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

Y. K. SAWA, N. TSUJI and S. MAEDA
Research Laboratory, Shionogi & Co., Ltd. Osaka, Japan

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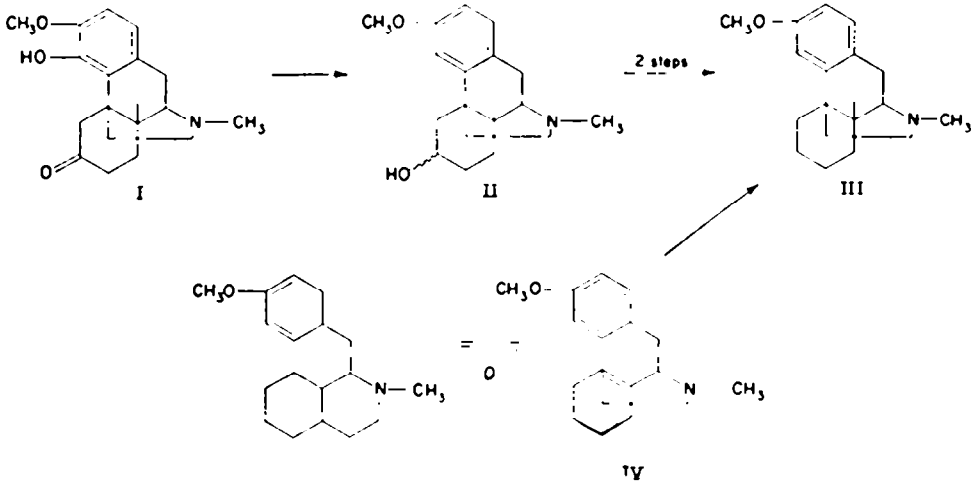
Abstract—Sinomenine, an alkaloid of the Japanese plant *Sinomenium acutum*, was converted to the 4-phenylether by the Ullmann reaction in a good yield. The Clemmensen reduction of sinomenine-phenylether and of its derivatives gave (±)-3-methoxy-4-phenoxy-N-methyl-Δ^{x}-morphinan.

Hydrogenation and successive sodium liquid ammonia reduction of (±)-3-methoxy-4-phenoxy-N-methyl-Δ^{x}-morphinan gave (±)-3-methoxy-N-methylmorphinan.

IN 1921, Speyer *et al.*[1] reported that the 4-hydroxyl group of dihydrothebainone (I) was eliminated by the Tafel reduction to yield dihydrothebacodine (II) and that desoxydihydrothebacodine (III), m.p. 146° was obtained from this compound.

In 1932, however, Small *et al.*[2] stated that they were unable to obtain dihydrothebacodine (II) by the reaction according to the method of Speyer *et al.*

In 1949, Grewe *et al.*[3] synthesized 3-methoxy-N-methylmorphinan (III) from 1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (IV) by ring-closure. Later, Schnider *et al.*[4] improved the method for preparing these octahydroisoquinoline derivatives and obtained many other morphinan derivatives.

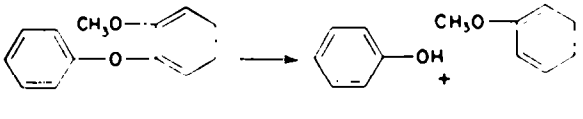


An outline of this paper was reported at the I.U.P.A.C. Symposium on the Chemistry of Natural Products in Melbourne, Australia, August (1960).

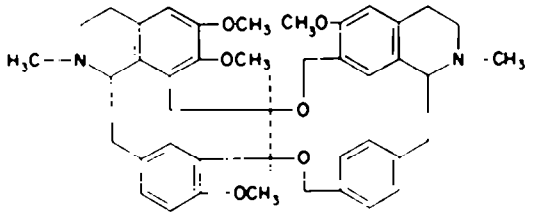
[1] E. Speyer and S. Siebert, *Ber. Dtsch. Chem. Ges.* **54**, 1519 (1921).
[2] L. F. Small and F. L. Cohen, *J. Amer. Chem. Soc.* **54**, 802 (1932).
[3] R. Grewe, A. Mondon and E. Nolte, *Liebigs Ann.* **564**, 161 (1949).
[4] O. Schnider and A. Grüssner, *Helv. Chim. Acta* **32**, 821 (1949); O. Schnider and A. Grüssner, *Ibid.* **34**, 2211 (1951); O. Schnider, A. Brossi and K. Vogler, *Ibid.* **37**, 710 (1954).

They reported that (--)-3-methoxy-N-methylmorphinan (III) does not melt at 146°, but at 109–111°. As a result of their work, it has been certified that desoxydihydrothebacodine obtained by Speyer *et al.* is not (—)-3-methoxy-N-methyl-morphinan. And since then no one has succeeded in eliminating the 4-hydroxyl group of the alkaloids related to morphine.

