Tetrahedron Vol. 24, pp. 6185 to 6196 Pergamon Press 1968. Printed in Great Britain

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

SYNTHESIS OF (−)-14 HYDROXY-3-METHOXY-N-METHYLMORPHINAN DERIVATIVES

Y. K. SAWA and H. TADA

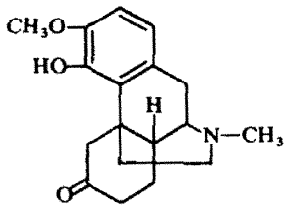
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

Abstract—Ullmann reaction of 14-hydroxydihydrothebainone followed by sodium liquid ammonia reduction gave (−)-14-hydroxy-3-methoxy-6-oxo-N-methylmorphinan in high yield. Starting from this compound 6-methyl derivatives were synthesized.

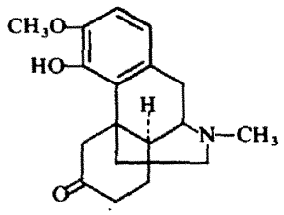
IN PREVIOUS papers,[1,2] the elimination of the 4-hydroxyl group in dihydrothebainone (I) and β-dihydrothebainone (II) was described. Pharmacological study revealed that some of these 4-deoxy compounds are more active than the respective starting phenolic compounds I and II. The elimination of the 4-OH group in 14-hydroxydihydrothebainone (III) was undertaken as this compound has not yet been prepared. It is well known that hydrogen peroxide oxidation[3,4] of thebaine (IV) in acidic medium gives a high yield of 14-hydroxycodeinone (V), stannous chloride reduction[5,6] of which opens the cyclic ether link to afford 14-hydroxythebainone (VI) and that reduction[6] of α,β-unsaturated ketone system of VI easily gives 14-hydroxydihydrothebainone III, which is also the product when 14-hydroxycodeinone oxime (VII) is reduced in alkaline solution.[6] Recently it was reported[7] that reduction of 14-hydroxydihydrocodeinone (VIII) with zinc and conc. hydrochloric acid gives 14-hydroxytetrahydrodesoxycodeine (IX), whereas reduction with zinc-ammonium chloride in aqueous alcohol affords 14-hydroxydihydrothebainone III and Wolff-kishner reduction[8] 14-hydroxydihydrodesoxycodeine-D (X) and 14-hydroxydihydrodesoxycodeine-C (XI).

The starting 14-hydroxydihydrothebainone III was prepared by the method of Seki[7] via 14-hydroxydihydrocodeinone VIII and also according to Speyer[6] via 14-hydroxycodeinone oxime VII. The properties of the product III agree with the literature reports. The Ullmann reaction was carried out by the method described[9] to give phenyl ether (XII) in 83% yield. This compound does show the following m.ps—120–121°, 131–132°, and 168–170°. After standing, however, all these products melt at 168–170°. Protection of the carbonyl group was accomplished with ethylene glycol and TsOH to give 91% of the ketal (XIII), m.p. 166–168°. Sodium-liquid ammonia reduction followed by hydrolysis afforded, in a yield of 90%, 14-hydroxy-3-methoxy-6-oxo-N-methylmorphinan (XIV), m.p. 194–196°, $[\alpha]_D$ −111·4°.

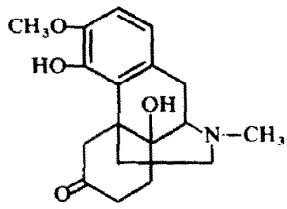
Its IR spectrum shows CO absorption at 1715 cm^{-1} and hydrogen-bonded OH absorption at 3433 cm^{-1}. This OH group, though tertiary, is easily acetylated under N_2 with acetic anhydride alone to give the acetate, m.p. 129–130°, in quantitative yield. Huang-Minlon reduction of the ketonic compound XIV yielded 14-hydroxy-3-methoxy-N-methylmorphinan (XV), m.p. 143–144·5°, $[\alpha]_D$ −76·6°, and azine deriva-



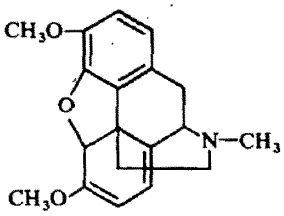
I



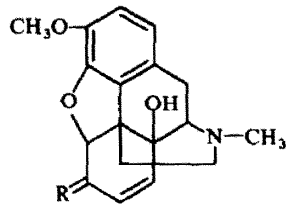
II



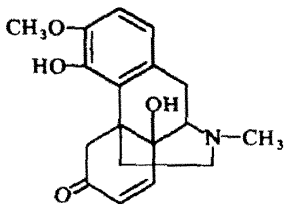
III



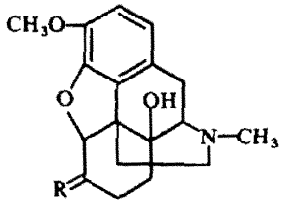
IV



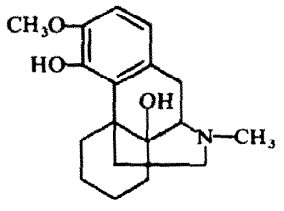
V: R = O
VII: R = N—OH



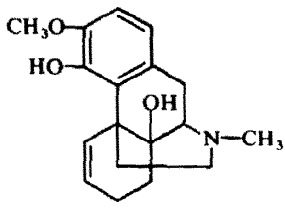
VI



VIII: R = O
X: R = H_2



IX

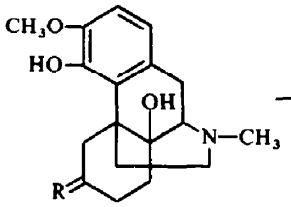


XI

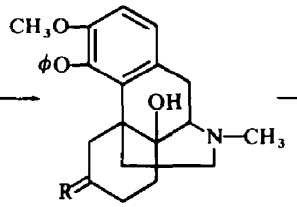
tive (XVI), m.p. 259–261°, $[\alpha]_D$ −311·2°, in 45% and 25% yields, respectively. Structure of the latter was based on the elementary analysis and the mol wt determination.

Reduction of the 6-oxo group by the action of zinc was also studied. The Clemmensen reduction gave the non-ketonic compound XV in 19% yield and the unchanged material in 31% yield, whereas reduction with zinc dust in conc. hydrochloric acid increased the yield of XV to 79%. This compound was also prepared by the following alternative route: 14-hydroxytetrahydrodesoxycodeine IX → 14-hydroxytetrahydrodesoxycodeine phenylether (XVII) → XV.

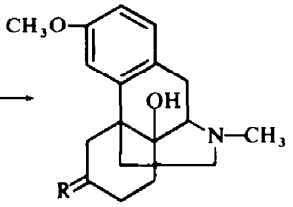
As stated before, it is known that Wolff-Kishner reduction[8] of 14-hydroxydihydrocodeinone VIII gives 14-hydroxydihydrodesoxycodeine-C XI and 14-hydroxydihydrodesoxycodeine-D X, the latter still retains the 4,5-ether link in the molecule. The Ullmann reaction of XI gave the phenylether (XVIII) in a yield of 77%. This compound has two crystalline forms: prisms, m.p. 134–135° and needles, m.p. 119–120°. The IR spectrum of the former differs from that of the latter in nujol, but is identical in chloroform solution.



