acetic acid. The solution was cooled to 0°, and a solution of 0.12 g. of sodium nitrite in 2.5 ml. of water was added in 0.5-ml. portions over a 10-minute period. The reaction was allowed to proceed for 10 minutes at 0°, 100 ml. of ice-cold water was added to the reaction mixture and the tripeptide azide was filtered off and washed successively with cold water, 5% $NaHCO_3$ and water. A solution of the azide in 19 ml. of cold tetrahydrofuran was added to an aqueous solution (14 ml.) of L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteine (0.45 g., 0.001 mole) and triethylamine (0.1 g., 0.001 mole) and stirred for 24 hr. at 4° and for 12 hr. at room temperature. After addition of 50 ml. of water to the reaction mixture, the precipitate was filtered off and washed with 25 ml. of hot ethyl acetate and 50 ml. of 0.5 *N* HCl and dried; wt. 0.9 g., m.p. 209–211°. A sample was recrystallized from 90% aqueous tetrahydrofuran–water; m.p. 213–214°, $[\alpha]^{24}_D$ −24.4° (*c* 0.9, 90% aqueous tetrahydrofuran).

Anal. Calcd. for $C_{54}H_{62}O_{12}N_8S_3$: C, 58.4; H, 5.62; N, 10.1. Found: C, 58.3; H, 5.66; N, 9.79.

This protected hexapeptide also was prepared by coupling S-benzyl-N-tosyl-L-cysteinyl-L-tyrosyl-L-phenylalanine with L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteine by the mixed anhydride method with isobutyl chlorocarbonate in a mixture of tetrahydrofuran and dimethylformamide. The yield of purified product, m.p. 213–214°, was 59%.

Carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide Hydrobromide.—The dihydrobromide of L-prolyl-L-arginylglycinamide[14] (1.92 g., 0.004 mole) was dissolved in 4 ml. of dimethylformamide, and 0.67 ml. of triethylamine was added with stirring. The mixture was cooled and the triethylamine hydrobromide was removed by filtration and washed with 1.5 ml. of cold dimethylformamide in three portions, the washings being added to the main filtrate. The monohydrobromide was purified by two precipitations from dimethylformamide solution with chloroform and then washed with chloroform and ether and dried *in vacuo* over P_2O_5 and NaOH. This material was dissolved in 15 ml. of dimethylformamide, and carbobenzoxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteine azide (2.8 g., 0.0046 mole) in 10 ml. of dimethylformamide was added. The mixture was stirred at room temperature for 3 hr. The crude product was then precipitated with ethyl acetate, filtered off, washed with ethyl acetate and chloroform, and dried.

The material was purified by countercurrent distribution in 2-butanol–0.5% acetic acid (130 transfers), and the Sakaguchi color reaction[25] was used for preparation of the distribution curve. The solutions from the tubes containing the protected hexapeptide amide hydrobromide (*K* 0.88) were concentrated on the rotary evaporator[26] and then lyophilized to give 2.87 g. (73%) of white, amorphous powder, $[\alpha]^{22}_D$ −34.8° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{40}H_{56}O_{10}N_{12}S\cdot HBr$: C, 49.2; H, 5.87; N, 17.2. Found: C, 48.8; H, 6.07; N, 17.0.

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[25] A. A. Albanese and J. E. Frankston, *J. Biol. Chem.*, **159**, 185 (1945).

[26] L. C. Craig, J. C. Gregory and W. Hausmann, *Anal. Chem.*, **22**, 1462 (1950).

NEW YORK, N. Y.

[CONTRIBUTION FROM THE SHIONOGI RESEARCH LABORATORY, SHIONOGI & CO., LTD.]

A Partial Synthesis of Caranine[1]

BY KEN'ICHI TAKEDA, KATSUMI KOTERA AND SATOSHI MIZUKAMI

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Reduction of the chlorohydrin IV, obtained by chlorination of lycorine (I), with zinc in acetic acid afforded three products: caranine (III), isocaranine (XII) and the diene derivative XIII. The dehydration reactions of caranine and isocaranine and the basic double-bond migrations of the diene derivative XIII were examined, and structures were established for these products. Lithium aluminum hydride was found to be the most effective reagent for conversion of the chlorohydrin to caranine.

Caranine is an alkaloid isolated from the bulbs of some *Amaryllidaceae plants* by W. C. Wildman and co-workers in 1955.[2,3] The structure III was proposed by them[4,5] recently. During the course of our investigations on the stereochemistry of dihydrolycorine, it was found that monodesoxydihydrolycorine (XIV) was identical with α-dihydrocaranine, obtained by the hydrogenation of caranine over platinum in acetic acid. This fact provided unequivocal evidence that caranine has the same carbon skeleton as lycorine.[6,7] Hence, it seemed of interest of synthesize caranine from lycorine (I).[8,9]

For this purpose, we first attempted to synthesize caranine through the reduction of the monotosylate II of lycorine as shown in Chart I, but neither the mono- nor the ditosylate was obtained under the various conditions. The next approach was the preparation of lycorine chlorohydrin by a procedure analogous to that used for the chlorination of dihydrolycorine.[10] Treatment of lycorine with phosphoryl chloride containing a trace of concentrated hydrochloric acid at 37° for 45 minutes gave the chlorohydrin IV, $C_{16}H_{18}ClNO_3$, m.p. 150° dec., in a 10% yield along with a large amount of anhydrolycorinium salt V.