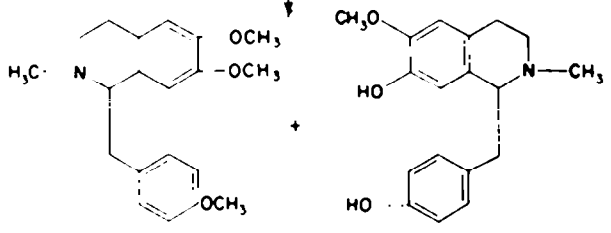
Sowa[5] succeeded in cleaving 2-methoxydiphenylether (V) into anisol and phenol by treating it with sodium in liquid ammonia and Tomita[6] applied this reaction to some alkaloids of the biscoclaurine group and obtained two kinds of coclaurine



V



Isotetrandrine



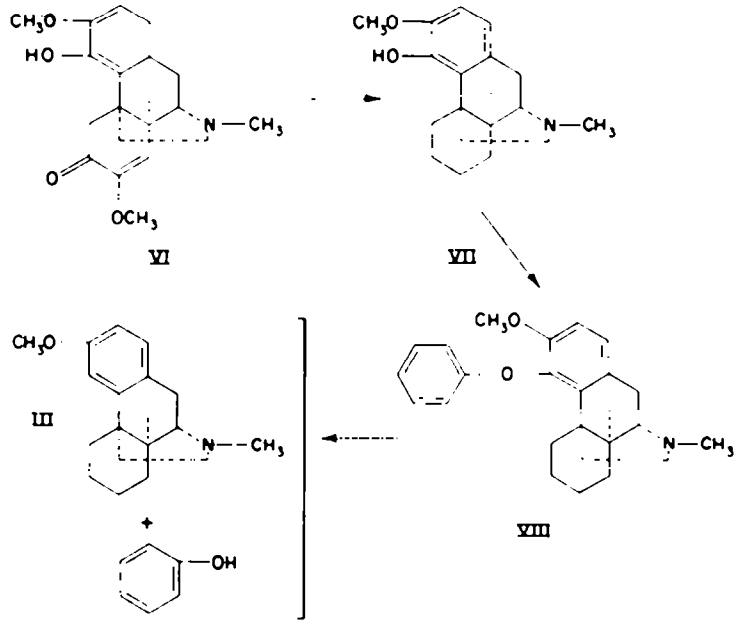
derivatives. These compounds all have the methoxyl group in the *ortho*-position of the ethereal oxygen linkage and no substituent in the *para*-position of same.

Sinomenine is an alkaloid isolated from the roots of *Sinomenium acutum* Rehed *et* Wils by Ishiwari[7] in 1920 and its structure was determined as VI by Kondo and Ochiai[8] and also by Goto.[9]

Desmethoxydesoxodihydrosinomenine i.e. (--)-tetrahydrodesoxycodeine (VII) was prepared from sinomenine (VI) by the Clemmensen reduction. We carried out the Ullmann reaction on this compound (VII) with bromobenzene in a pyridine solution in the presence of finely powdered potassium carbonate and copper and its 4-phenylether (VIII) was obtained in about 50 per cent yield.

[5] P. A. Sartovetto and F. J. Sowa, *J. Amer. Chem. Soc.* **59**, 603 (1937); A. L. Kranzfelder and F. J. Sowa, *Ibid.* **59**, 1488 (1937); F. C. Weber and F. J. Sowa, *Ibid* **60**, 94 (1938).
[6] M. Tomita, F. Fujita and F. Murai, *Yakugaku Zasshi* **71**, 226 (1951); M. Tomita, Y. Inubushi and H. Niwa, *Ibid.* **72**, 206 (1952).
[7] N. Ishiwari, *Chugai Iji Shimpo* **959**, 1 (1920).
[8] H. Kondo and F. Ochiai, Yakugaku Zasshi, No. 549, 913 (1927).
[9] K. Goto and H. Sudzuki, *Bull. Chem. Soc. Japan* **4**, 163 (1929).

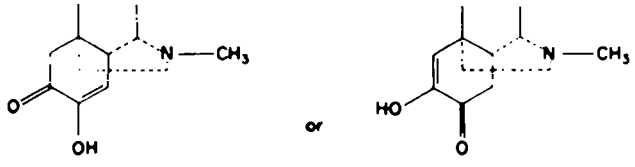
Treatment of this compound (VIII) with metallic sodium in liquid ammonia at −55°– −60° gave (+)-3-methoxy-N-methylmorphinan (III) in about 95 per cent yield together with phenol as expected. This compound melted at 109–111° and was not depressed on admixture with an authentic sample obtained by the method of Schnider.



