Tetrahedron. Vol. 24, pp 261 to 266. Pergamon Press. 1968 Printed in Great Britain

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

STRUCTURE OF THE KETAL DERIVATIVES PREPARED FROM 7-OXO-DIHYDROTHEBAINONE

Y. K. SAWA, K. OKABE and T. MIYAMOTO

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

(*Received in Japan* 14 *March* 1967; *accepted for publication* 17 *April* 1967)

Abstract—Ketalization of 7-oxo-dihydrothebainone gave 6,6;7,7- and 6,7;6,7-diketal derivatives depending on the amount of TsOH. The structure of these compounds has been confirmed by NMR study and chemical method.

IN THE previous paper[1] it was reported that the ketalization of 7-oxo-dihydrothebainone (the antipode of sinomeninone; I) afforded two ketal derivatives, i.e. ketal-A (III), m.p. 205–207°, $[\alpha]_D$ −59·9° and oily ketal-B (II) and that the properties of the ketal-A, except for rotation, were identical with those of the ketal compound, m.p. 207°, prepared from sinomeninone by Goto *et al.*[2] Examination of this ketalization revealed that reaction with 2·3 mole of TsOH gave mainly the ketal-B (II), whereas reaction with 1·24 mole of TsOH afforded the ketal-A (III) and the ketal-B (II) in yields of 32% and 64%, respectively.

As stated before[1] the Ullmann reaction of both compounds and the successive sodium–liquid ammonia reduction followed by hydrolysis gave the same 4-deoxy-7-oxo-dihydrothebainone (VI), m.p. 190–191°.

These facts suggested that a new ketal system was formed on the ketalization of the α-dicarbonyl group. Inspection of Dreiding models shows that a 6,7;6,7 diketal system is also feasible besides a 6,6;7,7 diketal system. Recently Caspi *et al.*[3] studied the NMR of the ketal derivatives of cortisone and revealed that a compound of the 20,21-bisdioxolane type (VII) showed rather sharp bands due to ketal moieties at 6·03 and 6·13 τ, whereas that of the naphthodioxane type (VIII) had multiple bands extending from 5·96 to about 6·63 τ.

We examined the NMR spectra of 4-deoxy-ketal-A (V), 4-deoxy-ketal-B (IV), ketal of 4-deoxydihydrothebainone (X) and ketal of 7-oxo-derivative (XVIII), which was synthesized from sinomenine as described later. In the NMR spectra 4-deoxy-ketal-A V shows multiple split bands extending from 5·6 to 6·7 τ, whereas the other three products give far narrower bands at about 6·1 τ.

These facts suggested that the ketal groups of V might belong to the naphthodioxane type. Then the hydrolysis of both ketal derivatives, IV and V, was reexamined. Though boiling with 20% HClaq afforded the same 4-deoxy-7-oxo-dihydrothebainone VI, hydrolysis with 10% HClaq gave interesting results; 4-deoxy-ketal-A V was easily hydrolyzed to the above mentioned diketone VI, whereas 4-deoxy-ketal-B IV gave, in a yield of 2·6%, a new compound (IX), m.p. 148–149°, $[\alpha]_D$ −109·2° in addition to