The structure of chlorohydrin IV was deduced from its conversion to monoacetyllycorine (VI), m.p. 231–232°, with potassium acetate in acetone. This substance on acetylation or alkaline hydrolysis furnished diacetyllycorine (VII) or lycorine (I), respectively, and this monoacetyl derivative also was obtained by the direct acetylation of lycorine with acetyl chloride in pyridine at 0°, along with diacetyllycorine.

On the other hand, S. Uyeo and his co-workers[11] obtained on partial hydrolysis of diacetyllycorine

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[1] The outline of this paper was read at the 16th International Congress of Pure and Applied Chemistry in Paris, France, July 19, 1957.

[2] L. H. Mason, E. R. Puschett and W. C. Wildman, THIS JOURNAL, 77, 1253 (1955).

[3] H. M. Fales, E. W. Warnhoff and W. C. Wildman, *ibid.*, 77, 5885 (1955).

[4] E. W. Warnhoff and W. C. Wildman, *Chemistry & Industry*, 348 (1956).

[5] E. W. Warnhoff and W. C. Wildman, THIS JOURNAL, 79, 2192 (1957).

[6] K. Takeda and K. Kotera, *Chemistry & Industry*, 347 (1956).

[7] K. Takeda and K. Kotera, *Pharm. Bull. Japan*, 5, 234 (1957).

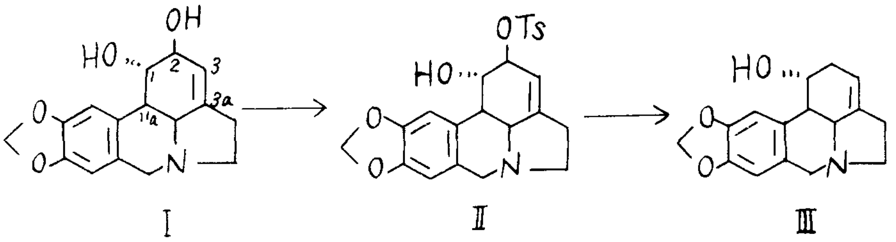
[8] Configuration of the hydroxyl groups in lycorine was assigned according to that of dihydrolycorine (*cf.* refs. 6, 7).

[9] Caranine was obtained from lycorine by the action of sodium in amyl alcohol by W. C. Wildman (*cf.* ref. 5, footnote 14a).

[10] K. Takeda and K. Kotera, unpublished observation.

[11] Y. Nakagawa, S. Uyeo and H. Yajima, *Chemistry & Industry*, 1238 (1956).

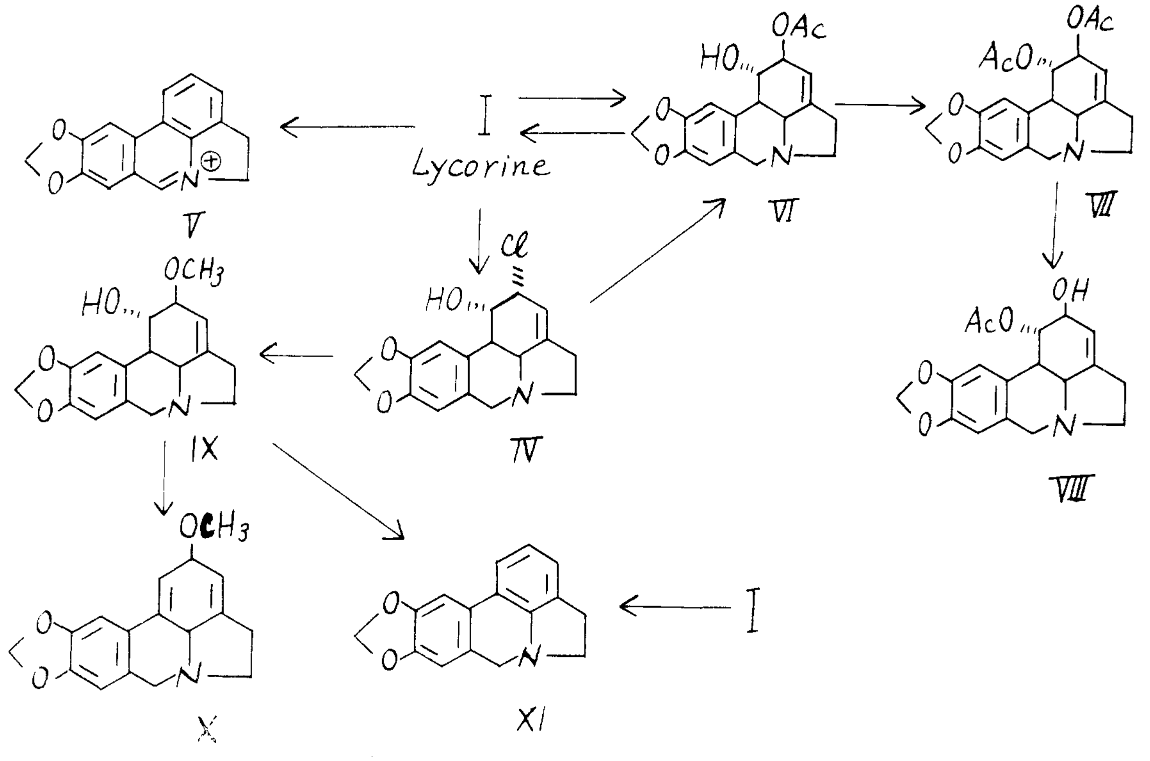
CHART I



another monoacetyllycorine, m.p. 215–216°, which on acetylation or alkaline hydrolysis also gave diacetyllycorine or lycorine, respectively, and on active manganese dioxide oxidation afforded an α,β-unsaturated ketone.