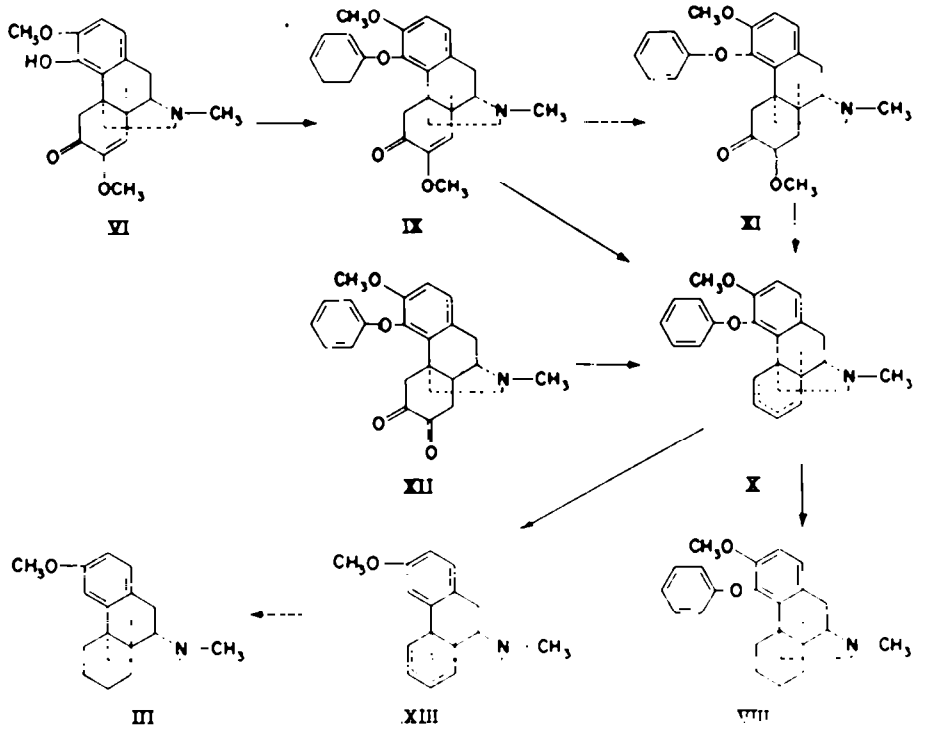
In order to expand the application of this reaction, sinomenine was analogously treated with bromobenzene by the Ullmann reaction to yield its 4-phenylether (IX) in about 85 per cent yield. When the Clemmensen reduction of this compound was carried out, the 6-carbonyl and the 7-enolmethylether groups were eliminated simultaneously and (+)-3-*methoxy*-4-*phenoxy*-*N*-methyl-Δ^x-morphinan (X) was obtained in about 90 per cent yield. However, the location of this double bond in ring C has not yet been determined. This compound (X) was also obtained from dihydrosinomenine-4-phenylether (XI) and sinomeninone-4-phenylether* (XII) by the Clemmensen reduction.

Hydrogenation of the unsaturated compound (X) over Adams' platinoxide afforded (±)-3-methoxy-4-phenoxy-N-methylmorphinan (VIII) in an excellent yield and sodium-liquid-ammonia reduction of X gave (±)-3-methoxy-N-methyl-Δ^x-morphinan (XIII) in about 90 per cent yield. This desoxy base XIII was also hydrogenated to (±)-3-methoxy-N-methylmorphinan (III) in a very good yield.

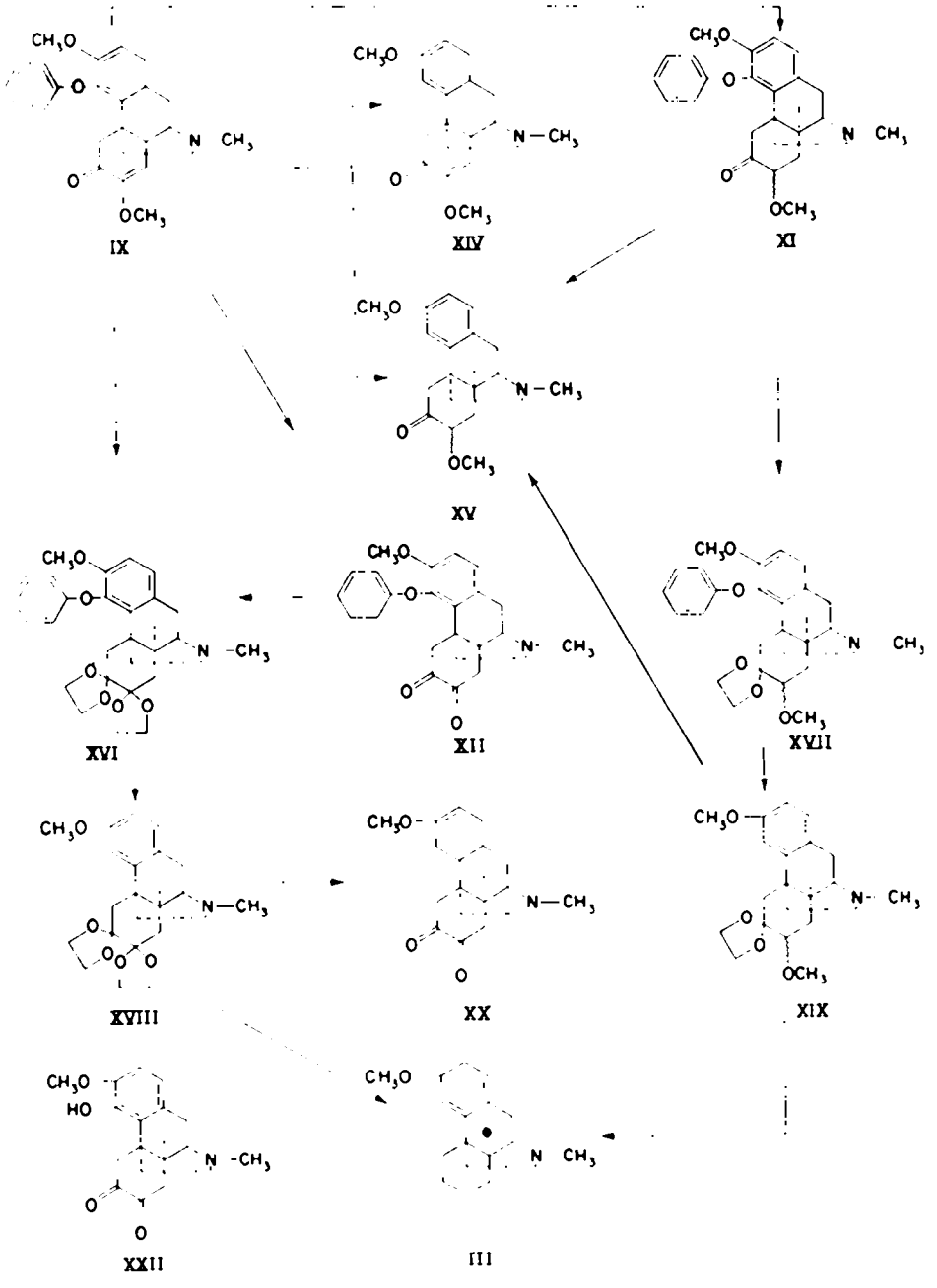
* We allot the diketon system to this compound tentatively because this compound may be:



