3.4 g. of hydrazine hydrate (80%) was deposited with stirring. The reaction mixture became yellow. 4-Hydrazino-3,6-dichloropyridazine was deposited gradually by standing at room temperature. After the reaction mixture was warmed on a water bath for 30 mins. and cooled, the crystals were collected and recrystallized from EtOH. Yield, 3.6 g. of m.p. 195~196°C (decomp.). Anal. Calcd. for C₇H₅N₂Cl₂: C, 26.81; H, 2.23; N, 30.28. Found: C, 27.03; H, 2.16; N, 30.44.

4-Hydrazinopyridazine Hydrochloride (VI)—A mixture of 2 g. of (V), 100 cc. EtOH, 10 cc. distilled water, and 0.8 g. Pd-C (ca. 8%) was hydrogenated at atmospheric pressure. After the calculated quantities of hydrogen was absorbed the catalyst was filtered off and washed with a small amount of water. The filtrate was evaporated in vacuo on a water bath and the residue was recrystallized from EtOH. Yield, 1.1 g. of needles, m.p. 240~242°C (decomp.). Anal. Calcd. for C₇H₅N₂·HCl: C, 32.75; H, 4.71; N, 38.22. Found: C, 32.77; H, 4.63; N, 37.71.

Reaction of 3,4,6-Trichloropyridazine with Glacial Acetic Acid. Formation of 3,4- or 3,5-Dichloro-6-pyridazine (VII)—Twenty grams of (I) was refluxed with 65 cc. of glacial AcOH for 1.5 hrs. After cool, the reaction mixture was poured into 300 cc. of water and deposited crystals were recrystallized from water. Yield, 6.3 g. of needles, m.p. 203~204°C. Anal. Calcd. for C₇H₅Cl₃·Cl₂: C, 29.09; H, 1.21. Found: C, 30.14; H, 1.38.

Catalytic Reduction of (VII)—A mixture of 3 g. of (VII), 1.5 g. NaOH, 1.4 g. Pd-C (8%), and 50 cc. of distilled water was hydrogenated at atmospheric pressure. After filtration of the catalyst, the filtrate was neutralized with dil. HCl (1:1) and evaporated on a water bath using water aspiration. The residue was extracted with hot AcOEt and 6-pyridazine (VIII), m.p. 96~99°C, deposited on standing at room temperature. Yield, 0.6 g. The melting point becomes 70~71°C as it forms a monohydrate in the air.

Reaction of 3,4,5-Trichloropyridazine with Glacial Acetic Acid. Formation of 4,5-Dichloro-6-pyridazine (X)—Eight grams of 3,4,5-trichloropyridazine (IX) was refluxed with 25 cc. of glacial AcOH for 1 hr. After cool, the reaction mixture was poured into 60 cc. of water and the deposited crystals were recrystallized from water. Yield, 2.5 g. of prisms, m.p. 199~200°C. The mixed melting point with an authentic sample was not depressed.

Reaction of 3,6-Dichloropyridazine with Glacial Acetic Acid. Formation of 3-Chloro-6-pyridazine (XII)—Two grams of 3,6-dichloropyridazine (XI) was refluxed with 7 cc. of glacial AcOH for 1 hr. After cool, the mixture was poured into 30 cc. of water and 0.7 g. of crude 3-chloro-6-pyridazine, m.p. 95~96°C, was obtained. It was recrystallized from AcOEt and dried in a vacuum desiccator. Yield, 0.62 g. of m.p. 138~139°C.

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Norio Sugimoto and Hiroshi Kugita: Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. XIV. Synthesis of 6-Hydroxy-4a,10-trimethylene-1,2,3,4,4a,9,10,10a-octahydrophenanthridine (Supplement).

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The synthesis of 6-hydroxy-4a,10-trimethylene-1,2,3,4,4a,9,10,10a-octahydrophenanthridine has been reported in earlier paper of this series and some considerations were made on the steric configuration of this compound this time.

The relationship between the configuration and synthetic method may be presented in the following manner, following past synthetic experiments.

