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The Synthesis of *dl*-α-Dihydrocaranone and γ-Lycorane

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dl-α-Dihydrocaranone (XII) has been synthesized stereoselectively, using the ring-closure reaction via benzyne intermediate of *N*-(2-bromo-4, 5-methylenedioxybenzyl)octahydroindole-6-one (X) with lithium piperidide in tetrahydrofuran. *dl*-γ-Lycorane (III) has been obtained by the Hauptmann reduction of XII.

The stereoisomers of lycorane derived from lycorine have been studied by Takeda and Kotera.[1] They established the stereochemistry of all of the possible isomers, α-, β-, γ- and δ-lycorane (I, II, III and IV). Recently, the stereoselective synthesis of *dl*-α- and β-lycorane has been reported by Hill,[2] but γ- and δ-lycorane have not yet been synthesized. The present investigation was undertaken in order to synthesize γ-lycorane stereoselectively, considering the biosynthesis[3] of the Amaryllidaceae alkaloids.

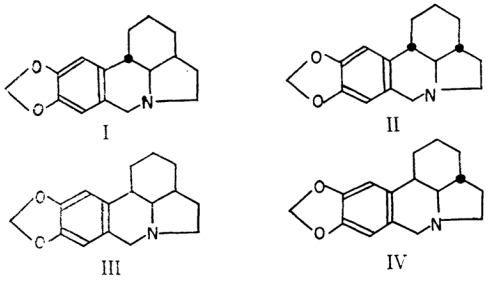

Fig. 1. The four stereoisomers of lycorane.

2-Bromo-4, 5-methylenedioxybenzyl bromide (V) was treated with 2, 5-dihydro-4-methoxyphenethylamine (VI) to give monobenzyl (VII) and di-benzyl (VIII) derivatives, which were then separated and purified by chromatography on silica gel. The ratio of VII to VIII was 3 : 1.

The monobenzyl derivative, VII, was hydrolyzed with 2 N hydrochloric acid into a 3-cyclohexenone

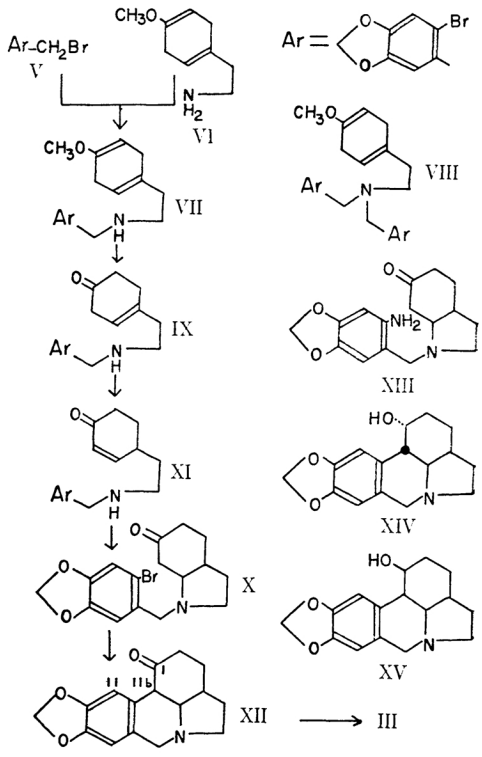

Fig. 2.

1) a) K. Takeda, K. Kotera, S. Mizukami and M. Kobayashi, *Chem. Pharm. Bull.*, **8**, 483 (1960); b) K. Kotera, *Tetrahedron*, **12**, 240 (1961); b) K. Kotera, ibid., **12**, 248 (1961).

2) R. K. Hill, J. A. Joule and L. J. Loeffler, *J. Am. Chem. Soc.*, **84**, 4951 (1962).

3) A. R. Buttersby, *Proc. Chem. Soc.*, **1963**, 189; D. H. R. Barton, ibid., **1963**, 293; A. R. Battersby, R. Binks, S. W. Breuer, H. M. Fales, W. C. Wildman and R. J. Highet, *J. Chem. Soc.*, **1964**, 1595.

(IX) hydrochloride, $C_{16}H_{18}NO_3 \cdot HCl$, m.p. 163°C. The NMR spectrum ($CDCl_3$) of the free base showed a vinyl proton multiplet at 4.35τ (1H) and a NH proton singlet at 5.2 τ (Fig. 3). The 3-cyclohexenone, IX, was refluxed in an 8 N hydrochloric acid - ethanol solution to yield *N*-(2-bromo-4, 5-methylenedioxybenzyl)-octahydroindole-6-one (X), which was then purified by chromatography on silica gel.