Accordingly, this monoacetyllycorine, m.p. 215–216°, was assigned structure VIII, and the position of a double bond in lycorine was proved to be between C_3 and C_{3a} by these chemical means. These results showed that our monoacetyllycorine, m.p. 231–232°, must be the isomer which is acetylated at the C_2 hydroxyl group (as in VI) and that the chlorine atom of the chlorohydrin must be attached at C_2. The probable configuration of the chlorine atom on the chlorohydrin seems to be *cis* to the C_1-hydroxyl function, since the C_2-quasiaxial hydroxyl group of lycorine would be replaced by chlorine as a result of Walden inversion. Furthermore, action of a weakly alkaline reagent such as sodium carbonate on the chlorohydrin in methanol did not afford an epoxide but a monomethyl ether, $C_{17}H_{19}NO_4$ (IX), m.p. 162–163°. The C_1-hydroxyl and the C_2-methoxyl groups of this monomethyl ether would be *trans* to each other from another Walden inversion. Further evidence for the position of this chlorine atom comes from the fact that dehydration of the monomethyl ether IX by phosphoryl chloride in pyridine at room temperature for five hours afforded a dehydro derivative, $C_{17}H_{17}NO_3$ (X), m.p. 129–130°, together with a small amount of anhydrolycorine (XI). Because the ultraviolet spectrum of the former compound showed maxima at 266 mμ (log ε 4.08) and 311 mμ (log ε 3.88), the double bond produced by dehydration must be conjugated with the aromatic ring.

Anhydrolycorine (XI), the structure of which was already confirmed by synthetic study,[12] could be obtained not only from anhydrolycorinium chloride[12] but also directly from the treatment of lycorine with phosphoryl chloride at 100° followed by the action of methanolic potash.



We next examined the dehalogenation of the chlorohydrin IV by zinc dust and acetic acid Gentle refluxing of the chlorohydrin IV with zinc in acetic acid afforded three products Two of them possessed the same formula, $C_{16}H_{17}NO_3$, and melted at 177–178° ([α]D −203.1°) and 187–188° ([α]D −245.0°), respectively. The former substance was found to be identical with natural caranine

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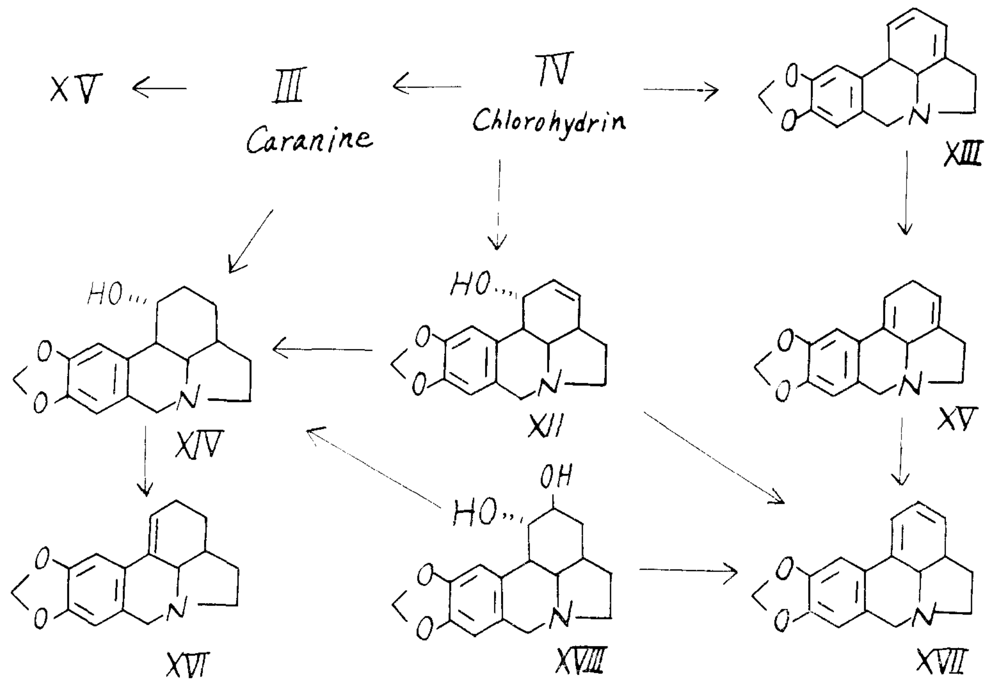
[12] L. G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima and N. Yanaihara, *J. Chem. Soc.*, 4622 (1954).