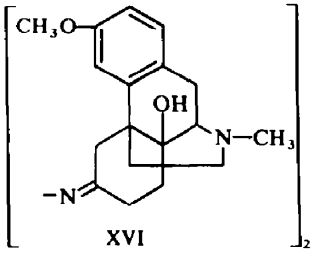
III: R = O
IX: R = H_2



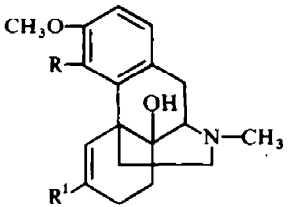
XII: R = O
XIII: R = O
O
XVII: R = H_2



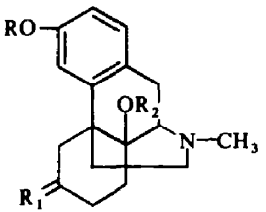
XIV: R = O
XV: R = H_2



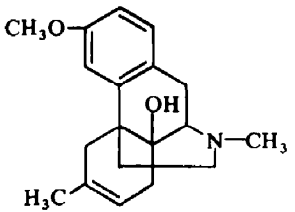
XVI



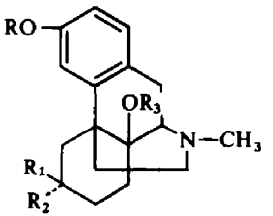
	R	R_1
XVIII:	ϕO—	H
XIX:	H	H
XXX:	H	CH_3



	R	R_1	R_2
XX:	H	O	H
XXI:	H	H_2	H
XXIX:	CH_3	O	Ac
XXXII:	CH_3	CH_2	H
XXXVII:	H	CH_2	H



XXXI



	R	R_1	R_2	R_3
XXII:	CH_3	H	OH	H
XXIII:	CH_3	OH	H	H
XXIV:	H	H	OH	H
XXV:	H	OH	H	H
XXVI:	CH_3	H	OAc	Ac
XXVII:	CH_3	OAc	H	Ac

	R	R_1	R_2	R_3
XXVIII:	CH_3	CH_3	OH	H
XXXIII:	CH_3	H	CH_3	H
XXIV:	CH_3	CH_3	H	H
XXXV:	H	H	CH_3	H
XXXVI:	H	CH_3	H	H

Sodium-liquid ammonia reduction of both products afforded high yields of the same 14-hydroxy-3-methoxy-N-methyl-Δ^5-morphinan (XIX), m.p. 128·5–130°. Catalytic hydrogenation of the unsaturated compound XIX also gave a high yield of the 14-hydroxy-3-methoxy-N-methylmorphinan XV.

It has been observed[10] that the tertiary OH group survives under the drastic conditions of the demethylation. Therefore the demethylation with 48% HBr was examined. The reaction of XIV and XV, on heating with the reagent for 15 min, yielded the expected phenolic compounds (XX and XXI) in yields of 61% and 72%, respectively.

Starting from the above-mentioned ketonic compounds several reactions were attempted. Sodium borohydride reduction of the 3-methoxy-6-oxo derivative XIV gave the 6-hydroxyl compound A (XXII), m.p. 94–96°, and the 6-hydroxyl compound B (XXIII), m.p. 153–155°, in yields of 39% and 40%, respectively. The same reduction of 3-hydroxy-6-oxo compound XX afforded a mixture of trihydroxy compounds, the separation of which was easily achieved by alumina chromatography. Trihydroxy derivative A (XXIV) was eluted with 2% MeOH–$CHCl_3$ in a yield of 81% and further elution with 5% MeOH–$CHCl_3$ gave a 12·6% yield of another epimeric triol derivative B (XXV), m.p. 215–215·5°. Methylation of the triol XXIV with phenyltrimethylammonium methoxide afforded a high yield of the above-mentioned low melting hydroxy compound XXII. Thus the relationship between both series was proved. In order to elucidate the configuration of the 6-hydroxyl groups, acetylation of these reduction products was studied. On treatment of the diol-A XXII and diol-B XXIII with acetic anhydride under N_2 afforded the diacetate-A (XXVI), m.p. 186–187·5°, and the diacetate-B (XXVII), m.p. 203–204°, in high yields respectively. The NMR spectra of the former acetate shows a signal (in ppm units) at 5·00 (triplet like, C_6—H) and signals at 2·15 (C_{14}—OAc) and 1·62 (C_6—OAc), whereas the latter shows a signal at 4·67 (broad, C_6—H) and signals at 2·18 (C_{14}—OAc) and 2·05 (C_6—OAc). These facts show that the diol-A XXII is 6α,14-dihydroxy-3-methoxy-N-methylmorphinan and that the diol-B XXIII is 6β,14-dihydroxy-3-methoxy-N-methylmorphinan. Next we tried the introduction of the Me group to C_6 because C_6-methyl compounds in the morphine series, in general, have strong activity. The reaction of 14-hydroxy-3-methoxy-6-oxo-N-methylmorphinan XIV with lithiummethyl gave a 30% yield of a methylol derivative (XXVIII), m.p. 108–109°, together with unchanged starting material in 41% yield. However, the same reaction of 14-acetoxy derivative (XXIX) increased the yield of XXVIII to 81·5%. In this case no epimeric compound was isolated showing only one side attack of the reagent occurs. Dehydration of XXVIII was achieved by the action of perchloric acid in acetic acid and also by the thionyl chloride-pyridine method.

These reactions gave a mixture of the anhydro compounds, separation of which was successfully performed by the perchlorate formation followed by purification from alcohol giving the pure Δ^5-6-methyl compound (XXX), m.p. 124–125°, and the Δ^6-6-methyl compound (XXXI), m.p. 135–136°. It is of interest to note that the acid catalyzed dehydration gives XXX and XXXI in a ratio 35:65, whereas in the base catalyzed reaction the ratio is 77:23 judging from $[\alpha]_D$ value of each crude product. The assignment of the structure of these compounds was based on NMR study. The NMR spectrum of the former shows a signal (in ppm units) for the C_5 proton at 5·65 ($W_{\frac{1}{2}}$ 4·5 c/s) and a Me signal at 1·77 and in the latter a signal for the C_7 proton

is at 5·14 ($W_{\frac{1}{2}}$ 7·5 c/s) and a Me signal at 1·70. The low field shift of the C_5 proton is attributable to the anisotropy of the benzene ring. In connection of this study, the Wittig reaction of XIV was examined. In the case of morphinan (B/C *cis*) and isomorphinan (B/C *trans*) series this reaction gave high yields of the desired compounds. The reaction in the 14-hydroxymorphinan series, however, was found to be sluggish giving 6-exo-methylene-14-hydroxy-3-methoxy-N-methylmorphinan (XXXII), m.p. 181–182° and the unchanged material in yields of 44% and 25%, respectively.

