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THE AMARYLLIDACEAE ALKALOIDS

TRANSFORMATION OF LYCORINE INTO HIPPEASTRINE

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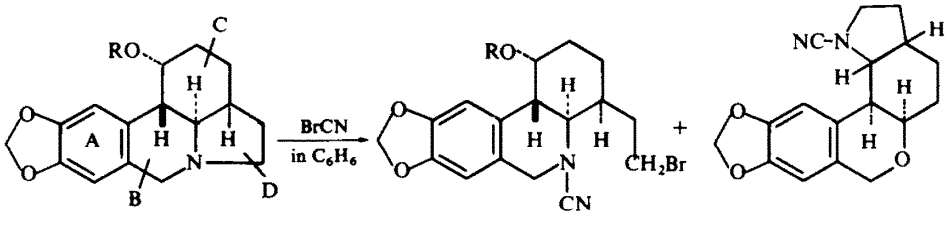
Abstract—Deoxy-N-cyanodihydronorhippeastrine (IX), obtained by the von Braun reaction of dihydrolycorine (VII), has been converted into deoxydihydrohippeastrine (XIV). Degradation of diacetyllycorine (XVIIIb) with cyanogen bromide and subsequent treatment of the degradation products with 5% ethanolic potassium hydroxide afford a neutral (XIXa) and two basic products (XX and XXI), of which, XIXa and XX may be transformed *via* a secondary amine XXIIa into hippeastrine (XVII). The structure determination of XXI was based on the structure elucidation of its two hydrogenation products, XXIVa and XXVa. The stereochemical relationships between dihydrolycorine and dihydrohippeastrine (XVI), and also between lycorine (XVIIIa) and hippeastrine (XVII) have been accomplished. Thus the absolute configurations of dihydrohippeastrine and hippeastrine are unequivocally established.

MIZUKAMI[1] reported previously that acetyl-ω-bromo-N-cyano-α-dihydrosecocaranine (IIa) formed in the treatment of α-dihydrocaranine acetate (Ia) with cyanogen bromide results from the cleavage of the D-ring, whereas, when α-dihydrocaranine (Ib) is subjected to the von Braun degradation reaction, ring cleavage, not only in the D-ring but also in the B-ring, results in two products, IIb and III in the ratio of 2:1. The transformation of III to deoxy α-dihydrolycorenine (IV) established the stereochemical relation between caranine- and lycorenine type alkaloids.

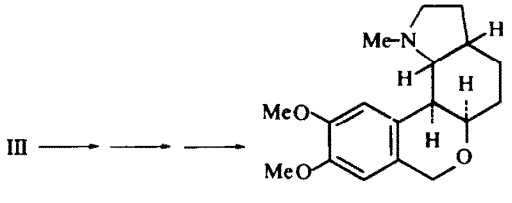
Chart 1



Ia: R = Ac
b: R = H

IIa: R = Ac
b: R = H

III

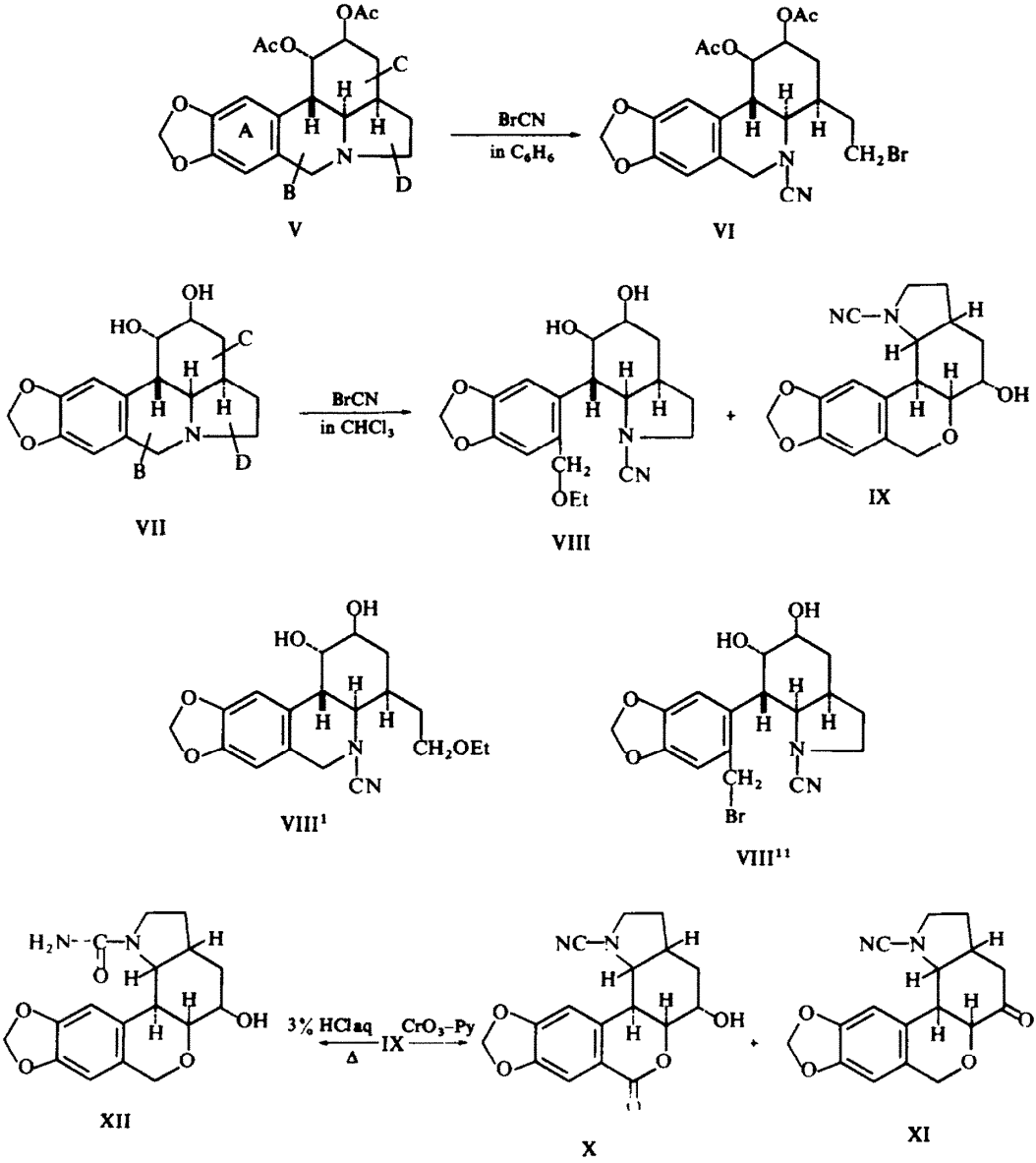


IV

This work prompted the conversion of dihydrolycorine (VII) into deoxydihydrohippeastrine (XIV) and then the direct transformation of lycorine (XVIIIa) into hippeastrine (XVII) which is of chemical as well as biogenetic interest.[2] The results obtained are the subject of this paper.

