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# 250. **Toshiro Ibuka and Masahiko Kitano**[*1] : Studies on the Alkaloids of Menispermaceous Plants. CCXXXVII.[*2] Alkaloids of *Stephania japonica* MIERS. (Suppl. 17[*2]). Structure of Homostephanoline. (3).[*3]

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The constitution of homostephanoline was investigated and the complete constitution (I) including the absolute stereostructure was presented.

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Homostephanoline, one of the basic constituents of *Stephania japonica* MIERS (Japanese name "Hasunohakazura"), was first isolated in pure form by Kondo and Sanada1) in 1928. The alkaloid possesses the molecular formula $C_{20}H_{25}O_5N=C_{16}H_{12}O\cdot(OH)\cdot(N\text{-}CH_3)\cdot(OCH_3)_3$2), and afforded hasubanonine (II) on methylation with diazomethane.2) Recently, degradative and spectroscopic investigations by Tomita and his coworkers3) serve to establish the stereo-structure of hasubanonine (O-methylhomostephanoline). Information regarding the position of hydroxyl group of homostephanoline was provided by Hofmann degradation of O-ethylhomostephanoline followed by acetolysis of the methine base to afford 3-acetoxy-6-ethoxy-1,5-dimethoxyphenanthrene (IV).[*3] Therefore, the structure of homostephanoline is shown by formula I.[*3]

In this paper, the authors report a confirmatory study on the structure of homostephanoline, which supplements the earlier result.

O-ethylhomostephanoline (III) was obtained by ethylation of homostephanoline (I) with diazoethane as colorless oily substance which was characterized as its hydrobromide, m.p. 230~238°. The nuclear magnetic resonance (NMR) spectrum[*4] of III confirmed the presence of a methyl of ethoxyl group at 8.25τ (3H), three methoxyl groups at 5.93 (3H), 6.05 (3H) and 6.35τ (3H), and N-methyl group at 7.47τ. The IR spectrum of III revealed the presence of a conjugated carbonyl group at 1660 cm$^{-1}$ and an enolic double bond band at 1600 cm$^{-1}$.[*5]

Reduction of O-ethylhomostephanoline (III) with sodium borohydride in aqueous methanol provided two epimeric alcohols, dihydro-O-ethyl-homostephanoline-A (Va) and -B (Vb), as in the case of borohydride reduction of hasubanonine.3,4) Vb was more strongly adsorbed on a chromatographic alumina column and had lower Rf value on the thin-layer chromatography (TLC) than its epimer Va. These findings indicate that the hydroxyl group of Va has the *quasi*-axial and that of Vb has *quasi*-equatorial

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[*3] (2). Y. Watanabe, M. Matsui, K. Ido: Yakugaku Zasshi, **85**, 584 (1965).

[*4] All NMR spectra were taken on Varian Associates A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard.

