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83. Ken'ichi Takeda, Katsumi Kotera, Satoshi Mizukami, and Miyoko Kobayashi: The Conversion of Dihydrolycorine to (−)-α-Lycorane.

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In 1928, Kondo and Tomimura1) reported that dihydrolycorine (I) lost two molecules of water on treatment with phosphoryl chloride yielding anhydrodihydrolycorine2) (II). It was later found here, however, that when the reaction was carried out under mild conditions in the presence of a trace of hydrochloric acid, a chlorine-containing crystalline base, $C_{16}H_{18}O_3NCl$, is isolated along with a small amount of anhydrodihydrolycorine (II). The chloro compound was characterized also as the hydrochloride and the O-acetate. The latter derivative indicated that it contained an acetylable hydroxyl group. The chloro compound is, therefore, designated as dihydrolycorine chlorohydrin. Treatment of this chlorohydrin with methanolic potassium hydroxide gave the known methyl ether3) (III). Methanolic potassium hydroxide, sodium hydrogencarbonate, or potassium acetate or even chromatography over activated alumina afforded, in contrast to lycorine chlorohydrin,2) an epoxide (IV) which was identical with the product obtained previously by the interaction of dihydrolycorine monotosylate with potassium hydroxide.3) Since on treatment with dilute hydrochloric acid the epoxide reverted to dihydrolycorine chlorohydrin, the chlorine and the hydroxyl group in the latter compound must be vicinal, *trans* and diaxial, as represented by the formula (V). These results and the fact that the epoxide (IV) could be converted by dilute sulfuric acid into dihydrolycorine3) indicated clearly that the chlorohydrin was produced from dihydrolycorine with complete retention of configuration. This would be explainable by postulating that the reaction proceeded through a protonated epoxide as an intermediate as shown in Chart 1.

Reduction of the chlorohydrin or its acetate with zinc dust in acetic acid yielded a monoene[*2] (VI), $C_{16}H_{17}O_2N$, whose ultraviolet spectrum indicated, as expected, non-conjuga-

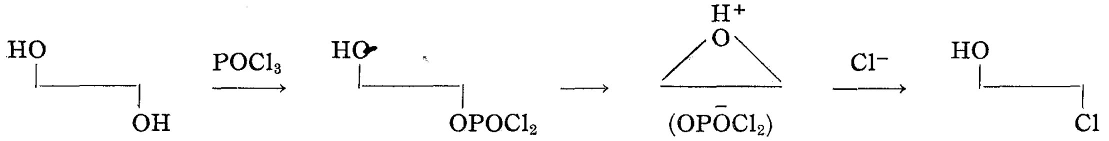


Chart 1.

[*1] Imafuku, Amagasaki, Hyogo-ken (武田健一, 小寺勝美, 水上 聰, 小林美代子).

