b]pyridazine (XVb), 3,8-Dimethyl-6-hydrazino-*s*-triazolo[4,3-*b*]pyridazine (XVIa), and 3,7-Dimethyl-6-hydrazino-*s*-triazolo[4,3-*b*]pyridazine(XVIb)—(XIIIa), (XIVb), (XIVa), and (XIVb) were respectively heated with excess of 80% $N_2H_4 \cdot H_2O$ for 1 hr. After cooling, the crystals were collected and recrystallized from MeOH. All of them were colorless leaflets.

Summary

In the reaction of 3,6-dichloro-4-methylpyridazine (I) with hydrazine hydrate, ammonia, sodium hydroxide, sodium methoxide, or potassium hydrogen sulfide, mono-substituted compounds were obtained. The position of methyl group in those compounds and the relationship among them were cleared up. Examination was also made on whether substitution in (I) occurred in 3- or in 6-position according to the change of conditions.

6-Chloro-8-methyl-*s*-triazolo[4,3-*b*]pyridazine and 6-chloro-7-methyl-*s*-triazolo[4,3-*b*]-pyridazine were prepared from 3-hydrazino-4-methyl-6-chloropyridazine and 3-hydrazino-5-methyl-6-chloropyridazine, and were derived to their 6-hydrazino derivatives.

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U.D.C. 547.837

41. Ken'ichi Takeda and Katsumi Kotera : The Stereochemistry of Dihydrolycorine.[1]

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The structure of lycorine, the most abundantly and widely occurring member of alkaloids of the Amaryllidaceae, has been studied with great interest and discussed vigorously from the chemical as well as biogenetical standpoint for these several years. Although the structure of dihydrolycorine, obtained by the catalytic reduction of lycorine, has been firmly established as the formula (I),[2,3] there still remained some problems to be solved conclusively on the stereochemistry of dihydrolycorine (I), such as the relationship of the two hydroxyl groups or B/C and C/D ring junctions.

In the present paper we wish to report the results of experiments on these problems.

Dihydrolycorine monotosylate, which was readily prepared by the action of tosyl chloride in pyridine at room temperature, afforded a substance, m.p. 148.5°, $C_{16}H_{17}O_3N$, when treated with 1% methanolic potassium hydroxide. The infrared spectrum of this substance indicated no hydroxyl nor carbonyl group. This substance gave monoacetyldihydrolycorine with hot acetic acid, which on either acetylation or alkaline hydrolysis furnished diacetyldihydrolycorine (Ia) or dihydrolycorine (I), respectively. This monoacetyldihydrolycorine was also obtained by the direct acetylation of dihydrolycorine with acetyl chloride in pyridine at 0° together with almost the same amount of diacetyldihydrolycorine. On the other hand, dihydrolycorine was directly obtained from the above-mentioned substance with dilute sulfuric acid at 100°. It is clear from these facts that the substance, $C_{16}H_{17}O_3N$, is an epoxide (II). Although there are many studies on the

* Imafuku, Amagasaki, Hyogo-ken (武田健一, 小寺勝美).

1) The investigations described in this paper were outlined in a preliminary communication to the Chemistry & Industry, **1956**, 347.

2) L.G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W.I. Taylor, B.R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima, N. Yanaihara : J. Chem. Soc., **1954**, 4622.

3) S. Takagi, W.I. Taylor, S. Uyeo, H. Yajima : J. Chem. Soc., **1955**, 4003.