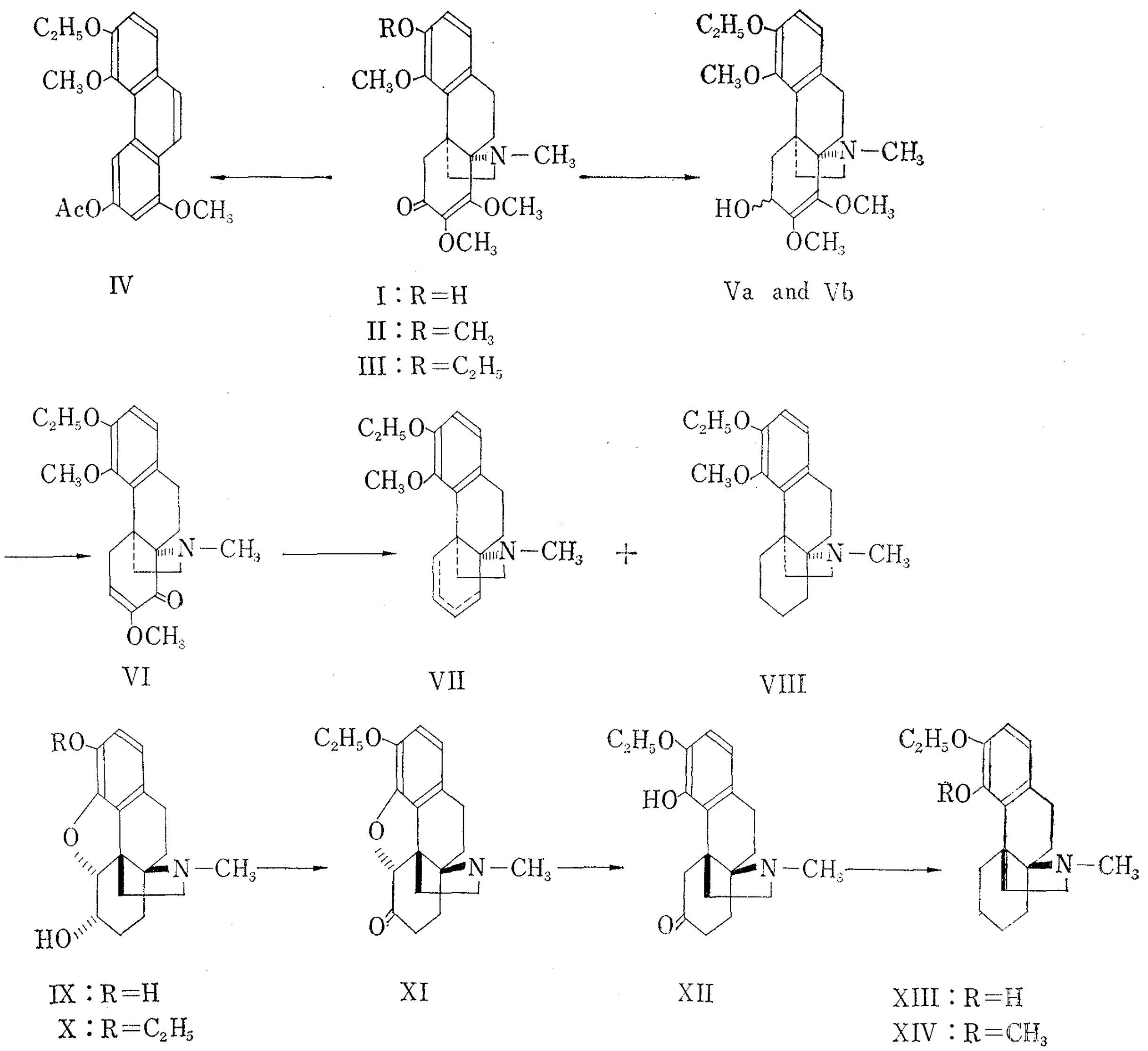
[*5] Otherwise specified, all IR spectra were taken in chloroform solution.

1) H. Kondo, T. Sanada: Yakugaku Zasshi, **48**, 1141 (1928).

2) M. Tomita, Y. Watanabe: *Ibid.*, **76**, 856 (1956).

3) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, M. Matsui: Tetrahedron Letters, No. 40, 2937 (1964); *Idem*: This Bulletin, **13**, 538 (1965).

4) T. Ibuka, M. Kitano: This Bulletin, **15**, 1808 (1967).



configuration.[3~6] Reduction of 1,3-dicarbonyl compounds provides a synthetic route of $\alpha,\beta$-unsaturated ketones since the reduction product undergoes an allylic rearrangement when treated with aqueous acid.[7] Both Va and Vb on mild treatment with dilute hydrobromic acid caused demethanolization producing a conjugated carbonyl compound (VI), m.p. 150°, $C_{21}H_{27}O_4N$, showing a carbonyl absorption at 1665 $cm^{-1}$ and an enolic double bond at 1645 $cm^{-1}$ in its infrared (IR) spectrum, and an olefinic proton at 4.31$\tau$ as triplet and two methoxyl groups at 6.05 and 6.41$\tau$ in its NMR spectrum.

Clemmensen reduction[8] of VI afforded an olefinic (VII) and a saturated compound (VIII), and this reduction sequence, from VI to VII and VIII, had analogy in the case of hasubanonine derivative.[3] The olefinic compound (VII), mp. 102°, $M^+$ : 313, showed a methoxyl group at 6.10$\tau$, a methyl of ethoxyl group at 8.54$\tau$, and two olefinic protons at 3.8~4.7$\tau$ in its NMR spectrum. Catalytic hydrogenation of VII over platinum dioxide

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5) *a*) D.H.R. Barton : Experientia, **6**, 316 (1950); *Idem* : J. Chem. Soc., **1953**, 1027; D.H.R. Barton, R. C. Cookson : Quart. Rev. Chem. Soc., **10**, 44 (1956).