Catalytic hydrogenation of these olefinic compounds on PtO_2 and on Pd-C gave a mixture of methyl derivatives. Gas chromatography indicated that the reduction product with PtO_2 consists mainly of the 6α-methyl derivative (XXXIII) and the reduction product with Pd–C is mainly the 6β-methyl derivative (XXXIV). The configuration of the Me groups was based on NMR spectroscopic studies. The NMR spectrum of the base XXXIII shows a Me signal at 0·67 and that of the base XXXIV at 0·92 (in ppm units).

Some of the above-mentioned products were demethylated for pharmacological tests. Several compounds were found to be more potent analgesics than morphine, when tested in rats by the Damour-Smith method and in mice by the Haffner method. The activity of these compounds will be reported in detail by Kido of this laboratory.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were obtained in $CHCl_3$ with Nihon Bunko DS-201 recording spectrometer. NMR spectra were recorded in $CDCl_3$ unless otherwise stated and peaks were measured using TMS as an internal reference.

14-Hydroxydihydrothebainone (III)

(a) *From 14-hydroxycodeinone oxime* (VII). A soln of 7·9 g the oxime VII in 80 ml 10% NaOH was hydrogenated in the presence of 7·9 g 5% Pd-$SrCO_3$. Hydrogen uptake ceased after 2·5 hr. After removal of the catalyst, excess NH_4Cl was added to the filtrate, and the soln was extracted with dichloromethane. The crude product was chromatographed over alumina developing with benzene–$CHCl_3$ (1:1). Recrystallization of the solid material from ligroin afforded 5·7 g (74·6%) 14-hydroxydihydrothebainone, m.p. 144–145°, $[\alpha]_D^{25}$ −89·5° ± 2° (*c*, 1·035, Chf).

(b) *From 14-hydroxydihydrocodeinone* (VIII). A soln of VIII was reduced with Zn powder in the presence of NH_4Cl according to Seki,[8] m.p. 144–146°, 69·4%.

14-Hydroxydihydrothebainone diacetate

Compound III was heated with excess Ac_2O under N_2 for 5 hr. The crude acetate was recrystallized from alcohol, m.p. 184–186°, $[\alpha]_D^{26}$ −83·0 ± 2° (*c*, 1·051, Chf); ν_{max} 1764 (C_4—AcO), 1739 (C_{14}—AcO) and 1712 cm^{-1} (>C=O) (Nujol); NMR: 2·35 (C_4—AcO) and 2·17 ppm (C_{14}—AcO). (Found: C, 65·92; H, 6·84; N, 3·73. $C_{22}H_{27}O_6N$ requires: C, 65·82; H, 6·78; N, 3·49%).

14-Hydroxydihydrothebainone 4-methyl ether

Compound III was methylated with $NPhMe_3OMe$. The crude product was recrystallized from alcohol, m.p. 154–155°, $[\alpha]_D^{25}$ −84·8° ± 2° (*c*, 1·080, Chf); ν_{max} 3400 (C_{14}—OH) and 1709 cm^{-1} (>C=O). (Found: C, 69·09; H, 7·78; N, 4·16. $C_{19}H_{25}O_4N$ requires: C, 68·86; H, 7·60; N, 4·23%).

14-Hydroxydihydrothebainone 4-phenyl ether (XII)

A soln of 31·7 g of III and 31·7 g bromobenzene in 100 ml pyridine was refluxed under stirring with 30 g finely powdered K_2CO_3 and 3·3 g metallic Cu for 6 hr, during which time the separated water was azeotropically removed. The reaction mixture was treated as described in the previous paper.[9] The crude product (43 g) was chromatographed over alumina and eluted with benzene and $CHCl_3$. The residues

after distillation of the solvents were combined and recrystallization from ether gave 32·85 g (83·5%) 4-phenyl ether XII, m.p. 131–132°, $[\alpha]_D^{25}$ −17·8° ± 2° (*c*, 1·064, Chf), which on standing raised its m.p. to 168–170°; $[\alpha]_D^{25}$ −19·4° ± 2° (*c*, 1·011, Chf); ν_{max} 3380 (C_{14}—OH) and 1710 cm^{-1} (>C=O). (Found: C, 73·47; H, 7·12; N, 3·61. $C_{24}H_{27}O_4N$ requires: C, 73·26; H, 6·92; N, 3·56%).

In some runs this compound showed m.p. 120–122°. It was found that each IR spectrum in $CHCl_3$ was identical.

The 14-acetate, prepared with Ac_2O recrystallized from alcohol, m.p. 209–211°, $[\alpha]_D^{24}$ −40·4° ± 2° (*c*, 1·031, Chf); ν_{max} 1720 cm^{-1} (C_{14}—AcO and C=O). (Found: C, 72·13; H, 6·80; N, 3·27. $C_{26}H_{29}O_5N$ requires: C, 71·70; H, 6·71; N, 3·22%).

6,6-*Ethylenedioxy*-14-*hydroxy*-3-*methoxy*-4-*phenoxy*-N-*methylmorphinan* (XIII)

A soln of 39·3 g of XII and 60 g ethylene glycol in 380 ml benzene was refluxed under stirring with 23·7 g TsOH for 4 hr, during which time the separated water was azeotropically removed. The soln was treated with dil. ammonia and washed with water. The alkaline water layer was extracted with benzene. Distillation of the solvent from the combined extracts gave the non-ketonic product (44 g), which was recrystallized from MeOH to give 40 g (91·5%) of XIII, m.p. 166–168°, $[\alpha]_D^{29}$ +5·7° ± 2° (*c*, 2·080, Chf); ν_{max} 3480 cm^{-1} (C_{14}—OH). (Found: C, 71·43; H, 7·29; N, 3·11. $C_{26}H_{31}O_5N$ requires: C, 71·37; H, 7·14; N, 3·20%).

6,6-*Ethylenedioxy*-14-*hydroxy*-3-*methoxy*-N-*methylmorphinan*

A soln of 30 g of XIII in 80 ml toluene was added dropwise to 500 ml liquid ammonia at −55° and the mixture treated with 4·3 g metallic Na. The residue after evaporation of the liquid ammonia was extracted with toluene, and washed with water. The crude product obtained from the extract was chromatographed over alumina and developed with $CHCl_3$.

The crystalline material (23·5 g) was recrystallized from alcohol to give 21·4 g (90·4%) 6,6-ethylenedioxy-14-hydroxy-3-methoxy-N-methylmorphinan, m.p. 171–172°, $[\alpha]_D^{26}$ −64·6° ± 2° (*c*, 1·072, Chf); ν_{max} 3460 cm^{-1} (C_{14}—OH). (Found: C, 69·39; H, 7·92; N, 3·92. $C_{20}H_{27}O_4N$ requires: C, 69·54; H, 7·88; N, 4·06%).

