[Chem. Pharm. Bull. 15(12)1944~1947(1967)]

UDC 547.94.02 : 582.675.4

251. Toshiro Ibuka and Masahiko Kitano*1 : Studies on the Alkaloids of Menispermaceous Plants. CCXXXIX.*2 Synthesis of Hasubanan Derivative from Sinomenine.*3

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Synthesis of hasubanan derivative from sinomenine is described.

(Received March 16, 1967)

The hasubanan skeleton (I) of hasubanonine,[1] metaphanine,[2] prometaphanine,[3] homostephanoline,[4] and cepharamine[5] is closely related to morphinan (II), and the difference between two groups is that the ethanamine chain of hasubanan forms five membered ring, whereas of morphinan forms six membered one. In this report the authors wish to present the transformation of morphinan derivative to hasubanan alkaloid.

The starting material chosen for the transformation was demethoxydeoxodihyrosinomenine (IV)[6] obtained from Clemmensen reduction of sinomenine (III). Acetylation of IV with acetic anhydride in dry pyridine afforded the acetate (V), m.p. 106°, $C_{20}H_{27}O_3N$. The acetate (V) showed acetate carbonyl band at 1755 cm^{-1} in the IR spectrum.*4 Oxidation of V with chromium trioxide in aqueous acetic acid[7,8] gives rise to the keto-acetate (VI), m.p. 195°, $C_{20}H_{25}O_4N$ (M^+ 343). The compound (VI) showed two carbonyl absorptions at 1769 cm^{-1} (acetate) and 1672 cm^{-1} (conj. ketone) in its IR spectrum and a signal attributable to C-9 proton at 7.02τ as doublet (J=3.0 c.p.s.) in its NMR spectrum.*5

Saponification of the keto-acetate (VI) with potassium hydroxide in aqueous ethylene glycol afforded the hydroxy-ketone (VII),[7] m.p. 214°, $C_{18}H_{23}O_3N$ (M^+ 301), showing a carbonyl absorption at 1670 cm^{-1} and a hydroxyl group at 3500 cm^{-1} in its IR spectrum. It is noteworthy that the hydroxyl group at C-4 of 10-oxo-compound (VII) is negative with Gibbs' reagent.[9]

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*2 This paper constitutes a part of a series entitled "Studies on the Alkaloids of Menispermaceous Plants" by Masao Tomita. Part CCXXXVIII: T. Ibuka, M. Kitano: This Bulletin, **15**, 1808 (1967).

*3 A preliminary communication of this work appeared in Tetrahedron Letters, No. 50, 6233 (1966).

*4 All IR spectra were taken in chloroform solution.

*5 All NMR spectra were taken on Varian Associates A-60 recording spectrometer in deuteriochloroform with tetramethylsilane as an internal standerd.

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2) M. Tomita, T. Ibuka, Y. Inubushi, K. Takeda: Tetrahedron Letters, No. 48, 3605 (1964); *Idem*: This Bulletin, **13**, 695 (1965); *Idem*: *Ibid.*, **13**, 704 (1965); T. Ibuka: Yakugaku Zasshi, **85**, 579 (1965).

3) M. Tomita, T. Ibuka, Y. Inubushi: Tetrahedron Letters, No. 48, 3617 (1964); *Idem*: Yakugaku Zasshi, **87**, 381 (1967).

4) Y. Watanabe, M. Matsui, K. Ido: Yakugaku Zasshi, **85**, 584 (1965); T. Ibuka M. Kitano: This Bulletin, **15**, 1939 (1967).

5) M. Tomita, M. Kozuka: Tetrahedron Letters, No. 50, 6229 (1966).

6) H. Kondo, E. Ochiai: Ann., **470**, 224 (1929); *Idem*: Yakugaku Zasshi, **44**, 8 (1924); K. Okabe: Shionogi's Ann. Rep., **11**, 49 (1961).

7) T. Sasaki, K. Kanematsu: The 21th Annual Meeting of the Pharmaceutical Society of Japan, Abstracts, p. 303 (1965). *Idem*: This Bulletin, **15**, 1415 (1967).