6) S. Winstein, N.J. Holness : J. Am. Chem. Soc., **77**, 5562 (1955).

7) *a*) W.F. Gannon, H.O. House : Org. Syn., Vol. 40, 14 (1960). *b*) M. Stiles, A. Longroy : Tetrahedron Letters, No. 10, 337 (1961).

8) H. Kondo, E. Ochiai : Ann., **470**, 224 (1929); *Idem* : Yakugaku Zasshi, **44**, 8 (1924); K. Okabe : Shionogi's Ann. Rep., **11**, 49 (1961); Y.K. Sawa, N. Tsuji, S. Maeda : Tetrahedron, **15**, 144 (1961).

in 10% aq. acetic acid gave the saturated compound (VIII), which was characterized as its hydrobromide, m.p. 235~236°, $C_{20}H_{29}O_2N \cdot HBr$, $[\alpha]_D^{29}$ +60° (MeOH).

The validity of the structure of VIII was verified by comparison of VIII with an authentic sample of XIV derived from dihydroindolinomorphine (IX)⁹⁾ (VIII is the enantiomer of XIV).

Ethylation of IX with diazoethane afforded O-ethyldihydroindolinomorphine (X) as colorless needles, m.p. 133~137°, $C_{19}H_{25}O_3N$, $M^+$ 315. Oppenauer oxidation of X with benzophenone and potassium *tert.* butoxide in benzene gave a carbonyl compound (XI), showing a carbonyl group at 1728 $cm^{-1}$ in its IR spectrum. Reduction of XI with zinc dust and ammonium chloride in boiling ethanol[9,10)] afforded a phenolic compound (XII), m.p. 141°, $C_{19}H_{25}O_3N$, whose IR spectrum showed a hydroxyl group at 3470 $cm^{-1}$ and a carbonyl group at 1700 $cm^{-1}$. Huang-Minlon reduction of XII gave a compound (XIII), m.p. 102~105°, $C_{19}H_{27}O_2N$, which on methylation with Rodionov reagent[11)] in boiling toluene afforded a compound (XIV), characterized as its hydrobromide, m.p. 236~237°, $C_{20}H_{29}O_2N \cdot HBr$, $[\alpha]_D$ −44° (MeOH).

As shown in Table I, properties of VIII derived from homostephanoline (I) were identical with those of XIV derived from dihydroindolinomorphine (IX) except the sign of rotation.

On the basis of above results, the structure of homostephanoline is unambiguously assigned to the formula I including the position of hydroxyl group.

Table I.

| | | VIII | XIV |
|---|---|---|---|
| Free base | IR ($CHCl_3$) | identical | |
| | NMR ($CDCl_3$) | | |
| | TLC | | |
| Hydrobromide | formula | $C_{20}H_{29}O_2N \cdot HBr$ | $C_{20}H_{29}O_2N \cdot HBr$ |
| | appearance | colorless prisms | colorless prisms |
| | m.p. | 235~236° (decomp.) | 236~237° (decomp.) |
| | IR (KBr) | identical | |
| | $[\alpha]_D$: (MeOH) | +60° | −44° |

## Experimental[*6]

**O-Ethylhomostephanoline (III)**——To a solution of homostephanoline (I) (3.7 g.) in MeOH (540 ml.) was added excess ether solution of diazoethane and the mixture was allowed to stand 7 days at room temperature. The excess diazoethane was decomposed with 3% AcOH and the solvent was evaporated. The residual oil was dissolved in 3.5% HCl and extracted with ether and the aq. layer was made alkaline with aq. $NH_4OH$ and extracted with ether. The extract was washed, dried over $MgSO_4$, and the solvent was evaporated to give colorless oil (2.2 g.), which was characterized as its hydrobromide, m.p. 230~238°. *Anal.* Calcd. for $C_{22}H_{29}O_5N \cdot HBr \cdot \frac{1}{2}H_2O$: C, 55.35; H, 6.34. Found: C, 55.51; H, 6.25.