14-*Hydroxy*-3-*methoxy*-6-*oxo*-N-*methylmorphinan* (XIV)

A soln of 30·9 g the above-cited ketal derivative in 310 ml N HCl was heated on a water bath for 10 min. The soln was made basic with NH_4OH. The ppts were collected, washed with water and dried yielding 26·8 g (99·4%), m.p. 193–195°. For analysis a small sample was recrystallized from alcohol, m.p. 194–196°, $[\alpha]_D^{26}$ −111·4° ± 2° (*c*, 1·027, Chf); ν_{max} 3433 (C_{14}—OH) and 1715 cm^{-1} (>C=O). (Found: C, 71·52; H, 7·79; N, 4·50. $C_{18}H_{23}O_3N$ requires: C, 71·73; H, 7·69; N, 4·65%). The picrate, recrystallized from alcohol, m.p. 197·5–199·5°.

14-*Acetoxy*-3-*methoxy*-6-*oxo*-N-*methylmorphinan* (XXIX)

A soln of 30 g of XIV in 300 ml Ac_2O was heated on a water bath under N_2 for 2 hr. The excess reagent was removed by distillation under reduced press. The residue was treated with dil NH_4OH, and extracted with dichloromethane. The product (34 g) was purified by chromatography over alumina followed by recrystallization from pet ether, m.p. 130–131°, $[\alpha]_D^{22}$ −153·4° ± 2° (*c*, 1·080, Chf); ν_{max} 1725 (C_{14}—AcO) and 1713 cm^{-1} (>C=O). (Found: C, 69·76; H, 7·40; N, 4·11. $C_{20}H_{25}O_4N$ requires: C, 69·95; H, 7·33; N, 4·08%).

3,14-*Dihydroxy*-6-*oxo*-N-*methylmorphinan* (XX)

A soln of 5 g of XIV in 25 ml 48% HBr was refluxed for 15 min. The soln was diluted with water, made alkaline with dil NH_4OH with cooling, and extracted with $CHCl_3$. The crude product was chromatographed over alumina and developed with $CHCl_3$ and with MeOH–$CHCl_3$. The material (3·05 g) eluted with 2% MeOH–$CHCl_3$ was recrystallized from $CHCl_3$–EtOH to afford 2·9 g (61%) of the demethylated XX, m.p. 231–233°, $[\alpha]_D^{25}$ −134·5° ± 2°, (*c*, 1·065, Chf). (Found: C, 71·20; H, 7·67; N, 4·88. $C_{17}H_{21}O_3N$ requires: C, 71·05; H, 7·37; N, 4·87%).

The 3,14-diacetate was prepared in the usual manner, but it did not crystallize on standing. Treatment

of the oily diacetate with excess of MeI gave the methiodide, m.p. 252–254° after recrystallization from hot water. (Found: C, 51·35; H, 5·62; N, 2·82; I, 24·42. $C_{21}H_{25}O_5N \cdot CH_3I$ requires: C, 51·47; H, 5·50; N, 2·73; I, 24·72%).

Reduction of 14-*hydroxy-dihydrothebainone* 4-*phenyl ether* (XII)

(a) *Huang-Minlon reduction.* A soln of 1 g XII in 20 ml diethylene glycol was heated with 0·6 ml 80% hydrazine hydrate at 110° for 1 hr, and then 0·7 g KOH pellets were added to the soln. The reaction mixture was heated at 200° for 6 hr. After dilution with 100 ml water excess NH_4Cl was added, and extraction with dichloromethane gave 1·01 g of the crude reduction products, which were chromatographed over alumina and developed with benzene to afford 0·207 g (21·5%) crystalline material. Compound XVII melted at 111–112·5° after recrystallization from alcohol, $[\alpha]_D^{25}$ −31·8° ± 2° (*c*, 1·028, Chf); ν_{max} 3460 cm^{-1} (C_{14}—OH). (Found: C, 75·88; H, 8·05; N, 3·56. $C_{24}H_{29}O_3N$ requires: C, 75·96; H, 7·70; N, 3·69%).

(b) *Clemmensen reduction.* A soln of 1 g of XII in 30 ml conc HCl was heated with amalgamated Zn (prepared from 10 g Zn powder and 2 g $HgCl_2$ in usual manner) for 3 hr, during which time 2 ml conc HCl was added every ½ hr. The insoluble material was removed by decantation, and washed with water. The water layers were combined, made basic with dil. NH_4OH, and extracted with dichloromethane. The crude material (1·03 g) was chromatographed on alumina and elution with benzene gave 0·478 g (49·6%) the crystalline non-ketonic product, m.p. 104–109°. Recrystallization from alcohol raised its m.p. to 110–112°. Further elution with $CHCl_3$ gave 0·26 g the unchanged starting ketone.

(c) *Zinc-hydrochloric acid reduction.* To a mixture of 3 g of XII and 20 g Zn powder 50 ml conc HCl was added in 2 portions. The mixture was agitated for 10 min and heated on a water bath for a further 10 min. Similar treatment as in (b) gave 2·98 g of the oily material, which showed 3 spots on TLC (Dragendorf reagent). Chromatography on alumina developing with benzene followed by recrystallization from 95% alcohol gave 0·688 g (23·8%) of the desired product, m.p. 112–114°. Further elution with benzene–$CHCl_3$ and with $CHCl_3$ recovered 0·14 g the unchanged material (4·6%) together with an unknown product.

Reduction of 14-*hydroxy*-3-*methoxy*-6-*oxo*-N-*methylmorphinan* (XIV)

(a) *Huang-Minlon reduction.* Compound XIV (1 g) was reduced as described for XII. The crude product (0·85 g) was chromatographed on alumina and eluted with benzene. The crystalline material (0·58 g) was purified from alcohol to yield 0·43 g (45%) of XV, m.p. 143–144·5°, $[\alpha]_D^{25}$ −76·6° ± 2° (*c*, 1·029, Chf); ν_{max} 3455 cm^{-1} (C_{14}—OH) (Found: C, 75·11; H, 8·81; N, 4·86. $C_{18}H_{25}O_2N$ requires: C, 75·22; H, 8·77; N, 4·87%).

Further elution with $CHCl_3$ gave 0·237 g the crystalline material, which was recrystallized from alcohol to give azine derivative XVI, m.p. 259–261°, $[\alpha]_D^{30}$ −311·2° ± 2° (*c*, 1·007, Chf), ν_{max} 3460 (C_{14}—OH) and 1640 cm^{-1} (>C=N—). (Found: C, 72·03; H, 7·93; N, 9·36. $C_{36}H_{46}O_4N_4$ requires: C, 72·21; H, 7·74; N, 9·36%). Mol. wt: 645·5 (Rast). $C_{36}H_{46}O_4N_4$ requires: 598·8.