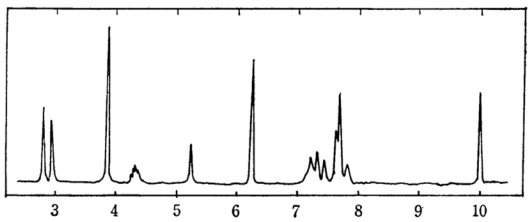

Fig. 3. NMR spectrum of XI (60 Mc.).

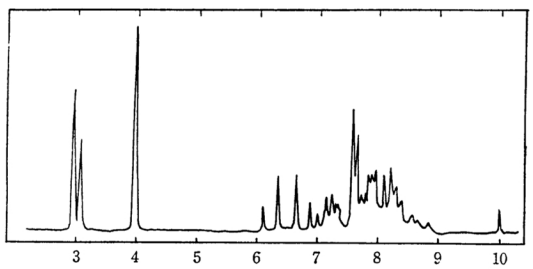

Fig. 4. NMR spectrum of X (60 Mc.).

The formation of the octahydroindole ring was deduced from the following facts. The NMR spectrum of this base showed a benzyl proton quartet at 6.4 τ (2H, AB type) (Fig. 4). The observed nonequivalence of the benzyl protons may arise from different magnetic shielding due to a molecular asymmetry resulting from the formation of the octahydroindole ring[4]. This base was then converted to its hydrochloride, $C_{16}H_{18}BrNO_3 \cdot HCl \cdot H_2O$, m.p. 123—125°C. The infrared spectrum of the hydrochloride exhibited the characteristic bands of an ammonium salt of the tertiary amine in the 2500—2700 cm^{-1} region. The more stable cis-fused octahydroindole ring may be obtained in this case.

The product obtained from α-dihydrocaranine (XIV) by Oppennauer oxidation was reported by Kotera[1] to be homogeneous α-dihydrocaranone (XII), which was isomeric at C_{11b} as compared with XIV. He suggested that another isomeric dihydrocaranone, the C_{11b} epimer of XII, might be unavailable due to non-bonded interaction between the C_{11}-aromatic proton and C_1-carbonyl-oxygen. Therefore, we considered the benzyl-octahydroindole, X, which has a cis-fused ring, would give XII upon treatment with strong bases.

Recently, Bunnett and his coworkers[5] reported many experiments on ring-closure reactions via benzyne intermediates. They mainly used potassium amide as the basic reagent.

The reaction of X with sodium or potassium amide in liquid ammonia did not give XII, but an amino-substituted derivative (XIII) solely. On the other hand, the treatment of X with lithium piperidide in tetrahydrofuran gave XII as the main product. This product was purified with chromatography over silica gel (35—40% yield) and recrystallized from methanol to give prisms, m.p. 147.5—149.5°C. The infrared spectrum in a chloroform solution was identical with that of the authentic *l*-α-dihydrocaranone.

dl-α-Dihydrocaranone, XII, was converted into its thioketal, m.p. 113.5—115°C, which was then desulfurized to *dl*-γ-lycorane, m.p. 101—102°C, by the method of Kotera.[1c]

The infrared spectrum of this compound was identical with that of the authentic *dl*-γ-lycorane. The reduction of XII with lithium aluminium hydride gave a mixture of two isomeric dihydrocaranines. The isomers were separated efficiently by silica gel chromatography into *dl*-1-epi-γ-dihydrocaranine, (XV), m.p. 135.5—136.5°C and *dl*-γ-dihydrocaranine, (C_1-epimer of XV), m.p. 180—181°C. The ratio of the isomers was 6 : 1. The infrared spectrum of the main product in a chloroform solution was identical with that of the authentic *l*-1-epi-γ-dihydrocaranine.

Experimental*1

2-Bromo - 4, 5 - methylenedioxybenzyl Bromide (V).*2—This was prepared by the method of Naik.[6]

2, 5-Dihydro-4-methoxyphenethylamine (VI).—This compound was prepared by a method similar to that described by Clarke.[7]

2-Bromo-4, 5 - methylenedioxybenzyl - (2, 5-dihydro-4-methoxyphenethyl)amine (VII).—A solution of 7 g. of V and 7.5 g. of VI in 500 ml. of absolute ethyl ether was kept at room temperature for one week. After the filtration of the deposited hydrobromide of VI, the solvent was removed under reduced pressure. The oily residue was then chromatographed over 130 g. of silica gel. Elution with a chloroform - ethyl ether solution (95 : 5 — 90 : 10) gave 2 g. of a dibenzyl derivative, VIII, as the first fraction. The product

4) Cf. R. K. Hill and T. H. Chan, *Tetrahedron*, **21**, 2015 (1965); G. M. Whitesides, J. J. Grocke, D. Holtz, H. Steinberg and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 1058 (1965); R. Grasky R. Huisgen, K. K. Sun and R. M. Moriarty, *J. Org. Chem.*, **30**, 74 (1965).