**Reduction of O-Ethylhomostephanoline (III) with Sodium Borohydride**——III (1.5 g.) was dissolved in 10% MeOH (20 ml.) and sodium borohydride (1.0 g.) was added in small portions. After standing for 6 hr. at room temperature, the excess sodium borohydride was decomposed with dil. AcOH. The solvent was evaporated under reduced pressure to dryness, and 20 ml. of dil. $NH_4OH$ was added and extracted with ether.

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

9) S. Okuda, K. Tsuda, S. Yamaguchi: "The 7th Symposium on the Chemistry of Natural Products, Japan" (Fukuoka, Oct., 1963), symposium abstract, p. 72 (1963). cf. *Idem*: J. Org. Chem., **27**, 4121 (1962); *Idem*: This Bulletin, **13**, 1092 (1965).

10) C. Schöpf, T. Pfeifer: Ann., **483**, 157 (1930).

11) *a*) W. Rodionov: Bull. soc. chim. France, **39**, 305 (1926). *b*) I. Seki: Ann. Takamine Lab., **12**, 56 (1960). *c*) K. Okabe: Yakugaku Zasshi, **82**, 1498 (1962). *d*) M. Tomita, T. Ibuka, M. Kitano: Tetrahedron Letters, No. 50, 6233 (1966). *e*) M. Tomita, T. Ibuka, Y. Inubushi, K. Takeda: This Bulletin, **13**, 695 (1965).

The extract was washed, dried over $MgSO_4$, and evaporated to give colorless oil (1.5 g.). The oil was dissolved in minimum amount of benzene, and was chromatographed over alumina column and elution with the same solvent gave dihydro-O-ethylhomostephanoline-A (Va) (380 mg.) as first eluate, and then -B (Vb) (208 mg.) as second eluate.

**Treatment of Dihydro-O-ethylhomostephanoline-A (Va) with dil. Hydrobromic Acid**——A solution of Va (220 mg.) in MeOH (13 ml.) was refluxed with 48% HBr (1 ml.) for 5 hr. The solvent was evaporated and the residue was dissolved in small volume of $H_2O$ and made alkaline with $NH_4OH$ and extracted with ether $CHCl_3$ (4:1) mixture. The extract was washed, dried over $MgSO_4$, and evaporated to give a crystalline solid. Recrystallization from acetone gave the conjugated carbonyl compound (VI) (82 mg.) as yellow prisms, m.p. 150°. IR $\nu_{\max}^{CHCl_3}$ $cm^{-1}$ : 1665 (C=O), 1645 (C=C). *Anal.* Calcd. for $C_{21}H_{27}O_4N$ : C, 70.56; H, 7.61. Found : C, 70.65; H, 7.84.

**Treatment of Dihydro-O-ethylhomostephanoline-B (Vb) with dil. Hydrobromic Acid**——To a solution of Vb (650 mg.) in MeOH (20 ml.) was added 48% HBr (1 ml.) and heated on a water bath for 5 hr. The solvent was evaporated and the residue was diluted with $H_2O$ and extracted with ether. The aq. layer was made alkaline with $NH_4OH$ and extracted with ether. The ether extract was washed, dried over $MgSO_4$, and evaporated to give crystalline masses. Recrystallization from acetone gave VI as yellow prisms, m.p. 146~149°. The IR spectrum of VI derived from Vb was superimposable with that of VI derived from Va, and the mixed melting point did not depress.

**Clemmensen Reduction of the Conjugated Carbonyl Compound (VI)**——VI (1.5 g.) was dissolved in 20 ml. of conc. HCl, and amalgamated zinc prepared from mossy zinc (20 g.), mercuric chloride (2 g.) and 3% HCl (10 ml.) was added in portions over a period of 2 hr. with stirring. After the addition was completed, the mixture was heated at 70~80° for 7 hr., during which time 7 ml. of conc. HCl was added in portions. The acidic layer is decanted and after made alkaline with $NH_4OH$, extracted with ether. The ether extract was washed, dried over $MgSO_4$, and evaporated to give brown oily substance, which was chromatographed over alumina column from benzene, and elution with the same solvent gave two compounds; olefinic (VII) (7 mg.) as first eluate, and saturated compound (VIII) (20 mg.) as second eluate. The saturated compound (VIII) was identical with the authentic sample (XIV) derived from dihydroindolinomorphine (IX) in terms of their, a) IR spectra (in $CHCl_3$), b) NMR spectra (in $CDCl_3$), c) mass spectra, and d) TLC. VIII was characterized as its hydrobromide, m.p. 235~236°, colorless prisms. $[\alpha]_D^{29}+60°$ (c=1.00, MeOH). *Anal.* Calcd. for $C_{20}H_{29}O_2N\cdot HBr$ : C, 60.60; H, 7.63. Found : C, 60.71; H, 7.69. The olefinic compound (VII) was recrystallized from ether as colorless prisms, m.p. 102°. MS, $M^+$ 313.

