Tetrahedron, 1960, Vol. 11, pp. 89 to 95. Pergamon Press Ltd. Printed in Northern Ireland

STEREOCHEMICAL RELATIONS BETWEEN LYCORINE, CARANINE, PLUVIINE, AND LYCORENINE

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(*Received* 4 *May* 1960)

Abstract—Treatment of α-dihydrocaranine (VI) with ethanolic potassium hydroxide followed by hydrolysis of the resulting ethoxymethylether (VIII) and methylation with diazomethane afforded α-dihydropluviine (XII). The product, XVIII, obtained by the von Braun reaction of α-dihydrocaranine, was converted into α-deoxydihydrolycorenine (XXIII) without affecting asymmetric centres of the respective compounds. Thus the configurational relationship between lycorine, caranine, pluviine, and lycorenine have been clarified.

PLUVIINE[1] and lycorenine[2,3] are both alkaloids isolated from the bulbs of *Lycoris radiata* and other plants of Amaryllidaceae. Although the structures of these alkaloids have been established, very little was known of the stereochemistry until Uyeo *et al.*[4] recently assigned to them the configurations I and II respectively. The present author has worked independently on the stereochemistry of the alkaloids and this paper provides further evidence supporting these configurations.

In previous papers,[5,6] the configuration of dihydrolycorine was discussed and its absolute configuration (III) was recently established by Nakagawa and Uyeo[7]. Since caranine,[8-12] an alkaloid from Amaryllidaceae, was obtained by elimination of the hydroxyl group attached to carbon 2 of lycorine without any configurational change and likewise α-dihydrocaranine,[5,6] a hydrogenation product of caranine, was derived from dihydrolycorine, caranine and α-dihydrocaranine are structurally related to lycorine (IV) and dihydrolycorine, and configurations V and VI may be assigned to them respectively.

It has been established that the structure of pluviine differs from that of caranine by two methoxyl groups and a methylenedioxy group. Similarity of the behaviour of the two alkaloids toward a variety of reagents and biogenesis of this group of the alkaloids, indicates that pluviine and caranine, and α-dihydropluviine and α-dihydrocaranine, have similar configurations.

As proof, the conversion of the methylenedioxy group in α-dihydrocaranine into methoxyl groups under conditions which would not affect configurations of functional groups and the skeleton of the base was undertaken.

[1] H. G. Boit, S. Uyeo and H. Yajima, *Chem. Ber.* **90**, 363 (1957).
[2] T. Kitagawa, W. I. Taylor, S. Uyeo and H. Yajima, *J. Chem. Soc.* 1066 (1955).
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[5] K. Takeda and K. Kotera, *Chem. & Ind.* 347 (1956).
[6] K. Takeda and K. Kotera, *Pharm. Bull. Japan* **5**, 234 (1957).
[7] Y. Nakagawa and S. Uyeo, *J. Chem. Soc.* 3736 (1959).
[8] L. H. Mason, E. R. Puschett and W. C. Wildman, *J. Amer. Chem. Soc.* **77**, 1253 (1955).
[9] H. M. Fales, E. W. Warnhoff and W. C. Wildman, *J. Amer. Chem. Soc.* **77**, 5885 (1955).
[10] E. W. Warnhoff and W. C. Wildman, *Chem. & Ind.* 348 (1956).
[11] E. W. Warnhoff and W. C. Wildman, *J. Amer. Chem. Soc.* **79**, 2192 (1957).
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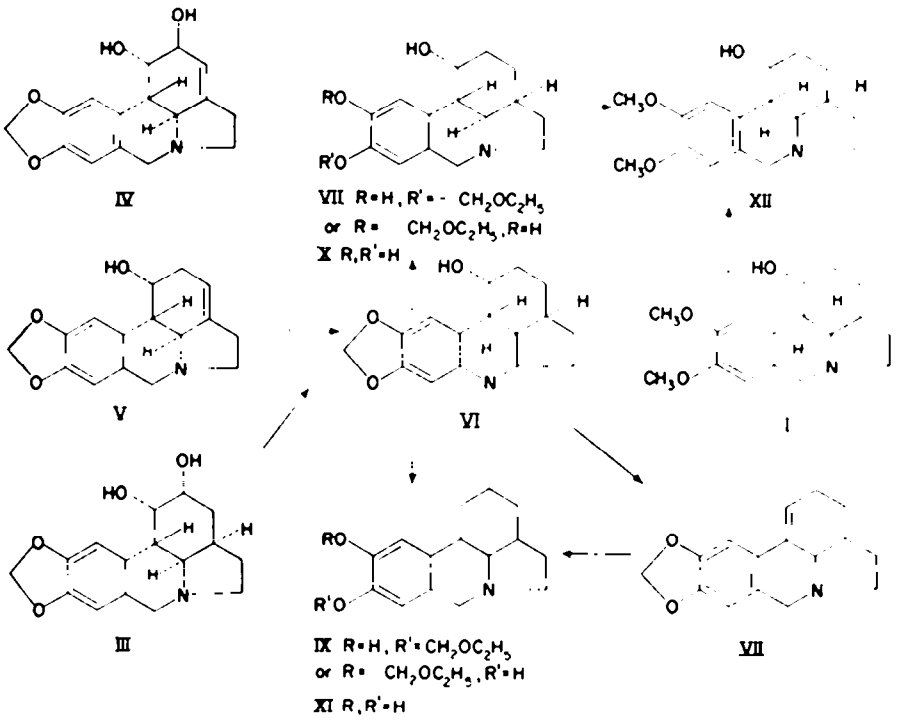