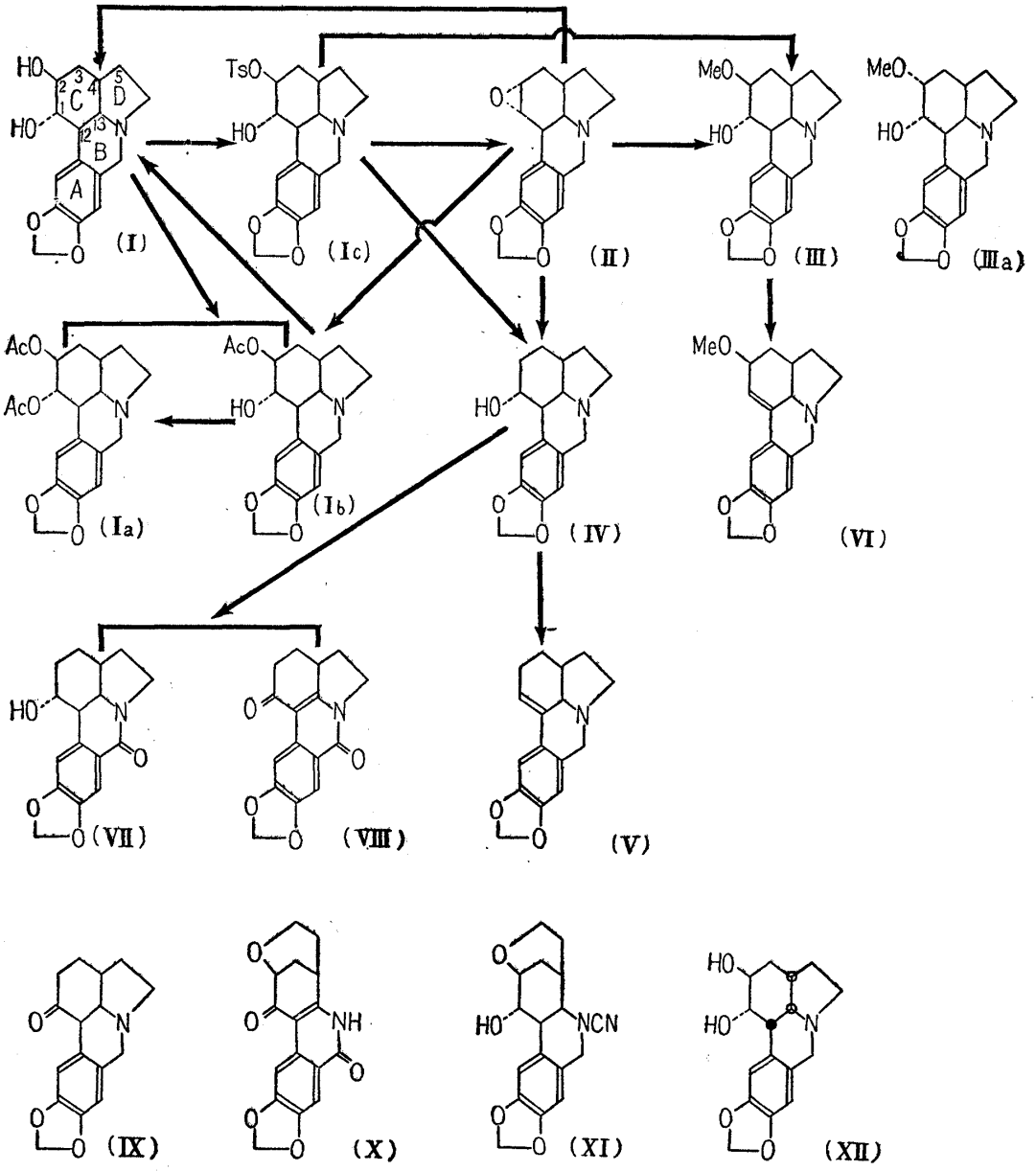

Chart 1.

ring-opening reactions of epoxides in the field of steroids or sapogenins,[4] as to the nitrogen-containing compounds, it may be said that there are only a few examples. In spite of this fact, it can also be deduced that the two vicinal hydroxyl groups produced by the ring-opening of the epoxide (II) are *trans* to each other and diaxial in configuration[4] (provided that the ring system does not undergo conformational change).

Reduction of dihydrolycorine monotosylate or the epoxide (II) with lithium aluminum hydride gave the same monodesoxy derivative (IV), $C_{16}H_{19}O_3N$, m.p. 169~170°.[1,5] It was proved that this compound is identical with dihydrocaranine[6] obtained by the catalytic

4) A. Fürst, Pl. A. Plattner: Abstract of Papers, 12th Internatl. Congr. Pure and Applied Chem., N.Y., 1951, p. 409; D.H.R. Barton: J. Chem. Soc., **1953**, 1027; A. Fürst, R. Scotoni, Jr.: Helv. Chim. Acta, **36**, 1332 (1953); *ibid.*, **36**, 1410(1953).