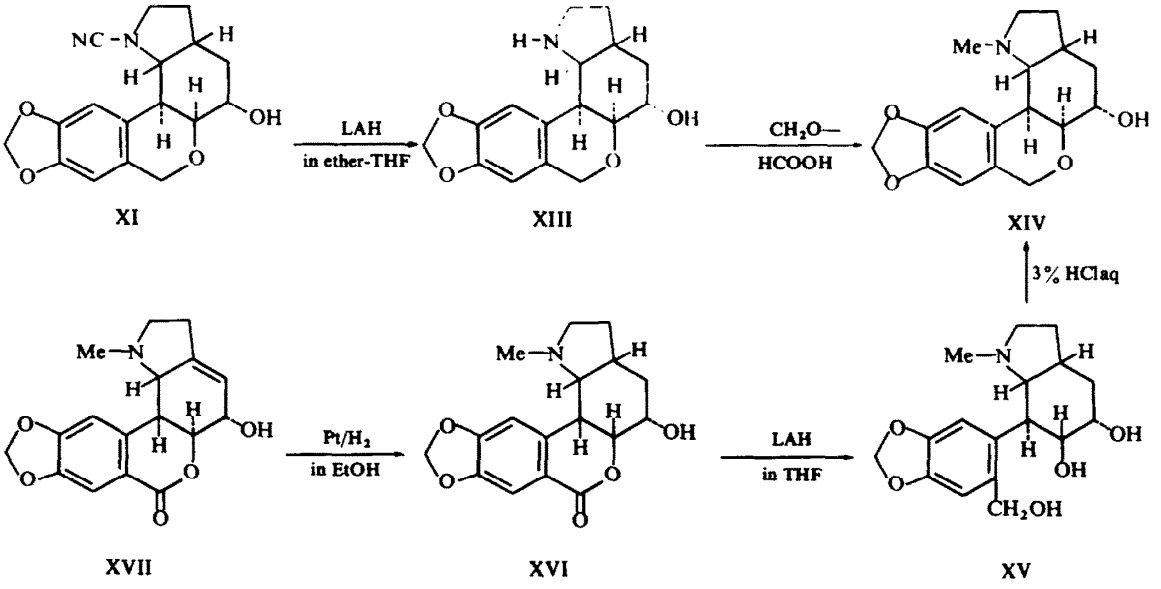
Previously Kondo and Katsura,[3] and later Uyeo *et al.*[4] carried out the von Braun reaction of diacetyldihydrolycorine (V) giving an almost quantitative yield of diacetyl ω-bromo-N-cyanodihydrosecolycorine (VI). Re-examination of their works proved that there is no degradation product due to the cleavage of the B-ring.

Chart 2



In order to obtain degradation products of the B-ring necessary for the present purpose, we undertook the von Braun degradation of dihydrolycorine (VII), which appeared difficult because of a low solubility of VII in the usual organic solvents, but heating under reflux in a large excess of chloroform gave two products, $C_{19}H_{24}O_5N_2$, m.p. 144°, $[\alpha]_D^{24}$ +36·2° and $C_{17}H_{18}O_4N_2$, m.p. 222°, $[\alpha]_D^{19}$ +100·6°. Other products resulting from D-ring cleavage may also be present, but were not examined. The first product VIII is different from the known substance VIII'[4] in chemical properties, analytical values, and IR and NMR spectra and it was assumed that it is produced by the reaction of the intermediate VIII'' with ethanol which was present as antioxidant in the commercial chloroform. The second product has no bromine and exhibits IR absorptions at 2198 cm^{-1} and 3460 cm^{-1}, characteristic of a CN and an OH group, respectively, and was expected to have the structure IX. Oxidation of IX with chromic acid–pyridine complex afforded two products, X and XI, in a ratio of 1 : 8, the structures of which were based on the IR and UV spectral data. Formation of X with a lactone moiety suggested that the expected structure of IX is correct and this was confirmed by the following experiments. The conversion of a N–CN group to a secondary amine may be achieved with mineral acids or by a LAH reduction.[4,5] Gentle refluxing of IX with 30% sulfuric acid or 10% hydrochloric acid afforded no secondary amine XIII and resulted in the formation of undetectable water-soluble substances but when IX was heated at 50–60° with 3% hydrochloric acid, a urea derivative XII, m.p. 240–241° (dec) was formed instead of the expected amine XIII. The conversion of XII into XIII in an alkaline or acid medium was unsuccessful and the LAH reduction of IX to XIII also failed in refluxing THF or ether, but when IX was carefully reduced by gentle refluxing in ether–THF (5:1 v/v) for 10 hr under a nitrogen atmosphere, the secondary amine XIII, m.p. 155–156°, $[\alpha]_D$ −23·1°, was obtained although the yield was not good (about 32%).