For the preparation of 4-desoxy compounds containing substituents in ring C, sinomenine-4-phenylether (IX) was treated with sodium in liquid ammonia and desoxysinomenine (XIV) and desoxydihydrosinomenine (XV) were obtained. The latter was also obtained from dihydrosinomenine-4-phenylether (XI) in an excellent



yield by the similar reduction. Treatment of sinomenine-4-phenylether (IX) with ethylene glycol and *p*-toluene-sulphonic acid gave the 6,7-diethylene glycol ketal (XVI) of sinomeninone-4-phenylether in about 65 per cent yield. The infra-red spectrum of this compound showed no absorption band due to the enol methylether and the carbonyl groups. Furthermore, the structure of this compound was confirmed on admixture with the sample obtained from sinomeninone-4-phenylether (XII). Dihydrosinomenine-4-phenylether (XI) was also converted to the 6-ethylene glycol ketal derivative (XVII) in a very good yield. These ketal derivatives XVI and XVII were treated with sodium in liquid ammonia to yield the ketal derivatives of the 4-desoxy compounds XVIII and XIX respectively. Treatment of the ketal derivatives XVIII and XIX with dilute hydrochloric acid afforded the corresponding carbonyl compounds XX and XV. The infra-red spectrum of desoxysinomeninone (XX) showed an absorption band due to α,β-unsaturated ketone as in the case of sinomeninone (XXII). The Clemmensen reduction of the 6-ethylene glycol ketal (XIX) of desoxydihydrosinomenine and the 6,7-diethylene glycol ketal (XVIII) of desoxysinomeninone did not afford the unsaturated compound, but (+)-3-methoxy-N-methyl-morphinan (III) contrary to the case of the 4-phenylethers of the sinomenine derivatives.


IX
XIV
XI
XV
XVI
XII
XVII
XVIII
XX
XIX
XXII
III

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. The infra-red spectra were determined by Messrs. Y. Matsui and M. Takasuka on a Koken D.S. 301 infra-red spectrophotometer.

Sinomenine-4-phenylether (IX)

A solution of 16·5 g sinomenine in 50 cc freshly distilled dry pyridine was refluxed with 15·7 g bromobenzene, 10·3 g finely powdered K_2CO_3 and 0·5 g copper for 15 hr. The mixture was filtered while hot and washed with hot pyridine. The solvent was removed by distillation and the residue in benzene, filtered, washed 3 times with water and dried over K_2CO_3. The benzene solution was chromatographed on alumina and the benzene eluate gave 22 g of the crude base. Recrystallization from benzene gave 20·7 g of the pure benzene adduct. (85%), m.p. 122–124°. $[\alpha]_D^{19}$ – 111·9° ± 2° (*c*, 0·940, alc.). (Found: C, 76·92; H, 7·09; N, 2·76. $C_{31}H_{37}O_4N{\cdot}C_6H_6$ requires: C, 76·99; H, 6·88; N, 2·90%).

The pyridine adduct separated on cooling the reaction mixture and crystallizing from pyridine, m.p. 120–123°, $[\alpha]_D^{19}$ –116·4° ± 2° (*c*, 0·975, alc.). (Found: C, 74·51; H, 6·67; N, 5·78. $C_{31}H_{37}O_4N{\cdot}C_5H_5N$ requires: C, 74·35; H, 6·66; N, 5·78%).

The free base was crystallized from ether, m.p. 142–143°, $[\alpha]_D^{18}$ –137·8° ± 2° (*c*, 0·994, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1690 cm^{-1} (conjugated C=O); 1632 cm^{-1} (enol methylether.) (Found: C, 73·94; H, 7·07; N, 3·27. $C_{31}H_{37}O_4N$ requires: C, 74·05; H, 6·75; N, 3·45%).

The picrate was prepared in ether and crystallized from alcohol, m.p. 230–231°. (Found: C, 58·95; H, 4·93; N, 8·83. $C_{31}H_{37}O_4N{\cdot}C_6H_3O_7N_3$ requires: C, 58·67; H, 4·77; N, 8·83%).

The methiodide was prepared in and crystallized from alcohol, m.p. 206° (dec), $[\alpha]_D^{19}$ –121·5° ± 2° (*c*, 0·969, alc.). (Found: C, 56·46; H, 6·04; N, 24·2; I, 21·31. $C_{31}H_{37}O_4N{\cdot}CH_3I$ requires: C, 56·66; H, 6·11; N, 2·36; I, 21·39%).

Dihydrosinomenine-4-phenylether (XI)

A solution of 12 g of the benzene adduct of sinomenine-4-phenylether in 100 cc alcohol was hydrogenated over 100 mg Adams' catalyst at room temp. After absorption of 700 cc hydrogen, the solution was filtered and evaporated to dryness. The residue in a small amount of alcohol was treated with an alcoholic solution of picric acid. The yield of yellow crystalline picrate m.p. 208° (dec.), was almost quantitative. (Found: C, 58·02; H, 5·27; N, 8·32. $C_{31}H_{39}O_4N{\cdot}C_6H_3O_7N_3$ requires: C, 58·84; H, 5·07; N, 8·80%).