5) In our earlier communication,[1] we reported that this substance, m.p. 169~170°, has a diamorph, m.p. 150°. However, further investigation showed that the latter would probably be the former contaminated with a small amount of impurity, and not a diamorph (cf. Experimental Section).

6) The authors wish to thank Dr. W.C. Wildman for his private communication to establish the identity of these substances.

reduction of caranine, an alkaloid isolated from some Amaryllidaceae plants by Wildman, *et al.*[7], with platinum in acetic acid. This result shows that the stereochemical relationship between dihydrolycorine and dihydrocaranine must be the same. Action of phosphoryl chloride upon the monodesoxy derivative in pyridine gave an unsaturated compound, $C_{16}H_{17}O_2N$, m.p. 86~87°. The ultraviolet absorption spectrum of this substance shows that the double bond produced by this reaction must be conjugated to the aromatic A-ring (cf. Fig. 1, Curve A). From these results, the structures of the monoacetate, monotosylate, monodesoxy derivative, and the unsaturated compound are well established by the formulae (Ib), (Ic), (IV), and (V), respectively.

Treatment of the monotosylate (Ic) with 10% methanolic potassium hydroxide gave the monomethyl ether (III), m.p. 195~196°, $C_{17}H_{21}O_4N$, as mentioned earlier.[1] At that time, we considered that the methoxyl group at C-2 of the monomethyl ether (IIIa) and the hydroxyl group at C-1 has a *cis*-configuration as a result of the Walden inversion. However, this compound is also obtained from the epoxide (II) by the action of 10% methanolic potassium hydroxide. From these facts, it can be concluded that the most probable course of methoxylation of the monotosylate proceeds with intermediate formation of the epoxide ring and that the methoxyl group at C-2 has the same configuration as the hydroxyl group at C-2 of dihydrolycorine (the correct structure of the monomethyl ether is represented as (III)).

Treatment of the monomethyl ether (III) with phosphoryl chloride in pyridine at room temperature readily gave an unsaturated compound, $C_{17}H_{19}O_3N$, m.p. 155~156°. The structure of this unsaturated compound assigned to (VI) was confirmed by the result of ultraviolet absorption spectrum (cf. Fig. 1, Curve B.).

Though attempts to obtain the monoketone (IX) by the chromic acid-pyridine oxidation of monodesoxydihydrolycorine (IV) failed, all the products obtained has a lactam moiety in the B-ring : i.e., one of the two oxidation products, m.p. 242~243°, $C_{16}H_{17}O_4N$, was assigned as (VII) from the ultraviolet and infrared absorption data and the structure of the other one, m.p. 249~250°, $C_{16}H_{13}O_4N$, was assumed to be (VIII) from the ultraviolt absorption data in comparison with that of the keto-lactam (X) obtained from

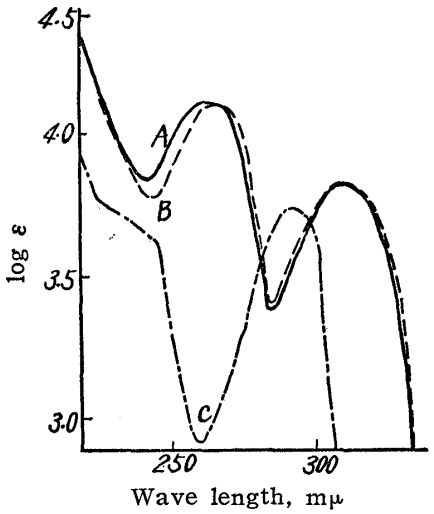

Fig. 1. Ultraviolet Absorption Spectra
(A) Unsaturated Compound (V). (B) Unsaturated Compound (VI). (C) Epoxide (II).

