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59. Shojiro Uyeo,*1 Tsunehiro Kitagawa,*2 and Yoshitomo Yamamoto*1 : Oxidation of the Hydrogenation Products of Lycorenine and Homolycorine.

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In the course of studies on the alkaloids of the Amaryllidaceae, we[1] have shown that catalytic hydrogenation of lycorenine afforded α- and β-deoxydihydrolycorenine (I and II) and homolycorine gave α- and β-dihydrohomolycorine (III and IV).

In this paper we wish to report the results obtained by oxidation of these products by either potassium permanganate or potassium dichromate.

First, α-deoxydihydrolycorenine (I), which contains a *cis*-fused perhydroindole ring-system, was oxidized by potassium permanganate in acetone to give a neutral compound, $C_{18}H_{23}O_4N$. It exhibited an ultraviolet absorption spectrum that resembled that of the starting material and indicated in the infrared spectrum an amido carbonyl band at 1681 cm^{-1}. Since reduction of this with lithium aluminum hydride reverted to α-deoxydihydrolycorenine, it must be either an N-formyl derivative resulted by oxidation of the N-methyl group or a lactam formed by oxidation of the α-methylene in the five-membered heterocyclic ring. The nuclear magnetic resonance spectrum revealed that this is a five-membered lactam, α-deoxydihydro-2-oxolycorenine (V), since it exhibited three protons from an N-methyl group at +1.90 p.p.m. (water as external reference).

In contrast to this mode of reaction, potassium dichromate oxidation of α-deoxydihydrolycorenine (I) in sulfuric acid gave, as a result of oxidation of the benzylic methylene, α-dihydrohomolycorine (III), which on further oxidation with potassium permanganate gave a five-membered lactam, α-dihydro-2-oxohomolycorine (VI). The structure of this product was proved by its reduction with lithium aluminum hydride to the known α-hexahydrohomolycorine (VII)[1] and transformation of α-deoxydihydro-2-oxolycorenine (V) to this compound by its dichromate oxidation in sulfuric acid. As can be seen from these experimental results, compounds of the α-series gave rise to lactams on oxidation with potassium permanganate and to lactones with potassium dichromate.

On the other hand, compounds of the β-series having a *trans*-fused perhydroindole ring system behaved differently toward the oxidizing agents. Thus, oxidation of β-deoxydihydrolycorenine (II) with potassium permanganate in acetone afforded predominant amount of a basic product which on chromatography on alumina furnished a new compound, $C_{18}H_{25}O_4N$ besides β-dihydrohomolycorine (IV).

Since this compound exhibited in the ultraviolet spectrum absorptions at 233 mμ (log ε, 3.97) and 282 mμ (log ε, 3.52) which were superimposable upon those of the starting material, and in the infrared spectrum a band at 3155 cm^{-1} corresponding to a hydroxyl group, and formed an oxime, $C_{18}H_{26}O_4N_2$, whose ultraviolet spectrum was very similar to that of lycorenine oxime,[2] it is clear that this compound is β-dihydrolycorenine (VIII) possessing a hemiacetal moiety in the molecule as does lycorenine.

On the other hand, oxidation of β-deoxydihydrolycorenine with potassium dichromate in sulfuric acid afforded β-dihydrohomolycorine in good yield. Further oxidation of this with potassium permanganate furnished a neutral compound, $C_{18}H_{21}O_5N$, which

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1) T. Kitagawa, S. Uyeo, N. Yokoyama : J. Chem. Soc., **1959**, 3741.

2) H. Kondo, T. Ikeda : Ann. Rept. ITSUU Lab., 3, 55 (1952).

exhibited, along with a δ-lactone band at 1706 cm^{-1} in the infrared spectrum, a band of an amido carbonyl at 1667 cm^{-1}. Since it could be reduced to β-hexahydrohomolycorine (IX)$^{1)}$ by lithium aluminum hydride, this must be either a five-membered lactam or an N-formyl compound. Between these two possibilities, the latter (XII) was preferred on the basis of the following evidence. Heating with 10% ethanolic sodium hydroxide resulted in a conversion of the amide (XII) into a new neutral compound, $C_{17}H_{21}O_4N$, which indicated in the ultraviolet spectrum absorptions characteristic of dihydroisocarbostyrils (Fig. 1), and in the infrared spectrum a hydroxyl band at 3367 cm^{-1} and an amido carbonyl at 1631 cm^{-1} corresponding to a sixmembered lactam. Reduction of this with lithium alminum hydride gave a compound that was shown to be identical with β-dihydropluviine (X)$^{1)}$ obtained by catalytic hydrogenation of pluviine in methanol over palladium-carbon.