Attempts to cleave the methylenedioxy group in α-dihydrocaranine with aluminium chloride or bromide were not successful, but treatment of the base with ethanolic potassium hydroxide under nitrogen in a sealed tube gave a satisfactory result. The reaction mixture yields, along with α-anhydrodihydrocaranine (VII), two phenolic bases which were separated by chromatography and may be represented by the formulae VIII and IX, according to the result obtained by treatment of safrol[13–15] with the same reagents. It is highly improbable that any configurational changes take place during the reaction, since some starting material was recovered unchanged. Hydrolysis of the phenols VIII and IX, with hydrochloric acid afford demethylene-α-dihydrocaranine (X) and demethylene-α-anhydrodihydrocaranine (XI) respectively, characterized as hydrochlorides.

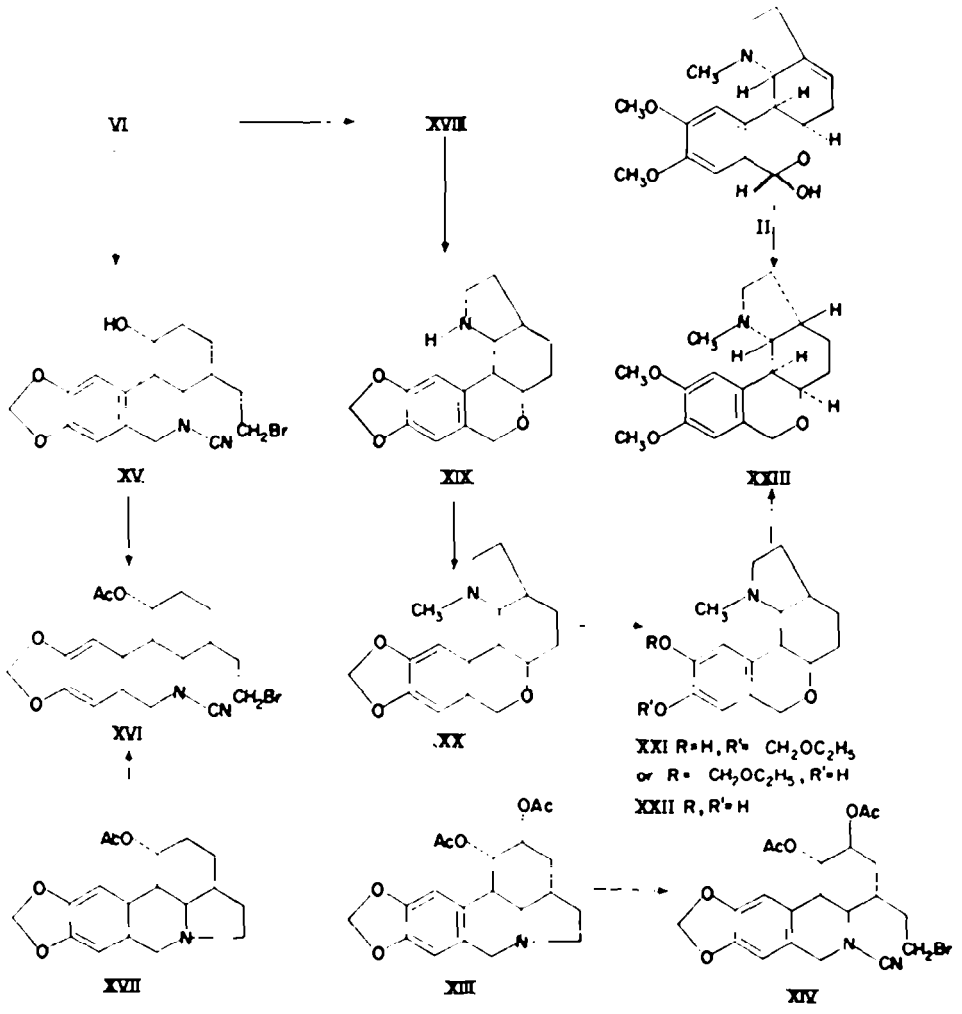
Both the phenols X and XI, give a green ferric chloride test and the analytical values, infra-red and ultra-violet spectra are in good agreement with the assigned structures. As expected, demethylene-α-anhydrodihydrocaranine (XI) is also obtained by treatment of α-anhydrodihydrocaranine (VII) with potassium hydroxide in ethanol in a sealed tube followed by hydrolysis with hydrochloric acid. Isolation of the free demethylene-α-dihydrocaranine from its hydrochloride failed, since the phenolic base is so soluble in water that it could not be extracted from its aqueous solution with organic solvents. Therefore, methylation of the free hydroxyl groups in demethylene-α-dihydrocaranine (X) was carried out with diazomethane using its hydrochloride in methanol. The resulting non-phenolic base is identical with α-dihydropluviine