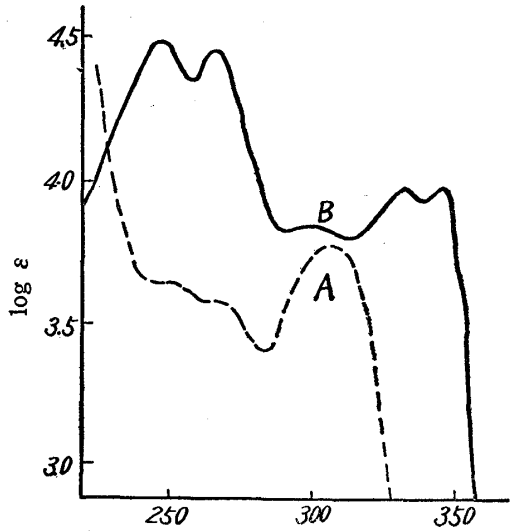

Fig. 2. Ultraviolet Absorption Spectra
(A) Lactam (VII). (B) Keto-lactam (VIII).

7) L.H. Mason, E.R. Puschett, W.C. Wildman : J. Am. Chem. Soc., **77**, 1253(1955); H.M. Fales, E.W. Warnhoff, W.C. Wildman : *ibid.*, **77**, 5885(1955); E.W. Warnhoff, W.C. Wildman : Chemistry & Industry, **1956**, 348.

dihydrolycorine by the degradation method of von Braun (cf. Fig. 2, Curves A and B)[3]. As to the course of this oxidation, it may be deduced that the lactam (VII) was first formed and this lactam successively afforded (VIII).

As has been pointed out previously,[3,8] diacetyl-ω-bromo-N-cyanodihydrosecolycorine by the alkaline treatment yielded the ether (XI), hence the hydroxyl group at C-2 and the ethylene residue in the D-ring must lie on the same side of the C-ring.

Since the hydroxyl group at C-2 is axial, the ethyl residue in the D-ring is also attached axial to the C-ring. The pyrrolidine D-ring must, therefore, be *cis*-fused (i.e. C-N bond is equatorial) to the C-ring, *trans*-fusion through two vicinal axial linkages being sterically impossible.

Considering the afore-mentioned fact that the monodesoxy derivative (IV) or the monomethyl ether (III) respectively yielded the corresponding unsaturated compounds by the ready elimination of the hydroxyl group at C-1, it is adequate to assume that the hydrogen atom at C-12 would be *trans* to the C-1 hydroxyl group and axial to the C-ring, hence this indicates that the aromatic A-ring is equatorial to the C-ring. Otherwise, the aromatic A-ring being axial to the C-ring, such conformation would not be favorable for reason of its unstability. It is, therefore, presumed that the juncture between rings B and C would be *trans*.

Consequently, dihydrolycorine has B/C and C/D rings *trans*- and *cis*-fused, respectively, and two vicinal axial hydroxyl groups. Dihydrolycorine, then, might be shown sterically by the formula (XII) or its mirror image.

The authors are indebted to Dr. W. I. Taylor and Prof. S. Uyeo for valuable discussions and to Dr. H. Kondo, Professor Emeritus of the University of Tokyo, for his kind guidance and encouragement. The authors wish also to express their thanks to Messrs. T. Iyeki and K. Miyahara and Misses N. Morita, H. Nakai, and T. Tange for the microanalyses and to Mr. M. Narisada for the measurement of the infrared spectra.

Experimental[9]

Monotosylate (Ic)—Dihydrolycorine (I) (500 mg.) and tosyl chloride (1.0 g.) were dissolved in pyridine (10 cc.) under cooling with ice and the solution was allowed to stand for 17 hrs. at room temperature. The reaction mixture was concentrated at 50~60°(bath temperature) *in vacuo* and the residue was poured into water. This aqueous mixture was basified with Na_2CO_3 and extracted several times with $CHCl_3$. The combined $CHCl_3$ solution was washed well with water, dried over Na_2SO_4, and evaporated *in vacuo* to give a crystalline residue (450 mg.) which was washed thoroughly with ice-cold Me_2CO to afford a crude monotosylate (250 mg.), m.p. 143~145°(decomp.). Recrystallization from EtOAc gave a pure sample, rosettes, m.p. 144~146°(decomp.); U. V. : λ_{max} 290 mμ (log ε 3.56). *Anal.* Calcd. for $C_{23}H_{25}O_6NS$: C, 62.26; H, 5.68; N, 3.16. Found : C, 62.35; H, 5.88; N, 3.06.