5) J. F. Bunnett and B. F. Hautfiord, *J. Am. Chem. Soc.*, **83**, 1691 (1961); J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962); J. F. Bunnett, T. Kato, R. R. Flynn and J. A. Skorcz, ibid., **28**, 1 (1963).

*1 All melting points are uncorrected.

*2 We are grateful to the Shiono-Koryo Co., Ltd., for its gift of piperonal for use as a starting material.

6) R. G. Naik and T. S. Wheeler, *J. Chem. Soc.*, **1938**, 1780.

7) C. B. Clark and A. R. Pinder, ibid., **1958**, 1967.

was then recrystallized from benzene - petroleum ether to give prisms, m. p. 88—89°C.

Found: C, 51.93; H, 4.48; N, 2.44. Calcd. for $C_{25}H_{25}O_5NBr_2$: C, 51.83; H, 4.35; N, 2.42%.

As a second fraction, 6 g. of a monobenzyl derivative (VII) were eluted.

4-[*N*-(2-Bromo-4, 5-methylenedioxybenzyl)-2'-aminoethyl]-3-cyclohexene-1-one (IX).—To a solution of 6.6 g. of the monobenzyl derivative (VII) in 150 ml. of ethanol, 300 ml. of a 2 N hydrochloric acid solution was added; the mixture was then allowed to stand at room temperature for 24 hr. The needles which thus formed were filtered (4.4 g.) and recrystallized from 1-propanol to give the 3-cyclohexenone (IX) hydrochloride, m. p. 163°C; infrared spectrum: ν_{max}^{Nujol} 1705 cm^{-1} (C=O), 2740 cm^{-1} (NH_2^+).

Found: C, 49.63; H, 4.95; N, 3.57. Calcd. for $C_{16}H_{19}NO_3BrCl$: C, 49.44; H, 4.93; N, 3.60%.

***N*-(2-Bromo-4, 5-methylenedioxybenzyl)octahydroindole-6-one (X).**—A solution of 4.5 g. of 3-cyclohexenone IX, or its hydrochloride in 200 ml. of ethanol and 200 ml. of 8 N hydrochloric acid was refluxed for 6—7 hr. The solvent was then evaporated under reduced pressure. The residue was dissolved in 100 ml. of water, and the solution was basified with a 10% sodium hydroxide solution and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed over silica gel. Elution with a chloroform-methanol-triethylamine solution (98.5 : 1 : 0.5) gave 3.7 g. of oily octahydroindolone, X. Its hydrochloride shows a m. p. of 123—125°C (infrared spectrum: ν_{max}^{Nujol} 1705 cm^{-1} (C=O), 2650 cm^{-1} (NH^+)).

Found: C, 46.97; H, 5.35; N, 3.44. Calcd. for $C_{16}H_{18}BrNO_3 \cdot HCl \cdot H_2O$: C, 47.25; 5.21; N, 3.20%.

The Reaction of Octahydroindolone (X) with Sodium Amide.—A solution of 360 mg. of the octahydroindolone, X, in 20 ml. of absolute ethyl ether was treated with a solution of sodium amide, prepared from 0.2 g. of sodium metal in 200 ml. of liquid ammonia, for 2.5 hr. After the addition of 0.3 g. of ammonium chloride and 30 ml. of ethyl ether, the ammonia was evaporated. Cold water was added to the mixture, and it was extracted with ether. The ethereal extracts were washed with water, dried, and evaporated to dryness. The residue was then chromatographed over a silica gel column. Elution with a chloroform-methanol-triethylamine solution (98.5 : 1.0 : 0.5) gave 250 mg. of an oily amino-substituted derivative, XIII, which was then derived to its acetate, prisms, m. p. 143—144°C.

Found: C, 65.62; H, 6.62; N, 8.53. Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48%.

The Reaction of Octahydroindolone (X) with Lithium Piperidide.—Into 580 mg. of octahydroindolone, X, in 120 ml. of tetrahydrofuran, a tetrahydrofuran solution of lithium piperidide, which had been prepared from 1 ml. of piperidine and 2 ml. of 4 N *n*-butyllithium in hexane, was added at 40—45°C with stirring under a nitrogen stream over about a one-hour period. After the mixture had then been stirred for a further 10—12 hr., the orange-yellow reaction mixture was cooled to 10°C, neutralized with ammonium chloride. After the addition of water, the resulting two layers were separated and the aqueous layer was extracted with ether. The tetrahydrofuran layer and the extracts were combined, and washed with a saturated aqueous solution of sodium chloride. The solvent was removed under reduced pressure, and the residue was chromatographed over 10 g. of silica gel. Elution with a chloroform - ethyl ether - methanol solution (94 : 5 : 1) gave 180 mg. of XII, which was then recrystallized from methanol to give prisms, m. p. 147.5—149.5°C.

Found: C, 70.94; H, 6.35; N, 5.34. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16%.

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