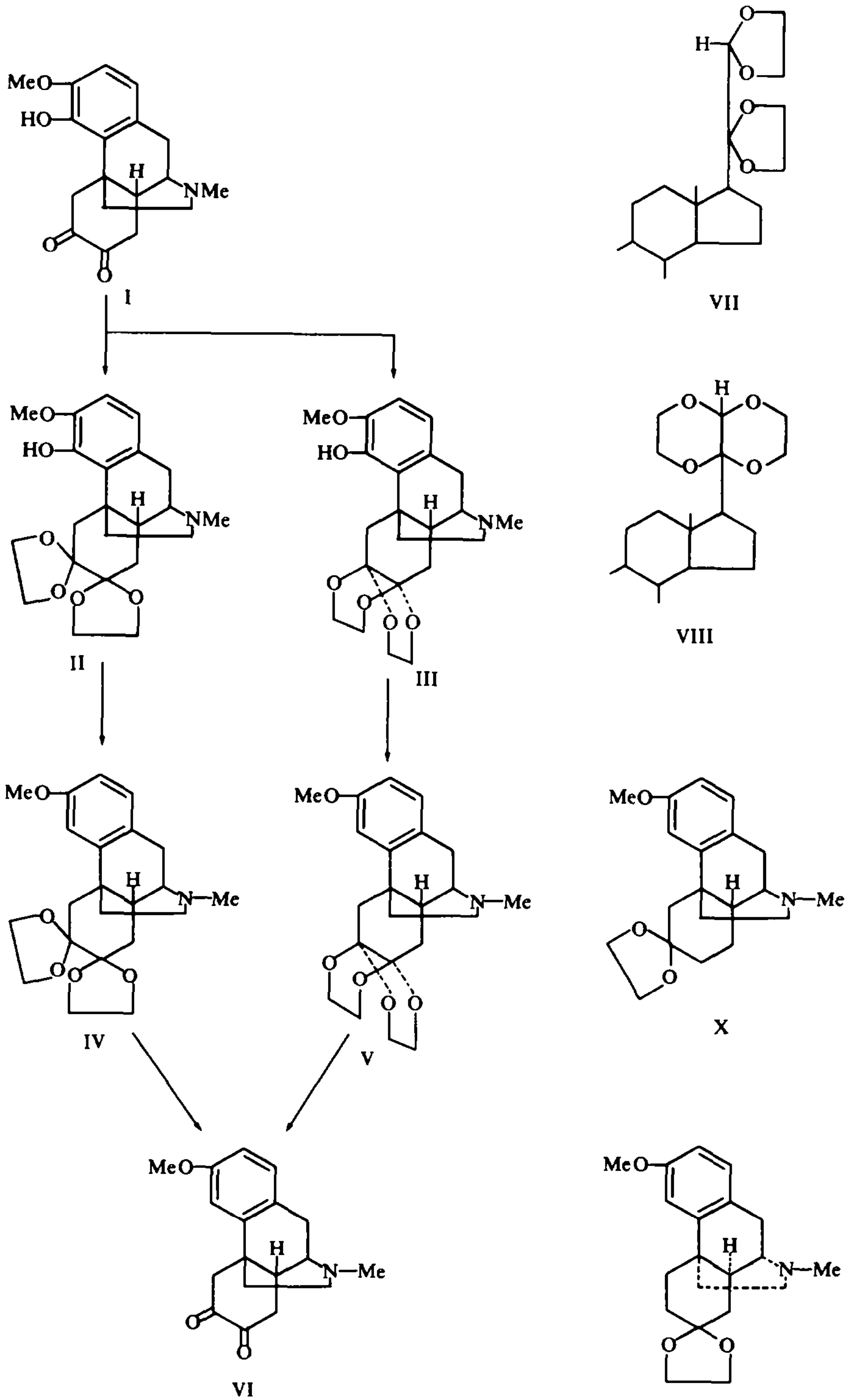
