

## ELIMINATION OF THE 4-HYDROXYL GROUP OF THE ALKALOIDS RELATED TO MORPHINE—II\*

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**Abstract** Dihydrothebaine- $\phi$ , dihydrothebainone- $\Delta^5$ -enol methylether and dihydrothebainone were converted to the respective 4-phenylethers by Ullmann reaction in good yields. These phenylether derivatives were reduced to 4-desoxy compounds by sodium-liquid ammonia reduction.

Clemmensen reduction of the phenylether and the desoxy derivatives gave (·)-3-methoxy-4-phenoxy-N-methyl-morphinan and (-)-3-methoxy-N-methylmorphinan respectively.

In a previous paper† the elimination of the 4-hydroxyl group of sinomenine and its derivatives was reported. The present paper is concerned with the synthesis of (-)-3-methoxy-N-methylmorphinan and its derivatives.

Recently, many N-methylmorphinan derivatives were synthesized from 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline derivatives by Grewe<sup>1</sup> and by Schnider.<sup>2</sup>

Among these compounds (-)-3-hydroxy-N-methylmorphinan has been found to have 3-5 times the activity of morphine as an analgesic. Elimination of the 4-hydroxyl group of thebaine derivatives may give some pharmacologically interesting compounds. The methods employed are the same as those used previously in the sinomenine series but using thebaine as a starting material.

In 1950, Bentley<sup>3</sup> succeeded in scission of the 4-5 oxygen bridge of thebaine (I) by the sodium-ammonia reduction and obtained dihydrothebaine- $\phi$  (II) in excellent yield.

Under conditions similar to those used for sinomenine, dihydrothebaine- $\phi$  (II) was converted to the 4-phenylether (III) in 85 per cent yield. Hydrogenation of this compound over palladium-strontium carbonate gave the 4-phenylether of dihydrothebainone- $\Delta^5$ -enol methylether (IV) and successive treatment with dilute hydrochloric acid gave dihydrothebainone-4-phenylether (V) in about 70 per cent yield based on dihydrothebaine- $\phi$ -phenylether (III).

The Ullmann reaction of dihydrothebainone- $\Delta^5$ -enol methylether (VI) and of dihydrothebainone (VII) gave their respective phenylethers in about 70 per cent yield. Sodium-liquid ammonia reduction of dihydrothebaine- $\phi$ -phenylether (III) afforded desoxydihydrothebaine- $\phi$  (VIII) in 90 per cent yield. After hydrogenation, this compound was treated with dilute hydrochloric acid to give desoxydihydrothebainone (IX) in 50 per cent yield. Sodium-ammonia reduction of the crude phenylether of

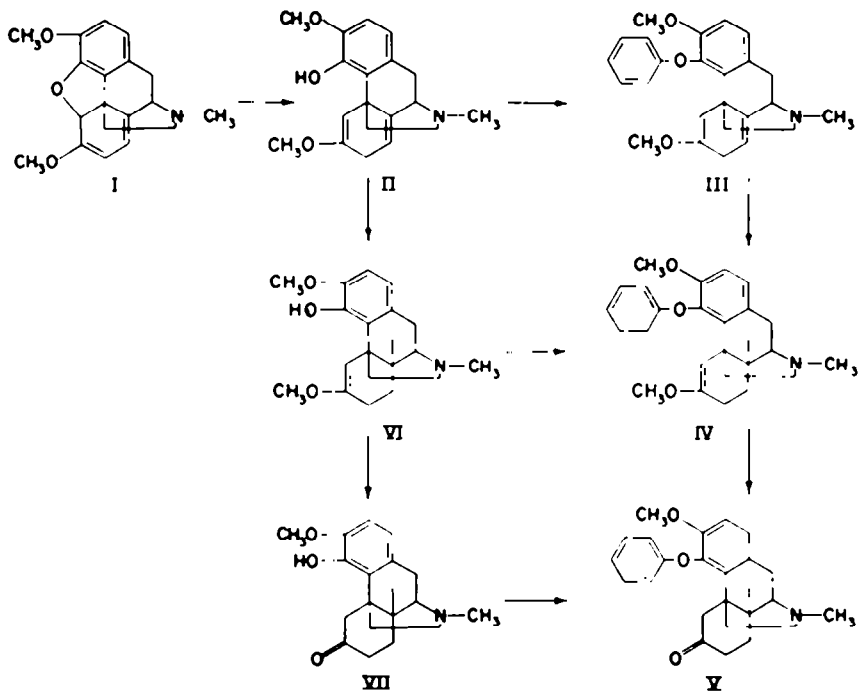
\* An outline of this paper was reported at the I.U.P.A.C. Symposium on the Chemistry of Natural Products in Melbourne, Australia, August, 1960.