[13] Hirao, *Nippon Kagaku Zasshi* **54**, 194 (1933).
[14] Hiraizumi, *Nippon Kagaku Zasshi* **55**, 605 (1934).
[15] Ono and Imoto, *Nippon Kagaku Zasshi* **59**, 364 (1933).

(XII). Thus the structural and configurational relationship between α-dihydropluviine (XII) and α-dihydrocaranine (VI) and between pluviine (I) and caranine (V) are verified.

An investigation was undertaken to cleave the pyrrolidine ring of α-dihydrocaranine (VI) by the von Braun reaction, analogous to that employed by Kondo and Katsura[16] for the fission of the pyrrolidine moiety of diacetyldihydrolycorine (XIII) to give diacetyl-ω-bromo-N-cyanodihydrosecolycorine (XIV) as the sole product.

Treatment of α-dihydrocaranine (VI) with cyanogen bromide in boiling benzene afforded, in contrast to the previous case, two products, $C_{17}H_{19}O_3N_2Br$ and $C_{17}H_{18}O_3N_2$ in a ratio of two to one.

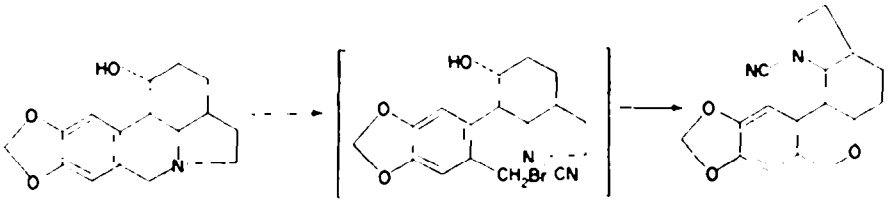


Compound XV contains bromine and exhibits infra-red absorptions at 4·48 and 2·90 μ characteristic of a CN and an OH group, respectively. The acetate (XVI) is

[16] H. Kondo and H. Katsura, *Yakugaku Zasshi* **59**, 733 (1939).

identical with the product obtained by the von Braun reaction of α-acetyldihydrocaranine (XVII).[11] Considering the similarity with diacetyl-ω-bromo-N-cyanodihydrosecolycorine (XIV) and the ease with which pyrrolidine rings can be cleaved with cyanogen bromide, structure XV is assigned to the compound, $C_{17}H_{19}O_3N_2Br$.