(b) *Clemmensen reduction.* A soln of 2·75 g XIV in 30 ml conc HCl was heated with amalgamated Zn (prepared from 30 g Zn powder and 2 g $HgCl_2$) for 7 hr, during which time 2 ml conc HCl was added every ½ hr. The crude product was chromatographed on alumina. The material (0·84 g) obtained from the benzene eluate was recrystallized from alcohol to afford 0·5 g (19%) of XV, m.p. and the mixed m.p. with the above-mentioned product 142–143°. The product (0·92 g) obtained by the further elution with benzene–$CHCl_3$ (1:1) was purified from alcohol to give 0·845 g (31%) the unchanged starting ketone, m.p. 191–192°.

(c) *Zinc-hydrochloric acid reduction.* The compound XIV (5 g) was reduced with 33 g Zn powder and 83 ml conc. HCl as for XII and treated as above. The crude material (4·7 g) was chromatographed over alumina and eluted with benzene to give 3·81 g (79·8%) the crystalline non-ketonic compound, which was recrystallized from alcohol, 3·74 g (78·6%), m.p. 145–146°.

(d) *Desulfurization of the thioketal of* XIV. To a soln of 3 g XIV and 9 g ethanedithiol 9 ml BF_3-etherate was added and the soln kept at room temp for 3 days. The soln was poured into 200 g ice-water, and extracted with benzene. The water layer was made alkaline, and extracted with $CHCl_3$. The crude product was recrystallized from alcohol to give 2·38 g (63·5%) the thioketal, m.p. 183–185°, $[\alpha]_D^{30}$ +38·6° ± 2° (*c*, 1·069, Chf). (Found: C, 63·72; H, 7·25; N, 3·46; S, 17·26. $C_{20}H_{27}O_2NS_2$ requires: C, 63·62; H, 7·21; N, 3·71; S, 16·99%).

A soln of 1 g of the thioketal in 50 ml MeOH was refluxed with Raney-Ni (prepared from 20 g Ni-Al alloy) for 8 hr. The residue (0·42 g) obtained from the MeOH soln was recrystallized from alcohol to give 0·36 g (47·3%) the non-ketonic compound XV, m.p. 143·5–144·5°.

Ullmann reaction of 14-*hydroxytetrahydrodesoxycodeine* (IX)

A soln of 3 g IX and 3 g bromobenzene in 10 cc pyridine was refluxed with 0·33 g Cu powder and 3 g finely powdered K_2CO_3 for 6 hr. The crude product was chromatographed on alumina and eluted with benzene. The crystalline material (3·45 g) was recrystallized from alcohol to give 3·07 g (82%) of XVII, m.p. 109–111°. This product was identical with that prepared from XII by comparison of IR spectra.

Sodium liquid ammonia reduction of 14-*hydroxy*-3-*methoxy*-4-*phenoxy*-N-*methylmorphinan* (XVII)

A soln of XVII (1 g) in 2 ml toluene and 30 ml liquid ammonia was reduced with 0·3 g metallic Na. Excess of the reagent was destroyed with NH_4Cl, and liquid ammonia was allowed to evaporate. The residue was treated with toluene and dil alkali, and washed with water. The crystalline material (0·735 g) was recrystallized from alcohol to give 0·714 g (94%) of XV, m.p. and mixed m.p. with the product prepared from XIV, 143·5–144·5°. The picrate was prepared in ether and recrystallized from alcohol, m.p. 191–193°. The 14-acetate, recrystallized from pet. ether, m.p. 100–101°, $[\alpha]_D^{24}$ −111·0° ± 2° (*c*, 1·042, Chf), ν_{max} 1727 cm^{-1} (C_{14}—AcO). (Found: C, 73·02; H, 8·36; N, 4·29. $C_{20}H_{27}O_3N$ requires: C, 72·92; H, 8·26; N, 4·25%).

3,14-*Dihydroxy*-N-*methylmorphinan* (XXI)

A soln of 0·4 g of XV in 4 ml 48% HBr was refluxed for 15 min. The crude phenolic compound (0·36 g) was recrystallized from 95% alcohol to afford 0·275 g (72·3%) of pure product, m.p. 246–248°, $[\alpha]_D^{25}$ −80·3° ± 2° (*c*, 1·048, Chf), ν_{max} 3375 cm^{-1} (C_3— and C_{14}—OH). (Found: C, 74·51; H, 8·43; N, 5·38. $C_{17}H_{23}O_2N$ requires: C, 74·69; H, 8·48; N, 5·12%).

This compound is easily methylated to the starting methoxy derivative by the action of $PhNMe_3OMe$. The 3,14-diacetate, prepared in usual manner, did not crystallize on standing, ν_{max} 1764 (C_3—AcO) and 1727 cm^{-1} (C_{14}—AcO).

The Ullmann reaction of 14-*hydroxydihydrodesoxycodeine*-C (XI)

A soln of 9 g XI and 9 g bromobenzene in 30 ml pyridine was refluxed in the presence of 1 g Cu powder and 9 g finely powdered K_2CO_3 for 6 hr. The crude product was chromatographed over alumina and eluted with benzene–$CHCl_3$ (1:1) to give 9·8 g of crystalline material. Recrystallization from alcohol afforded 8·7 g (77%) of XVIII, m.p. 134–135°, $[\alpha]_D^{23}$ −33·6° ± 2° (*c*, 1·041, Chf), ν_{max} 3400 (C_{14}—OH) and 1650 cm^{-1} (>C=C<), NMR: 5·92 (C_5—H) and 5·35 ppm (C_6—H). (Found: C, 76·23; H, 7·38; N, 3·83. $C_{24}H_{27}O_3N$ requires: C, 76·36; H, 7·21; N, 3·71%).

Catalytic hydrogenation of this compound gave the XVII in high yield.

Sodium liquid ammonia reduction of 14-*hydroxydihydrodesoxycodeine*-C *phenyl ether* (XVIII)

A soln of 9 g of XVIII in 20 ml toluene and 250 ml liquid ammonia was reduced with 2·4 g metallic Na at −55°. The crude reduction product was recrystallized from alcohol to yield 6·15 g (90·4%) of XIX, m.p. 128·5–130°, $[\alpha]_D^{22}$ −7·4° ± 2° (*c*, 1·089, Chf), ν_{max} 3370 cm^{-1} (C_{14}—OH), NMR: 5·89 ppm (C_5— and C_6—H). (Found: C, 75·75; H, 8·12; N, 5·04. $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; N, 4·91%). Catalytic reduction of this compound over PtO_2 gave XV in high yield.

Sodium borohydride reduction of 14-*hydroxy*-3-*methoxy*-6-*oxo*-N-*methylmorphinan* (XIV)

To a soln of 4 g XIV in 80 ml MeOH was added 2 g $NaBH_4$ in small portions, and the soln was kept under stirring for 4 hr at room temp. AcOH (10 ml) was added to destroy the excess reagent, the solvent removed, the residue treated with dil NH_4OH and extracted with $CHCl_3$. Distillation of the solvent gave 3·75 g the crude product, which was chromatographed over alumina.