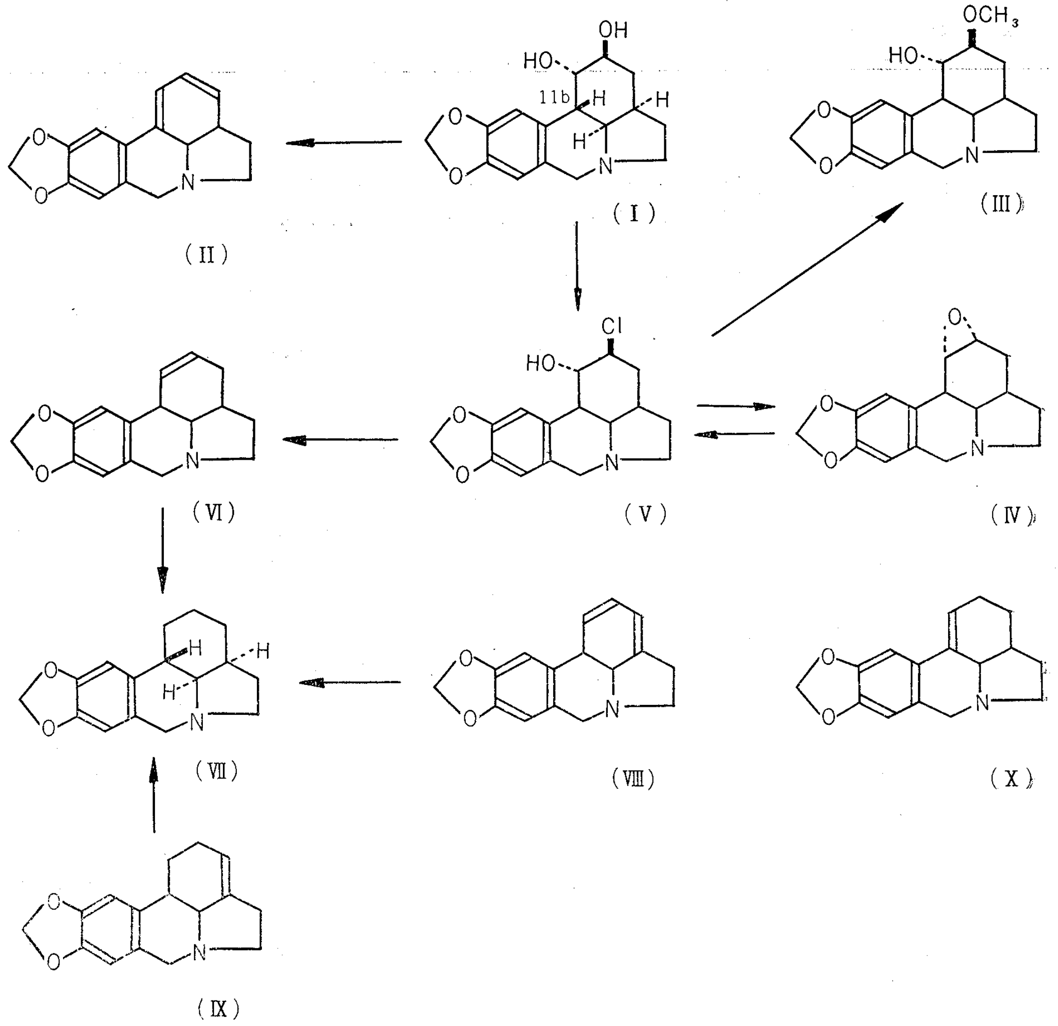
[*2] An attempt to convert this into its lactam by oxidation with chromium trioxide in pyridine failed, the only products isolated being anhydrolycorinone described by L. G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto. S. Uyeo, H. Yajima, and N. Yanaihara (J. Chem. Soc., **1954**, 4622) and anhydrodehydrolycorinone obtained earlier by J. W. Cook, J. D. Loudon, and P. McCloskey (J. Chem. Soc., **1954**, 4176).

1) H. Kondo, K. Tomimura: Yakugaku Zasshi, **48**, 227(1928).

2) K. Takeda, K. Kotera, S. Mizukami: J. Am. Chem. Soc., **80**, 2562(1958).

3) K. Takeda, K. Kotera: This Bulletin, **5**, 234(1957).

tion of the double bond with the aromatic ring. A strong band in its infrared spectrum at 14.90 μ would be attributable to a *cis*-disubstituted ethylenic bond, in good agreement with the expected structure. Conversion of halohydrins to the corresponding olefins by treatment with zinc dust and acetic acid has been reported in the literature and it was also shown that lycorine chlorohydrin was converted into the diene (VIII) by this method.2)



Hydrogenation of the monoene (VI) in the presence of Adams catalyst in acetic acid yielded a saturated compound, $C_{16}H_{19}O_2N$, m.p. 82~83°, $[\alpha]_D$ −31°, which was designated (−)-α-lycorane and characterized also as its hydrochloride of m.p. 254~255° (decomp.), $[\alpha]_D$ +27.9°. It was highly probable that the configurations at all asymmetric centers in (−)-α-lycorane (VII) are the same as those of the parent compound, dihydrolycorine,3) since the sequence of reactions leading to this was carried out under the conditions which did not affect any of the asymmetric centers, and a migration of the double bond of the monoene (VI) to such as α-anhydrodihydrocaranine (X)3) during the hydrogenation was highly improbable. Detailed discussions on this problem will be made in a forthcoming paper.