On the other hand, $C_{17}H_{18}O_3N_2$ isolated from the mother liquors of XV shows a CN band in the infra-red spectrum at 4·54 μ but neither a hydroxyl nor a carbonyl band could be detected. Since two oxygen atoms in the molecule belong to a methylenedioxy group, the remaining third oxygen is considered present as an ether group. In view of this, it seemed plausible that the compound XVIII results from cleavage of the piperideine instead of the pyrrolidine ring in α-dihydrocaranine (VI) followed by elimination of hydrogen bromide to give an oxygen bridge as follows:



VI XVIII

Unequivocal evidence for this structure is given by the following reactions: Treatment of $C_{17}H_{18}O_3N_2$ with lithium aluminium hydride in ether gives in good yield a basic product (XIX), $C_{16}H_{19}O_3N$, which exhibits a NH band in the infra-red spectrum at 3·00 μ but no CN absorption.

Methylation of the secondary amine XIX with formaldehyde and formic acid affords the N-methyl derivative XX, $C_{17}H_{21}O_3N$, which was treated in a sealed tube with ethanolic potassium hydroxide at 180–190° as mentioned for the cleavage of the methylenedioxy group in α-dihydrocaranine. The resulting XXI exhibits no infra-red absorptions typical of a methylenedioxy group at about 9·6 and 10·7 μ but a hydroxyl band at 2·78 μ. Hydrolysis with dilute hydrochloric acid of XXII gives a dihydroxy derivative characterized as the hydrochloride and giving a green ferric chloride test. Methylation of the phenolic hydroxyl groups was accomplished by treatment of the base with excess ethereal diazomethane, giving a non-phenolic base, $C_{18}H_{25}O_3N$, m.p. 123–124°, $[\alpha]_D$ · 18·7°, which is identical with α-deoxydihydrolycorenine (XXIII) in m.p., mixed m.p., optical rotation and infra-red spectrum.

Since in the conversion of α-dihydrocaranine (VI) into α-deoxydihydrolycorenine (XXIII) no asymmetric centre was affected, the stereochemical relationship between these two bases is established and the configurations of α-deoxydihydrolycorenine and lycorenine can be deduced from that of α-dihydrocaranine (VI) and represented by formulae XXIII and II. The experimental evidence establishes that the asymmetric carbons in caranine (V), pluviine (I), and lycorenine (II) have the same configuration as those in lycorine (IV), which is in accordance with the accepted biogenesis of these alkaloids.

EXPERIMENTAL

Melting points are not corrected.

Methylenedioxy ring-opening of α-dihydrocaranine (VI) *with ethanolic potassium hydroxide.*

KOH (750 mg) was added to a solution of α-dihydrocaranine (VI, 600 mg) in 95% ethanol (25 ml). The reaction mixture was heated under nitrogen in a sealed tube at 180-190° for 1·5 hr. The solvent was removed under reduced pressure and the residue divided into benzene- and water-soluble fractions. Evaporation of the dried benzene left a colourless oil (210 mg) which gave on crystallization from ethanol, unchanged α-dihydrocaranine (100 mg) m.p. 165–168°, undepressed on admixture with the starting material. The mother liquor was chromatographed in benzene over alumina. The benzene eluate yielded α-anhydrodihydrocaranine (VII, 60 mg) as needles, m.p. 83–84°, identical in m.p. and infra-red spectrum with the authentic sample obtained by Takeda and Kotera. On further elution with chloroform, additional unchanged α-dihydrocaranine (20 mg) was recovered. The water-soluble fraction was filtered, saturated with ammonium chloride, and extracted with chloroform. Concentration of the dried extract gave a brown oil (425 mg) which was dissolved in chloroform–benzene (6:1) and chromatographed on alumina (20 g). Elution with chloroform–benzene (6:1) gave a colourless oil which could not be crystallized. Treatment with 5% HCl gave after crystallization from water, 40 mg of the hydrochloride of XI as needles, m.p. 260° (decomp); $[\alpha]_D^{27}$ −34° (*c*, 0·42 in 70% ethanol); λ_{max} 263, 306 mμ; log ε, 4·06, 3·66; λ_{max} 2·95, 2·97 (OH), 6·20 μ. This gave a green ferric chloride test. (Found: C, 62·62; H, 6·64; N, 5·10. $C_{18}H_{17}O_4N$·HCl·1/2H_2O requires: C, 62·39; H, 6·63; N, 4·85%).