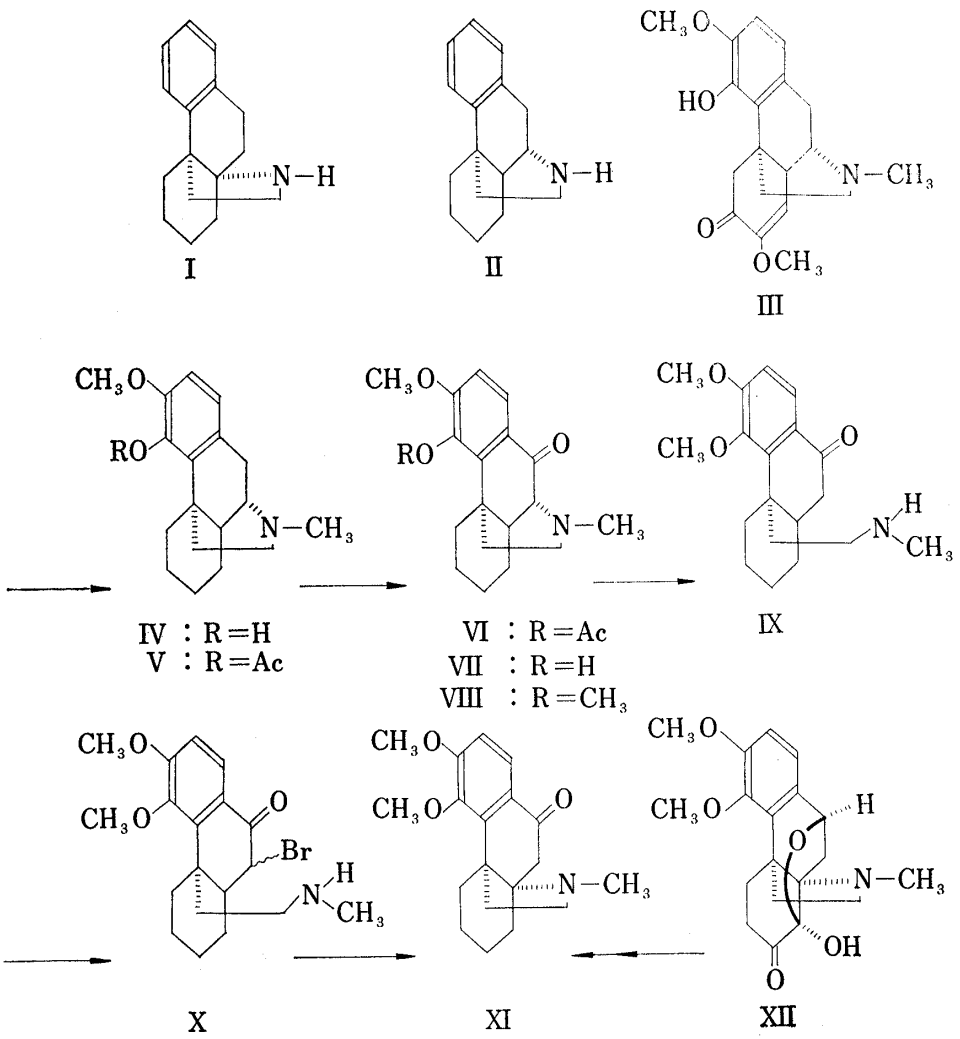
8) cf. H. Rapoport, S. Masamune: J. Am. Chem. Soc., **77**, 4330 (1955); *Idem*: *Ibid.*, **77**, 6359 (1959). See also H.L. Holmes, C.C. Lee: *Ibid.*, **69**, 1996 (1947).

9) M. Tomita, S. Uyeo: Yakugaku Zasshi, **61**, 449 (1941).

Methylation of Ⅶ with Rodionov reagent[10] in boiling toluene afforded the ketone (Ⅷ) as an oily substance, M^+ 315, which was characterized as its methiodide, m.p. 267～268°, $C_{20}H_{28}O_3NI$. Reduction of the ketone (Ⅷ) with zinc in boiling acetic acid gave rise to the ketone (Ⅸ) as an oily substance.

The dehydrogenation experiments designed for the purpose of the introducing of a double bond between C-9 and C-14 into Ⅸ with DDQ[11] or selenium dioxide were not encouraging. Hofmann degradation of Ⅷ likewise failed to yield any characterizable product. In view of these difficulties, bromination of the ketone (Ⅸ) in acetic acid was carried out to afford the bromo-ketone (X), which was not purified or analyzed but was immediately treated with the mixture of lithium chloride and lithium carbonate in N,N-dimethylformamide[12] at 120° to give the desired 3,4-dimethoxy-10-oxo-N-methylhasubanan (Ⅺ), m.p. 143～144°, whose molecular ion peak appeared at m/e 315 in its mass spectrum.