A sample of the picrate was converted to the free base by partition between ether and dil NaOH. The ether extracts were washed with dil NaOH and water, dried, filtered and chromatographed on alumina, yielding a colorless oil which crystallized on standing. Crystallization from ether gave pure dihydrosinomenine-4-phenylether, m.p. 149–154°, $[\alpha]_D^{24}$ –5·9° ± 2° (*c*, 0·904, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1730 cm^{-1} (unconjugated >C=O). (Found: C, 73·84; H, 7·25; N, 3·41. $C_{31}H_{39}O_4N$ requires: C, 73·68; H, 7·17; N, 3·44%).

The methiodide crystallized from alcohol, m.p. 255°(dec). (Found: C, 56·57; H, 5·82; N, 2·44; I, 23.21. $C_{31}H_{39}O_4N{\cdot}CH_3I$ requires: C, 56·83; H, 5·87; N, 2·55; I, 23·10%).

Sinomeninone-4-phenylether (XII)

A solution of 12 g of the benzene adduct of sinomenine-4-phenylether in 120 cc 10% HCl was heated for 2 hr on a water bath. Upon cooling, the solution was made basic with 20% Na_2CO_3 and the crystalline product washed with water and crystallized from methanol yielding 8·45 g pure sinomeninone-4-phenylether (84%), m.p. 212–214°. $[\alpha]_D^{25}$ –64·7° ± 2° (*c*, 1·043, chloroform). I.R. $\lambda_{max}^{CHCl_3}$ 3535 cm^{-1} (OH); 1678 cm^{-1} (conjugated >C=O). (Found: C, 72·37; H, 6·61; N, 3·35; OCH_3: 10·80. $C_{24}H_{25}O_4N{\cdot}1/2CH_3OH$ requires: C, 72·21; H, 6·68; N, 3·44; OCH_3, 11·42%).

The hydrochloride crystallized from 10% HCl m.p. 97° (dec). $[\alpha]_D^{19}$ –61·9° ± 2° (*c*, 0·47; alc.). (Found: C, 64·96; H, 6·39; N, 2·92; Cl, 8·19; OCH_3, 7·50. $C_{24}H_{25}O_4N{\cdot}HCl{\cdot}H_2O$ requires: C, 64·64; H, 6·33; N, 3·14; Cl, 7·95; OCH_3, 6·96%).

6,7-Diethylene glycol ketal of sinomeninone-4-phenylether (XVI)

(a) *From sinomenine-4-phenylether*. A benzene solution of 4 g of the benzene adduct of sinomenine-4-phenylether and 10 cc ethylene glycol was refluxed with 3·5 g toluene-*p*-sulphonic acid for 7 hr, with an "azeotropic" receiver to collect the volatile products. Upon cooling, 10% Na_2CO_3 was added to give a slightly alkaline reaction and the 2 layers separated. The alkaline solution was extracted with chloroform and the crude base chromatographed on alumina, the chloroform eluate yielding 3 g of the crude product. Crystallization from ethylacetate yielded 2·6 g pure diketal derivative (65%), m.p. 198–200°. $[\alpha]_D^{29}$ −37·6 ± 2° (*c*, 1·037, alc.). (Found: C, 70·32; H, 6·94; N, 2·96. $C_{28}H_{33}O_6N$ requires: C, 70·12; H, 6·94; N, 2·92%). The infra-red spectrum showed no absorption band due to enol methylether and carbonyl groups.

The methiodide was prepared in and crystallized from alcohol, m.p. 120°. $[\alpha]_D^{21}$ −21·0° ± 2° (*c*, 1·093, methanol). (Found: C, 54·81; H, 6·18; N, 2·00; I, 19·69. $C_{28}H_{33}O_6N{\cdot}CH_3I$ requires: C, 54·46; H, 5·99; N, 2·19; I, 19·85%).

(b) *From sinomeninone-4-phenylether* (XII). A benzene solution of 5 g sinomeninone-4-phenylether and 10 cc ethylene glycol was refluxed with 4 g toluene-*p*-sulphonic acid for 7 hr as described above. The reaction mixture yielded 4·76 g of the diketal derivative (81%), m.p. 198–200° and this was not depressed on admixture with the sample obtained from sinomenine-4-phenylether.

Ethylene glycol ketal of dihydrosinomenine-4-phenylether (XVII)

A benzene solution of 2·6 g dihydrosinomenine-4-phenylether and 5 cc ethylene glycol was refluxed with 2 g toluene-*p*-sulphonic acid for 7 hr, and yielded 2·9 g of the compound as a syrup (essentially quantitative). $[\alpha]_D^{17}$ −56·2° ± 2° (*c*, 1·0, alc.).

The methiodide was prepared in and crystallized from alcohol, m.p. 260° (dec). $[\alpha]_D^{26}$ −46·2° ± 2° (*c*, 1·165, alc.). (Found: C, 56·65; H, 6·13; N, 2·29; I, 21·75. $C_{27}H_{33}O_6N{\cdot}CH_3I$ requires: C, 56·66; H, 6·11; N, 2·36; I, 21·39%).