Further elution with chloroform methanol (50:1 and 30:1) gave colourless oil (300 mg) which could not be crystallized. Treatment with 5% HCl gave the hydrochloride of X, (287 mg) m.p. 250–255° (decomp). The analytical sample was obtained by recrystallization from water, m.p. 267–270° (decomp); $[\alpha]_D^{27}$ −56° (*c*, 0·26 in 70% ethanol); λ_{max} 285 mμ; log ε, 3·78; λ_{max} 2·93 (OH), 6·21 μ. (Found: C, 58·72; H, 7·00; N, 4·72. $C_{18}H_{19}O_5N$·HCl·1/2H_2O requires: C, 58·72; H, 6·89; N, 4·57%).

Attempts to isolate the free phenolic base from the hydrochloride of X failed, since it could not be extracted from its aqueous solution by a variety of solvents. The picrate was prepared in dilute ethanolic solution and crystallized from ethanol as yellow plates, m.p. 201–202°. (Found: C, 49·95; H, 4·79; N, 11·00. $C_{18}H_{19}O_5N$·$C_6H_3O_7N_3$·H_2O requires: C, 49·61; H, 4·76; N, 11·02%).

Methylenedioxy ring-opening of α-anhydrodihydrocaranine with ethanolic potassium hydroxide. α-Anhydrodihydrocaranine (VII; 300 mg) was treated with KOH (375 mg) in 95% ethanol (12 ml) as for α-dihydrocaranine. α-Anhydrodihydrocaranine (136 mg), m.p. and mixed m.p. 83–85°, was recovered unchanged. The phenolic fraction was chromatographed on alumina (5 g). Elution with chloroform–benzene (1:1, 2:1, 3:1, 4:1, 5:1 and 6:1) gave a colourless oil (110 mg) which was hydrolysed with HCl to give after concentration the hydrochloride of XI (80 mg) as needles, m.p. 257–261° (decomp), identical with the phenolic by-product obtained by treatment of α-dihydrocaranine with potassium hydroxide as described above.

Methylation of demethylene-α-dihydrocaranine (X) *with diazomethane.* To a solution of the hydrochloride of X (200 mg) in methanol (25 ml) was added ethereal diazomethane (150 ml) prepared from nitrosomethylurea (10 g). The mixture was kept at room temp for 4 days. Excess of the diazomethane was decomposed with dil HCl, the mixture concentrated and the resulting oil dissolved in dil HCl, filtered and basified with 10% NaOH. Extraction with benzene and evaporation after washing with 10% NaOH and drying gave a brown oil (70 mg), which was chromatographed in benzene on alumina (5 g). Elution with benzene–ethyl acetate (5:1 and 4:1) gave α-dihydropluviine (XII, 20 mg). The analytical sample, m.p. 135–137°, recrystallized from acetone, $[\alpha]_D^{23}$ −83·4° (*c*, 0·31 in ethanol); λ_{max} 232, 282 mμ; log ε; 3·79, 3·62, was identical by mixed m.p. and infra-red spectrum with an authentic specimen. (Found: C, 70·30; H, 8·12; N, 4·58. Calc. for $C_{17}H_{23}O_3N$: C, 70·56; H, 8·01; N, 4·84%).