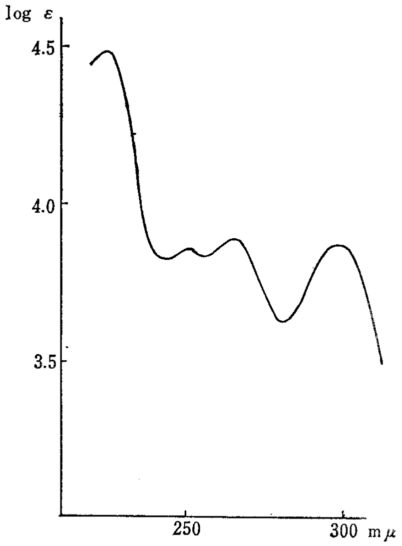
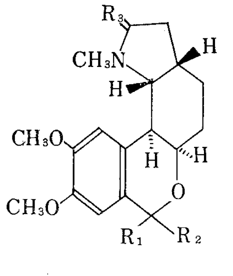


Fig. 1. Ultraviolet Absorption Spectrum of β-Dihydro-7-oxopluviine

Thus the structure of the hydrolysis product can be formulated as β-dihydro-7-oxopluviine (XI) which is satisfactorily rationalized as arising from the intermediate formed by deformylation of the amide and hydrolysis of the lactone grouping in XII by an intramolecular cyclization involving the carboxyl and imino groups. It is noteworthy



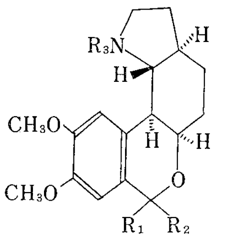
I : $R_1=R_2=H, R_3=H_2$

III : $R_1, R_2=O, R_3=H_2$

V : $R_1=R_2=H, R_3=O$

VI : $R_1, R_2=O, R_3=O$

XIII : $R_1=H, R_2=OH, R_3=H_2$

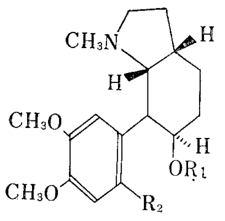


II : $R_1=R_2=H, R_3=CH_3$

IV : $R_1, R_2=O, R_3=CH_3$

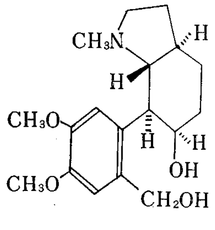
VIII : $R_1=H, R_2=OH, R_3=CH_3$

XII : $R_1, R_2=O, R_3=CHO$

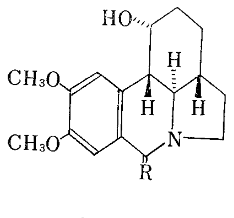


VII : $R_1=H, R_2=CH_2OH$

XIV : $R_1=CH_3CO, R_2=CHO$



IX



X : $R=H_2$

XI : $R=O$

that this sequence of reactions provided a further confirmative evidence for the stereochemical relationship between β-dihydrohomolycorine and β-dihydropluviine.

In view of the results mentioned above, it may be concluded that potassium dichromate in sulfuric acid preferentially attacks the benzylic position of the compounds of both α- and β-series. On the other hand, stereospecific oxidation was observed in the case of potassium permanganate; the compounds of the β-series, in contrast to those of α-series, were first oxidized at the benzylic position of ring B leading to a hemiacetal and then to a lactone, while the vicinity of the nitrogen atom was not so readily attacked by this reagent as in the case of the α-series and only under drastic conditions the N-methyl group rather than the α-methylene in the heterocyclic ring was oxidized to the N-formyl group.