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

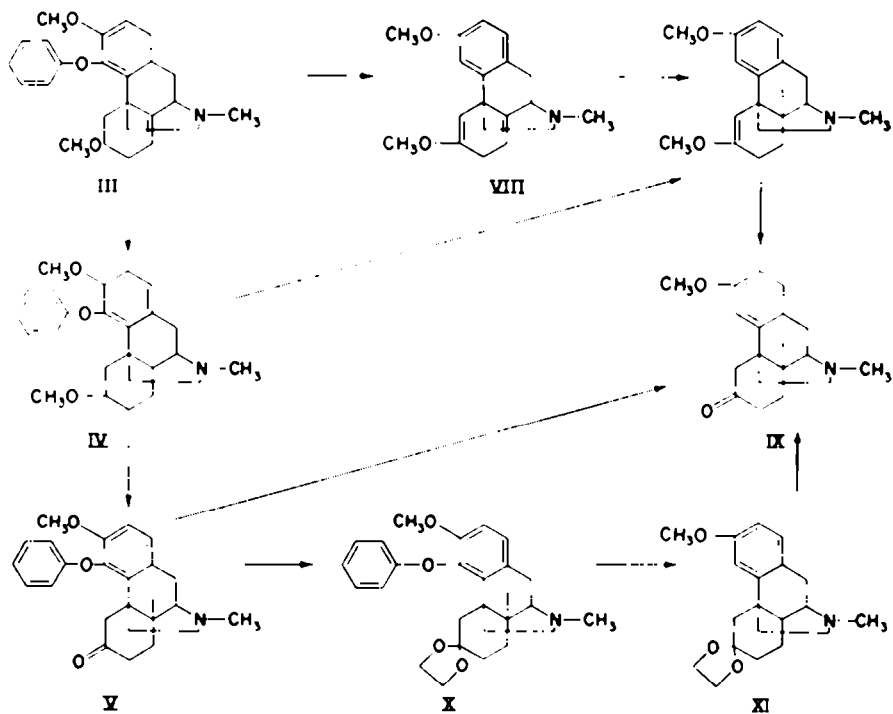
<sup>1</sup> R. Grewe and A. Mondon, *Chem. Ber.* 81, 279 (1948); R. Grewe, A. Mondon and E. Nolte, *Liebigs Ann.* 564, 161 (1949).

<sup>2</sup> O. Schnider and A. Grüssner, *Helv. Chim. Acta* 32, 821 (1949); *Ibid* 34, 2211 (1951); O. Schnider, A. Brossi and K. Vogler, *Ibid* 37, 710 (1954); *Ibid* 33, 1437 (1950).

<sup>3</sup> K. W. Bentley and R. Robinson, *Experientia* 6, 353 (1950); K. W. Bentley, R. Robinson and A. E. Wain, *J. Chem. Soc.* 1952, 958.

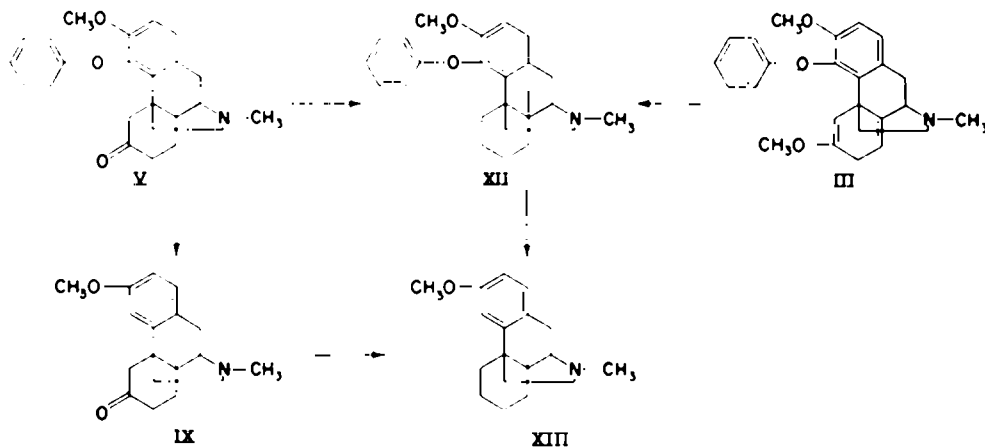


dihydrothebainone- $\Delta^5$ -enol methylether (IV) and successive hydrolysis also gave the same carbonyl compound (IX) in 85 per cent yield. Dihydrothebainone-4-phenylether (V) was treated with ethylene glycol and *p*-toluene sulfonic acid in order to protect the