Its acetate prepared by the action of Ac_2O and pyridine on (Ic) afforded a pure sample, needles, m.p. 177~178°(decomp.) on recrystallization from Et_2O. *Anal.* Calcd. for $C_{25}H_{27}O_7NS$: C, 61.82; H, 5.61; N, 2.88. Found : C, 61.77; H, 5.87; N, 3.01.

Epoxide (II)—a) From (Ic) : A solution of the crude monotosylate (Ic), m.p. 143~145°(decomp.) (100 mg.), and KOH (150 mg.) in MeOH (15 cc.) was heated under reflux for 1 hr. The reaction mixture was diluted with water, concentrated *in vacuo* to remove MeOH, and extracted with a benzene-Et_2O mixture. The organic layer was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was chromatographed on alumina and the crystalline product, which was eluted with benzene, gave colorless prisms (35 mg.), m.p. 148~148.5°, $[\alpha]_D^{19}$ −215.4°(c=0.975, benzene) on recrystallization from MeOH. U. V. : λ_{max} 290 mμ (log ε 3.68) (cf. Fig. 1, Curve C). *Anal.* Calcd. for $C_{16}H_{17}C_3N$: C, 70.81; H, 6.31; N, 5.16. Found : C, 70.89; H, 6.44; N, 5.35.

b) From (Ic)-Acetate : When a solution of (Ic)-acetate (90 mg.) and KOH (100 mg.) in MeOH (10 cc.) was worked up in the same way as described before, the crude epoxide (35 mg.), m.p. 145~146°, was obtained.

The Monomethyl Ether (III) from (Ic)—To a boiling solution of methanolic KOH prepared with

8) H. Kondo, H. Katsura : J. Pharm. Soc. Japan, **59**, 733(1939).

9) All melting points are uncorrected. The ultraviolet absorption spectra were taken in 90% EtOH solution using a Beckman Model DU Spectrophotometer and the infrared absorption spectra were determined with a Perkin-Elmer Single-beam Infrared Spectrophotometer, Model 12 c.

KOH (1.0 g.) in MeOH (9 cc.) and water (1 cc.), the crude monotosylate (Ic), m.p. 143~144°(decomp.) (100 mg.), was added and this solution was heated under reflux for 3 hrs. After cooling, the reaction mixture was diluted with water and evaporated to remove MeOH under reduced pressure and the crystalline precipitate (30 mg.), m.p. 189~193°, was obtained. Recrystallization from EtOH gave a pure sample, prisms, m.p. 195~196°, $[\alpha]_D^{19}$ −85.7°(c=1.23, EtOH). U. V. : λ_{max} 291 mμ (log ε 3.68), I. R. : λ_{max}^{Nujol} 9.15 μ (-OCH_3). *Anal.* Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62; OCH_3, 10.23. Found : C, 67.30; H, 7.03; N, 4.95; OCH_3, 10.48.

Ring-opening Reaction of the Epoxide (II) with Acetic Acid—The epoxide (II) (200 mg.) in glacial AcOH (6 cc.) was heated under reflux for 10 mins. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in water, filtered, basified with Na_2CO_3, and extracted with benzene. The organic layer was washed with water, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. Trituration of the residue with Me_2CO gave crystals (150 mg.), m.p. 165~168°, which were recrystallized twice from the same solvent, affording monoacetyldihydrolycorine (Ib), needles, m.p. 170~171°, $[\alpha]_D^{25}$ −180.6°(c=1.65 $CHCl_3$). U. V. : λ_{max} 290 mμ (log ε 3.64). *Anal.* Calcd. for $C_{18}H_{21}O_5N$: C, 65.25; H, 6.34; N, 4.23. Found : C, 65.05; H, 6.40; N, 4.06.

Acetylation of Dihydrolycorine (I)—Dihydrolycorine (I) (200 mg.) was added to a mixture of AcCl (150 mg.) and pyridine (4 cc.) under cooling with ice and this mixture was stored in the refrigerator for 10 hrs. The reaction mixture was poured into a large amount of ice water, made basic with Na_2CO_3, and extracted with Et_2O. The ethereal layer was washed several times with water, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on alumina. The benzene eluted residue was recrystallized from EtOH to colorless needles (40 mg.), m.p. 173~175°, which showed no depression on admixture with the authentic diacetyldihydrolycorine, m.p. 174~175°. Trituration of the benzene-Et_2O (1:1) eluate with Et_2O gave a crystalline product (50 mg.) which was recrystallized from the same solvent to colorless needles, m.p. 170~171°, undepressed on admixture with monoacetyldihydrolycorine, m.p. 170~171°, prepared from the epoxide (II) as described above and both substances gave identical infrared spectra.