(III) by mixed melting point determination and by comparison of their infrared spectra.[13] The second compound, m.p. 187–188°, on hydrogenation either over platinum in acetic acid or over palladium in ethanol gave the same α-dihydrocaranine XIV[4-7] in good yield. Thus, the second compound seems to be an isomer of caranine due to the difference of the position of a double bond. It was named isocaranine (XII). From the behavior of this substance on catalytic hydrogenation, the double bond seems to be in the C_2–C_3 position and neither tri- nor tetrasubstituted. The third product, $C_{16}H_{15}NO_2$ (XIII), m.p. 112–113°, $[\alpha]_D$ $-349.8°$, was a diene derivative which contained no hydroxyl group. The ultraviolet spectrum, 235 mμ (log ϵ 3.78) and 292 mμ (log ϵ 3.82), showed that neither double bond of this substance was conjugated with the aromatic ring. Treatment of this diene with either a 2% ethanolic solution of potassium hydroxide under reflux or contact with alumina for a rather long time furnished, by a prototropic shift, an isomer XV, m.p. 154–155°, $[\alpha]_D$ $-113.6°$, in which one double bond had moved into conjugation with the aromatic nucleus. Its ultraviolet spectrum was identical with that of isosafrol and the compound XVI obtained by the dehydration of α-dihydrocaranine.[6,7] On the other hand, XIII was not affected by concentrated hydrochloric acid in methanol. From these experimental results, the most probable structure for this diene is XIII. Reactions of the chlorohydrins with zinc dust and acetic acid analogous to those of IV have been reported by other authors in the steroid field.[14-17]

A further correlation of structure between these three substances was obtained by dehydration with phosphoryl chloride. With phosphoryl chloride in pyridine at room temperature, isocaranine (XII) gave the so-called anhydrodihydrolycorine (XVII), m.p. 104–105°, $[\alpha]_D$ $-77.3°$, which was obtained directly from dihydrolycorine (XVIII) by the same reagent without pyridine by Kondo and Tomimura 30 years ago.[18,19] This compound was proved to be the diene derivative having double bonds fully conjugated with the aromatic ring as shown by its ultraviolet spectrum, 309 mμ (log ϵ 3.94) and 337 mμ (log ϵ 4.02). Since this diene was rather easily reduced on catalytic reduction to its tetrahydro derivative,[20] the assignment of formula XVII seems to be reasonable.

On the other hand, when caranine (III) was treated with phosphoryl chloride in the same manner, the above-mentioned isomeric diene XV was obtained readily. The fact that caranine afforded the isomeric diene XV with one conjugated double bond under the same conditions as in the case of isocaranine indicated that double-bond migration does not occur during this type of dehydration reaction. Furthermore, this diene XV afforded anhydrodihydrolycorine (XVII) in a 40% yield when treated with 20% ethanolic potash under reflux for four hours, with a 20% recovery of the starting material XV. As mentioned above, in alkaline medium, the double bond at C_1–C_2 of the diene XIII migrated much more easily than did that at C_3–C_{3a} of the diene XV.

These findings were well predicted by the structures III, XII, XIII and XV which had been assigned to caranine, isocaranine, the diene, m.p.

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[13] The authentic specimen of caranine was kindly supplied by Dr. W. C. Wildman.

[14] L. F. Fieser and R. Ettorre, THIS JOURNAL, **75**, 1700 (1953).

[15] L. F. Fieser and X. A. Domingquez, *ibid.*, **75**, 1704 (1953).

[16] J. Elks, G. H. Phillipps, D. A. H. Taylor and L. J. Wyman, *J. Chem. Soc.*, 1739 (1954).

[17] E. J. Corey and J. J. Ursprung, THIS JOURNAL, **78**, 5041 (1956).

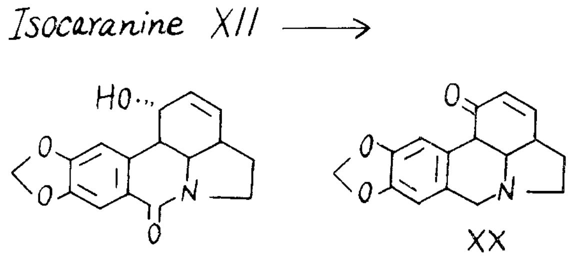
[18] H. Kondo and K. Tomimura, *J. Pharm. Soc. Japan*, **48**, 227 (1928).

[19] H. Kondo, K. Takeda and K. Kotera, *Ann. Report. ITSUU Lab.*, **5**, 66 (1954).

[20] K. Takeda and K. Kotera, unpublished observation.

112–113°, and another diene, m.p. 154–155°, respectively.

When isocaranine (XII) was oxidized with manganese dioxide, only a trace of a neutral substance was obtained, the structure of which was assumed to be XIX and not the anticipated α,β-unsaturated ketone XX, solely on the basis of the ultraviolet and infrared spectra. There was insufficient material for further work.



XIX XX

Finally, reduction of the chlorohydrin IV with lithium aluminum hydride in ether afforded only caranine (III) in a 60% yield and did not give other products, in contrast to reduction using zinc in acetic acid.

Experimental[21]

Attempted Tosylation of Lycorine (I).—A mixture of 400 mg. of lycorine (I), 270 mg. of tosyl chloride and 4 ml. of pyridine was stored in the refrigerator overnight. This reaction mixture was worked up in the usual manner.[7] The crystalline product obtained in this case was 200 mg. of the starting material. When a mixture of 400 mg. of lycorine (I), 600 mg. of tosyl chloride and 4 ml. of pyridine was allowed to stand at room temperature (*ca.* 25°) for 18 hours, the starting material could not be recovered. However, neither mono- nor ditosylate was obtained.