Although we have prepared β-dihydrolycorenine as mentioned above, we were not successful in obtaining α-dihydrolycorenine (XIII) either by hydrogenation of lycorenine or by oxidation of α-deoxydihydrolycorenine. α-Dihydrolycorenine has now been obtained by partial reduction of α-dihydrohomolycorine with lithium aluminum hydride under controlled conditions, and characterized as its acetate (XIV), $C_{20}H_{27}O_5N$, which exhibits in the ultraviolet spectrum absorptions almost identical with those of acetyllycorenine[3] at 234 (log ε, 4.12), 281 (log ε, 3.97), and 311 mμ (log ε, 3.83), proving the structure (XIII).

Experimental[*3]

Oxidation of α-Deoxydihydrolycorenine (I). a) With Potassium Permanganate——To a stirred solution of 200 mg. of α-deoxydihydrolycorenine in 20 ml. of Me_2CO was added dropwise 200 mg. of $KMnO_4$ in 10 ml. of H_2O at 0~5° and stirring was continued for 20 min. Then, 10 ml. of H_2O was added, and the excess $KMnO_4$ was destroyed by passing SO_2 gas into the mixture. Most of the solvent was removed under reduced pressure, the residue extracted with three 20 ml. portions of benzene, and the extracts were washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave 40 mg. of a crystalline residue which was recrystallized from Me_2CO to give α-deoxydihydro-2-oxolycorenine (V) as colorless prisms, m.p. 192~194°. $[\alpha]_D$ $-57.5°$ (c=1.07). UV: λ_{max} 284 mμ (log ε 3.64). IR: ν_{max} 1681 cm^{-1} (lactam). NMR (H_2O as internal reference): +1.90 p.p.m. (N-CH_3), +0.86 p.p.m. (OCH_3). *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 67.93; H, 7.29; N, 4.42.

The combined foregoing aqueous layer and washings were made alkaline with aq. NH_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. K_2CO_3, and evaporated. The resulting basic oil (210 mg.) was chromatographed in benzene over Al_2O_3. The eluate afforded 90 mg. of the starting material.

b) With Potassium Dichromate——To a solution of 20 mg. of α-deoxydihydrolycorenine in 1 ml. of 18% H_2SO_4 was added slowly 13 mg. of $K_2Cr_2O_7$ and the mixture was stirred on a boiling water bath for 5 min. After cooling, the solution was diluted with 3 ml. of H_2O, made alkaline with aq. NH_3, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. K_2CO_3, and evaporated to give 15 mg. of a residue. Recrystallization from Me_2CO afforded colorless needles, m.p. 189~190°. A mixture melting point with authentic α-dihydrohomolycorine (III) was undepressed.

Reduction of α-Deoxydihydro-2-oxolycorenine (V) with Lithium Aluminum Hydride——A mixture of 20 mg. of α-deoxydihydro-2-oxolycorenine and 20 mg. of $LiAlH_4$ in 10 ml. of anhyd. tetrahydrofuran was refluxed for 3 hr. After cooling, the excess reagent was destroyed by the dropwise addition of H_2O. The resulting precipitate was filtered and washed with tetrahydrofuran, and the combined filtrate and washings were evaporated to give 15 mg. of the crystalline material. Recrystallization from MeOH afforded needles, m.p. 126~127°. A mixture melting point with an authentic sample of I was not depressed.

Oxidation of α-Dihydrohomolycorine (III) with Potassium Permanganate——To a stirred solution of 200 mg. of α-dihydrohomolycorine in 20 ml. of Me_2CO was added 200 mg. of pulverized $KMnO_4$. Stirring was continued at 15~20° for 20 hr., and the excess $KMnO_4$ was destroyed by the dropwise addition of MeOH. The resulting precipitate was filtered and washed with $CHCl_3$. The combined filtrate and washings were evaporated to dryness. The residue was taken up in 10 ml. of 5% HCl and the solution was

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[*3] All melting points are uncorrected. Optical rotations were determined in abs. EtOH. IR spectra were determined in Nujol mull and UV spectra were determined in 95% EtOH.