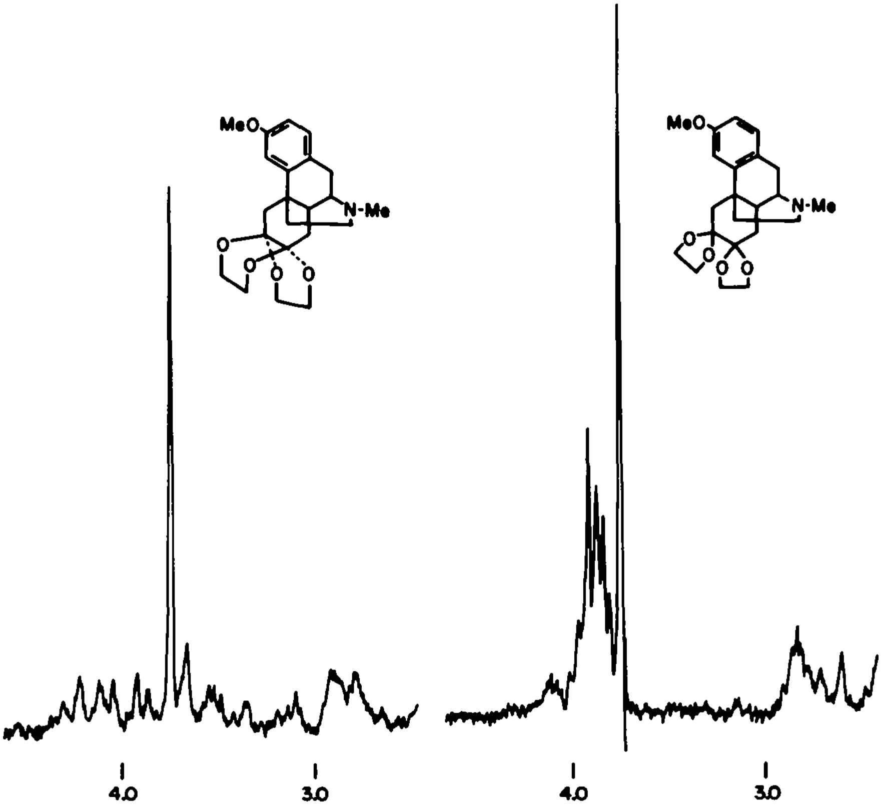