Lycorine Chlorohydrin (IV).—A mixture of 10 g. of lycorine (I) and 35 g. of phosphoryl chloride was warmed on the water-bath, its temperature being raised from 21 to 35° over a period of 10 minutes. When one drop of 35% hydrochloric acid (using a capillary tube of diameter *ca.* 1 mm.) was added to this mixture at 35°, a reaction started with gentle foaming. One additional drop of 35% hydrochloric acid was added 4 times at 5-minute intervals at the same temperature.

The suspended crystals were dissolved gradually to give a yellowish solution. After further warming at 37° for 10 minutes and cooling, this solution was added dropwise to 1500 ml. of ice-cold water. While being cooled with ice, this aqueous solution was basified with 200 ml. of 10% sodium hydroxide followed by 300 ml. of 10% sodium carbonate and extracted with 1000 ml. of ether. The ethereal layer was washed with water, dried over sodium sulfate and concentrated to 30 ml. Scratching with a glass rod gave 1.15 g. of a crystalline product, m.p. 148–150° dec., a portion of which was recrystallized from ether to give a pure sample, prisms, m.p. 150° dec., $[\alpha]^{23.5}\text{D}$ +63.09° (*c* 0.097, ethanol); ultraviolet spectrum: $\lambda_{\max}$ 292 mμ (log ε 3.68).

Anal. Calcd. for $C_{16}H_{16}ClNO_3$: C, 62.83; H, 5.27; N, 4.58; Cl, 11.60. Found: C, 62.47; H, 5.43; N, 4.40; Cl, 11.61.

When 4.0 g. of the chlorohydrin residue was allowed to stand at room temperature for several days, it mostly changed to an ether-insoluble, but water-soluble substance.[22] This was dissolved in water, acidified with dilute sulfuric acid and converted to its reineckate. The above-mentioned alkaline mother liquor also was worked up according to the same procedure to obtain the quaternary ammonium salt as its reineckate. Dissolved in a mixture of water and acetone 1:3, the combined reineckate was treated with Amberlite IRA 400. The free quaternary base thus obtained was converted to 3.0 g. of its chloride, m.p. 280–281° dec., with dilute hydrochloric acid. This chloride was shown to be identical with the authentic anhydrolycorinium chloride by mixed melting point determination and by comparison of their ultraviolet spectra.

Acetylation of Lycorine (I) with Acetyl Chloride in Pyridine.—To a mixture of 50 mg. of acetyl chloride and 4 ml. of pyridine was added 250 mg. of lycorine (I) under cooling with ice, and this mixture was stored in the refrigerator (0–5°) for 17 hours. The crystals disappeared and a glassy oil precipitated at the bottom. This reaction mixture was poured into a large amount of ice-cold water, basified with 10% sodium carbonate and extracted with a benzene–ether mixture. The organic layer was washed with water and dried over sodium sulfate. The residue obtained on evaporation of the solvent under reduced pressure was chromatographed on 15 g. of alumina.[23] The fraction eluted with ethyl acetate and benzene (1:20) gave, on crystallization from ethanol, 30 mg. of colorless scales, m.p. 214–215° dec., undepressed on admixture with an authentic specimen of diacetyllycorine (VII), m.p. 214–215° dec. Elution with a mixture of benzene and ethyl acetate (5:1) gave 120 mg. of crude VI. Recrystallization from ethanol gave 100 mg. of colorless needles, m.p. 231–232°, $[\alpha]^{23.5}\text{D}$ +22.37° (*c* 0.192, ethanol); infrared spectra: 5.835, 8.09 μ (Nujol), and 2.77, 5.79 μ ($CHCl_3$); ultraviolet spectrum: $\lambda_{\max}$ 291 mμ (log ε 3.67).

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.74; H, 5.86; N, 3.95.

This monoacetyllycorine (VI) on either acetylation (with acetic anhydride in pyridine) or saponification (with methanolic potash) afforded diacetyllycorine (VII), m.p. 214–215° dec., or lycorine (I), m.p. 280° dec., respectively.

Conversion of Lycorine Chlorohydrin (IV) to Monoacetyllycorine (VI).—A mixture of 100 mg. of crude lycorine chlorohydrin, 500 mg. of anhydrous potassium acetate, 10 ml. of acetone and 1 ml. of water was heated under reflux for three hours. This reaction mixture was diluted with water and extracted with a benzene–ether mixture. The organic layer was washed with water, dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed on 10 g. of alumina. The benzene–ethyl acetate (4:1) eluate was rechromatographed on 5 g. of alumina. A mixture of benzene and ether (1:1) eluted crystalline fractions. Recrystallization from ethanol gave 10 mg. of needles, m.p. 230–231°. Its melting point showed no depression on admixture with the above-mentioned monoacetyllycorine (VI), and its infrared spectrum was identical with that of the authentic specimen.