In this connection it would be interesting to mention that Wildman and Fales4) converted lycorine by treatment with sodium in amyl alcohol in part into lycorene (IX) which gave on hydrogenation in acetic acid (−)-α-lycorane, identical in all respects with the

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4) H. M. Fales, W. C. Wildman: J. Am. Chem. Soc., 80, 4395(1958).

present sample.[*3] In this case there is even less chance for the involvement of C-11b. (−)-α-Lycorane was also the product of hydrogenation, as expected, when the diene (VIII) was reduced in acetic acid in the presence of Adams catalyst.

Experimental[*4]

Action of Phosphoryl Chloride on Dihydrolycorine (I)—A mixture of 3.5 g. of dihydrolycorine (I) and 12.5 g. of $POCl_3$ was gradually heated to 75° during the course of 15 min. and one drop of 35% HCl was added. The reaction started with gentle foaming and suspended crystals disappeared, giving a yellowish solution. After a further 25 min. of heating at 75~80°, the mixture was cooled and added dropwise into 1000 cc. of ice-cold water. The mixture was neutralized with 10% NaOH, basified with 10% Na_2CO_3, and extracted with 600 cc. of Et_2O. Et_2O layer was washed with H_2O, dried over Na_2SO_4, and concentrated to 50 cc. On standing, crystals deposited and were collected to give 1.55 g. of the chlorohydrin (V), m.p. 148~149° (decomp.). An analytical sample was obtained by crystallization from Et_2O as prisms, m.p. 151~152° (decomp.), $[\alpha]_D^{28}$ −15.77° (c=0.089, EtOH). UV λ_{max} 290 mμ (log ε 3.75). *Anal.* Calcd. for $C_{16}H_{18}O_3NCl$: C, 62.41; H, 5.89; N, 4.55; Cl, 11.52. Found: C, 62.74; H, 6.05; N, 4.59; Cl, 10.88.

Hydrochloride: Needles from H_2O, m.p. 235° (decomp.), $[\alpha]_D^{22}$ +11.7° (c=0.41, EtOH). *Anal.* Calcd. for $C_{16}H_{18}O_3NCl \cdot HCl \cdot \frac{1}{2}H_2O$: C, 54.50; H, 5.68; N, 3.98; Cl, 20.10. Found: C, 54.23; H, 5.93; N, 4.01; Cl, 19.95.

O-Acetate: Prisms from EtOH, m.p. 188~189° (decomp.), $[\alpha]_D^{22}$ −20.1° (c=0.44, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{20}O_4NCl$: C, 61.78; H, 5.76; N, 4.00. Found: C, 61.80; H, 5.60; N, 4.24.

The mother-liquor freed from the chlorohydrin (V) was chromatographed in benzene over 30 g. of alumina. The benzene eluate gave a crystalline product which was recrystallized from MeOH to 20 mg. of anhydrodihydrolycorine (II) as needles, m.p. 104~105°.

Elution with 10:1 benzene-Et_2O gave a fraction, which on recrystallization from MeOH yielded 160 mg. of a product as prisms, m.p. 148~148.5°, which was identical with the epoxide[*5] (IV) in m.p., mixed m.p., and IR spectrum.