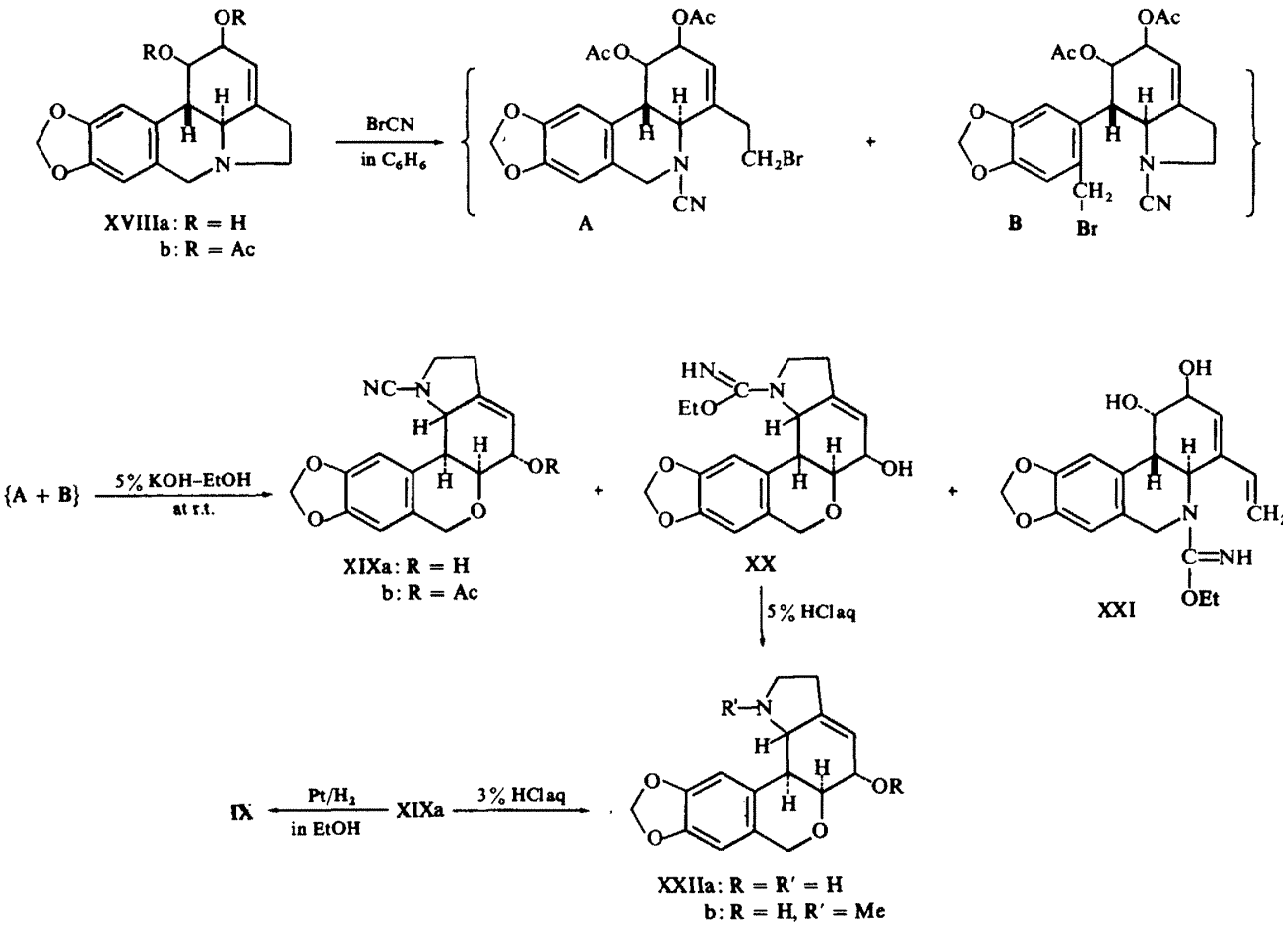
Chart 3



XI XIII XIV

XVII XVI XV

Chart 4


OR
RO
H
H
O
O
N
XVIIIa: R = H
b: R = Ac
BrCN
in C6H6
OAc
AcO
CH2Br
CN
A
B
CH2
Br
{A + B}
5% KOH-EtOH
at r.t.
NC
OR
XIXa: R = H
b: R = Ac
HN
EtO
OH
XX
HO
CH2
C=NH
OEt
XXI
5% HClaq
R'
IX
Pt/H2
in EtOH
XIXa
3% HClaq
XXIIa: R = R' = H
b: R = H, R' = Me

probably on account of the unstability of XIII. Methylation of XIII with formaldehyde and formic acid afforded an N–Me derivative XIV, m.p. 109–110°, $[\alpha]_D$ +62·6°, characterized as the hydrochloride, m.p. 285–286° (dec), $[\alpha]_D$ +8·7°. The hydrochloride was identical with that of deoxydihydrohippeastrine, derived from dihydrohippeastrine (XVI)[6] *via* triol XV by a LAH reduction followed by a ring closure with 3% hydrochloric acid.[7] As expected, dihydrolycorine (VII) could be converted into deoxydihydrohippeastrine (XIV), derived from the hydrogenation product of hippeastrine (XVII). Thus the chemical relation between dihydrolycorine and dihydrohippeastrine has been established.

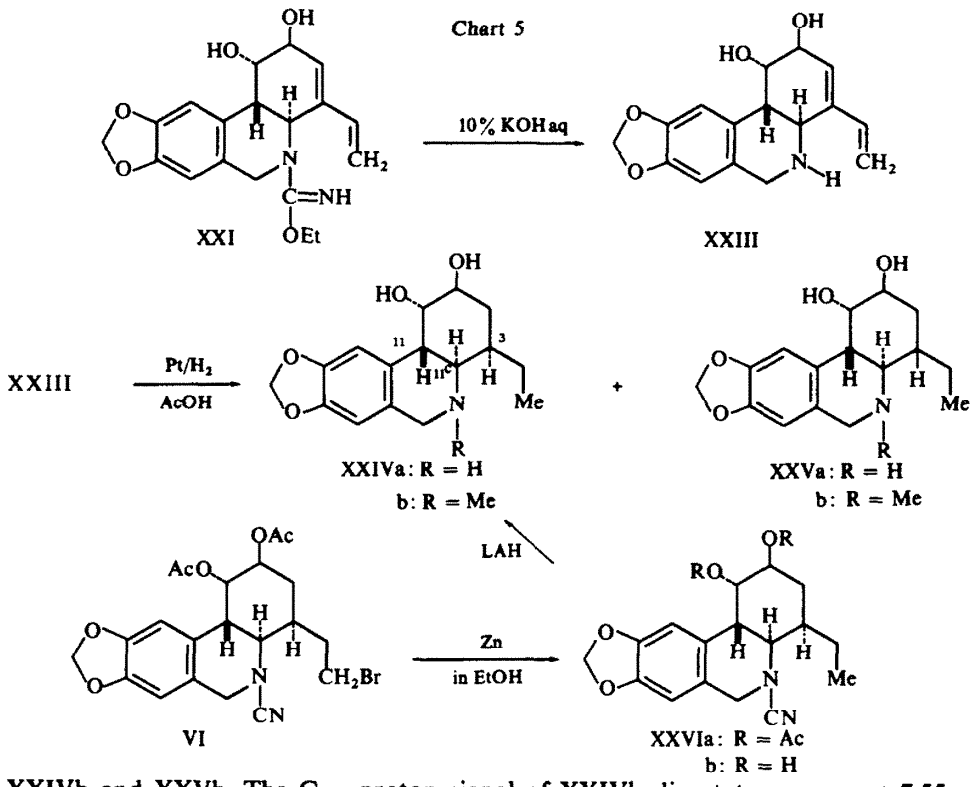
The von Braun degradation of lycorine resulted in the complete recovery of the starting material, because of insolubility in the usual organic solvents, but treatment of diacetyllycorine (XVIIIb) with cyanogen bromide in refluxing benzene afforded the products, A and B, detectable in equal intensity as poorly isolable spots on a thin layer plate.* As separation of the products seemed difficult, the mixture was treated with 5% ethanolic potassium hydroxide at room temperature, affording one neutral and two basic products. Hydrogenation of an oily neutral product with platinum oxide in ethanol gave deoxy-N-cyanodihydronorhippeastrine (IX) with the structure assigned as XIXa, the acetate XIXb of which was obtained in a crystalline state, m.p. 196–197°, $[\alpha]_D$ +276·4°. Of the two basic products, an oily one was converted by refluxing in 5% hydrochloric acid to a secondary amine XXIIa, m.p. 239–240° (dec), $[\alpha]_D$ +87·30, which was also obtained from XIXa by heating in 3% hydrochloric acid. Consequently, the structure of the oily basic product could be an iminoether derivative, XX, which was confirmed by analysis and IR spectrum. An iminoether XX could readily be formed by a further action of the alkaline reagent on XIXa. In this case, the easy hydrolysis of XIXa and XX with mineral acid to a secondary amine XXIIa contrasts with the difficulty in the case of IX. N-Methylation of the secondary amine XXIIa gave deoxyhippeastrine (XXIIb), characterized as the hydrochloride, m.p. 270–271° (dec), $[\alpha]_D$ +331·5°. This hydrochloride was also obtained from hippeastrine (XVII) by LAH reduction followed by a ring closure with 3% hydrochloric acid. On acetylation, oxidation with chromic acid–pyridine complex and hydrolysis of the acetoxyl group, deoxyhippeastrine (XXIIb) was reversely converted into hippeastrine itself. Uyeo *et al.*[7] have reported the reverse conversion of hippeastrine into lycorine β-methiodide.†