Conversion of Lycorine Chlorohydrin (IV) to the Monomethyl Ether IX.—A mixture of 60 mg. of the crude chlorohydrin IV, 100 mg. of anhydrous potassium carbonate, 10 ml. of methanol and 2 ml. of water was heated under reflux for half an hour. After dilution with water and removal of the methanol, this reaction mixture was extracted with a benzene–ether mixture. Though the residue gave 40 mg. of a crystalline product under scratching, it was purified by chromatography on 8 g. of alumina. The product eluted with a mixture of benzene and ether (3:2) was recrystallized from ether to give 20 mg. of colorless plates, m.p. 162–163°, $[\alpha]^{28}\text{D}$ −72.7° (*c* 1.68, ethanol); infrared spectrum (Nujol): 3.13 (–OH), 9.25 μ ($-OCH_3$); ultraviolet spectrum: $\lambda_{\max}$ 292 mμ (log ε 3.67).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65; OCH_3, 10.28. Found: C, 67.57; H, 6.21; N, 4.55; OCH_3, 10.22.

Dehydration of the Monomethyl Ether IX.—A mixture of 400 mg. of the monomethyl ether IX, 2 g. of phosphoryl chloride and 6 ml. of pyridine was allowed to stand at room temperature (*ca.* 25°) for five hours. The reaction mixture was carefully poured into 150 ml. of ice-cold water, dissolved completely, basified with 10% sodium carbonate and extracted with benzene. The benzene extract was

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[21] All melting points are uncorrected. The ultraviolet spectra were taken in 95% ethanol solution, unless otherwise stated, using a Beckman model DU spectrophotometer. The infrared absorption spectra were determined with a Perkin-Elmer model 12 C single beam infrared spectrophotometer.

[22] This fact probably shows that anhydrolycorine (XI) was first produced and then was converted to anhydrolycorinium salt (V) (*cf.* ref. 12).

[23] Unless otherwise stated, alumina used in this experiment was Merck reagent standardized for chromatographic adsorption analysis according to Brockmann.

washed with water, dried over sodium sulfate and evaporated to dryness. Dissolved in a mixture of benzene and petroleum ether (2:1), the residue was chromatographed on 20 g. of alumina. Benzene–petroleum ether (2:1) eluted a crystalline product, which on recrystallization from ethanol afforded 6 mg. of colorless scales, m.p. 111–112°, undepressed on admixture with an authentic specimen of anhydrolycorine (XI). Elution with benzene–ether (7:1 to 5:1) gave another crystalline product, which on recrystallization from ethanol afforded 80 mg. of colorless needles, m.p. 129–130°, $[\alpha]^{29.5}\text{D}$ −104.1° (c 0.137, ethanol); ultraviolet spectrum: $\lambda_{\max}$ 266 mμ (log ϵ 4.08), 311 mμ (log ϵ 3.88); infrared spectrum: 9.47 μ (-OCH_3).

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94; OCH_3, 11.03. Found: C, 71.97; H, 6.23; N, 5.23; OCH_3, 11.23.

Conversion of Lycorine (I) to Anhydrolycorine (XI) and the Monomethyl Ether IX.—A mixture of 5 g. of lycorine (I) and 17 g. of phosphoryl chloride was heated at 100° for 15 minutes. The reaction mixture was poured dropwise into 1500 ml. of ice-cold water, dissolved completely, basified with 100 ml. of 10% sodium hydroxide followed by 150 ml. of 10% sodium carbonate and extracted with 1000 ml. of ether. After evaporation, the ether extract gave 3.9 g. of a glassy oil which was heated under reflux for one hour in 130 ml. of methanol and 13 ml. of water with 1.3 g. of potassium hydroxide. The reaction mixture was diluted with water and extracted with a mixture of benzene and ether (10:3). The organic layer was washed well with water, dried over sodium sulfate and evaporated to dryness. The residue was dissolved in 200 ml. of a mixture of benzene and petroleum ether (5:1), and chromatographed on 100 g. of alumina. Benzene–petroleum ether (5:1) eluted a crystalline product, which on recrystallization from ethanol afforded 670 mg. of colorless scales, m.p. 110–111°, undepressed on admixture with the authentic anhydrolycorine (XI). Three fractions of benzene–ether (10:1, 3:1, 1:1) eluted another crystalline product, which on recrystallization from ether afforded 510 mg. of colorless needles, m.p. 162–163°, undepressed on admixture with the authentic specimen of the monomethyl ether IX.

Reaction of Lycorine Chlorohydrin (IV) with Zinc Dust in Acetic Acid.—A mixture of 3.5 g. of the chlorohydrin IV, 25 g. of zinc dust, 200 ml. of glacial acetic acid and 20 ml. of water was heated vigorously under reflux using a free flame for three hours. The zinc dust was dissolved completely. After cooling, the precipitated zinc acetate was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water and filtered. Hydrogen sulfide was passed into this aqueous solution. The zinc sulfide thus precipitated was removed by filtration, and the filtrate was basified with sodium carbonate and extracted with benzene. By purification of 1.50 g. of the benzene-soluble material on 45 g. of alumina, the following three products were obtained. The first substance was eluted with benzene almost without being adsorbed. Recrystallization from ether gave 400 mg. of XIII, prisms, m.p. 112–113°, $[\alpha]^{25}\text{D}$ −349.8° (c 1.423, ethanol); ultraviolet spectrum: $\lambda_{\max}$ 235 mμ (log ϵ 3.78), 292 mμ (log ϵ 3.82).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.75; H, 5.93; N, 5.62.