Conversion of the Chlorohydrin (V) or its Acetate into the Epoxide (IV)—a) To a solution of 100 mg. of the chlorohydrin (V) in 10 cc. of MeOH, a solution of 90 mg. of KOH in 1 cc. of H_2O was added. After being kept for 5 min. at 25°, the mixture was diluted with H_2O, extracted with 30 cc. of benzene, and the benzene layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness under a reduced pressure. The residue on recrystallization from MeOH afforded 62 mg. of colorless prisms (75% yield), m.p. 148~148.5°, identical with the epoxide (IV).

b) A mixture of 50 mg. of the acetyl derivative of (V) and 300 mg. of $NaHCO_3$ in 10 cc. of MeOH was heated under reflux for 1 hr. When the reaction mixture was worked up in the same way as described above, 15 mg. of the crude epoxide (IV), m.p. 146~148°, was obtained.

c) A mixture of 200 mg. of (V), 13 cc. of MeOH, 7 cc. of H_2O, and 1.0 g. of anhyd. AcOK was heated under reflux for 2 hr. On working up in the same way as described above, 80 mg. of the crude epoxide (IV), m.p. 145~147°, was obtained.

d) A solution of 100 mg. of (V) in 20 cc. of benzene was passed through a column of 15 g. of alumina. Elution with benzene and 10:1 benzene-Et_2O gave a fraction which, on recrystallization from MeOH, afforded 50 mg. of the pure epoxide (IV), m.p. 148~148.5°.

Monomethyl Ether (III) from the Chlorohydrin (V)—To a boiling solution of 8.0 g of KOH in 80 cc. of MeOH and 8 cc. of H_2O, 1.0 g. of (V) was added and the mixture was refluxed for 2 hr. When cool, the reaction mixture was diluted with H_2O and extracted with benzene, which was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness under a reduced pressure. Two crystallizations of the residue from MeOH afforded 750 mg. of colorless plates, m.p. 195~196°, identical with the monomethyl ether[3)] (III).

Reaction of the Epoxide (IV) with Hydrochloric Acid—A mixture of 60 mg. of the epoxide (IV), 6 cc. of MeOH, and 1 cc. of 10% HCl was heated under reflux for 0.5 hr. The mixture was diluted

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[*3] The authors are grateful to Dr. Wildman for a direct comparison of this sample of (−)-α-lycorane with his own.

[*4] All m.p.s are uncorrected. Unless otherwise stated, the ultraviolet spectra were taken in 95% EtOH solution using a Beckman Model DU spectrophotometer. Alumina used for chromatography in the present series of experiment was Merck's Reagent Grade, standardized according to Brockmann. The infrared absorption spectra were measured with a Perkin-Elmer Model 12C, single-beam infrared spectrophotometer.

[*5] The epoxide (IV) probably came from the chlorohydrin (V) by the action of alumina (see the next section (d)).

with H_2O, basified with Na_2CO_3, and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over Na_2SO_4, and concentrated to give 40 mg. of colorless prisms, m.p. 151~152° (decomp.), identical with the chlorohydrin (V) in m.p., mixed m.p., and IR spectrum.

Reduction of the Chlorohydrin (V) or its Acetate with Zinc Dust in Acetic Acid—a) A mixture of 200 mg. of the chlorohydrin (V), 2.0 g. of Zn dust, 15 cc. of AcOH, and 1.5 cc. of H_2O was refluxed for 1 hr. When cool, the precipitated inorganic substance was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue dissolved in H_2O was treated with H_2S and after removal of ZnS the filtrate was basified with Na_2CO_3 and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness to give a monoene (VI) which on recrystallization from Et_2CO-H_2O yielded 96 mg. of colorless scales, m.p. 85~86°, $[\alpha]_D^{25}$ −139.0° (c=1.00, EtOH), UV λ_{max} 290 mμ ($\log \varepsilon$ 3.72); IR λ_{max}^{Nujol} 14.90 μ (*cis*-CH=CH-). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.99; H, 6.46; N, 5.57.

b) A mixture of 100 mg. of the acetyl derivative of (V), 4.0 g. of Zn dust, 20 cc. of AcOH, and 2 cc. of H_2O was treated in the same way as described above and yielded 40 mg. of (VI), m.p. 84~86°.