The remaining basic product, m.p. 205–206° (dec), $[\alpha]_D$ −133·5°, also appeared to be an iminoether derivative, XXI, from the IR spectrum and its structure was determined in the following manner. XXI was treated with 10% potassium hydroxide, giving the secondary amine XXIII, m.p. 234–236° (dec), $[\alpha]_D$ −53·4°, which on hydrogenation with platinum oxide in acetic acid afforded, after absorbing about 2·4 molar equivs of hydrogen, two products, XXIVa, m.p. 210°, $[\alpha]_D$ −170·0° and XXVa, m.p. 267–269° (dec), $[\alpha]_D$ −100·9°. These were found to be stereoisomers at C_{3a} based on the results of the NMR spectra (100 Mc, $CDCl_3$) of the diacetates of

* TLC of the product (SiO_2, $CHCl_3$: MeOH 30:1, conc H_2SO_4) showed two spots, not perfectly separately at about R_f 0·6, one of which coloured dark-grey and the other black. From our empirical knowledge regarding the relation between the structures and the colours developed with concentrated sulfuric acid, we presumed the structures of the products as A and B, respectively.

† Very recently, the absolute configurations of diastereoisomeric methiodides in the lycorine-type alkaloids have distinctly been determined.

Chart 5



XXIVb and XXVb. The C_{11c}-proton signal of XXIVb diacetate appears at 7·55 τ (d-d, J = 11 and 4 c/s) and that of XXVb diacetate is at 7·18 τ (d-d, J = 11 and 9 c/s). In both spectra the larger coupling constants (11 c/s) correspond to those between C_{11c}- and C_{11b}-protons, showing a *trans* relation of the B/C-ring juncture. The smaller coupling constants (4 and 9 c/s) are attributable to those between C_{11c}- and C_{3a}-protons and show clearly that the relation between the C—N bond and the ethyl group is *cis* in the former and *trans* in the latter.* Furthermore, one of the reduction products, XXIVa, was chemically correlated with the known compound VI. Treatment of VI with zinc dust in ethanol gave the product XXVIa by a reductive elimination of the bromine atom. The LAH reductions of XXVIa and XXVIb afforded a secondary amine, identical with XXIVa. Accordingly, the α-configuration of the C_{3a}-hydrogen of XXIVa is confirmed. The other reduction product XXVa must have the β-configuration at C_{3a}. Therefore, the iminoether XXI is formed by dehydrobromination of the intermediate A with base and has a conjugated diene system, as shown in the formula.

Very recently, our group studied the stereochemistry and absolute configurations of lycorine derivatives using NMR, CD and ORD spectroscopy[9,10] and X-ray analysis of dihydrolycorine hydrobromide,[11] and showed that the previously proposed stereochemistry[12] and absolute configurations[13] are correct.

Thus the stereochemistry and absolute configurations of dihydrohippeastrine (XVI) and hippeastrine (XVII) have been determined and agree with Uyeo *et al.*[7]

* The NMR study on the diacetates of the C_{3a}-stereoisomers, XXIVb and XXVb, has been performed leading to the interesting results, which will be presented elsewhere in details.

EXPERIMENTAL

All m.ps determined in capillary tubes were uncorrected. Specific rotations were measured with Rudolf Photoelectric Polarimeter Model 200. NMR spectra were taken in $CDCl_3$ soln containing TMS as an internal standard using a Varian A-60 spectrophotometer. UV spectra were determined with a Hitachi EPS-2 recording spectrophotometer and IR spectra with a Nippon Bunko DS-201B spectrometer. Unless otherwise stated, solutions were dried over anhyd Na_2SO_4.

von Braun reaction of dihydrolycorine (VII)

A suspension of dihydrolycorine (4·5 g) in Chf (300 ml) was added dropwise to a soln of cyanogen bromide (4·5 g) in Chf (100 ml) with stirring at room temp. The mixture was refluxed for 3 hr and after cooling, filtered to remove a small amount of an amorphous substance produced during the reaction. The filtrate was washed thoroughly with H_2O, 5% HCl aq and again with H_2O, dried and evaporated *in vacuo* giving a brownish residue (2·76 g), which on recrystallization from acetone afforded IX (654 mg), as prisms m.p. 220–222°. The mother liquor was evaporated under reduced press and the residue (1·85 g) chromatographed on neutral Al_2O_3 (activity grade III). The fractions eluted with benzene–Chf (6:5) were combined and crystallized from acetone to give an additional crop (357 mg) of IX, m.p. 220–222°; total 1·011 g. Further recrystallization from acetone gave pure IX as white prisms, m.p. 222°, $[\alpha]_D^{19}$ +100·6° (*c*, 0·707 EtOH). ν_{max}^{Nujol} 3460 cm^{-1} (OH), 2198 cm^{-1} (N—CN). λ_{max}^{EtOH} 236·1 mμ (ε 4000), 292 mμ (ε 4530). (Found: C, 64·99; H, 5·89; N, 9·07. $C_{17}H_{18}O_4N$ requires: C, 64·95; H, 5·77; N, 8·91%.) The yellowish residue (859 mg) obtained from the mother liquor was rechromatographed over neutral Al_2O_3 (act III). Elution with benzene–Chf (5:4) gave crystalline fractions, which on recrystallization from benzene–AcOEt afforded colourless rods of VIII, (150 mg) m.p. 141–142°. Further recrystallization from benzene–AcOEt gave a pure sample for analysis, m.p. 144–145°, $[\alpha]_D^{24}$ +36·2° (*c*, 1·046 Chf). ν_{max}^{Nujol} 3550 cm^{-1}, 3350 cm^{-1} (OH), 2213 cm^{-1} (N—CN). λ_{max}^{EtOH} 240 mμ (ε 5180), 287 mμ (ε 3730). NMR: 5·60 τ (s, —$\underline{CH_2}$—O—), 8·77 τ (*t*, *J* = c/s, —O—CH_2—$\underline{CH_3}$). (Found: C, 63·41; H, 6·86; N, 7·87. $C_{19}H_{24}O_5N_2$ requires: C, 63·32; H, 6·71; N, 7·77%.)