The second substance was eluted with benzene–ethyl acetate (4:1). This compound was recrystallized from ethyl acetate to give 120 mg. of a pure sample, prisms, m.p. 177–178°, $[\alpha]^{30}\text{D}$ −203.1° (c 0.90, chloroform); infrared spectrum: 3.13 μ (-OH); ultraviolet spectrum: $\lambda_{\max}$ 240 mμ (log ϵ 3.55), 291 mμ (log ϵ 3.67). The melting point of this compound showed no depression on admixture with an authentic sample of natural caranine and its infrared spectrum was in full agreement with that of caranine.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.87; H, 6.52; N, 5.12.

Elution with benzene–ethyl acetate (1:1) gave the third substance, which on recrystallization from ethyl acetate afforded 250 mg. of pure isocaranine (XII), prisms, m.p. 187–188°, $[\alpha]^{22}\text{D}$ −245.0° (c 1.00, chloroform); infrared spectrum: 3.13 μ (-OH); ultraviolet spectrum: $\lambda_{\max}$ 291 mμ (log ϵ 3.67).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.89; H, 6.46; N, 5.11.

Treatment of 50 mg. of isocaranine with 1 ml. of acetic anhydride in 1 ml. of pyridine gave 50 mg. of its acetate, which was recrystallized from ether to afford a pure sample as colorless needles, m.p. 125–126°.

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.89; H, 6.20; N, 4.57.

Catalytic Reduction of Isocaranine (XII). (a) **Over Platinum in Acetic Acid.**—When a solution of 80 mg. of isocaranine (XII) in 5 ml. of glacial acetic acid was shaken in hydrogen in the presence of 30 mg. of platinum oxide for half an hour, 12.1 ml. of hydrogen was absorbed. The reaction mixture was worked up in the usual manner. The crystalline product, m.p. 166–169°, was recrystallized from acetone to give 70 mg. of colorless prisms, m.p. 169–170°. The melting point of this compound was not depressed on admixture with the authentic specimen of monodesoxydihydrolycorine (XIV) and its infrared spectrum was in full agreement with that of XIV.

(b) **With 10% Palladium–Charcoal Catalyst in Ethanol.**—A solution of 55 mg. of isocaranine (XII) in 10 ml. of ethanol was shaken in hydrogen in the presence of 100 mg. of 10% palladium–charcoal catalyst. After half an hour, absorption of hydrogen ended. However, this reaction mixture was shaken in hydrogen for four additional hours and then worked up in the usual manner. Recrystallization from ethyl acetate afforded 40 mg. of colorless prisms, m.p. 169–170°, identical with monodesoxydihydrolycorine.

Double Bond Migration of the Diene Derivative XIII. (a) **With Alumina.**—Dissolved in petroleum ether, 50 mg. of the diene derivative XIII was chromatographed on 10 g. of alumina. No crystalline product was eluted with mixtures of petroleum ether (b.p. 45–57°) and benzene (10:0, 3:1, 2:1). Eluates of petroleum ether and benzene (1:1, 1:4, 0:10) afforded crystalline fractions. Recrystallization from ether gave 40 mg. of colorless needles, m.p. 154–155°, $[\alpha]^{21}\text{D}$ −113.6° (c 1.11, ethanol); ultraviolet spectrum: $\lambda_{\max}$ 265 mμ (log ϵ 4.02), 310 mμ (log ϵ 3.81).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.60; H, 6.01; N, 5.52.

(b) **With 2% Ethanolic Potash.**—In 20 ml. of 2% ethanolic potash, 100 mg. of the diene derivative XIII was heated under reflux for two hours. The reaction mixture was diluted with water, concentrated and extracted with benzene. The benzene layer was washed with water, dried over sodium sulfate and evaporated to dryness under reduced pressure. Recrystallization of the residue from ether afforded 86 mg. of colorless needles, m.p. 153–154°, of a compound which was identical with that obtained with alumina as described above.

Action of Methanolic Hydrochloric Acid on the Diene Derivative XIII.—A solution of 45 mg. of the diene derivative XIII, 5 ml. of methanol and 1 ml. of 35% hydrochloric acid was heated under reflux for two hours. The reaction mixture was diluted with water, basified with 10% sodium carbonate and extracted with ether. The ethereal layer was washed with water, dried over sodium sulfate and evaporated to dryness. Recrystallization from ether afforded 30 mg. of colorless needles, m.p. 108–110°, undepressed on admixture with the authentic starting material.

Double Bond Migration in the Diene Derivative XV.—In 10 ml. of 20% ethanolic potash, 50 mg. of the diene derivative XV was heated under reflux for four hours. The reaction mixture was worked up in the usual manner. The residue was chromatographed on 10 g. of alumina. Elution with petroleum ether and benzene (1:1) afforded a crystalline product, which was recrystallized from ether to give 20 mg. of colorless needles, m.p. 102–104°, undepressed on admixture with the authentic sample of anhydrodihydrolycorine (XVII) and showed the same ultraviolet absorption spectra. Finally, benzene–petroleum ether (2:1) eluted 10 mg. of the starting material.