Further Acetylation of Monoacetyldihydrolycorine (Ib)—A mixture of monoacetyldihydrolycorine (Ib) (100 mg.), Ac_2O (4 cc.), and pyridine (0.4 cc.) was allowed to stand overnight at room temperature. The reaction mixture was worked up in the usual manner. The crystalline product thus obtained was recrystallized from EtOH to give a pure sample (90 mg.) as needles, m.p. 174~175°, undepressed on admixture with the authentic diacetyldihydrolycorine (Ia) prepared by the procedure of H. Kondo and Katsura.[8] The infrared spectrum of each substance also showed that both substances were identical.

Saponification of Monoacetyldihydrolycorine (Ib)—Saponification of monoacetyldihydrolycorine (Ib) (30 mg.) obtained from the epoxide with KOH (300 mg.) in MeOH (10 cc.) gave dihydrolycorine (I), needles, m.p. 250°(decomp.), undepressed on admixture with the authentic specimen.

Ring-opening Reaction of the Epoxide (II) with Dilute Sulfuric Acid—The epoxide (II) (20 mg.) in 10% H_2SO_4 (4 cc.) was heated at 100° for 2 hrs. When the reaction mixture was basified with Na_2CO_3 and allowed to stand at room temperature, a crystalline product precipitated slowly. Recrystallization from MeOH gave a pure sample as needles, m.p. 250°(decomp.), undepressed on admixture with the authentic specimen of dihydrolycorine (I).

The Monomethyl Ether (III) from the Epoxide (II)—To a boiling solution of methanolic KOH prepared from KOH (1.1 g.), MeOH (9 cc.), and water (1 cc.) was added the crude epoxide (II), m.p. 145~147°(120 mg.), and this solution was worked up by the same procedure with that from the monotosylate (Ic) as described before. The crude product (90 mg.), m.p. 189~193°, was obtained. Recrystallization from EtOAc gave a pure sample (60 mg.), prisms, m.p. 195~196°, which was undepressed on admixture with the authentic monomethyl ether (III) obtained directly from the monotosylate (Ic).

The Monodesoxy Derivative (IV)—a) Reduction of the Epoxide (II) with $LiAlH_4$: To a solution of the epoxide (II) (1.0 g.) in dry Et_2O (80 cc.), $LiAlH_4$(500 mg.) in dry Et_2O (40 cc.) was added dorpwise with stirring over a period of 1 hr. and stirring was continued for 1 hr. more at room temperature. Water (60 cc.) was slowly added to the reaction mixture and then benzene (60 cc.) was added. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue (820 mg.) solidified, and after purification via hydrochloride, needles, m.p. 263~264°(decomp.), were recrystallized from Me_2CO to colorless prisms (630 mg.), m.p. 169~170°, $[\alpha]_D^{21}$ −103.2°(c=0.95, EtOH), U. V. : λ_{max} 291 mμ (log ε 3.67). *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.29; H, 7.01; N, 5.13. Found : C, 70.51; H, 7.40; N, 5.08.

The mother liquor from which no further hydrochloride of this product, m.p. 169~170°, could be obtained, was basified with Na_2CO_3 and extracted with benzene. The benzene layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. Trituration of the residue with a small amount of Me_2CO gave a crystalline product, which was recrystallized from EtOH to colorless needles (50 mg.), m.p. 149~150°, $[\alpha]_D^{25}$ −72.2°(c=1.50, $CHCl_3$). The analytical values correspond to the formula, $C_{16}H_{19}O_3N$. *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.29; H, 7.01; N, 5.13. Found : C, 70.27, 70.48; H, 7.04,