3) T. Kitagawa, W.I. Taylor, S. Uyeo, H. Yajima: J. Chem. Soc., **1955**, 1066.

extracted with three 20 ml. portions of benzene. The extracts were washed with H_2O and dried over anhyd. Na_2SO_4. Removal of the solvent gave 50 mg. of a crystalline mass. This was further purified by chromatography over Al_2O_3, using benzene as eluent. The material (45 mg.) thus obtained was recrystallized from Me_2CO-petr. ether to give α-dihydro-2-oxohomolycorine (VI) as colorless prisms, m.p. 229~230°. $[\alpha]_D$ $-74.0°$(c=0.95). UV λ_{max} mμ (log ε): 226 (3.89), 267 (3.48), 302 (3.23). IR ν_{max} cm^{-1}: 1721 (lactone), 1675 (lactam). *Anal.* Calcd. for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.28; H, 6.42; N, 4.25.

The foregoing aq. acidic phase was made alkaline with aq. NH_3 and extracted with $CHCl_3$. The extract was washed wtih H_2O, dried over anhyd. K_2CO_3, and evaporated to leave 100 mg. of an oil which was chromatographed in benzene over Al_2O_3. The eluate gave 50 mg. of the starting material.

Oxidation of α-Deoxydihydro-2-oxolycorenine (V) with Potassium Dichromate——To a solution of 20 mg. of α-deoxydihydro-2-oxolycorenine in 1 ml. of 18% H_2SO_4 was slowly added 25 mg. of $K_2Cr_2O_7$. The mixture was heated for 5 min. on a boiling water bath. After cooling, 3 ml. of H_2O was added and the solution was extracted with benzene. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. Removal of the solvent left 13 mg. of a crystalline mass which on recrystallization from Me_2CO gave colorless prisms, m.p. 229~230°. A mixture melting point with VI was not depressed, and the IR spectrum of the product was identical with that of VI.

Reduction of α-Dihydro-2-oxohomolycorine (VI) with Lithium Aluminum Hydride——Using 20 mg. of α-dihydro-2-oxohomolycorine and 20 mg. of $LiAlH_4$ and applying the procedure described above for the reduction of V, there was obtained 15 mg. of a crude product. Recrystallization from Me_2CO gave colorless needles of α-hexahydrohomolycorine (VII),[1] m.p. 174~175°. A mixture melting point with an authentic sample was not depressed.

Oxidation of β-Deoxydihydrolycorenine (II). a) With Potassium Permanganate——To a stirred solution of 250 mg. of β-deoxydihydrolycorenine in 60 ml. of Me_2CO, was added dropwise 250 mg. of $KMnO_4$ in 5 ml. of H_2O at a temperature below 15°, and stirring was continued for 1 hr. at 15~20°. Then, 20 ml. of H_2O was added and the excess $KMnO_4$ was destroyed by passing SO_2 gas into the solution. Most of the Me_2CO was removed under reduced pressure, the residue was extracted with three 20 ml. portions of benzene, and the extracts were washed with H_2O and dried over anhyd. Na_2SO_4. Removal of the solvent gave a small amount of crystalline material which was not investigated further. The combined aqueous layer and washings were made alkaline with aq. NH_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. K_2CO_3, and evaporated to dryness, giving 200 mg. of oily material. This was chromatographed over Al_2O_3. The first eluate with 100 ml. of benzene gave 150 mg. of β-dihydrohomolycorine (IV) as colorless needles, m.p. 158~159°, after crystallization from Me_2CO. A mixture melting point with an authentic sample was undepressed. The second eluate with 150 ml. of benzene-AcOEt (9:1) gave 50 mg. of β-dihydrolycorenine (VIII) as colorless needles, m.p. 158~159°, after crystallization from Me_2CO. $[\alpha]_D$ $+66.8°$(c=0.45). UV λ_{max} mμ (log ε): 233 (3.97), 282 (3.52). IR: ν_{max} 3155 cm^{-1}(OH). *Anal.* Calcd. for $C_{18}H_{25}O_5N$: C, 67.69; H, 7.89; N, 4.34. Found: C, 67.44; H, 8.05; N, 4.39.