Dehydration of Isocaranine (XII).—A mixture of 140 mg. of isocaranine (XII), 1 g. of phosphoryl chloride and 3 ml. of pyridine was allowed to stand at room temperature overnight. The reaction mixture was poured dropwise into 100 ml. of ice-cold water, dissolved completely, basified with 10% sodium carbonate and extracted with benzene. The benzene-soluble material was chromatographed on 10 g. of neutral alumina.[24] A mixture of benzene and petroleum

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(24) Normal alumina was neutralized by the procedure of Reichstein (*cf.* T. Reichstein and C. W. Shoppee, *Disc. Faraday Soc.*, **7**, 305 (1949).

ether (2:1) eluted a crystalline product, which on recrystallization from ether afforded 40 mg. of colorless needles, m.p. 104–105°, $[\alpha]^{21}D$ −77.3° (*c* 0.99, benzene). This substance was found to be identical with anhydrodihydrolycorine (XVII) by melting point determination and by comparison of the ultraviolet spectra.

Dehydration of Caranine (III).—A mixture of 180 mg. of caranine (III), 1 g. of phosphoryl chloride and 3 ml. of pyridine was worked up by a procedure analogous to that used for isocaranine (XII) as described above. The residue obtained by evaporation of the benzene extract afforded on recrystallization from ether 110 mg. of colorless needles, m.p. 153–154°, identical with the diene derivative XV obtained by the alkaline double bond migration of the diene derivative XIII.

Manganese Dioxide Oxidation of Isocaranine (XII).—A solution of 100 mg. of isocaranine (XII) in 33 ml. of benzene was shaken with 1.0 g. of manganese dioxide[25] at room temperature (25–30°) for ten hours. After removal of manganese dioxide by filtration, the benzene solution was extracted with dilute hydrochloric acid. The acidic aqueous layer was basified with 10% sodium carbonate and extracted with benzene. This benzene layer afforded 20 mg. of the starting material. The original benzene solution containing nonbasic substances was worked up in the usual manner. In trituration with ethanol, the residue afforded a small amount of crystalline product, which was purified by sublimation in high vacuum. Though this compound melted at 264–265°, not enough was obtained to carry out an analysis. Its ultraviolet spectrum was similar to that of dihydrolycorinone[26] and its infrared spectrum showed peaks at 2.95 μ (-OH) and 6.11 μ $(-\underset{\underset{\displaystyle O}{\|}}{C}-N-)$. Moreover, using manganese dioxide prepared by Attenburrow's method,[27] oxidation was carried out in chloroform solution changing the reaction temperature or reaction time as follows: 5°, 20°, 25° or 0.25, 0.5, 0.75, 1, 6 hours, respectively. However, the anticipated α,β-unsaturated ketone was not obtained.

Reduction of Lycorine Chlorohydrin (IV) with Lithium Aluminum Hydride in Ether.—A solution of 40 mg. of the chlorohydrin IV in 130 ml. of dry ether with 40 mg. of lithium aluminum hydride was heated under reflux for four hours. Water was added and the reaction mixture was filtered. The ethereal layer was separated, evaporated to dryness, and dissolved in 15 ml. of benzene. The residue was chromatographed on 10 g. of alumina. A mixture of benzene and ether (5:1) eluted a crystalline product, which on recrystallization from ethanol afforded 20 mg. of colorless prisms, m.p. 176–177°, undepressed on admixture with an authentic sample of caranine (III).

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IMAFUKU, AMAGASAKI, JAPAN

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Alkaloids of the Amaryllidaceae. XI. The Structures of Alkaloids Derived from 5,10b-Ethanophenanthridine[1,2]

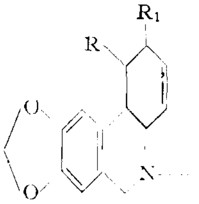
BY W. C. WILDMAN

RECEIVED DECEMBER 2, 1957

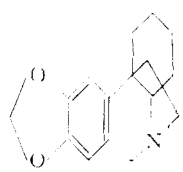
A combination of degradative and synthetic evidence has proved that the alkaloids crinine, powelline, buphanidrine and buphanisine are represented by structures IX, XVI, XX and XXIV, respectively.

The isolation and characterization of the alkaloid crinine from two unidentified *Crinum* species was reported by this Laboratory in 1955.[3] In a paper submitted after our communication, Boit[4] independently reported the isolation of an alkaloid, crinidine, from *Crinum moorei* J. D. Hook. Crinine and crinidine possessed identical molecular formulas and functional groups. Direct comparison of the two alkaloids by infrared spectra and mixture melting point determination showed them to be identical. Since that time, crinine has been isolated from *Boöphone fischeri* Baker,[5] *Crinum powellii* Hort.[6,7] and *Nerine bowdenii* W. Watson.[7]

Sharing with caranine (I, R = OH, R_1 = H)[1] the relatively simple molecular formula $C_{16}H_{17}NO_3$, crinine was found to contain the same functional groups, *viz.*, one methylenedioxyphenyl group, one hydroxyl and one aliphatic double bond. The latter is neither conjugated with the aromatic ring nor contiguous with the hydroxyl function. Since crinine occurs frequently in bulbs which are rich also in lycorine (I, R, R_1 = OH),[8,9] a tentative hypothesis was advanced that crinine might possess the isomeric structure I (R = H, R_1 = OH). Support for this was obtained from the facile oxidation of crinine to a ketone, oxocrinine, by manganese dioxide. The infrared spectrum of oxocrinine showed no hydroxyl absorption but pos-



I



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