Elution with benzene–$CHCl_3$ (1:1) and with $CHCl_3$ afforded crystalline material, which were combined and recrystallized from benzene–pet. ether (1:4) to give 1·6 g (39·8%) of XXII, m.p. 94–96°, $[\alpha]_D^{25}$ −32·1° ± 2° (*c*, 1·038, Chf), $\nu_{max}^{CCl_4}$ 3593 (C_6—OH) and 3442 cm^{-1} (C_{14}—OH). (Found: C, 71·37; H, 8·48; N, 4·76. $C_{18}H_{25}O_3N$ requires: C, 71·25; H, 8·31; N, 4·62%).

Further elution with 2% MeOH–$CHCl_3$ gave the crystalline product, which was recrystallized from benzene–pet. ether (4:1) to give 1·56 g (38·8%) of XXIII, m.p. 153–155°, $[\alpha]_D^{25}$ −91·4° ± 2° (*c*, 1·042, Chf), $\nu_{max}^{CCl_4}$ 3618 (C_6—OH) and 3441 cm^{-1} (C_{14}—OH). (Found: C, 71·37; H, 8·31; N, 4·36. $C_{18}H_{25}O_3N$ requires: C, 71·25; H, 8·31; N, 4·62%).

Sodium borohydride reduction of 3,14-*dihydroxy-6-oxo*-N-*methylmorphinan* (XX)

A soln of 2·9 g XX in 50 ml MeOH was reduced with 2 g $NaBH_4$ as above, and excess of the reagent was destroyed by the action of AcOH. After removal of the solvent the residue was dissolved in water, made basic with NH_4OH, saturated with NaCl, and extracted repeatedly with $CHCl_3$. The crude product (3·5 g) was chromatographed over alumina and eluted with 2% MeOH–$CHCl_3$. Removal of the solvent gave 2·38 g of XXIV as amorphous solid, which was converted to the hydrochloride. It melted at 165–190° (under foaming) after recrystallization from acetone–water. $[\alpha]_D^{28}$ −18·0° ± 2° (*c*, 0·979, alc). (Found: C, 55·33; H, 7·94; N, 4·03; Cl, 10·01; H_2O, 13·31. $C_{17}H_{23}O_3N \cdot HCl \cdot 2.5H_2O$ requires: C, 55·05; H, 7·88; N, 3·78; Cl, 9·56; H_2O, 12·14%).

Further elution with 5% MeOH–$CHCl_3$ gave 0·74 g the epimeric alcohol, which was recrystallized from alcohol to give 0·51 g of XXV, m.p. 215–215·5°, $[\alpha]_D^{29}$ −82·6° ± 2° (*c*, 0·981, alc). (Found: C, 67·86; H, 8·75; N, 4·33. $C_{17}H_{23}O_3N \cdot C_2H_5OH$ requires: C, 68·03; H, 8·71; N, 4·18%). The hydrobromide, m.p. 293° (dec).

Methylation of trihydroxy-N-*methylmorphinan* (XXIV)

The amorphous triol XXIV (0·289 g) was methylated by the action of $PhNMe_3OMe$. The crude product (0·256 g) was purified by alumina chromatography developing with benzene followed by recrystallization from benzene–pet. ether, m.p. 95–96° and identical with XXII was demonstrated by mixed m.p.

Acetylation of the 6α,14-*dihydroxy*-3-*methoxy*-N-*methylmorphinan* (XXII)

The compound XXII (0·2 g) was heated with excess Ac_2O under N_2 for 5 hr, and the crude product twice recrystallized from 95% alcohol to give 0·215 g of XXVI, m.p. 186–187·5°, $[\alpha]_D^{26}$ −90·6° ± 2° (*c*, 1·024, Chf), ν_{max} 1726 cm^{-1} (C_6 and C_{14}—AcO), NMR: 5·00 (C_6—H), 2·15 (C_{14}—AcO) and 1·62 ppm (C_6—AcO). (Found: C, 68·20; H, 7·66; N, 3·28. $C_{22}H_{29}O_5N$ requires: C, 68·19; H, 7·54; N, 3·62%).

A soln of the above-mentioned diacetate (0·865 g) in 20 ml MeOH was refluxed for 6 hr. The residue obtained from removal of the solvent was chromatographed over SiO_2. The less polar product (0·127 g) eluted with 2% MeOH–$CHCl_3$ was identified as the starting diacetate. Further elution with the same solvent gave a mixture of the diacetate and the monoacetate. The more polar product (0·314 g) developed with 5% MeOH $CHCl_3$ was purified from alcohol to give 0·244 g (31·6%) 6α-acetoxy-14-hydroxy-3-methoxy-N-methylmorphinan, m.p. 142·5–144°, $[\alpha]_D^{24}$ −39·4° ± 2° (*c*, 1·041, Chf); ν_{max} 3370 (C_{14}—OH) and 1720 cm^{-1} (C_6—AcO). NMR: 5·00 (C_6—H) and 1·60 ppm (C_6—AcO). (Found: C, 69·62; H, 8·06; N, 3·99. $C_{20}H_{27}O_4N$ requires: C, 69·54; H, 7·88; N, 4·06%).

Acetylation of 6β,14-*dihydroxy*-3-*methoxy*-N-*methylmorphinan* (XXIII)

Acetylation of XXIII as above followed by recrystallization of the crude product from alcohol gave the diacetate, m.p. 203–204°, $[\alpha]_D^{26}$ −105·3° ± 2° (*c*, 0·990, Chf); ν_{max} 1728 cm^{-1} (C_6—AcO and C_{14}—AcO); NMR: 4·67 (C_6—H), 2·18 (C_{14}—AcO) and 2·05 ppm (C_6—AcO). (Found: C, 67·89; H, 7·40; N, 3·77. $C_{22}H_{29}O_5N$ requires: C, 68·19; H, 7·54; N, 3·62%).

A soln of 0·2 g XXIII in 2 ml Ac_2O was kept at room temp overnight. Dilution with water, conversion to alkaline and extraction with benzene gave 0·234 g the crude acetate, which was chromatographed on alumina and developed with benzene. Recrystallization of the crystalline material from benzene–pet. ether afforded the 6β-acetoxy-14-hydroxy derivative, m.p. 173–174°, $[\alpha]_D^{25}$ −79·4 ± 2° (*c*, 1·003, Chf); ν_{max} (*c*, 0·989, Chf); ν_{max}^{Nujol} 1761 (C_3—AcO) and 1731 cm^{-1} (C_6—AcO and C_{14}—AcO); NMR: 4·67 (C_6—H), C, 69·40; H, 7·95; N, 4·07. $C_{20}H_{27}O_4N$ requires: C, 69·54; H, 7·88; N, 4·06%).