CHART I

the compound VI. The compound IX had the formula $C_{20}H_{25}O_4N$ and showed a carbonyl band at 1730 cm^{-1} and a band due to a ketal moiety at 1040 cm^{-1} in the IR spectrum.



These facts suggest that either the 6-ketal or the 7-ketal moiety is hydrolyzed to the ketonic group. Further hydrolysis of the keto-ketal derivative IX with 20% HClaq gave the diketonic compound VI in high yield.

Huang-Minlon reduction of IX afforded non-ketonic compounds (XI), $C_{20}H_{27}O_3N$, m.p. 112–113°, $[\alpha]_D$ −25·3° and (XII) $C_{20}H_{27}O_3N$, m.p. 163–166°, $[\alpha]_D$ −115·2°, in yields of 46% and 22%, respectively. The structure of the former was assigned to the ketal of 3-methoxy-7-oxo-N-methylmorphinan XI by comparing the IR spectrum in chloroform with that of the sample prepared from sinomenine. The latter had absorption bands due to a OH group at 3600 cm^{-1} and to an enol ether group at 1670 cm^{-1}. Hydrolysis of this compound with 2% HClaq also gave the 7-oxo-N-methylmorphinan derivative XIII.

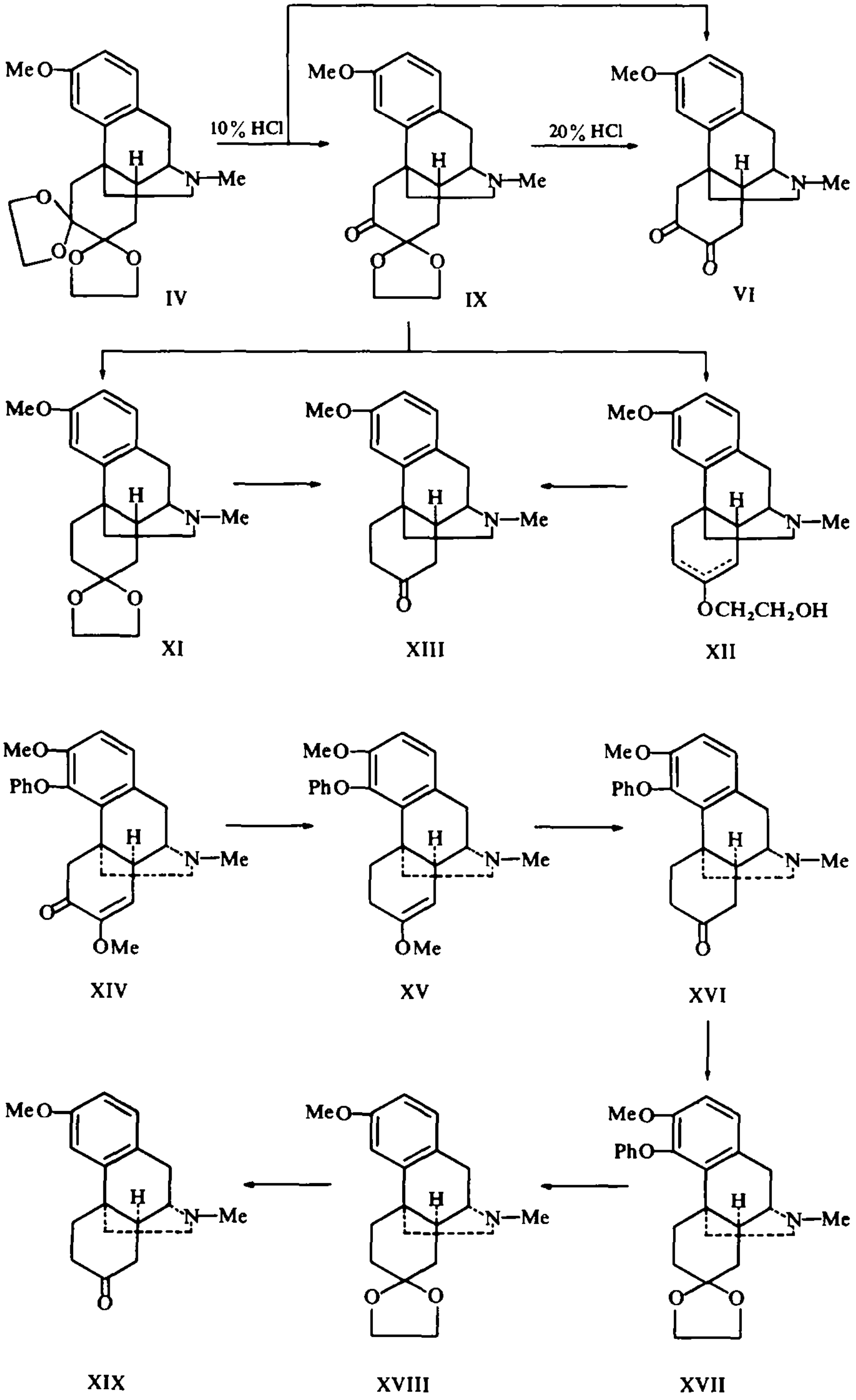

MeO
N—Me
H
10% HCl
20% HCl
IV
IX
VI
XI
XIII
XII
OCH₂CH₂OH
PhO
OMe
XIV
XV
XVI
XIX
XVIII
XVII

CHART II

These facts show that the structure of the high melting substance is represented as 7-(β-hydroxyethoxy)-3-methoxy-N-methyl-Δ^6 or Δ^7-morphinan XII. Accordingly the structure of 4-deoxy-ketal-B IV must be 6,6;7,7-bisethylenedioxy-3-methoxy-N-methylmorphinan and that of 4-deoxy-ketal-A V 6,7;6,7-bisethylenedioxy-3-methoxy-N-methylmorphinan. It is of interest to note that the naphthodioxane group is easily hydrolyzed compared with the oxolane group.