6-carbonyl group and successive sodium-ammonia reduction of the product gave the ethylene glycol ketal of desoxydihydrothebainone (XI). The action of dilute hydrochloric acid on the ketal derivative gave desoxydihydrothebainone i.e. (-)-3-methoxy-6-oxo-N-methylmorphinan (IX) in 75 per cent yield based on dihydrothebainone-4-phenylether.

Sodium-ammonia reduction of dihydrothebainone-4-phenylether (V) also gave the same desoxy base, but in a poor yield. Furthermore, tetrahydrodesoxycodine-4-phenylether (XII) was obtained from dihydrothebainone-4-phenylether (V) and dihydrothebaine- $\phi$ -phenylether (III) by the Clemmensen reduction in yields of 85 and 25 per cent respectively.



The 4-phenoxy group of tetrahydrodesoxycodine (XII) was also eliminated by sodium-ammonia reduction to yield (-)-3-methoxy-N-methylmorphinan (XIII) in almost quantitative yield. The Clemmensen reduction of desoxydihydrothebainone (IX) also gave the same compound (XIII) in 55 per cent yield. A number of these new 4-desoxy compounds have been screened for analgesic and antitussive activity, but the pharmacology of these compounds will be reported elsewhere.

#### EXPERIMENTAL

All melting points are uncorrected. Analyses of the compounds were carried out by Messrs. K. Miyahara, Y. Daikatsu, T. Takaoka and Miss U. Kasugai of our laboratory. The infra-red spectra were determined by Messrs. Y. Matsui and M. Takasuka on a Koken D.S. 301 infra-red spectrophotometer.

##### *Dihydrothebaine- $\phi$ -4-phenylether*

A pyridine solution of 47.1 g dihydrothebaine- $\phi$  and 5.71 g bromobenzene was refluxed for 10 hr under stirring with 32.4 g finely powdered  $K_2CO_3$  and 4.7 g copper. The reaction mixture was treated as in the case of sinomenine-4-phenylether. The benzene eluate gave 50.38 g dihydrothebaine- $\phi$ -4-phenylether (86%) which crystallized from isopropanol, m.p. 135-136°,  $[\alpha]_D^{20} = 34.1^\circ$ ; 2' (c, 0.973, alc.). I.R.  $\lambda_{max}^{CHCl_3}$  1710  $cm^{-1}$ , 1665  $cm^{-1}$  ( $\begin{matrix} H \\ | \\ -C-C-OCH_3 \end{matrix}$ ). (Found: C, 77.17; H, 7.10; N, 3.66.  $C_{24}H_{27}O_2N$  requires: C, 77.09; H, 6.99; N, 3.60%.)

The methiodide was prepared in and crystallized from alcohol, m.p. 191-192°. (Found: C, 57.98; H, 6.26; N, 2.12.  $C_{24}H_{27}O_2N \cdot CH_3I \cdot C_7H_8OH$  requires: C, 58.23; H, 6.28; N, 2.42%.)

The picrate was prepared in ether and crystallized from alcohol, m.p. 187–188°. (Found: C, 60.05; H, 5.04; N, 9.00.  $C_{23}H_{21}O_3N_3C_6H_3O_7N_3$  requires: C, 60.18; H, 4.89; N, 9.06%.)

#### 4-Phenylether of dihydrothebainone- $\Delta^3$ -enol methyl ether

(a) *From dihydrothebaine- $\phi$ -4-phenylether.* Twenty grams of dihydrothebaine- $\phi$ -4-phenylether was hydrogenated over 16 g palladium strontium carbonate (5% Pd) in 300 cc alcohol. After absorption of 1290 cc hydrogen in 15 hr and filtration of the catalyst, the solvent was removed to yield 20.2 g of crude product, m.p. 92–95°. A small sample was recrystallized from pet. ether for analysis, m.p.

106–107°.  $[\alpha]_D^{25}$  55.4 : 1° (c, 2.069, alc.). I.R.  $\lambda_{max}^{CHCl_3}$  1662  $cm^{-1}$   $\left( \begin{array}{c} H \\ | \\ -C \quad C \begin{array}{l} \diagup \\ \diagdown \end{array} \\ \quad \quad \quad OCH_3 \end{array} \right)$ . (Found: C, 76.49; H, 7.47; N, 3.46.  $C_{28}H_{30}O_3N$  requires: C, 76.69; H, 7.47; N, 3.58%.)