The catalytic reduction of 2-(β-cyanoethyl)-2-(m-methoxyphenyl)cyclohexanone (I), prepared from 2-(m-methoxyphenyl)cyclohexanone and acrylonitrile, at high temperature and pressure, with Raney nickel as the catalyst, first effects reduction of the nitrile to form the amino ketone compound and this undergoes intramolecular condensation to the octahydroquinoline compound (II). The hydrogenation of this compound (II),

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if the phenyl group is above the plane of the octahydroquinoline ring, would begin with the attack of hydrogen on the double bond from the rear and the hydrogenated decahydroquinoline compound (III) would be in trans configuration. This is also known from the fact that its acetylation affords 1-acetyldecahydroquinoline (III'), m.p. 108~109°, in almost quantitative yield, as uniform crystals. This trans configuration for decahydro compound (III) would explain the facile progress of the Pictet–Spengler reaction of (III) with formic acid and formaldehyde, giving the product in a good yield, and the position of the amino group and ortho–position of the phenyl ring, as constructed on the molecular model, would be such that would easily undergo condensation with formaldehyde, more easily than in the compounds with cis configuration. The cyclization of this trans-compound to 3-methoxy-9-aza compound (IV) would give a compound with cis-fused B/C ring and trans–fused C/D ring, having the same steric configuration as that of morphine. This compound was demethylated with 48% hydrobromic acid to 3-hydroxy-9-aza compound (V). The compound obtained by methylation of (V) with dimethyl sulfate in alkali hydroxide was identified with the starting compound (IV), by the identity of their hydrochloride (m.p. 249°) and methiodide (m.p. 235~236°). This has established beyond doubt that the compound (V) listed in the title has the same configuration as that of morphine and this fact may be further endorsed by the powerful analgesic action found in this compound (V).

Recently, Wildman reported that crinine, powelline, buphanidrine, and buphanamine, the components of plants of Amaryllidaceae family, were all d–nor compounds of the same skeletal structure (V) and, since it had been found by Eddy that these compounds possessed a strong analgesic action, it may fully be assumed that series of these compounds also have the same steric configuration as that of morphine.

The writers are indebted to the kind encouragement of Dr. Fujisawa, the Director of this Laboratory, during the course of the present work.

**Experimental**

6-Methoxy-4a,10-trimethylene-1,2,3,4,4a,9,10,10a-octahydrophenanthridine—To the solution of the hydroxy compound (V) (0.3 g.) dissolved in 10% KOH solution (5 cc.), Me₂SO₄ (1.0 g.) was added and shaken vigorously for about 10~15 mins., neutralized with HCl, and KI added. Yellow crystal-

line solid was separated and filtered to obtain the methiodide of (IV) (0.3 g.) as yellow needles (AcOEt + MeOH), m.p. 235–236°. A mixed melting point of this compound with the authentic sample of methiodide of (IV) was not depressed.

A mixture of the methiodide of the methoxy compound (IV) (0.2 g) was warmed with moisted fresh AgCl on a water bath and converted to the methochloride. AgI was filtered off and the combined filtrate was concentrated to dryness. The residue was distilled in vacuo (2 mm. Hg) to yield colorless, very viscous oil at 240° (bath temp.). Hydrochloride: Colorless needles (AcOEt + EtOH), m.p. 249°. This compound was determined as the starting material (IV) by admixture.

Summary

Some considerations were made on the steric configuration of 3-hydroxy-9-aza-des-N-morphinan synthesized previously. It was thereby established that the octahydroquinoline formed during the course of its synthesis has a trans-configuration and that its cyclized product and demethylated, objective compound have the same steric configuration as that of morphine.

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Shoji Shibata, Junzo Shoji, Akihiro Ohta, and Mitsuo Watanabe: Metabolic Products of Fungi. XI.* Some Observation on the Occurrence of Skyrin and Rugulosin in Mold Metabolites, with a Reference to Structural Relationship between Penicilliopsis and Skyrin.

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