(±)-3-*Methoxy-4-phenoxy-N-methyl-*Δ^{α}*-morphinan* (X)

(a) *From sinomenine-4-phenylether* (IX). Amalgamated zinc (prepared from 20 g mossy zinc and 2 g mercuric chloride) was added in small portions to a hot solution of 3·6 g of the benzene adduct of sinomenine-4-phenylether in 25 cc conc HCl during 2 hr. The mixture was heated on a water bath with stirring for 6 hr, during which time 15 cc conc HCl was added every 2 hr. The solution was cooled to room temp, diluted with water, made basic with dil NaOH and extracted with benzene. The solvent was distilled off under red. press. and 2·7 g of product obtained. An alcoholic solution of the product was refluxed with 0·5 g hydroxylamine hydrochloride and 0·5 g sodium acetate for 1 hr. The solvent was distilled off and the residue in water made alkaline with dil NaOH and extracted with ether. The product was chromatographed on alumina and the ether eluate gave 2·43 g of a syrup (90%). $[\alpha]_D^{28}$ −52·4 ± 3° (*c*, 0·722, alc.). The free base did not crystallize, but its methanol adduct was obtained as needles when this syrup was treated with methanol. m.p. 91–96°. $[\alpha]_D^{28}$ +51·5° ± 2° (*c*, 1·028, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1660 cm^{-1} (CH—CH). (Found: C, 76·47; H, 8·02; N, 3·51; OCH_3, 14·55. $C_{24}H_{27}O_2N{\cdot}CH_3OH$ requires: C, 76·30; H, 7·94; N, 3·56; OCH_3, 15·77%).

The methiodide was prepared in and crystallized from alcohol, m.p. 228°. $[\alpha]_D^{24}$ −34·4° ± 2° (*c*, 1·016, alc.). (Found: C, 58·63; H, 6·67; N, 2·82; I, 23·43. $C_{24}H_{27}O_2N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 59·01; H, 6·60; N, 2·55; I, 23·10%).

The picrate was prepared in and crystallized from alcohol, m.p. 211–212°. (Found: C, 60·88; H, 5·44; N, 9·29. $C_{24}H_{27}O_2N{\cdot}C_6H_3O_7N_3$ requires: C, 61·01; H, 5·12; N, 9·49%).

(b) *From dihydrosinomenine-4-phenylether* (XI). 3·0 g dihydrosinomenine-4-phenylether was heated with 60 cc conc HCl and amalgamated zinc (prepared from 20 g mossy zinc and 2 g mercuric chloride) for 6 hr and yielded 2·36 g of crude product (89%). The methanol adduct m.p. 91–96° was undepressed on admixture with the sample obtained from sinomenine-4-phenylether.

(c) *From sinomeninone-4-phenylether* (XII). A mixture of 2·0 g sinomeninone-4-phenylether, 50 cc conc HCl and amalgamated zinc (prepared from 13 g mossy zinc and 1 g mercuric chloride) was heated for 6 hr on a water bath yielding 1·62 g of the crude base (91·5%). The methanol adduct m.p. 91–96° was not depressed on admixture with the sample.

(+)-3-*Methoxy*-4-*phenoxy*-N-*methylmorphinan* (VIII)

(a) *From desmethoxydesoxodihydrosinomenine* ((+)-*tetrahydrodesoxycodeine*; VII). A pyridine solution of 5·74 g desmethoxydesoxydihydrosinomenine, i.e. (+)-tetrahydrodesoxycodeine and 6·28 bromobenzene was refluxed with 3·14 g finely powdered K_2CO_3 and 1 g copper for 15 hr. Upon cooling, the reaction mixture was treated as in the case of the Ullmann reaction of sinomenine. The benzene eluate gave 5·5 g of crude product which crystallized from pet. ether yielding 3·7 g pure (+)-3-methoxy-4-phenoxy-N-methylmorphinan (51%), m.p. 95–96°. $[\alpha]_D^{31}$ +9·5° ± 2° (*c*, 1·20, alc.). (Found: C, 79·29; H, 8·06; N, 3·76. $C_{24}H_{29}O_2N$ requires: C, 79·30; H, 8·04; N, 3·85%).

The picrate was prepared in and crystallized from alcohol, m.p. 222°. (Found: C, 60·57; H, 5·49; N, 9·30. $C_{24}H_{29}O_2N{\cdot}C_6H_3O_7N_3$ requires: C, 60·80; H, 5·44; N, 9·46%).

The methiodide was prepared in ether and crystallized from alcohol, m.p. 237–238°. $[\alpha]_D^{18}$ +6·1° ± 2° (*c*, 0·948, alc.). (Found: C, 58·75; H, 6·88; N, 2·40; I, 23·57. $C_{24}H_{29}O_2N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 58·80; H, 6·95; N, 2·54; I, 23·01%).

(b) *From* (+)-3-*methoxy*-4-*phenoxy*-N-*methyl*-Δ^x-*morphinan* (X). A solution of 1·2 g of the methanol adduct of (+)-3-methoxy-4-phenoxy-N-methyl-Δ^x-morphinan in 30 cc glacial acetic acid was hydrogenated over 50 mg Adams' catalyst at room temp. After consumption of one mole equivalent of hydrogen, the solution was filtered, concentrated, made basic with 20% NaOH and extracted with ether. The crude base was chromatographed on alumina and the ether eluate yielded 1·2 g of the saturated compound which crystallized from pet. ether yielding pure product m.p. 95–96° which was not depressed on admixture with the sample obtained by the Ullmann reaction.