Oxidation of IX *with* CrO_3*-pyridine*

Compound IX (1·02 g) in pyridine (10 ml) was oxidized with the Sarett's reagent prepared from CrO_3 (0·8 g) and pyridine (8 ml) at room temp for 18 hr. The reaction mixture was diluted with H_2O and extracted with Chf. The extract was thoroughly washed with H_2O, dried and evaporated *in vacuo* to give an oily residue which was dissolved in Chf, and the soln washed with 5% HCl aq and H_2O, dried and evaporated to give a reddish-brown oil (1·05 g). Chromatography on 5% H_2O-containing Al_2O_3 (30 g) gave a crystalline product (334 mg) eluted with benzene–Chf (7:1), which on recrystallization from Chf–MeOH gave XI (221 mg) as prisms, m.p. 231–233° (dec). Concentration of the mother liquor gave an additional crop of XI (31 mg), m.p. 230–233° (dec). For analysis, the first crop was recrystallized from Chf–MeOH to give pure XI, m.p. 231–233° (dec), $[\alpha]_D^{24·5}$ +66·5° (*c*, 0·986 Chf). ν_{max}^{Nujol} 2305 cm^{-1} (N—CN), 1720 cm^{-1} (C=O). λ_{max}^{EtOH} 236 mμ (ε 3840), 292 mμ (ε 4600). (Found: C, 65·58; H, 5·43; N, 8·77. $C_{17}H_{16}O_4N_2$ requires: C, 65·37; H, 5·16; N, 8·97%.) Further elution with benzene–Chf (7:1) afforded crystalline fractions, which on crystallization from acetone gave prisms (208 mg), m.p. 219–222°, identical with the starting material by comparison of m.p., mixed m.p. and IR spectra. Further fractions eluted with benzene–Chf (1:2) were recrystallized from MeOH giving colourless needles (35 mg), m.p. 219–220°. Recrystallization from MeOH gave an analytical sample of X, m.p. 219–220°, $[\alpha]_D^{24·5}$ +54·6° (*c*, 0·50 Chf). ν_{max}^{Nujol} 3399 cm^{-1} (OH), 2212 cm^{-1} (N—CN), 1703 cm^{-1} (6-membered ring lactone). λ_{max}^{EtOH} 309·5 mμ (ε 5870), 270 mμ (ε 5170). (Found: C, 62·13; H, 5·01; N, 8·37. $C_{17}H_{16}O_5N_2$ requires: C, 62·19; H, 4·91; N, 8·53%.)

Conversion of IX *into urea derivative* XII

A suspension of IX (52 mg) in 3% HCl aq (2·5 ml) was heated at 50–60° for 1 hr. Evaporation followed by trituration with acetone yielded a crystalline solid, which was recrystallized from acetone to give XII (38 mg) as colourless prisms. An analytical sample was obtained after two recrystallizations from acetone, m.p. 240–241° (dec), $[\alpha]_D^{26}$ −7·2° (*c*, 1·06 EtOH). ν_{max}^{Nujol} 1605, 1654 cm^{-1} ($NCONH_2$). (Found: C, 61·48; H, 6·30; N, 8·51. $C_{17}H_{20}O_5N_2$ requires: C, 61·43; H, 6·07; N, 8·43%.)

Attempted hydrolyses of IX *and* XII *to* XIII *with mineral acids or caustic alkali*

(i) A suspension of IX (50 mg) in 30% H_2SO_4 aq (3 ml) was refluxed for 2 hr. The reaction mixture was diluted with H_2O and washed with Chf. The aqueous layer was filtered to remove an amorphous substance,

basified with 5% Na_2CO_3 aq and extracted with Chf. The extract was washed with H_2O and dried. Evaporation of the solvent gave no residual product.

(ii) A suspension of XII (20 mg) in 20% ethanolic KOH was heated under reflux for 2 hr. After cooling, the crystals deposited (28 mg) were collected by filtrations and recrystallized from acetone to give prisms, m.p. 240–241° (dec). The IR spectrum was identical with that of the starting material.

Reduction of IX *with* LAH

A soln of IX (510 mg) in THF (27 ml) was added dropwise to a suspension of LAH (600 mg) in abs ether (100 ml) with stirring over a period of 20 min. After stirring for 10 hr at 40° under N_2, a small amount of H_2O to the reaction mixture was added to decompose excess LAH. The resulting ppt was filtered off and the filtrate and the washings were combined, dried and evaporated to give an oily residue. The Chf soln of the residue was extracted with 3% HCl aq, and the acidic layer made alkaline with 5% NaOH aq and extracted thoroughly with Chf. The extract was dried and evaporated to dryness *in vacuo* at room temp. Trituration of the oily residue (323 mg) with acetone gave a crystalline product which was carefully recrystallized from acetone in a following manner: the crystalline product was dissolved in acetone at room temp, the soln concentrated at about 40° under N_2 and allowed to stand at room temp to yield XIII (146 mg) as colourless needles, m.p. 155–156°, $[\alpha]_D^{24}$ −23·1° (*c*, 0·792 Chf). ν_{max}^{chf} 3615 cm^{-1} (OH). λ_{max}^{EtOH} 236 mμ (ε 3740), 292 mμ (ε 4600). (Found: C, 66·29; H, 6·75; N, 4·77. $C_{16}H_{19}O_4N$ requires: C, 66·42; H, 6·62; N, 4·84%.)