The compound (Ⅺ) thus obtained from sinomenine (Ⅲ) and the hasubanan derivative derived from metaphanine (Ⅻ)[2] were found to be identical in terms of their IR spectra,



10) W. Rodionov : Bull. soc. chim. France, **39**, 305 (1926); I. Seki : Ann. Takamine Lab., **12**, 56 (1960); K. Okabe : Yakugaku Zasshi, **82**, 1498 (1962).

11) D. Burn, D.N. Kirk, V. Petrow : Proc. Chem. Soc., **1960**, 14; D. Caine, J.B. Dawson : J. Org. Chem., **29**, 3108 (1964); G. Muller, J. Martell, C. Huynh : Bull. soc. chim. France, **1961**, 2000.

12) cf. N.L. Wendler, D. Taub, H. Kuo : J. Am. Chem. Soc., **82**, 5701 (1960); R.P. Holysz : *Ibid.*, **75**, 4432 (1953).

NMR spectra, MS spectra,[13] signs of specific rotation, and the mixed melting point did not depress.

Experimental*6

Acetylation of Demethoxydeoxodihydrosinomenine (IV)——Demethoxydeoxodihyrosinomenine (Ⅳ) (350 mg.) was treated with Ac_2O (2 ml.) and pyridine (2ml.) at room temperature for 20 hr. The excess Ac_2O and pyridine were removed *in vacuo* and the residue was made alkaline with 5% NH_4OH, and extracted with ether. The ether extract was washed, dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a crystalline solid. Recrystallization from ether gave 345 mg. of the acetate (V) as colorless pillars, m.p. 106°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1755 (OAc). *Anal.* Calcd. for $C_{20}H_{27}O_3N$: C, 72.92; H, 8.26. Found : C, 72.67; H, 8.21. Acetate (V) methiodide, m.p. 282° (acetone). Colorless prisms. *Anal.* Calcd. for $C_{21}H_{30}O_3NI$: C, 53.52; H, 6.42; N, 2.97. Found : C, 53.55; H, 6.59; N, 2.80.

Keto-Acetate (VI)——A mixture of the acetate (V) (250 mg.), AcOH (3 ml.), H_2O (0.5 ml.), and CrO_3 (100 mg.) was stirred for 48 hr. at room temperature. The reaction mixture was poured into ice-water and made alkaline with conc. NH_4OH and extracted with ether. The ether extract was washed, dried over $MgSO_4$, and evaporated to give an oily substance which was chromatograped over alumina from benzene and eluted with the same solvent. Recrystallization from acetone gave the keto-acetate (Ⅵ) as slightly yellow prisms, yield, 210 mg. m.p. 195°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1769 (acetate), 1672 (conj. ketone). NMR τ ($CDCl_3$) : two benzene protons, 1.95 (1*H*, doublet, J=8.5 c.p.s.), 3.03 (1*H*, doublet, J=8.5 c.p.s.); OCH_3, 6.11 (3*H*); N-CH_3, $OCOCH_3$ (overlapped), 7.67 (6*H*). *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.33; N, 4.08. Found : C, 69.95; H, 7,60; N. 3.85.

Hydroxy-Ketone (VII)——A mixture of the keto-acetate (Ⅵ) (270 mg.), ethylene glycol (3 ml.), H_2O (1 ml.), and KOH (1 g.) was refluxed for 20 hr. After cooling, H_2O was added, and then made ammoniacal alkaline with NH_4Cl, and extracted with ether. The ether extract was washed, dried over $MgSO_4$, and evaporated to give a crystalline solid. Recrystallization from acetone gave 200 mg. of the hydroxy-ketone (Ⅶ) as slightly yellow needles, m.p. 214°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1670 (conj. ketone), 3500 (hydroxyl). *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found : C, 71.44; H, 7.66; N, 4.61.