In connection with this study synthesis of (+)-3-methoxy-7-oxo-N-methylmorphinan (XIX) from sinomeninephenylether (XIV) was also studied. Huang-Minlon reduction of XIV afforded deoxosinomeninephenylether (XV) in 85% yield. Hydrolysis of XV gave the 7-oxo derivative (XVI), m.p. 179–180°. This compound is levo rotatory though it was prepared from sinomenine. Protection of the 7-oxo group with ethylene glycol and sodium-liquid ammonia reduction followed by hydrolysis gave the desired 3-methoxy-7-oxo-N-methylmorphinan (XIX), m.p. 105–106°, $[\alpha]_D$ +57·3°.

EXPERIMENTAL

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

Ketalization of 7-oxo-dihydrothebainone (I)

Ketalization of this compound with $TsOH \cdot H_2O$ (1·24 mole equiv) has been described.[1] The same reaction with $TsOH \cdot H_2O$ (2·5 mole equiv) gave an oily ketal-B II in quantitative yield.

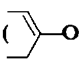
Hydrolysis of 4-deoxy-ketal-B(IV)

Hydrolysis of IV with 20% HClaq and of V with 20% HClaq has been described.[1] A soln of 9·73 g IV in 50 cc 10% HClaq was heated on a steam bath for 3·5 hr. The soln was made basic with dil. Na_2CO_3aq and extracted with chloroform. The crude products were recrystallized from benzene to give 7·12 g less soluble diketonic compound VI, m.p. and the mixed m.p. with 4-deoxy-7-oxo-dihydrothebainone 188–190°, 94·6%. The benzene soln was chromatographed on alumina and the elution with benzene gave 0·226 g IX, m.p. 146–148°, 2·6%. Recrystallization from ether raised its m.p. to 148–149°, $[\alpha]_D$ −109·2° ± 2° (*c*, 1·015, alc). (Found: C, 69·84; H, 7·46; N, 4·25. $C_{20}H_{25}O_4N$ requires: C, 69·95; H, 7·33; N, 4·08%).

Hydrolysis of the keto-ketal derivative (IX) *to 4-deoxy-7-oxo-dihydrothebainone* (VI)

Hydrolysis was performed by heating with 20% HClaq. The crude product was purified from ether, m.p. and the mixed m.p. with VI 198–199°.

Huang-Minlon reduction of the keto-ketal derivative (IX)

One gram of IX was converted to the hydrazone by heating with 5 g 80% hydrazine hydrate on the oil bath. The excess hydrazine was removed by distillation under reduced press., and 4·0 g diethylene glycol and 1 g KOH pellets were added to the residue. The mixture was heated at 185° for 3 hr and then diluted with water. The soln was extracted with benzene and washed with water. The crude products (0·95 g) were triturated with ether. The less soluble substance was purified from ether to give 0·216 g XII, m.p. 163–166°, 22·5%; $[\alpha]_D^{24}$ −115·2° ± 2° (*c*, 1·043, alc); IR 3600 cm^{-1} (OH), 1670 cm^{-1} ( OR). (Found: C, 73·04; H, 8·33; N, 4·67. $C_{20}H_{27}O_3N$ requires: C, 72·92; H, 8·26; N, 4·67%). The ether soln was chromatographed on alumina. The enol ether free substance (0·44 g) was first eluted with ether. Recrystallization from ether gave the pure XI, m.p. 112–113°, $[\alpha]_D^{24}$ −25·3° ± 2° (*c*, 1·033, alc). (Found: C, 73·02; H, 8·36; N, 4·47. $C_{20}H_{27}O_3N$ requires: C, 72·92; H, 8·26; N, 4·25%). Comparison of the IR spectra shows that this compound is the antipode of (+)-7,7-ethylenedioxy-3-methoxy-N-methylmorphinan.

Hydrolysis of (XI) and (XII)

(*a*) A soln of 0·285 g the ketal derivative XI in 3 cc 5% HClaq was heated on the steam bath for 1 hr. The soln was made basic and extracted with chloroform. The crude product was crystallized from ether to give 0·205 g XIII, m.p. 104–105°, $[\alpha]_D^{24\cdot5}$ $-62\cdot0^\circ \pm 2^\circ$ (*c*, 0·999, chloroform). (Found: C, 75·71; H, 8·23; N, 5·04. $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; N, 4·91%).