(b) *From dihydrothebainone- $\Delta^3$ -enol methylether.* A pyridine solution of 9.45 g dihydrothebainone- $\Delta^3$ -enol methylether and 9.4 g bromobenzene was refluxed for 15 hr with  $K_2CO_3$  and copper. The reaction mixture was treated as usual and the product was chromatographed on alumina. The benzene eluate gave 11.28 g of a syrup which on standing solidified, m.p. 93–97°. A small sample was recrystallized from pet. ether, m.p. 106–107°. This compound was not depressed on admixture with the sample obtained from dihydrothebaine- $\phi$ -4-phenylether.

#### Dihydrothebainone-4-phenylether

(a) *From the phenylether of dihydrothebainone- $\Delta^3$ -enol methylether.* A solution of 11.28 g of the crude phenylether of dihydrothebainone- $\Delta^3$ -enol methylether in 55 cc 2 N HCl was heated for 10 min on a water-bath, cooled to room temp. and made basic with ammonia. The precipitated oil solidified on standing (8.9 g) and was recrystallized from isopropanol, 8.18 g (69% based on dihydrothebainone- $\Delta^3$ -enolmethylether.) m.p. 145–146°.  $[\alpha]_D^{25}$  11.2° : 2° (c, 0.980, alc.). I.R.  $\lambda_{max}^{CHCl_3}$  1712  $cm^{-1}$  (—C—O). (Found: C, 73.08; H, 7.41; N, 3.87;  $H_2O$ , 3.92.  $C_{24}H_{27}O_3N \cdot H_2O$  requires: C, 72.88; H, 7.39; N, 3.45;  $H_2O$ , 4.55%.)

The hydrochloride crystallized from alcohol-ethyl acetate, m.p. 276–277° (dec). (Found: C, 66.94; H, 6.90; N, 3.12; Cl, 8.23.  $C_{24}H_{27}O_3N \cdot HCl \cdot H_2O$  requires: C, 66.73; H, 7.00; N, 3.25; Cl, 8.20%.)

(b) *From dihydrothebainone.* A pyridine solution of 9.04 g dihydrothebainone and 9.4 g bromobenzene was refluxed for 15 hr with 12.4 g finely powdered  $K_2CO_3$  and 1 g copper. The benzene eluate afforded 9.04 g of the crude base which recrystallized from isopropanol, m.p. 144–145°, 8.23 g (71%). The mixed m.p. with the sample prepared from the phenylether of dihydrothebainone- $\Delta^3$ -enol methylether, was 145–146°.

#### Desoxydihydrothebaine- $\phi$

A solution of 15 g dihydrothebaine- $\phi$ -4-phenylether in 150 cc toluene was added dropwise to 150 cc liquid ammonia at –50–55°. 2.8 g metallic sodium was added to this stirred solution. After 1 hr the reaction mixture was worked up as described in the previous paper. The crude base was recrystallized from pet. ether, m.p. 86–87°, 10.3 g (90%).  $[\alpha]_D^{25}$  24.9° : 2° (c, 2.113, alc.). I.R.

$\lambda_{max}^{CHCl_3}$  1707  $cm^{-1}$ , 1666  $cm^{-1}$   $\left( \begin{array}{c} H \\ | \\ -C \quad C \begin{array}{l} \diagup \\ \diagdown \end{array} \\ \quad \quad \quad OCH_3 \end{array} \right)$ . (Found: C, 76.99; H, 7.75; N, 4.66.  $C_{19}H_{23}O_2N$  requires: C, 76.73; H, 7.80; N, 4.71%.)

#### Desoxydihydrothebainone- $\Delta^3$ -enol methylether

(a) *From the phenylether of dihydrothebainone- $\Delta^3$ -enol methylether.* A solution of 10.1 g of the phenylether of dihydrothebainone- $\Delta^3$ -enol methylether in 40 cc toluene was reduced with 1.9 g metallic sodium in 300 cc liquid ammonia. After 1 hr the reaction mixture yielded 7.7 g of crude

product (almost quantitative). A small sample was recrystallized from pet. ether to give colorless needles, m.p. 103.5–104.5°.  $[\alpha]_D^{20} - 70.5^\circ \pm 2^\circ$  (c, 1.039, alc.). I.R.  $\lambda_{\max}^{\text{CHCl}_3}$  1664  $\text{cm}^{-1}$   $\left( \begin{array}{c} \text{H} \\ | \\ \text{C}-\text{C} \\ | \quad \diagdown \\ \quad \quad \text{OCH}_3 \end{array} \right)$ .