(−)-3-*Methoxy*-N-*methyl*-Δ^x-*morphinan* (XIII)

A solution of 0·98 g (+)-3-methoxy-4-phenoxy-N-methyl-Δ^x- morphinan in 60 cc dry ether was added dropwise to 150 cc liquid ammonia (treated previously with a small amount of metallic sodium at −55–60°). Another 0·3 g metallic sodium was added to this stirred solution keeping the temp at about −55°–−60°. When a blue coloration persisted for an hour, a small amount of ammonium chloride was added and the color disappeared. Liquid ammonia was evaporated and the residue was treated with water and ether and the ether extracts washed several times with dil NaOH. The ether layer gave 0·68 g of non-phenolic substance which crystallized on standing, (93%), m.p. 78–85°. Recrystallization from ether gave (−)-3-methoxy-N-methyl-Δ^x-morphinan, m.p. 90–94°. $[\alpha]_D^{20}$ −89·1° ± 2° (*c*, 0·968, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1660 cm^{-1} (CH CH). (Found: C, 80·03; H, 8·95; N, 4·98. $C_{16}H_{23}ON$ requires: C, 80·25; H, 8·61; N, 5·20%).

The picrate was prepared in and crystallized from alcohol, m.p. 183–184°. (Found: C, 58·11; H, 5·59; N, 10·80. $C_{16}H_{23}ON{\cdot}C_6H_3O_7N$ requires: C, 57·82; H, 5·26; N, 11·24%).

The hydrobromide crystallized from hot water, m.p. 117–122°. $[\alpha]_D^{20}$ −59·0° ± 3° (*c*, 0·721, water). (Found: C, 58·67; H, 7·31; N, 3·75; Br, 22·11. $C_{16}H_{23}ON{\cdot}HBr{\cdot}H_2O$ requires: C, 58·70; H, 7·12; N, 3·80; Br, 21·70%).

The methiodide was prepared in alcohol and crystallized from alcohol ether, m.p. 217–218° (dec). $[\alpha]_D^{31}$ −40·8° ± 2° (*c*, 1·001, alc.).

(+)-3-*Methoxy*-N-*methylmorphinan* (III)

(a) From (+)-3-*methoxy*-4-*phenoxy*-N-*methylmorphinan* (VIII). A solution of 0·97 g (+)-3-methoxy-4-phenoxy-N-methylmorphinan (VIII) in 50 cc dry ether was added dropwise to 100 cc liquid ammonia at −55–60° and 0·37 g metallic sodium was added to this stirred solution. After an hour the reaction mixture was worked up as described for (+)-3-methoxy-N-methyl-Δ^x-morphinan (XIII) and 0·688 g of the crude base obtained (95%) with m.p. 100–106°. Recrystallization from ether gave pure (+)-3-methoxy-N-methylmorphinan, m.p. 109–111°. $[\alpha]_D^{20}$ +48·1° ± 2° (*c*, 0·915, alc.). This m.p. showed no depression on admixture of (−)-3-methoxy-N-methylmorphinan obtained from 1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline. (Found: C, 79·80; H, 9·28; N, 4·90. $C_{18}H_{25}ON$ requires: C, 79·66; H, 9·29; N, 5·16%).

The combined alkaline solutions were made acidic and extracted with ether. The *p*-nitrobenzoate m.p. 129–130° was identified as phenyl *p*-nitrobenzoate.

(b) *From* (+)-3-*methoxy*-N-*methyl*-Δ^x-*morphinan* (XIII). A solution of 0·18 g (+)-3-methoxy-N-methyl-Δ^x-morphinan (XIII) in 6 cc glacial acetic acid was hydrogenated in the presence of 10 mg of Adams' catalyst at room temp yielding 0·18 g of the crude base which was purified from ether. The

m.p. 105 108°, was not depressed on admixture with an authentic sample of (−)-3-methoxy-N-methylmorphinan.

(c) *From 6,7-diethylene glycol ketal of desoxysinomeninone* (XVIII). A mixture of amalgamated zinc (prepared from 6·5 g mossy zinc), 1 g of the ketal derivative and 20 cc conc HCl was heated on a water bath for 5 hr. The crude base (0·7 g) was chromatographed on alumina and the product converted to the tartrate. After several recrystallizations from alcohol, the m.p. 193 194° (dec) was not depressed on admixture with the tartrate of (−)-3-methoxy-N-methylmorphinan, 0·4 g (37%).

(d) *From 6-ethylene glycol ketal of desoxydihydrosinomenine* (XIX). A mixture of amalgamated zinc (prepared from 13 g mossy zinc), 2 g of the ketal derivative and 40 cc conc HCl was heated on a water bath for 6 hr. The crude base (1·41 g) was converted to the tartrate and recrystallized from alcohol, m.p. 192–193° (dec), 0·89 g (38%).

Desoxysinomeninone (XX)

A solution of 3 g of 6,7-diethylene glycol ketal of sinomeninone-4-phenylether (XVI) in 100 cc dry toluene was added dropwise to 300 cc liquid ammonia at −55– −60° and 0·42 g metallic sodium was added to this stirred solution and the mixture treated as usual. The crude base was chromatographed on alumina and the ether eluate gave 2·35 g of the desoxy compound, m.p. 202–206°, (97%). Recrystallization from methanol raised the m.p. to 203 206°, $[\alpha]_D^{23}$ +49·8 ± 2° (*c*, 1·088, alc.). (Found: C, 68·46; H, 7·46; N, 3·57. $C_{22}H_{29}O_4N$ requires: C, 68·19; H, 7·54; N, 3·62%).