A mixture of 30 mg. of β-dihydrolycorenine, 30 mg. of $NH_2OH \cdot HCl$, and 20 mg. of anhyd. AcONa in 5 ml. of MeOH was refluxed for 3 hr. After removal of the solvent, the residue was taken up in 5 ml. of H_2O, and the solution was made alkaline with aq. NH_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd, K_2CO_3, and evaporated to yield 25 mg. of the crystalline oxime of VIII. Recrystallization from EtOH gave the analytical sample, prisms, m.p. 214~215°. UV λ_{max} mμ (log ε): 271 (4.04), 310 (3.62). *Anal.* Calcd. for $C_{18}H_{26}O_4N_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.24; H, 7.56; N, 8.00.

b) With Potassium Dichromate——Dichromate oxidation of 500 mg. of β-deoxydihydrolycorenine by the procedure as described for the dichromate oxidation of I yielded 330 mg. of crystalline material. Recrystallization from EtOH gave needles, m.p. 158~159°. A mixture melting point with an authentic sample of IV was undepressed.

Oxidation of β-Dihydrohomolycorine (IV) with Potassium Permanganate——To a stirred solution of 150 mg. of β-dihydrohomolycorine in 20 ml. of Me_2CO, 150 mg. of $KMnO_4$ in 5 ml. of H_2O was added at a temperature below 10°. Stirring was continued for 4 hr. at 20° and 20 ml. of H_2O was added. The excess reagent was destroyed by passing SO_2 gas into the solution, the solvent removed under reduced pressure and the residue extracted with three 20 ml. portions of benzene. The extracts were washed with H_2O and dried over anhyd. Na_2SO_4. Removal of the solvent yielded 15 mg. of β-dihydro-N-formylnorhomolycorine (XII). Recrystallization from Me_2CO-petr. ether gave the analytical sample as needles, m.p. 203~204°. $[\alpha]_D$ $+22.1°$(c=0.82). UV λ_{max} mμ (log ε): 227 (4.37), 268 (3.96), 302 (3.77). IR ν_{max} cm^{-1}: 1706 (lactone), 1667 (N-CHO). *Anal.* Calcd. for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.06; H, 6.48; N, 4.28.

The combined aqueous layer and washings were made alkaline with aq. NH_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated to yield 100 mg. of basic material. Chromatography of this product over Al_2O_3, using benzene as eluent, gave 90 mg. of the starting material.

Reduction of β-Dihydro-N-formylnorhomolycorine (XII) with Lithium Aluminum Hydride——To a solution of 20 mg. of β-dihydro-N-formylnorhomolycorine in 3 ml. of anhyd. tetrahydrofuran was added 20 mg. of $LiAlH_4$. After refluxing for 3 hr., the excess $LiAlH_4$ was decomposed by the cautious addition of H_2O. The resulting precipitate was filtered and washed with $CHCl_3$. The filtrate and washings were combined and evaporated to yield 15 mg. of crystals which on recrystallization from Me_2CO gave needles, m.p. 164~165°. A mixture melting point with authentic β-hexahydrohomolycorine (IX)[1)] was not depressed.

Deformylation of β-Dihydro-N-formylnorhomolycorine (XII)——A mixture of 40 mg. of β-dihydro-N-formylnorhomolycorine and 5 ml. of 10% EtOH-KOH was refluxed for 5 hr. and 5 ml. of H_2O was added. Most of the EtOH was removed under reduced pressure. The residue was extracted with three 20 ml. portions of $CHCl_3$ and the extracts were washed with H_2O. After drying and evaporation of the solvent, 35 mg. of β-dihydro-7-oxopluviine (XI) was obtained. Recrystallization form EtOH provided the analytical sample, colorless needles, m.p. 258~259°. $[\alpha]_D$ $-45.4°$ $(c=0.67)$. UV λ_{max} mμ (log ε) : 223 (4.46), 249 (3.84), 263 (3.89), 298 (3.79). IR ν_{max} cm^{-1} : 3378 (OH), 1629 (lactam). *Anal.* Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.23. Found : C, 66.70; H, 6.67; N, 4.28.

