha]_D^{27.5}$ −121·7° ± 2° (*c*, 1·019, alc.). (Found: C, 79·80; H, 8·50; N, 5·78. $C_{17}H_{21}ON$ requires: C, 79·96; H, 8·29; N, 5·49%.)

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