(Found: C, 76.44; H, 8.51; N, 4.48.  $\text{C}_{10}\text{H}_{13}\text{O}_2\text{N}$  requires: C, 76.22; H, 8.42; N, 4.68%.)

(b) *From desoxydihydrothebaine- $\phi$* . 2 g desoxydihydrothebaine- $\phi$  was hydrogenated over 0.25 g Adams' catalyst in 50 cc alcohol. After 22 hr and absorption of 1 mole  $\text{H}_2$ , the catalyst was removed and the filtrate concentrated to yield 2 g crude product. This base could not be crystallized but treatment with dil HCl gave 0.85 g desoxydihydrothebainone.

#### *Desoxydihydrothebainone*

(a) *From desoxydihydrothebainone- $\Delta^5$ -enol methylether*. A solution of 30.5 g desoxydihydrothebainone- $\Delta^5$ -enol methylether, m.p. 103.5–104.5°, in 150 cc 2 N HCl was heated for 10 min on a water bath. The cooled solution was diluted with NaOH until basic and the precipitated colorless solid washed with water and dried, 27.8 g (96%), m.p. 183–186°. A small sample was crystallized from alcohol for analysis, m.p. 187–188.5°.  $[\alpha]_D^{20} 97.3^\circ \pm 2^\circ$  (c, 2.094, alc.). I.R.  $\lambda_{\max}^{\text{CHCl}_3}$  1708  $\text{cm}^{-1}$  (>C=O). (Found: C, 76.02; H, 8.21; N, 4.80.  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$  requires: C, 75.75; H, 8.12; N, 4.91%.)

(b) *From the ketal of dihydrothebainone-4-phenylether*. A benzene solution of 3.77 g dihydrothebainone-4-phenylether and 10 cc ethylene glycol was refluxed with 3.66 g toluene-*p*-sulphonic acid for 8 hr, with an "azeotropic" receiver to collect the volatile products. After cooling, the reaction mixture was treated with 10%  $\text{Na}_2\text{CO}_3$  until basic, washed with water and dried yielding 4.18 g of crude ketal derivative as a syrup. A solution of 2.8 g of this crude ketal in 50 cc ether was added dropwise to 100 cc liquid ammonia and the mixture treated with 0.35 g metallic sodium. The reaction mixture yielded 2.42 g of the crude desoxy base, m.p. 82–90°. A small sample was crystallized from ether for analysis, m.p. 96–97°.  $[\alpha]_D^{20} 32.5^\circ \pm 2^\circ$  (c, 1.046, alc.). (Found: C, 72.85; H, 8.37; N, 4.12.  $\text{C}_{10}\text{H}_{11}\text{O}_2\text{N}$  requires: C, 72.92; H, 8.26; N, 4.25%.)

The methiodide\* was prepared in and crystallized from acetone, m.p. 241–242°. (Found: C, 53.59; H, 6.87; N, 2.75; I, 25.52.  $\text{C}_{10}\text{H}_{11}\text{O}_2\text{N}\cdot\text{CH}_3\text{I}\cdot\frac{1}{2}\text{CH}_3\text{COCH}_3$  requires: C, 54.00; H, 6.65; N, 2.80; I, 25.36%.)

A solution of 1.2 g of the crude ketal of the desoxy compound in 10 cc 5% HCl was heated for several min. The reaction mixture was made basic with dil ammonia yielding 1.01 g of the colorless solid, m.p. 183–186°. The carbonyl compound recrystallized from alcohol in small plates, m.p. 187–189°. The infra-red spectrum was identical with that of the sample prepared from desoxydihydrothebainone- $\Delta^5$ -enol methylether.

(c) *From dihydrothebainone-4-phenylether*. A solution of 10 g dihydrothebainone-4-phenylether in 100 cc toluene was added dropwise to 100 cc liquid ammonia and the mixture reduced with 2.6 g metallic sodium. The reaction mixture yielded a crystalline material insoluble in the toluene solution.

The residue (6.02 g) from the toluene was crystallized from alcohol and yielded 3.5 g (48%) of colorless plates, m.p. 187–189°. This compound was identified as desoxydihydrothebainone.