Reduction of β-Dihydro-7-oxopluviine (XI) with Lithium Aluminum Hydride——The reduction of 25 mg. of β-dihydro-7-oxopluviine with 30 mg. of $LiAlH_4$ in 5 ml. of anhyd. tetrahydrofuran was carried out in the same manner as described for the $LiAlH_4$ reduction of V. There was obtained 20 mg. of crystalline material which was recrystallized from Me_2CO to give needles, m.p. 172~173°. A mixture melting point with authentic β-dihydropluviine (X)[1)] was not depressed and the IR spectra of the both samples were identical.

Partial Reduction of α-Dihydrohomolycorine (III) with Lithium Aluminum Hydride——A solution of 317 mg. of α-dihydrohomolycorine in 25 ml. of anhyd. tetrahydrofuran was added dropwise with stirring to a suspension of 20 mg. of $LiAlH_4$ in 5 ml. of anhyd. tetrahydrofuran at −10°. After the addition had been completed, the mixture was stirred for 3 hr. at 10° and then for 30 min. at 20°. The excess reagent was decomposed by dropwise addition of H_2O. The resulting precipitate was removed by filtration and washed with several portions of $CHCl_3$. The combined filtrate and washings were evaporated to dryness, giving 300 mg. of crystalline material. This was chromatographed over Al_2O_3. The first eluate with 300 ml. of benzene gave 180 mg. of the starting material. The second eluate with an additional 500 ml. of benzene afforded 50 mg. of α-dihydrolycorenine (XIII) which was recystallized from Me_2CO-petr. ether giving needles, m.p. 159~160°. $[\alpha]_D$ $+14.2°$ $(c=0.57)$. UV λ_{max} mμ (log ε) : 231 (3.90), 282 (3.50). IR : ν_{max} 3279 cm^{-1} (OH). *Anal.* Calcd. for $C_{18}H_{25}O_4N \cdot 1/4 H_2O$: C, 66.77; H, 7.88; N, 4.64. Found : C, 66.75; H, 7.74; N, 4.39. The final eluate with 100 ml. of benzene-AcOEt (9:1) gave 35 mg. of crystalline material which was recrystallized from Me_2CO giving needles, m.p. 174~175°. A mixture melting point with an authentic sample of VII was not depressed.

Acetylation of α-Dihydrolycorenine (XIII)——A mixture of 70 mg. of α-dihydrolycorenine, 1 g. of Ac_2O, and one drop of conc. H_2SO_4 was allowed to stand at room temperature for 12 hr. The mixture was poured into ice-cold H_2O, made alkaline with Na_2CO_3, and extracted with three 10 ml. portions of $CHCl_3$. The extracts were washed with H_2O, dried over anhyd. K_2CO_3, and evaporated to give 50 mg. of a residue which was chromatographed over Al_2O_3. The eluate with $CHCl_3$ afforded 20 mg. of acetyl-α-dihydrolycorenine (XIV) as prisms, m.p. 101~103°, after recrystallization from EtOH. UV λ_{max} mμ (log ε) : 234 (4.12), 281 (3.97), 311 (3.83). IR ν_{max} cm^{-1} : 1739 (OAc), 1681 (CHO). *Anal.* Calcd. for $C_{20}H_{27}O_5N$: C, 66.49; H, 7.53. Found : C, 66.44; H, 7.84.

Summary

Oxidation of α-deoxydihydrolycorenine (I) with potassium dichromate in sulfuric acid gave α-dihydrohomolycorine and with potassium permanganate α-deoxydihydro-2-oxolycorenine (V) which reverted to I on treatment with lithium aluminum hydride. β-Deoxydihydrolycorenine (II) gave with potassium permanganate β-dihydrolycorenine together with β-dihydrohomolycorine which constituted the sole product of dichromate oxidation of (II) and gave on further oxidation with permanganate the N-formyl derivative (XII) which was converted into β-dihydro-7-oxopluviine (XI) on treatment with alcoholic sodium hydroxide. α-Dihydrolycorenine (XIII) was obtained only by reduction of α-dihydrohomolycorine with lithium aluminum hydride under controlled conditions.

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