Acetylation of 3,6α,14-*trihydroxy*-N-*methylmorphinan* (XXIV)

The compound XXIV (0·5 g) was heated with excess Ac_2O under N_2 for 10 hr. The crude product (0·687 g) was chromatographed over alumina with benzene. Recrystallization from 95% alcohol gave 0·53 g (73·8%) of the triacetate, m.p. 162–163·5°, $[\alpha]_D^{24}$ −80·5° ± 2° (*c*, 1·058, Chf); ν_{max}^{Nujol} 1770 (C_3—AcO) and 1732 cm^{-1} (C_6—AcO and C_{14}—AcO); NMR: 5·07 (C_6—H), 2·12 (C_{14}—AcO) and 1·65 ppm (C_6—AcO). (Found: C, 66·42; H, 7·03; N, 3·59. $C_{23}H_{29}O_6N$ requires: C, 66·49; H, 7·04; N, 3·37%).

Acetylation of 3,6β,14-*trihydroxy*-N-*methylmorphinan* (XXV)

Similar treatment of 0·28 g XXV gave 0·283 g of the triacetate, m.p. 166–168°, $[\alpha]_D^{30}$ −91·7° ± 2° (*c*, 0·989, Chf); ν_{max}^{Nujol} 1761 (C_3—AcO) and 1731 cm^{-1} (C_6—AcO and C_{14}—AcO); NMR: 4·67 (C_6—H),

2·17 (C_{14}—AcO) and 2·03 ppm (C_6—AcO). (Found: C, 66·42; H, 7·12; N, 3·45. $C_{23}H_{29}O_6N$ requires: C, 66·49; H, 7·04; N, 3·37%).

Reaction of 14-*hydroxy*-3-*methoxy*-6-*oxo*-N-*methylmorphinan* (XIV) *with methyllithium*

To a soln of MeLi in THF (prepared from 0·7 g metallic Li and 7·1 g MeI in ether and excess of the ether was removed by distillation after addition of THF) was added a soln of XIV (1 g) in THF under cooling, and the soln kept stirred at room temp for 5·5 hr. The soln was poured into dil AcOH, and the volatile compounds removed by distillation. The water layer was made basic with NH_4OH, and extracted with dichloromethane.

The crude material (0·98 g) was treated with ether to separate the insoluble material (0·41 g), which was identified as the starting material. The material (0·49 g) soluble in ether still showed the presence of the carbonyl compound in the IR spectrum. Treatment with hydroxylamine followed by chromatography on alumina with ether afforded 0·315 g (30%) non-ketonic compound, m.p. 107–109°.

Reaction of 14-*acetoxy*-3-*methoxy*-6-*oxo*-N-*methylmorphinan* (XXIX) *with methyllithium*

To a soln of MeLi in ether (prepared from 8·8 g metallic Li and 85 g MeI in 200 ml ether) a soln of 20 g XXIX in 200 ml ether was added at −5° during 20 min and the soln stirred at 0° for 5 hr. The crude product (18·9 g) obtained by the above-mentioned treatment was chromatographed on alumina, and developed with ether. Recrystallization of the crystalline material from ether afforded 15·08 g (81·6%) XXVIII, m.p. 108–109°, $[\alpha]_D^{23}$ −48·3° ± 2° (*c*, 1·068, Chf); $\nu_{max}^{CCl_4}$ 3595 (C_6—OH) and 3440 cm^{-1} (C_{14}—OH); NMR: 1·23 ppm (C_6—CH_3). (Found: C, 71·99; H, 8·59; N, 4·67. $C_{19}H_{27}O_3N$ requires: C, 71·89; H, 8·57; N, 4·41%).

This compound was undepressed on admixutre with the product described above.

Dehydration of 6α,14-*dihydroxy*-3-*methoxy*-6β,N-*dimethylmorphinan* (XXVIII)

(a) *Acid catalyzed dehydration.* A soln of 2·38 g XXVIII in 45 ml glacial AcOH was heated with 0·85 ml 60% perchloric acid at 100° for 10 min. The soln was diluted with 25 ml water, and the volatile compounds were removed by distillation under reduced press. The remaining soln was made alkaline with NH_4OH, and extracted with dichloromethane. Distillation of the solvent gave 2·23 g crystalline material, m.p. 85–100°, $[\alpha]_D^{23}$ −136·0° ± 2° (*c*, 1·007, Chf). The perchlorate obtained from the above basic product was recrystallized from aqueous alcohol to give 2·05 g the less soluble salt, m.p. 131–135°. Liberation of the salt and recrystallization of the base from alcohol gave 1·141 g of XXXI, m.p. 132·5–134°. $[\alpha]_D^{25}$ −181·5° ± 2° (*c*, 1·005, Chf); NMR: 5·14 ppm (C_7-vinyl proton). (Found: C, 76·26; H, 8·37; N, 4·74. $C_{19}H_{25}O_2N$ requires: C, 76·22; H, 8·42; N, 4·68%). Concentration of the mother liquor of the perchlorate gave 0·533 g the second crop, m.p. 200–232° (dec; sinterring at 145°) and 0·095 g the third crop, m.p. 230–235° (dec). These products were combined, and recrystallized from alcohol to give 0·298 g the second perchlorate, m.p. 239–241° (dec).

Conversion to the base followed by recrystallization from alcohol gave XXX, m.p. 122–124°, $[\alpha]_D^{25}$ −54·5° ± 2° (*c*, 1·007, Chf); NMR: 5·65 ppm (C_5-vinyl proton). (Found: C, 76·09; H, 8·48; N, 4·80. $C_{19}H_{25}O_2N$ requires: C, 76·22; H, 8·42; N, 4·68%).

(b) *Base catalyzed dehydration.* To a soln of 2·38 g XXVIII in 25 ml pyridine 3·6 g $SOCl_2$ was added with cooling, and the soln was kept stirred for 20 min. The soln was diluted with 50 g ice-water, and made strongly basic with NaOH aq. The pyridine was removed by distillation under reduced press, and the anhydro compound extracted with dichloromethane. Removal of the solvent gave 2·2 g the crystalline material, m.p. 100–110°, $[\alpha]_D^{22}$ −81·7° ± 2° (*c*, 1·042, Chf). The separation was performed by the same treatment as above, and 0·955 g of XXX, m.p. 122–124° and 0·244 g of XXXI, m.p. 134–135°, were obtained.

The Wittig reaction of 14-*hydroxy*-3-*methoxy*-6-*oxo*-N-*methylmorphinan* (XIV)

To a Wittig reagent prepared from 0·42 g metallic Li, 4·7 g bromobenzene and 10·7 g triphenylmethylphosphonium bromide in 50 ml ether, a soln of 3 g XIV in 140 ml THF was added, and the ether was fractionally distilled off. The soln was refluxed under N_2 for 42 hr, and poured onto 100 g ice. The soln was concentrated to about half volume, and extracted with $CHCl_3$. The basic product was extracted with dil phosphoric acid. The crude product (2·55 g) was chromatographed over alumina and eluted with benzene and $CHCl_3$. The material obtained from the benzene eluate was purified by crystallization from alcohol to give 1·297 g (43·7%) of XXXII, m.p. 181–182°, $[\alpha]_D^{23}$ −22·1° ± 2° (*c*, 1·033, Chf); ν_{max} 887 cm^{-1} (>C=CH_2); NMR: 4·63 ppm (>C=CH_2). Found: C, 76·28; H, 8·50; N, 4·89. $C_{19}H_{25}O_2N$ requires: C, 76·22;, H, 8·42; N, 4·68%).