Reaction of α-dihydrocaranine (VI) *with cyanogen bromide.* A solution of cyanogen bromide (250 mg) in dry benzene (8 ml) was added dropwise to a solution of α-dihydrocaranine (VI, 500 mg) in dry benzene (42 ml) and the mixture refluxed for 3 hr. The reaction mixture was washed with water, 5% HCl and again with water, and concentrated to 1/3 of its volume with separation of XV as needles (138 mg). The analytical sample m.p. 183–185° recrystallized from ethanol, $[\alpha]_D^{28}$ −173·4° (*c*, 0·51 in chloroform); λ_{max} 237, 291 mμ; log ε, 3·68, 3·70; λ_{max} 2·91 (OH), 4·49 μ (N–CN). (Found: C, 54·05; H, 5·07; N, 7·22; Br, 20·86. $C_{17}H_{19}O_3N_2Br$ requires: C, 53·83; H, 5·05; N, 7·39; Br, 21·08%).

The mother liquors from the above crystals were evaporated and the resulting brown oil dissolved in benzene and chromatographed on alumina (15 g). Elution with benzene afforded XVIII (125 mg)

which recrystallized from ethanol as colourless prisms, m.p. 187–188°; $[\alpha]_D^{16}$ −135·9° (*c*, 0·38 in chloroform); λ_{max} 236, 290 mμ; log ε, 3·64, 3·65; λ_{max} 4·54 μ (N-CN). (Found: C, 68·30; H, 6·30; N, 9·05. $C_{17}H_{18}O_3N_2$ requires: C, 68·44; H, 6·08; N, 9·39%). Further elution with benzene–ethyl acetate (3:1) gave additional XV (73 mg) as colourless needles, m.p. 183–185°.

Reaction of α-acetyldihydrocaranine (XVII) *with cyanogen bromide.* A solution of cyanogen bromide (250 mg) in dry benzene (4 ml) was added dropwise to a solution of α-dihydroacetylcaranine (XVII, 250 mg) in dry benzene (6 ml) and refluxed for 1 hr. The product (XVI, 230 mg) recrystallized from ethanol as colurless needles, m.p. 158°; $[\alpha]_D^{21}$ −127·4° (*c*, 0·58 in chloroform); λ_{max} 237, 291 mμ; log ε, 3·68, 3·71; λ_{max} 4·53 (N-CN), 5·79 μ (−OCOCH$_3$). (Found: C, 53·72; H, 5·22; N, 6·56; Br, 18·75. $C_{16}H_{21}O_4N_2Br$ requires: C, 54·15; H, 5·02; N, 6·65; Br, 18·98%).

Acetylation of XV. A solution of XV (150 mg) in dry pyridine (0·5 ml) and acetic anhydride (1 ml) was allowed to stand at room temp for 24 hr. The reaction mixture was poured into ice-cold water, basified with 10% aqueous sodium carbonate and extracted with benzene. Concentration of the dried extract gave the acetate (XVI, 100 mg) which after crystallization from ethanol, gave colourless needles, m.p. and mixed m.p. 158°. The infra-red spectrum in Nujol was also identical with that of XVI.

Reduction of XVIII *with lithium aluminium hydride.* A solution of XVIII (97 mg) in dry ether (70 ml) was refluxed with lithium aluminium hydride (200 mg) for 3 hr. After addition of water, the precipitate was filtered off and the filtrate and washings combined, dried and evaporated to give colourless needles (86 mg). Recrystallization from ethanol gave XIX (76 mg), m.p. 139–140°; $[\alpha]_D^{16}$ −6·5° (*c*, 0·42 in ethanol); λ_{max} 292 mμ; log ε, 3·66; λ_{max} 3·00 μ (N-H). (Found: C, 70·02; H, 7·11; N, 4·97. $C_{16}H_{19}O_3N$ requires: C, 70·31; H, 7·01; N, 5·13%).