(*b*) A soln of 0·04 g XII in 10 cc 2% HClaq was heated as above. The similar treatment gave the same 7-oxo compound.

Huang-Minlon reduction of sinomenine-phenylether (XIV)

The benzene adduct of sinomeninephenylether (4·83 g) was converted to the hydrazone by heating with 10 g 80% hydrazine hydrate. To the reaction mixture was added 10 cc diethylene glycol and 2·5 g KOH pellets and the mixture was heated under stirring at 185° for 3 hr. Dilution with water and extraction with benzene gave 4·16 g the crude products, which were chromatographed over alumina to give 3·34 g oily deoxosinomeninephenylether XV.

Hydrolysis of deoxosinomeninephenylether (XV)

Hydrolysis of the above mentioned compound (0·555 g) was achieved by heating with 5·6 cc 10% HClaq. Chromatography on alumina and recrystallization from ether gave 0·535 g the 7-oxo compound XVI, m.p. 179–180°; $[\alpha]_D^{25\cdot5}$ $-26\cdot4^\circ$ (*c*, 1·055, alc). (Found: C, 76·60; H, 7·29; N, 3·63. $C_{24}H_{27}O_3N$ requires: C, 76·36; H, 7·21; N, 3·71%).

Ketalization of the 7-oxo compound XVI

The above mentioned 7-oxo compound (30·7 g) in benzene was azeotropically ketalized with 51 g ethylene glycol and 15·2 g TsOH. The reaction mixture was treated in usual manner. The crude products were chromatographed on alumina and the benzene eluate was crystallized from MeOH yielding 28·74 g (80·6%) the solvate of the desired ketal XVII, m.p. 108–109° (dec); $[\alpha]_D^{24}$ $-29\cdot0^\circ \pm 2^\circ$ (*c*, 1·074, alc). (Found: C, 72·20; H, 7·82; N, 3·04. $C_{26}H_{31}O_4N \cdot \frac{1}{2}CH_3OH$ requires: C, 72·74; H, 7·60; N, 3·20%).

Sodium-liquid ammonia reduction of the ketal (XVII)

A soln of 27·76 g the solvate of the ketal in 120 cc toluene was added dropwise to 500 cc liquid ammonia at -55° and the mixture treated with 3·7 g metallic Na until the blue colour persisted for ½ hr. The non-phenolic substance was chromatographed on alumina and elution with benzene gave 22 g oily XVIII, which on standing crystallized. Recrystallization from petroleum ether gave the pure product, m.p. 113°, 17·37 g (83·3%); $[\alpha]_D^{24}$ $+25\cdot6^\circ \pm 2^\circ$ (*c*, 1·060, alc). (Found: C, 73·05; H, 8·42; N, 4·31. $C_{20}H_{27}O_3N$ requires: C, 72·92; H, 8·26; N, 4·25%).

Hydrolysis of (XVIII)

Hydrolysis of the above mentioned product (18·128 g) with 90 cc 10% HClaq, liberation with dil. Na_2CO_3 aq and extraction with chloroform gave 16·77 g the oily ketonic compound, which was triturated with pet ether to give the crystalline ketonic compound XIX, m.p. 105–106° after having been purified via the hydrobromide; $[\alpha]_D^{20}$ $+47\cdot8^\circ \pm 2^\circ$ (*c*, 1·062, alc). (Found: C, 76·06; H, 8·36; N, 4·79. $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; N, 4·91%).

Acknowledgement—We 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, K. Okabe and T. Miyamoto, *Tetrahedron* **21**, 1121 (1965).

[2] K. Goto, I. Yamamoto and T. Yamazaki, *Proceedings of Japan Academy* **37**, 282 (1960).

[3] E. Caspi, T. A. Wittstruck and N. Grover, *J. Org. Chem.* **28**, 763 (1963).