Recrystallization of the product obtained from the $CHCl_3$ eluate yielded unchanged 6-oxo compound (0·756 g, 25·4%). A similar reaction with XXIX gave the methylene derivative XXXII in 48·9% yield.

Reduction of the unsaturated compounds, XXX, XXXI *and* XXXII.

(a) A soln of 0·3 g of XXX in 10 ml 50% AcOH was hydrogenated on 0·03 g PtO_2. After the uptake of H_2 had ceased, the catalyst was removed by filtration and washed with a small amount of water. The combined soln was made alkaline with NH_4OH, and extracted with CH_2Cl_2. A gas chromatogram of the crude product ($[\alpha]_D$ −44·8°) showed two peaks at retention times at 10·2 and 11·6 min in a ratio of 12:88.

Two recrystallizations of the mixture from alcohol gave XXXIII, m.p. 110–111°, $[\alpha]_D^{23}$ −40·1° ± 2° (*c*, 1·058, Chf). ν_{max} 3440 cm^{-1} (C_{14}—OH); NMR: 0·67 ppm (C_6—CH_3). (Found: C, 75·64; H, 9·08; N, 4·68. $C_{19}H_{27}O_2N$ requires: C, 75·71; H, 9·03; N, 4·65%).

(b) A soln of 0·3 g of XXX in 10 ml 50% AcOH was catalytically reduced over Pd-C (prepared from 0·1 g $PdCl_2$), and the uptake of H_2 was rather sluggish compared with above case. The crude product had $[\alpha]_D$ −87·7° and showed two peaks at the same retention times as above in a ratio of 93:7 on a gas chromatogram.

Two recrystallization of the crude product from alcohol yielded XXXIV, m.p. 108–109°, $[\alpha]_D^{23}$ −90·1° ± 2° (*c*, 1·066, Chf); ν_{max} 3445 cm^{-1} (C_{14}—OH); NMR: 0·92 ppm (C_6—CH_3). (Found: C, 75·90; H, 9·26; N, 4·41. $C_{19}H_{27}O_2N$ requires: C, 75·71; H, 9·02; N, 4·65%). On admixture with XXXIII it melted at 80–100°.

(c) A soln of 0·3 g of XXXI in 10 ml 50% AcOH was hydrogenated in the presence of 0·3 g PtO_2. The crude reduction product ($[\alpha]_D$ −46·6°) showed two peaks in a ratio of 18:82 on a gas chromatogram indicating that XXXIII was predominantly present.

The same hydrogenation on Pd-C gave mainly XXXIV. A gas chromatogram of the reduction product ($[\alpha]_D$ −88·5°) showed two peaks in a ratio of 92:8.

(d) A soln of 0·3 g of XXXII in 10 ml 50% AcOH was reduced over Pt_2O. A gas chromatogram of the reduction product ($[\alpha]_D$ −47·5°) showed two peaks in a ratio of 11:89. This indicates that XXXIII is mainly produced. The similar catalytic reduction over Pd-C gave a mixture of 6α- and 6β-methyl derivatives. A gas chromatogram of the product ($[\alpha]_D$ −77·3°) indicated two peaks in a ratio of 76:24 showing this reduction gave mainly XXXIV.

3,14-*Dihydroxy*-6α,N-*dimethylmorphinan* (XXXV)

A soln of XXXIII (1 g) in 5 ml 48% HBr was refluxed for 20 min. The residue obtained after removal of excess reagent was dissolved in water, made basic with NH_4OH and extracted with CH_2Cl_2. The crude phenolic substance (0·795 g) was recrystallized from alcohol to give 0·652 g (68%) of XXXV, m.p. 221·5–222·5°, $[\alpha]_D^{23}$ −41·3° ± 2° (*c*, 1·036, Chf); ν_{max}^{Nujol} 3300 and 3260 cm^{-1} (C_3- and C_{14}-OH). (Found: C, 75·14; H, 8·87; N, 5·16. $C_{18}H_{25}O_2N$ requires: C, 75·22; H, 8·77; N, 4·87%).

3,14-*Dihydroxy*-6β,N-*dimethylmorphinan* (XXXVI)

A soln of 1·5 g XXXIV in 8 ml 48% HBr was refluxed for 20 min and treated as above. The crude phenolic substance was recrystallized from alcohol to give 1·247 g (87%) of XXXVI, m.p. 226–228° (dec, sinterring at 220°), $[\alpha]_D^{23}$ −93·8° ± 2° (*c*, 1·057, Chf); ν_{max}^{Nujol} 3215 cm^{-1} (C_3— and C_{14}—OH). (Found: C, 75·23; H, 8·87; N, 5·04. $C_{18}H_{25}O_2N$ requires: C, 75·22; H, 8·77; N, 4·87%).

3,14-*Dihydroxy*-6-*methylene*-N-*methylmorphinan* (XXXVII)

A soln of 2·9 g of XX was treated with triphenylphosphinemethylene (prepared from 0·7 g metallic Li, 7·85 g bromobenzene and 17·35 g triphenylmethylphosphonium bromide in THF) as for the 3-methoxy derivative XIV. The crude exo-methylene product (2·93 g) was chromatographed over alumina and eluted with $CHCl_3$. Removal of the solvent and recrystallization of the residue (1·5 g) from alcohol afforded 1·25 g (43%) of XXXVII, m.p. 239·5–240·5°, $[\alpha]_D^{24}$ −30·1° ± 2° (*c*, 0·957, Chf); ν_{max}^{Nujol} 3280 (C_3— and C_{14}—OH) 887 cm^{-1} (>C=CH_2). (Found: C, 75·54; H, 8·17; N, 4·96. $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; N, 4·91%). Methylation of this compound with $NPhMe_3OMe$ gave, in 77% yield, XXXII, m.p. 181·5–182·5°.

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

REFERENCES

[1] Y. K. Sawa, N. Tsuji, and S. Meda, *Tetrahedron* **15**, 154 (1961).
[2] Y. K. Sawa, M. Horiuchi, and K. Tanaka, *Ibid.* **21**, 1133 (1965).
[3] I. Kh. Fel'dman and A. I. Lyutenberg, *Chem. Abstr.* **40**, 6489 (1946).
[4] I. Seki, *Ann. Sankyo Res. Lab.* **12**, 52 (1960).
[5] M. Freund and E. Speyer, *Z. Angew. Chem.* **27**, i. 250 (1914).
[6] E. Speyer, *Liebigs Ann.* **430**, 1 (1923).
[7] I. Seki, *Ann. Sankyo Res. Lab.* **13**, 75 (1961).
[8] I. Seki, *Ibid.* **13**, 67 (1961); T. D. Perrine and L. F. Small, *J. Org. Chem.* **17**, 1540 (1952
[9] Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron* **20**, 2255 (1964).
[10] U. Wiess, *J. Org. Chem.* **22**, 1505 (1957).