The Eschweiler–Clarke reaction of XIII

A mixture of XIII (91 mg), 85% formic acid (0·2 ml) and 37% formalin (0·05 ml) was refluxed for 6 hr. The mixture was evaporated to dryness under reduced press, taken up in 5% HCl aq, filtered, basified with 5% NaOH aq and extracted with benzene. Evaporation of the dried extracts gave a yellow oil (100 mg), which on recrystallization from acetone–pet ether afforded XIV (51 mg) as colourless needles, m.p. 90–95°. A small portion was repeatedly recrystallized from the same solvent to give pure XIV for analysis, m.p. 109–111° $[\alpha]_D^{25.5}$ +65·6° (*c*, 1·13 Chf). ν_{max}^{Nujol} 3340 cm^{-1} (OH). (Found: C, 67·48; H, 7·36; N, 4·56. $C_{17}H_{21}O_4N$ requires: C, 67·31; H, 6·98; N, 4·62%.) The mother liquor was evaporated to dryness and the residue was dissolved in 5% HCl aq, filtered and evaporated to dryness under reduced press. Recrystallization from MeOH gave the hydrochloride of XIV as colourless prisms, m.p. 285–286° (dec) $[\alpha]_D^{25}$ +8·7° (*c*, 1·04 MeOH). ν_{max}^{Nujol} 3314 cm^{-1} (OH), (Found: C, 60·25; H, 6·70; N, 4·37. $C_{17}H_{21}O_4N \cdot HCl$ requires: C, 60·08; H, 6·53; N, 4·12%.)

Reduction of dihydrohippeastrine (XVI) *with* LAH

A soln of dihydrohippeastrine (85 mg) in THF (8 ml) was added dropwise to a suspension of LAH (114 mg) in THF (10 ml) with stirring at room temp. The mixture was refluxed with stirring for 5 hr and after cooling a small amount of H_2O was added. The ppt was filtered off, and the filtrate and washings were combined, dried and evaporated to dryness. The residue was dissolved in Chf and the soln was washed with H_2O and dried. Evaporation gave a yellowish oil (54 mg). The aqueous soln was saturated with NaCl and extracted with Chf. The Chf layer was dried and evaporated to leave an oily residue (19 mg). Trituration of the combined oily residue (73 mg) with acetone gave crude crystals which were recrystallized from acetone to yield XV (40 mg) as colourless prisms, m.p. 99–101°, $[\alpha]_D^{24}$ −9·4° (*c*, 0·876 Chf). ν_{max}^{Nujol} 3511 cm^{-1}, 3286 cm^{-1} (OH), 1700 cm^{-1} (C=O). λ_{max}^{EtOH} 241 mμ (ε 5160), 289 mμ (ε 4080). (Found: C, 63·40; H, 7·82; N, 3·70. $C_{17}H_{21}O_6N \cdot MeCOMe$ requires: C, 63·30; H, 7·70; N, 3·69%.)

Deoxydihydrohippeastrine (XIV)—HCl *from* XV

A suspension of XV (12 mg) in 5% HCl aq was heated at 90–93° for 2 hr. After cooling, the mixture was filtered, evaporated to dryness under reduced press and the residue was crystallized from acetone to give the hydrochloride of XIV as colourless prisms (8 mg), m.p. 285–287° (dec). The hydrochloride was identical with a sample of XIV HCl derived from dihydrolycorine in the m.p. mixed m.p., optical rotations and IR spectra.

von Braun reaction of diacetyllycorine (XVIIIb)

A soln of cyanogen bromide (3·7 g) in dry benzene (70 ml) was added to a soln of XVIIIb (5·1 g) in dry benzene (250 ml) and the mixture refluxed for 3 hr. The reaction mixture was washed with H_2O, 5% HCl aq and again H_2O, and dried. Evaporation of the solvent gave an oil (6·7 g), which showed two spots

(R_f, around 0·6) by TLC on silica gel using the solvent system (Chf: MeOH; 100:3) with the spray reagent of conc H_2SO_4. Attempts to separate two reaction products (A and B) by column- or preparative-TLC were unsuccessful.

Treatment of the reaction mixture (A *and* B) *with ethanolic potassium hydroxide*

A soln of the oily reaction mixture A and B (3·0 g) and KOH (7·8 g) in abs EtOH (130 ml) was allowed to stand at room temp for 3 hr. CO_2 was introduced, the ppted K_2CO_3 was filtered off, and the combined filtrate and washings were evaporated to dryness under reduced press. The residue was dissolved in Chf and the soln was shaken with 5% HCl aq to separate neutral and basic fractions.

(i) *Neutral fraction.* The Chf soln was washed with H_2O, dried and evaporated to give a yellow oil (366 mg), which was chromatographed over 5% water-containing Al_2O_3. Elution with benzene–Chf (7:3) gave an oily XIXa (256 mg), which showed one spot on TLC. Acetylation of XIXa (76 mg) with Ac_2O and pyridine after allowing to stand at room temp overnight gave a brown oil (80 mg). Trituration with benzene gave the crystalline acetate, which was recrystallized twice from MeOH to give XIXb (68 mg), m.p. 196–197°, colourless needles, $[\alpha]_D^{24.5}$ +276·4° (*c*, 1·058 Chf). ν_{max}^{Nujol} 2202 cm^{-1} (N—CN), 1730 cm^{-1} (OAc). λ_{max}^{EtOH} 237 mμ (ε 3930), 292 mμ (ε 4460). (Found: C, 64·46; H, 5·29; N, 7·79. $C_{19}H_{18}O_5N_2$ requires: C, 64·40; H, 5·12; N, 7·91%.)

(ii) *Basic fraction.* The preceding 5% HCl aq extract was basified with 5% NaOH aq and extracted with Chf. The soln was washed with H_2O and dried. Evaporation of the solvent gave an oily residue (1·67 g) which on trituration with acetone afforded XXI (650 mg) as colourless prisms, m.p. 203–205° (dec). A small portion of crude XXI on repeated recrystallization from acetone gave an analytical sample, m.p. 205–206° (dec), $[\alpha]_D^{24.5}$ −133·5° (*c*, 1·075 Chf). ν_{max}^{Nujol} 3340 cm^{-1} (OH), 1613 cm^{-1} (—C(OEt)=NH). λ_{max}^{EtOH} 292 mμ (ε 5020). (Found: C, 63·90; H, 6·39; N, 7·97. $C_{19}H_{22}O_5N_2$ requires: C, 63·67; H, 6·19; N, 7·82%.)

The combined mother liquors were adsorbed on column of Al_2O_3 (act III). Fractions eluted with benzene–Chf (1:1) gave an oily XX (85 mg) which showed the IR band at 1610 cm^{-1}, characteristic of an iminoether group and showed one spot on TLC. Further crops of XXI (60 mg), m.p. 203–205° (dec) were obtained by elution with Chf–MeOH (400:1) followed by recrystallization from acetone.

Catalytic hydrogenation of XIXa *over* PtO_2

Compound XIXa (105 mg) was dissolved in EtOH (5 ml) and hydrogenated with Adams' catalyst (65 mg) for 2·5 hr. Working up yielded an oily residue, which was crystallized from acetone to give m.p. 220–222°, as colourless prisms (60 mg), identical with IX in m.p., mixed m.p. and IR spectrum.