Oxidation of Monoene (VI) with Chromium Trioxide-Pyridine Complex[*2]—To a mixture of 200 mg. of CrO_3 and 2 cc. of pyridine, a solution of 190 mg. of the monoene (VI) in 2 cc. of pyridine was added dropwise while cooling in an ice-bath. The yellow complex disappeared gradually and the reaction mixture turned to a reddish-brown solution. It was allowed to stand for 25 hr. at room temperature. The mixture was diluted with H_2O, concentrated under a reduced pressure to remove pyridine, acidified with dil. HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, evaporated to dryness, and the residue was chromatographed in benzene over 10 g. of alumina. The benzene eluate gave a crystalline product which was sublimed in high vacuum and the sublimate was crystallized from EtOH to colorless prisms, m.p. 231~232°, identical in m.p., mixed m.p., and UV spectrum with authentic anhydrolycorinone. Elution of the residue with 9:1 benzene-Et_2O gave a fraction which was purified by sublimation in high vacuum followed by crystallization from EtOH to colorless needles, m.p. 216~218°, identical with anhydrodehydrolycorinone as shown by a mixed m.p. determination and comparison of the UV spectra.

(−)-α-Lycorane (VII)—a) From the Monoene (VI): A solution of 250 mg. of (VI) in 10 cc. of AcOH was hydrogenated in the presence of 50 mg. of the Adams catalyst, when 1.2 equivalent of H_2 was taken up in 2 hr. After filtration of the catalyst, most of AcOH was evaporated, the residue was dissolved in H_2O, and filtered. Basification of the filtrate with 10% Na_2CO_3 solution followed by extraction with petr. ether (b.p. 60~67°), and concentration of the dried extract gave 250 mg. of crude (−)-α-lycorane (VII), m.p. 76~80°. Two recrystallizations from petr. ether gave colorless prisms, m.p. 82~83°, $[\alpha]_D^{22}$ −31.0° (c=0.99, EtOH). UV: λ_{max} 290 mμ ($\log \varepsilon$ 3.70). No strong band corresponding to a *cis*-disubstituted ethylene group was observed in its IR spectrum. *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.65; H, 7.69; N, 5.53.

Hydrochloride: Clusters of needles (from H_2O), m.p. 254~255° (decomp.), $[\alpha]_D^{22}$ +27.9° (c=0.94, EtOH). *Anal.* Calcd. for $C_{16}H_{19}O_2N \cdot HCl$: C, 65.39; H, 6.86; N, 4.77. Found: C, 65.12; H, 7.12; N, 4.77.

b) From the Diene (VIII): A solution of 150 mg. of (VIII) in 3 cc. of AcOH was added to a suspension of 50 mg. of reduced PtO_2 in 2 cc. of AcOH. Reduction stopped in 2 hr. after almost 1 mole of H_2 had been absorbed. On working up in a similar manner as described above, 70 mg. of a crystalline product was obtained on recrystallization from petr. ether as prisms, m.p. 82~83°, $[\alpha]_D^{20}$ −29.8° (c=0.76, EtOH), identical in m.p., mixed m.p., optical rotation, and IR spectrum with (−)-α-lycorane (VII).

The authors are indebted to Prof. S. Uyeo, Dr. W. C. Wildman, and Dr. W. I. Taylor for valuable discussions.

Summary

Treatment of dihydrolycorine (I) with phosphoryl chloride under mild conditions yielded a chlorohydrin (V). Reduction of this hydrin with zinc in acetic acid followed by reduction with hydrogen and platinum oxide afforded (−)-α-lycorane (VII), the steric structure of which was considered, in view of the sequence of reactions used in this transformation, to be that of the ring-system of dihydrolycorine.

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