The Eschweiler–Clarke reaction of XIX. A mixture of XIX (95 mg), 85% formic acid (0·2 ml) and 37% formalin (0·05 ml) was refluxed for 6 hr. The mixture was then evaporated to dryness under reduced pressure, taken up in 5% HCl, filtered, basified with 10% aqueous sodium carbonate and extracted with benzene. Concentration of the dried extracts gave an oil (99 mg), which was taken up in light petroleum and chromatographed on alumina (5 g). Elution with light petroleum gave a crystalline product, which on recrystallization from light petroleum gave colourless prisms (XX, 79 mg) m.p. 82–84°; $[\alpha]_D^{25}$ +2° (*c*, 1·01 in ethanol); λ_{max} 292 mμ; log ε, 3·67. (Found: C, 71·08; H, 7·08; N, 4·80. $C_{17}H_{21}O_3N$ requires: C, 71·05; H, 7·37; N, 4·87%).

Methylenedioxy ring-opening of XX *with ethanolic potassium hydroxide.* A solution of XX (154 mg) and KOH (187 mg) in 95% ethanol (4 ml) was heated under nitrogen in a sealed tube at 180–190° for 1·5 hr. The mixture was concentrated to dryness under reduced pressure and the residue in water extracted with light petroleum. Concentration of the dried extract recovered unchanged starting material (30 mg). The aqueous layer was saturated with ammonium chloride and extracted with chloroform and dried. The residue was chromatographed in benzene on alumina (10 g). Elution with benzene afforded a crystalline product (120 mg) which was recrystallized from ether as colourless needles (XXI, 90 mg) m.p. 96–98°; $[\alpha]_D^{20}$ +30·7° (*c*, 0·55 in ethanol); λ_{max} 285 mμ; log ε, 3·40; λ_{max} 2·78 μ (OH), 6·25 μ. (Found: C, 68·64; H, 8·36; N, 3·96. $C_{16}H_{23}O_4N$ requires: C, 68·44; H, 8·16; N, 4·20%).

Action of hydrochloric acid on XXI. A solution of XXI (50 mg) in dil HCl was heated at 100° for a few min. The mixture was filtered, evaporated to dryness, and the residue crystallized from water to give the hydrochloride of XXII as colourless scales, m.p. 235–240° (decomp); $[\alpha]_D^{21}$ −37° (*c*, 0·81 in 70% ethanol); λ_{max} 288 mμ; log ε, 3·57. (Found: C, 61·42; H, 7·20; N, 4·41. $C_{16}H_{21}O_3N$·HCl requires: C, 61·60; H, 7·11; N, 4·49%).

Methylation of XXII *with diazomethane.* After refluxing XXI (140 mg) in 5% HCl (3 ml) for a few min, the mixture was basified with aqueous ammonia and extracted with ether. Concentration of the dried extract gave an oil (XXII, 100 mg) which in ether (10 ml) was treated with ethereal diazomethane (80 ml) prepared from nitrosomethylurea (5 g). After being kept at room temp for 4 days, the mixture was concentrated to dryness, the residue in ether, filtered and treated again with excess diazomethane for further 4 days. The excess diazomethane was destroyed by dropwise addition of 5% HCl, the ether evaporated, and the residue in dil HCl, filtered and basified with 10% aqueous sodium carbonate. Extraction with benzene and removal of the solvent afforded a residue (98 mg) which was chromatographed in benzene–light petroleum (1:1) on alumina (5 g). The benzene–light petroleum (1:1) eluate gave a crystalline product (XXIII, 30 mg) m.p. 118–120°. Three recrystallizations from methanol gave colourless needles, m.p. 123–124°; $[\alpha]_D^{16}$ −18·7° (*c*, 0·39 in ethanol); λ_{max}

285 mμ; log ε, 3·70. (Found: C, 71·05; H, 8·09; N, 4·64. Calc. for $C_{16}H_{23}O_3N$: C, 71·25; H, 8·31; N, 4·62%).

This was identical in m.p., mixed m.p., optical rotation and infra-red spectrum with authentic α-deoxydihydrolycorenine furnished by Prof. Uyeo. Further elution with chloroform and chloroform–methanol (10:1) gave a phenolic oil (40 mg) which was further methylated with diazomethane to α-deoxydihydrolycorenine (14 mg).

Acknowledgements—The author wishes to express his deep appreciation to Dr. K. Takeda, Director of this Laboratory, and to Prof. S. Uyeo of the University of Osaka for their valuable discussions.