**O-Ethyldihydroindolinomorphine (X)**——Dihydroindolinomorphine (IX) (1.2 g.) was dissolved in MeOH (20 ml.) and was added ether solution of diazoethane. After standing for 10 hr., the excess diazoethane was decomposed with 3% AcOH and the solvent was evaporated to give an yellow oily substance. The residual oil was dissolved in 3.5% HCl and extracted with ether, and then the aq. layer was made alkaline with $NH_4OH$ and extracted with ether. The ether extract was washed, dried over $MgSO_4$, and the solvent was evaporated to give crystalline solid. Recrystallization from ether gave O-ethyldihydroindolinomorphine (X) as colorless needles, m.p. 133~137°. *Anal.* Calcd. for $C_{19}H_{25}O_3N$ : C, 72.35; H, 7.99. Found : C, 72.08; H, 8.25.

**Oppenauer Oxidation of O-Ethyldihydroindolinomorphine (X)**——A solution of X (522 mg.) in anhyd. benzene (30 ml.) was added 5 g. of benzophenone and 1 g. of potassium *tert.* butoxide. The mixture was refluxed for 15 min. and extracted three times with 5% HCl, and the aq. layer was made alkaline with $NH_4OH$ and extracted with ether. The ether extract was washed, dried over $MgSO_4$, and evaporated to give the ketone (XI) as a slightly yellow oil (400 mg.). IR $\nu_{\max}^{CHCl_3}$ $cm^{-1}$ : 1728 (C=O).

**Reduction of the Ketone (XI) with Zinc and Ammonium Chloride**——To a solution of XI (462 mg.) in EtOH (30 ml.) was added zinc powder (1.2 g.) and $NH_4Cl$ (1.2 g.). The mixture was refluxed with stirring for 6 hr., and after cooling, the mixture was filtered and the filtrate was condensed under reduced pressure. The residue was extracted with $CHCl_3$, washed, dried over $MgSO_4$, and evaporated. The light brown oil was chromatographed over alumina column from benzene to give crystalline solid. Recrystallization from acetone gave XI as colorless needles, m.p. 141°. *Anal.* Calcd. for $C_{19}H_{25}O_3N$ : C, 72.35; H, 7.99. Found : C, 72.29; H, 8.12.

**Huang-Minlon Reduction of XII**——A mixture of XII (400 mg.) and 85% hydrazine hydrate (2 ml.) was heated at 120° for 1 hr., and after cooling, diethylene glycol (4 ml.) and KOH pellets (1 g.) was added, and the reaction mixture was heated for 3 hr. at 170~180°. After cooling, the reaction mixture was made ammoniacal alkaline with $NH_4Cl$ and then extracted with ether-$CHCl_3$ (3:1) mixture. The 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 crude compound (XIII). Yield, 206 mg. Recrystallization from acetone gave analytical sample (XIII) as colorless needles, m.p. 102~105°. IR $\nu_{\max}^{CHCl_3}$ $cm^{-1}$ : 3470 (OH). MS, $M^+$ 301. *Anal.* Calcd. for $C_{19}H_{27}O_2N$ : C, 75.71; H, 9.03. Found : C, 75.79; H, 9.28.

**Methylation of XIII with Rodionov Reagent**——XIII (200 mg.) was dissolved in anhyd. toluene (30 ml.), and then the Rodionov reagent (6 ml. of MeOH solution) was added. The mixture was heated at 100° for 1 hr. to remove MeOH, and then at 130° for 8 hr. with stirring. After cooling, $H_2O$ (20 ml.) was added and extracted with ether. The 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 XIV as colorless oil, which was characterized as its hydrobromide, m.p. 236~237°. $[\alpha]_D^{29} -44°$ (c=1.00. MeOH). *Anal.* Calcd. for $C_{20}H_{29}O_2N \cdot HBr$ : C, 60.60; H, 7.63. Found : C, 60.32; H, 7.92.

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