The crystalline material (0.51 g), insoluble in toluene, had m.p. 201–205° and recrystallized from alcohol to give colorless prisms, m.p. 203–205°. The infra-red spectrum did not indicate the absorption band due to carbonyl group but that of hydroxyl group. (Found: C, 75.24; H, 8.74; N, 5.01.  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$  requires: C, 75.22; H, 8.77; N, 4.87%). It appeared to be 4-desoxydihydrothebainol.

#### *Tetrahydrodesoxycodine-4-phenylether*

(a) *From dihydrothebainone-4-phenylether*. Amalgamated zinc (prepared from 20 g mossy zinc and 2 g mercuric chloride) was added in small portions to a hot solution of 3.0 g dihydrothebainone-4-phenylether in 25 cc conc HCl and 10 cc glacial acetic acid during 2 hr. The mixture was heated on a waterbath for 3 hr, during which time 8 cc conc HCl was added every  $\frac{1}{4}$  hr.

The solution was diluted, made basic with NaOH and extracted with benzene. The residue was treated with hydroxylamine in methanol and the crude product was chromatographed on alumina in

\* The infra-red spectrum of this compound showed the absorption band due to carbonyl group.

ether solution to yield 2.34 g tetrahydrodesoxycodeine-4-phenylether (85%), m.p. 92–93°.  $[\alpha]_D^{25} - 6.7^\circ \pm 2^\circ$  (c, 2.202, alc.). (Found: C, 79.13; H, 8.06; N, 3.54.  $C_{24}H_{29}O_3N$  require: C, 79.30; H, 8.04; N, 3.85%).

The picrate crystallized from alcohol, m.p. 218–219° (dec). (Found: C, 60.91; H, 5.64; N, 9.26.  $C_{24}H_{29}O_3N \cdot C_6H_3O_7N_3$  requires: C, 60.80; H, 5.44; N, 9.46%).

The methiodide recrystallized from alcohol, m.p. 239–240°.  $[\alpha]_D^{25} - 5.3^\circ \pm 2^\circ$  (c, 0.781, alc.). The infra-red spectrum of tetrahydrodesoxycodeine-4-phenylether in chloroform was identical with that of desmethoxydesoxodihydrosinomenine-4-phenylether.

(b) *From dihydrothebaine- $\phi$ -4-phenylether.* A mixture of 5 g dihydrothebaine- $\phi$ -4-phenylether, amalgamated zinc (prepared from 30 g mossy zinc) and 110 cc of conc HCl was heated for 6 hr.

After treatment with hydroxylamine, 4.89 g of the crude base was chromatographed and the eluate treated with picric acid. Recrystallization of the picrate raised the m.p. to 217–218° (dec). Liberation of the picrate with dil NaOH gave 1.15 g tetrahydrodesoxycodeine-4-phenylether (25%), m.p. 89–91°. The m.p. showed no depression when mixed with the sample obtained from dihydrothebaine-4-phenylether.

#### (–)-3-Methoxy-N-methylmorphinan

(a) *From tetrahydrodesoxycodeine-4-phenylether.* A solution of 2.34 g tetrahydrodesoxycodeine-4-phenylether in 100 cc ether was added dropwise to 100 cc liquid ammonia and the mixture treated with 0.55 g metallic sodium yielding 1.75 g of crude product, m.p. 104–107°. Chromatography of this material in ether over activated alumina, raised the m.p. to 106–108° and afforded 1.70 g of the desoxy base (97%).  $[\alpha]_D^{25} - 45.9^\circ \pm 2^\circ$  (c, 2.018, alc.).

Treatment of the base with 48% HBr gave (–)-3-hydroxy-N-methylmorphinan, m.p. 198–199°.  $[\alpha]_D^{25} - 39.8^\circ \pm 2^\circ$  (c, 3.009, alc.). This compound was not depressed on admixture with the sample prepared from (–)-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline according to Schnider.

(b) *From desoxydihydrothebaine.* A solution of 1 g desoxydihydrothebaine in 30 cc conc HCl was reduced with amalgamated zinc (prepared from 10 g mossy zinc). Treatment of the reaction mixture with hydroxylamine and additional chromatography on alumina gave 0.522 g of the desoxy base. The m.p., 108–109° was not depressed on admixture with an authentic sample of (–)-3-methoxy-N-methyl-morphinan,  $[\alpha]_D^{25} - 47.0^\circ \pm 2^\circ$  (c, 1.965, alc.).

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\* Amylenehydrate adduct.