Methylation of Hydroxy-Ketone (VII) with Rodionov Reagant——Ⅶ (700 mg.) was dissolved in anhyd. toluene (30 ml.) and the Rodionov reagent (10 ml. of MeOH solution) was added. The mixture was heated at 90° for 1 hr. to remove MeOH, and then at 130° (oil bath temperature) for 50 hr. After dimethylaniline was removed by steam distillation, the crude product was extracted with ether. The ether extract was washed, dried over $MgSO_4$, and evaporated. The residue was chromatographed over alumina column from benzene and elution with the same solvent gave the ketone (Ⅷ) as slightly yellow oil. Yield, 600 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1669 (conj. ketone). MS : M^+ 315. NMR τ ($CDCl_3$) : two benzene protons, 2.08 (1*H*, doublet, J=8.5 c.p.s.), 3.08 (1*H*, doublet, J=8.5 c.p.s.); $OCH_3 \times 2$, 6.05 (3*H*), 6.16 (3*H*); N-CH_3, 7.67 (3*H*); C_9-H, 7.03 (1*H*, doublet, J=3.0 c.p.s.). Ketone (Ⅷ) methiodide : recrystallized from acetone as an yellow prisms, m.p. 267~268°. *Anal.* Calcd. for $C_{20}H_{28}O_3NI$: C, 52.53; H, 6.17; N, 3.07. Found : C, 52.61; H, 6.38; N, 2.97.

Reduction of the Ketone (VIII) with Zinc in Acetic Acid——To a solution of 490 mg. of Ⅷ in 10 ml. of AcOH was gradually added 1 g. of zinc dust, and the mixture was heated under reflux for 15 hr. After standing overnight, the inorganic precipitate was removed by filtration, and the filtrate was made alkaline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried over $MgSO_4$ and evaporated to give the ketone (Ⅸ) (400 mg.) as colorless oily substance. The base (Ⅸ) showed a single spot on thin-layer chromatography. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1672 (conj. ketone). NMR τ ($CDCl_3$) : two benbene protons, 2.10 (1*H*, doublet, J=9.0 c.p.s.), 3.11 (1*H*, doublet, J=9.0 c.p.s.); $OCH_3 \times 2$, 6.08 (3*H*), 6.14 (3*H*); N-CH_3, 7.61 (3*H*).

Bromo-Ketone (X), and 3,4-Dimethoxy-10-oxo-N-methylhasubanan (XI)——To a solution of the ketone (Ⅸ) (400 mg.) in 3 ml. of AcOH was added over a period of 1 hr. a solution of 200 mg. of bromine in 1.4 ml. of AcOH and the mixture stirred at room temperature for 15 hr. The reaction mixture was made alkaline with conc. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried over $MgSO_4$ and evaporation of the solvent under reduced pressure gave the bromoketone (X) as brown oil (yield 500 mg.). The crude bromo-ketone (X) was dissolved in dry N,N-dimethylformamide (20 ml.), to which $LiCO_3$ (100 mg.) and LiCl (500 mg.) was added, and the mixture was heated at 120° (oil bath temperature) for 3 hr. under nitrogen. After cooling, H_2O (30 ml.) was added and extracted with ether. The ether extract was washed, dried over $MgSO_4$, and evaporated to left a brown oil which was chromatographed over silica gel column from $CHCl_3$. Trituration with a small amount of EtOH gave a crystalline solid (35 mg.). Recrystallization from EtOH gave the pure sample (Ⅺ) as colorless needles, m.p. 143~144°. $[\alpha]_D^{30}$ −38° (c=0.4, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1678 (conj. ketone). NMR τ ($CDCl_3$) : two benzene protons, 2.38 (1*H*, doublet, J=8.5 c.p.s.),

*6 All melting points were determined on a Yanagimoto Micro Melting Point Apparatus and uncorrected.

13) M. Tomita, A. Kato, T. Ibuka : Tetrahedron Letters, No. 15, 1019 (1965); *Idem* : Mass Spectroscopy (Japan), **13**, No. 30, 115 (1965).

3.18 (1*H*, doublet, J=8.5 c.p.s.); $OCH_3 \times 2$, 6.11 (3*H*), 6.12 (3*H*); N-CH_3, 7.82 (3*H*). MS : M^+ 315, m/e 259 (base peak[13]).

The authors express their deep appreciation to Professor M. Tomita, Kyoto University, for his continuing counsel and encouragement in this work. They wish to express their gratitude to Dr. T. Shingu of the Faculty for measurements of NMR spectra. They are also grateful to Miss Y. Mano and her collaborators for elementary analyses.