The methiodide was prepared in and crystallized from alcohol, m.p. 249 250°. $[\alpha]_D^{18}$ −33·5° ± 2° (*c*, 1·070, alc.).

This compound was converted to desoxysinomeninone (XX) by the action of 20% HCl. The m.p. 190–192° after recrystallization from hot benzene was not depressed on admixture with the sample obtained from desoxysinomenine (XXI). $[\alpha]_D^{17}$ −49·5° ± 2° (*c*, 0·986, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 3525 cm^{-1} (OH); 1725 cm^{-1} (W); 1679 cm^{-1} (S) (conjugated >C=O). (Found: C, 72·20; H, 7·15; N, 4·79. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; N, 4·68%).

The methiodide was prepared in and crystallized from methanol, m.p. 269 270° (dec). (Found: C, 51·51; H, 5·51; N, 3·14; I, 28·88. $C_{18}H_{21}O_3N{\cdot}CH_3I$ requires: C, 51·71; H, 5·48; N, 3·18; I, 28·76%).

Sodium ammonia reduction of sinomenine-4-phenylether (IX)

A solution of 2 g of the benzene adduct of sinomenine-4-phenylether (IX) in 70 cc dry toluene was added dropwise to 150 cc liquid ammonia at −50 −55° and 0·7 g metallic sodium added to this stirred solution. After ½ hr the mixture was treated as usual. 1·2 g of the crude base was treated with ether and 0·42 g of a white crystalline product collected (32%).

Desoxysinomenine (XIV) crystallized from ether, m.p. 163–173° (m.p. 180 182° by monoscope). $[\alpha]_D^{28}$ −24·2° ± 2° (*c*, 1·056, alc.). I.R. $\lambda_{max}^{CHCl_3}$ 1691 cm^{-1} (conjugated C=O); 1632 cm^{-1} (enol methyl-ether). (Found: C, 72·75; H, 7·60; N, 4·61; OCH_3, 19·94. $C_{19}H_{23}O_3N$ requires: C, 72·82; H, 7·40; N, 4·47; OCH_3, 19·81%).

The methiodide was prepared in and crystallized from alcohol, m.p. 247 248°. (Found: C, 52·61; H, 5·80; N, 3·01; I, 27·39. $C_{19}H_{23}O_3N{\cdot}CH_3I$ requires: C, 52·75; H, 5·76; N, 3·08; I, 27·87%). Treatment of desoxysinomenine (XIV) with 20% HCl gave desoxysinomeninone (XX) m.p. 190 192°.

Desoxydihydrosinomenine (XV)

This compound was obtained from the ether solution as a syrup, yield 0·7 g. The methiodide prepared in and crystallized from alcohol, melted at 222 225° and the infra-red spectrum was identical with that of desoxydihydrosinomenine obtained from dihydrosinomenine-4-phenylether (XI).

Desoxydihydrosinomenine (XV)

A solution of 2 g dihydrosinomenine-4-phenylether (XI) in 40 cc dry toluene was added dropwise to 200 cc liquid ammonia at −50– −55° and 0·6 g metallic sodium added to this stirred solution and the reaction mixture treated as usual. 1·45 g of desoxydihydrosinomenine was obtained as a syrup, (94%). I.R. $\lambda_{max}^{CHCl_3}$ 1728 cm^{-1} (C=O).

The methiodide prepared in and crystallized from alcohol, melted at 222 225°. (Found: C, 51·55; H, 6·53; N, 2·96. $C_{19}H_{16}O_3N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 52·49; H, 6·81; N, 2·78%). This methiodide was not depressed on admixture with the sample obtained from ethylene glycol ketal of desoxydihydrosinomenine.

Ethylene glycol ketal of desoxydihydrosinomenine (XIX)

A solution of 1 g 6-ethylene glycol ketal of dihydrosinomenine-4-phenylether in 20 cc dry toluene was added dropwise to 100 cc liquid ammonia at −50 −55° and 0·4 g metallic sodium added and the mixture worked up as usual. Recrystallization of 0·71 g of the crude product from ethyl acetate gave pure ethylene glycol ketal of desoxydihydrosinomenine (XIX), m.p. 177–179°. $[\alpha]_D^{24}$ −10·0° ± 2° (*c*, 1·001, alc.). (Found: C, 70·33; H, 8·37; N, 3·89. $C_{21}H_{29}O_4N$ requires: C, 70·17; H, 8·13; N, 3·90%).

The methiodide prepared in and crystallized from alcohol melted at 246–247°, $[\alpha]_D^{18}$ +3·3° ± 2° (*c*, 0·992, alc.). (Found: C, 52·60; H, 6·56; N, 2·87; I, 24·86. $C_{21}H_{29}O_4N{\cdot}CH_3I$ requires: C, 52·70; H, 6·43; N, 2·79; I, 25·31%). This ketal derivative was converted to desoxydihydrosinomenine (XXI) by treating it with 10% HCl but could not be made to crystallize.

The methiodide prepared in and crystallized from alcohol, melted at 225°. (Found: C, 52·14; H, 6·72; N, 2·75; I, 25·26. $C_{19}H_{23}O_3N{\cdot}CH_3I{\cdot}C_2H_5OH$ requires: C, 52·49; H, 6·81; N, 2·78; I, 25·21%).

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