7.19; N, 5.16. However, attempts to crystallize the salts of this product, such as hydrochloride, perchlorate, and picrate, were unsuccessful. Further purification by chromatography on alumina or by sublimation in high vacuum also failed. The ultraviolet spectrum of this substance, m.p. 149~150°, was similar to that of the product, m.p. 169~170°. The infrared spectrum of each substance in Nujol is similar in general, but not identical. One of the most remarkable differences consists in the point that the substance of the lower melting point has λ_{max}^{Nujol} 11.70 μ in contrast with λ_{max}^{Nufol} 11.83 μ of the product of the higher melting point. However, the infrared spectra of these substances both in $CHCl_3$ and in CCl_4 were nearly indistinguishable. Though the results of the infrared spectra indicate that these substances were to be identical, the mixed melting point determination shows an extremely slight depression (e.g. ca. 0.5° or less). Finally, by paper chromatography in BuOH : AcOH : H_2O (10:1:5), the substance, m.p. 169~170°, gave only one spot (Rf 0.55~0.57) by Dragendorff's reagent. On the other hand, the substance, m.p. 149~150°, gave two spots (Rf 0.55~0.57 and 0.48~0.50, respectively) by the same reagent. Accordingly, the substance, m.p. 149~150°, was found to be the substance, m.p. 169~170°, containing an impurity. This impurity was not studied at present.

b) Reduction of the Monotosylate (Ic) with $LialH_4$: To A solution of the monotosylate (Ic) (150 mg.) in dry Et_2O (20 cc.) and dry benzene (30 cc.), $LiAlH_4$(80 mg.) in dry Et_2O (10 cc.) was added dropwise with stirring during 15 mins. and then the reaction mixture was heated under reflux for 10 hrs., to which water (15 cc.) was added slowly. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was chromatographed on alumina. The benzene-Et_2O (1:1) eluate was recrystallized from Me_2CO to colorless prisms (20 mg.), m.p. 169~170°, which showed no depression on admixture with the monodesoxy derivative obtained from the epoxide as described above.

The Unsaturated Compound (V)—To a mixture of $POCl_3$ (1.0 g.) and pyridine (3 cc.), the monodesoxy derivative (IV) (250 mg.) was added under cooling with ice and this mixture was allowed to stand for 18 hrs. at room temperature. The reaction mixture was slowly poured into ice-cold water (100 cc.) and the solution was basified with Na_2CO_3 and extracted with petroleum ether (b.p. 59~69°). The organic layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue (180 mg.) almost solidified after a short time and was chromatographed on alumina. The crystalline product, which was eluted with benzene-petr. ether (2:1), was dissolved in dil. HCl. The acid solution was filtered and basified with Na_2CO_3. The crystalline product precipitated and was collected, washed well with water, and dried *in vacuo*. This product (110 mg.) melted at 84~85°. Recrystallization from Me_2CO-water gave a pure sample as colorless needles, m.p. 86~87°, $[\alpha]_D^{18}$ −226.7°(c=0.75, benzene). U. V. : λ_{max} 261, 310 mμ (log ε 4.12, 3.84). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.25; H, 6.71; N, 5.48. Found : C, 75.63; H, 7.09; N, 5.69.

The Unsaturated Compound (VI)—To a mixture of phosphoryl chloride (3 g.) and pyridine (10 cc.), the monomethyl ether (III) (250 mg.) was added under cooling with ice. The monomethyl ether (III) dissolved slowly and the reaction mixture, turned to a reddish-yellow solution, was allowed to stand for 18 hrs. at room temperature. After standing, the crystalline precipitate was collected and dissolved in water. The anticipated unsaturated base, m.p. 150~154°(200 mg.), was prectipitated from the water extract when this solution was basified with Na_2CO_3. Recrystallization from EtOH gave a pure sample, colorless needles, m.p. 155~156°, $[\alpha]_D^{19}$ −80.0°(c=1.00, EtOH). U. V. : λ_{max} 265, 310 mμ (log ε 4.09, 3.84). *Anal.* Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.75; N, 4.91; OCH_3, 10.88. Found : C, 71.70; H, 6.75; N, 5.03; OCH_3, 10.05.