Acid treatment of XIXa

A mixture of XIXa (504 mg) and 3% HCl aq (15 ml) was heated under reflux for 1 hr, then diluted with H_2O and washed with Chf. The aqueous soln was made alkaline with 10% NaOH aq and extracted with Chf. The extract was washed with H_2O and dried. Evaporation of the solvent gave a solid which was crystallized from EtOH to give XXIIa (167 mg) as colourless needles, m.p. 237–239° (dec). Further recrystallization gave an analytical sample, m.p. 239–240° (dec), $[\alpha]_D^{24.5}$ +87·3° (*c*, 0·654 Chf). The IR spectrum showed no N—CN absorption. λ_{max}^{EtOH} 235 mμ (ε 3860), 292 mμ (ε 4740). (Found: C, 66·99; H, 6·15; N, 4·71. $C_{16}H_{17}O_4N$ requires: C, 66·88; H, 5·96; N, 4·88%.)

The Eschweiler–Clarke reaction of XXIIa

A mixture of XXIIa (157 mg), 85% formic acid (0·4 ml) and 37% formalin (0·1 ml) was refluxed for 6 hr. The mixture was evaporated to dryness under reduced press, taken up in 5% HCl aq, filtered, basified with 10% NaOH aq and extracted with benzene. Evaporation of dried extract gave an oily residue (143 mg). The residue (84 mg) was dissolved in 5% HCl aq and evaporated to dryness under reduced press. Trituration with MeOH gave a solid which was crystallized from MeOH to yield the hydrochloride of XXIIb as colourless prisms, m.p. 270–271° (dec), $[\alpha]_D$ +131·5° (*c*, 1·115 H_2O–EtOH). ν_{max}^{Nujol} 3282 cm^{-1} (OH), λ_{max}^{EtOH} 293 mμ (ε 4810). (Found: C, 60·63; H, 6·09; N, 4·40. $C_{17}H_{19}O_4N \cdot HCl$ requires: C, 60·44; 5.97; N, 4·15%.)

Preparation of deoxyhippeastrine (XXIIb) *from hippeastrine* (XVII)

To a suspension of LAH (36 mg) in abs THF (3 ml) XVII (107 mg) was added. After refluxing for 5 hr, a small amount of H_2O was added to decompose the complex. The resulting ppt was filtered off, the filtrate

and the washings combined were dried and evaporated to give an oily residue. The residue was dissolved in Chf, dried and evaporated to leave an oily product (86 mg), which was again dissolved in 5% HCl aq (5 ml). The HCl soln was warmed at 90–95° for 2 hr and then evaporated *in vacuo* below 40°. The residual solid was crystallized from MeOH to give the hydrochloride of XXIIb (44 mg) as colourless prisms, m.p. 269–270° (dec), $[\alpha]_D^{26}$ +130·6° (*c*, 1·144, H_2O–EtOH) which was identical with XXIIb–HCl obtained above.

Conversion of XX *into* XXIIa

A soln of XX (59 mg) in 3% HCl aq (1·8 ml) was refluxed for 5 hr. After cooling, the soln was diluted with H_2O and washed with Chf. The aqueous layer was basified with 5% Na_2CO_3 aq and extracted with Chf. The extract was washed with 5% Na_2CO_3 aq and H_2O, dried and evaporated to give XXIIa which was crystallized from acetone as needles m.p. 237–239° (dec). The IR spectrum was identical with that of XXIIa obtained by treatment of XIXa with 5% HCl aq.

Conversion of deoxyhippeastrine (XXIIb) *into hippeastrine* (XVII)

Acetylation of deoxyhippeastrine (410 mg) with Ac_2O and pyridine gave the crude acetate (446 mg) as an oil. This acetate (310 mg) and CrO_3 (302 mg) in dry pyridine (3 ml) was allowed to stand for 24 hr at room temp and the mixture poured into ice-water (100 ml) and extracted with ether. The ethereal extract was washed with H_2O and dried. Removal of ether gave an oily residue (265 mg) which was chromatographed over neutral Al_2O_3. Elution with benzene: pet ether (3:1) afforded an oily substance which was identical with the starting acetate by comparison of the IR spectra. Further elution with benzene and benzene: AcOEt (100:1) gave hippeastrine acetate (60 mg) as an oil. The oily acetate (35 mg) was heated with 5% $KHCO_3$ in MeOH (3 ml) under reflux for 45 min. After removal of MeOH, the residue was diluted with H_2O and extracted with Chf. The extract was washed with H_2O and dried. Evaporation of the solvent and recrystallization of the residue (28 mg) from acetone gave prisms, m.p. 213–214°, which was identical with an authentic sample of hippeastrine in the m.p., mixed m.p., and the UV and IR spectra.

Treatment of iminoether XXI *with* 10% KOH *aq*

A suspension of XXI (645 mg) in 10% KOH aq (40 ml) gradually changed to a clear soln while refluxing for 1·5 hr. After cooling, the ppt formed was collected by filtration, washed with H_2O and EtOH. Recrystallization from MeOH gave XXIII (260 mg) as prisms, m.p. 234–236° (dec), $[\alpha]_D^{23}$ −53·4° (*c*, 0·245 MeOH). ν_{max}^{Nujol} 3335 cm^{-1} (OH), λ_{max}^{EtOH} 293 mμ (ε 5550). (Found: C, 67·03; H, 6·09; N, 5·19. $C_{16}H_{17}O_4N$ requires: C, 66·88; H, 5·96; N, 4·88%.)

Hydrogenation of XXIII *over* PtO_2

A soln of XXIII (102 mg) in AcOH (2 ml) was shaken in the presence of Adams' catalyst (20 mg) in an atom of H_2. After the absorption of H_2 (19·5 ml at 23°), the catalyst was removed by filtration and the filtrate evaporated. The residue was dissolved in H_2O (10 ml) and basified with Na_2CO_3 at about pH 8·0 to give a solid (66 mg), which on crystallization from MeOH gave XXVa as colourless needles, m.p. 268–270° (dec), $[\alpha]_D^{25}$ −100·9 (*c*, 0·226 MeOH). ν_{max}^{Nujol} 3250 cm^{-1} (OH). λ_{max}^{EtOH} 293 mμ (ε 4440), 234 mμ (ε 3450). (Found: C, 65·73; H, 7·27; N, 4·83. $C_{16}H_{21}O_4N$ requires: C, 65·95; H, 7·23; N, 4·81%.) The filtrate and the washings were combined, made more alkaline and then extracted with Chf. The extract was dried and concentrated to dryness *in vacuo*. Trituration of the oily residue (37 mg) with MeOH and recrystallization from the same solvent gave XXIVa (32 mg) as prisms, m.p. 210°, $[\alpha]_D^{26.5}$ −170·0° (*c*, 0·484 MeOH). λ_{max}^{Nujol} 3250 cm^{-1} (OH). λ_{max}^{EtOH} 292 mμ (ε 4750), 234 mμ (ε 3760). (Found: C, 63·11; H, 7·89; N, 4·49. $C_{16}H_{21}O_4N \cdot CH_3OH$ requires: C, 63·14; H, 7·79; N, 4·33%.)

Reaction of VI *with* Zn *in* EtOH

A mixture of VI (1·29 g), Zn-powder (12 g) and EtOH (120 ml) was refluxed under stirring for 5 hr. After cooling, the mixture was filtered and the Zn washed with EtOH. The filtrate combined with the washings was evaporated to dryness *in vacuo*. The residue was dissolved in Chf, and the soln washed with 5% HCl aq and then H_2O. The solvent was removed under reduced press and the resulting crystalline substance (1·0 g) was recrystallized from MeOH to give XXVIa as colourless prisms, m.p. 205–207°. Evaporation of the mother liquors and crystallization of the residue from MeOH gave an additional crop of XXVIa (180 mg) as prisms, m.p. 204–206°. A pure sample for analysis was obtained by further recrystallization

from MeOH as needles, m.p. 208–209°, $[\alpha]_D^{23}$ −90·2° (*c*, 1·051 Chf). ν_{max}^{Nujol} 1760, 1742 cm^{-1} (OAc), 2209 cm^{-1} (N—CN). (Found: C, 62·86; H, 6·16; N, 7·36. $C_{21}H_{24}O_6N$ requires: C, 62·99; H, 6·04; N, 7·00%.)

Saponification of XXVIa *with* 1% EtOH–KOH

A soln of XXVIa (240 mg) in 1% ethanolic KOH was allowed to stand at room remp for 2 hr. The soln was evaporated *in vacuo*, diluted with H_2O and extracted with Chf. The extract was dried and evaporated. The residue (197 mg) was crystallized from AcOEt to yield XXVIb (144 mg) as prisms, m.p. 195–196°. Recrystallization from the same solvent gave an analytical sample of XXVIb, m.p. 195–196°, $[\alpha]_D^{25·5}$ −179·8° (*c*, 1·024 Chf). ν_{max}^{Nujol} 2208 cm^{-1} (N—CN). (Found: C, 64·64; H, 6·47; N, 8·97. $C_{17}H_{20}O_4N_2$ requires: C, 64·54; H, 6·37; N, 8·86%.)

LAH *reduction of* XXVIb

A soln of XXVIb (92 mg) in dried THF (6 ml) was added dropwise with stirring to a suspension of LAH (96 mg) in dried THF (15 ml). After refluxing for 3 hr, a small amount of H_2O was added to the reaction mixture. The resulting ppt was filtered off, and the filtrate and the washings combined were dried and evaporated to give an oily residue (90 mg). Trituration with MeOH gave XXIVa as colourless prisms, m.p. 210°.

LAH *reduction of* XXVIa

A soln of XXVIa (414 mg) in dried THF (20 ml) was added dropwise with stirring to a suspension of LAH (500 mg) in THF (30 ml). After stirring for 3 hr under reflux, a small amount of H_2O was added to the mixture to decompose the complex. The ppt was filtered off, and the filtrate combined with washings concentrated to dryness *in vacuo*. The residue was dissolved in Chf, washed with H_2O and dried. After removal of the solvent under reduced press at 40°, the residue (269 mg) was crystallized from MeOH to give XXVIa as prisms, m.p. 209–210°. This product was identical in all respects with XXIVa obtained by the hydrogenation of XXIII and also by the LAH reduction of XXVIb.

The Eschweiler–Clarke reaction of XXIVa

A soln of XXIVa (628 mg), 85% formic acid (1·6 ml) and formalin (0·4 ml) was refluxed for 5 hr. The solvent was evaporated *in vacuo*, and the residue was dissolved in 5% HCl aq and filtered. The aqueous layer was basified with 5% NaOH aq, extracted with Chf, dried and evaporated to give XXIVb as an oil, which afforded the picrate as needles, m.p. 215° (from AcOEt–EtOH), $[\alpha]_D^{27·5}$ −103·9° (*c*, 0·976 Chf). (Found: C, 50·68; H, 5·31; N, 10·52. $C_{23}H_{26}O_{11}N_4 \cdot \frac{1}{2}H_2O$ requires: C, 50·68; H, 5·01; N, 10·31%.)

Acetylation of XXIVb

A soln of the oily XXIVb (520 mg), Ac_2O (7 ml) and pyridine (15 ml) was kept overnight at room temp. After concentration of the reaction mixture *in vacuo* at 40°, 5% Na_2CO_3 aq was added and the mixture was extracted with Chf. The extract was washed with H_2O and dried. Evaporation of the solvent gave a crystalline product (573 mg) which on crystallization from MeOH afforded colourless prisms (480 mg), m.p. 215–217°. Further recrystallization gave an analytical sample of XXIVb diacetate, m.p. 220–221°, $[\alpha]_D^{27·5}$ −97·2° (*c*, 1·162 Chf). ν_{max}^{Nujol} 1747 cm^{-1} (OAc). λ_{max}^{EtOH} 292·5 mμ (ε 4810), NMR: 7·55 τ (1H, d-d, 11·0, 4·0 c/s, H_{11e}). (Found: C, 64·61; H, 7·20; N, 3·83. $C_{21}H_{27}O_6N$ requires: C, 64·76; H, 6·99; N, 3·60%.)

Preparation of XXVb *diacetate*

A mixture of XXVa (144 mg), 85% formic acid (0·4 ml) and 37% formalin (0·09 ml) was refluxed for 5·5 hr. The mixture was evaporated to dryness *in vacuo*, and 5% Na_2CO_3 aq added to the residue, which was extracted with Chf and the soln successively washed with 5% Na_2CO_3 aq and H_2O. The dried Chf soln was evaporated to give an oily product (152 mg), which was subjected to the next reaction without further purification. The crude oily XXVb was acetylated with Ac_2O and pyridine. Working up and recrystallization from acetone gave XXVb diacetate as prisms, m.p. 200–201°, $[\alpha]_D^{22}$ −7·9° (*c*, 0·480 Chf), ν_{max}^{Nujol} 1750 cm^{-1} (OAc). λ_{max}^{EtOH} 293 mμ (ε 4930). NMR: 7·18 τ (1H, d-d, 11·0, 9·0 c/s, H_{11e}). (Found: C, 64·40; H, 6·88; N, 3·49. $C_{21}H_{27}O_6N$ requires: C, 64·76; H, 6·99; N, 3·60%.)

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