Oxidation of the Monodesoxy Derivative (IV) with Chromic Acid-Pyridine Complex—To a chromic acid-pyridine complex prepared from CrO_3 (250 mg.) and pyridine (2.5 cc.), the monodesoxy derivative (250 mg.) in pyridine (2.5 cc.) was added dropwise under cooling with ice. The yellow complex disappeared gradually and the mixture turned to a reddish-brown solution which was allowed to stand for 30 hrs. at room temperature. The reaction mixture was diluted with a large amount of water, evaporated under reduced pressure to remove the pyridine, acidified with dil. HCl, and extracted with benzene. The benzene layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on alumina. A crystalline product (40 mg.) was eluted with benzene-Et_2O (4:1) which was recrystallized from EtOH to colorless needles, m.p. 249~250°. U. V. : λ_{max} 245, 265, 330, 345 mμ (log ε 4.49, 4.46, 4.00, 3.99). I. R. : λ_{max}^{Nujol} 6.03 μ (conjugated >C=O), 6.11 μ (-N-C=O). *Anal.* Calcd. for $C_{16}H_{13}O_4N$: C, 67.84; H, 4.63; N, 4.95. Found : C, 67.56; H, 5.09; N, 4.75.

Another crystalline product (35 mg.) was eluted with benzene-Et_2O (1:1) which was recrystallized from EtOH to colorless plates, m.p. 242~243°. U. V. : λ_{max} 240 (inflexion), 265 (inflexion), 305 mμ (log ε 3.65, 3.59, 3.78). I. R. : λ_{max}^{Nujol} 2.98 μ (-OH) and 6.14 μ (-N-C=O). *Anal.* Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88. Found : C, 66.42; H, 6.24; N, 5.18.

Summary

The epoxide (II), the monomethyl ether (III), and the monodesoxy derivative (IV) of dihydrolycorine were obtained from dihydrolycorine (I) via its monotosylate (Ic). It has been determined from the results of the ring-opening reaction of the above-mentioned epoxide that the two vicinal hydroxyl groups in (I) are *trans* and diaxial. Furthermore, by the elimination reaction of the hydroxyl function, (III) and (IV) are easily convertible to the corresponding unsaturated compounds (V) and (VI), respectively. On the basis of these findings, it may be suggested that the stereochemical structure of dihydrolycorine (I) can be represented as shown in (XII).

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U.D.C. 547.857.07

42. Morizo Ishidate and Hidetaka Yuki: The Synthesis of 8-Substituted Purine Derivatives. I. Some 8-Substituted Derivatives of Hypoxanthine.

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Purine antagonists have been one of the subjects of intensive study on cancer chemotherapy during the past few years. 6-Mercaptopurine, 2,6-diaminopurine, and 8-azaguanine (5-amino-7-hydroxytriazolo[5,4-*d*]pyrimidine) have been demonstrated to act as the antagonist of precursors of nucleic acid components. These purine derivatives are in general sparingly soluble in water and in organic solvents. This lack of solubility is likely to bring about an unfavorable effect on the activity and a limitted application of the agents.

It seemed interesting to prepare more soluble purine derivatives which possess antagonizing activity.

Hitchings[1] demonstrated that the growth-promoting action of *Lactobacillus casei* produced by the addition of adenine was lost in the case of 9-methyladenine and that a marked growth inhibition in the rat and bacteria caused by 2,6-diaminopurine was not observed in the case of 9-methyl-2,6-diaminopurine. This is probably due to the fact that the hydrogen at 9-position of purine moiety is essential for the formation of nucleic acid *in vivo*.

Of purine derivatives only a few 8-substituted compounds are known in the literature. The present paper describes the preparation of some derivatives of hypoxanthine which are substituted at 8-position with hydrophilic groups such as -SH, -COOH, $-CH_2OH$, and $-CH_2CH_2COOH$, in order to investigate the biological property.

8-Mercaptohypoxanthine (II) was directly obtained in a good yield by the fusion of 4,5-diamino-6-hydroxypyrimidine (I) or its sulfate with thiourea. The compound (II) was further treated with monochloroacetic acid to give 8-carboxymethylthiohypoxanthine (III).

On the treatment of (I) with cyanoacetamide, 4-amino-5-cyanoacetamido-6-hydroxypyrimidine (IV) was produced. The cyclization of the latter to purine derivative by using alkali was unsuccessful, only to be hydrolysed to the starting material. The same

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1) G.H. Hitchings: J. Biol. Chem., **192**, 505(1951).