The reaction was carried out as described before. The resulting residue (0.660 g) was chromatographed on a column packed with 66 g of basic alumina (Brockmann II).

The eluent used was 225 ml of petroleum ether, and 25-ml fractions were collected. Fractions 1–5 gave 0.54 g of a mixture of 3α,5-cyclo-5α-cholestane (88.5%) and cholest-5-ene (11.5%) (analyzed by vpc).

The mixture (0.53 g) of 3α,5-cyclo-5α-cholestane and cholest-5-ene was chromatographed as described previously (reduction of 6β-methoxy-3α,5-cyclo-5α-cholestane) to give 3α,5-cyclo-5α-cholestane and cholest-5-ene.

Reduction of 6β-Methoxy-3α,5-cyclo-5α-androstan-17-one.—The reaction was carried out as described for 6β-methoxy-3α,5-cyclo-5α-cholestane, using 1.14 g of $LiAlH_4$, 4 g of $AlCl_3$, and 3.04 g of 6β-methoxy-3α,5-cyclo-5α-androstan-17-one.

The resulting residue (2.84 g) was chromatographed on a column packed with 85 g of alumina (Brockmann III). The eluents used were 420 ml of petroleum ether–benzene (1:1), 180 ml of benzene, and 90 ml of ether; 30-ml fractions were collected. After crystallization (from methanol–water mixture), fractions 1–15 gave 2.0 g of 17β-hydroxy-3α,5-cyclo-5α-androstan, mp 120–121°, $[\alpha]_D$ +76° ($CHCl_3$) [lit.[8] mp 122–124°, $[\alpha]_D$ +77° ($CHCl_3$)]; fractions 20–23 gave 0.3 g of 3β-methoxy-17β-hydroxyandrostan-5-ene, mp 139–141°, $[\alpha]_D$ −53° (ethanol 95%) [lit.[9] mp 142.5–143°, $[\alpha]_D$ −51° (ethanol 95%)].

Reduction of 6β-Methoxy-3α,5-cyclo-5α-pregnan-20-one.—The reaction was carried out as described for 6β-methoxy-3α,5-cyclo-5α-cholestane using 1.14 g of $LiAlH_4$, 4 g of $AlCl_3$, and 3.4 g of 6β-methoxy-3α,5-cyclopregnan-20-one. The resulting residue (3.11 g), containing a mixture of epimeric 20-ols, was oxidized in acetic acid (46 ml) by chromium trioxide (0.92 g) in water (5 ml). After 12 hr ice was added and the mixture was made alkaline with ammonia, the precipitated product was extracted with ether, and the ethereal solution was washed with water, dried, and evaporated. The resulting residue (3.06 g) was chromatographed on a column packed with 95 g of alumina (Brockmann III). The eluents used were 600 ml of petroleum ether and 300 ml of benzene; 100-ml fractions were collected. Fractions 1–6 gave after crystallization (from methanol) 2.19 g of 3α,5-cyclo-5α-pregnan-20-one, mp 107–109°, $[\alpha]_D$ +173° ($CHCl_3$) [lit.[8] mp 109–111°, $[\alpha]_D$ +179° ($CHCl_3$)].

Reduction of 3β-Tosyloxycholest-5-ene.—To 0.35 g of $LiAlH_4$ in 16 ml of ether was added 1.25 g of $AlCl_3$ in 16 ml of ether, at room temperature. 3β-Tosyloxycholest-5-ene (4 g) in 20 ml of benzene was added.

The reaction was carried out as described before. The resulting residue (2.9 g) was chromatographed on a column packed with 580 g of basic alumina (Brockmann II). The eluent used was 350 ml of petroleum ether, 50-ml fractions being collected. Fractions 1–5 gave 2.7 g of a mixture of 3α,5-cyclo-5α-cholestane (86%) and cholest-5-ene (14%) (analyzed by vpc).

The mixture (2.7 g) of 3α,5-cyclo-5α-cholestane and cholest-5-ene was chromatographed as described previously (reduction of 6β-methoxy-3α,5-cyclo-5α-cholestane) to give 3α,5-cyclo-5α-cholestane and cholest-5-ene.

$LiAlD_4$–$AlCl_3$ was used to isolate the 3-deuteriocholest-5-ene following the preparation scheme previously described.

Registry No.—6β-Methoxy-3α,5-cyclo-5α-cholestane, 2867-93-8; 6β-hydroxy-3α,5-cyclo-5α-cholestane, 465-54-3; 6β-methoxy-3α,5-cyclo-5α-androstan-17-one, 14425-92-4; 6β-methoxy-3α,5-cyclo-5α-pregnan-20-one, 32249-55-1; 3β-tosyloxycholest-5-ene, 1182-65-6; lithium aluminum hydride, 16853-85-3; aluminum chloride, 7446-70-0.

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The Structure of Lycorenine and the 7-Hydroxy Alkaloids Derived from the [2]Benzopyrano[3,4-*g*]indole Nucleus[1]

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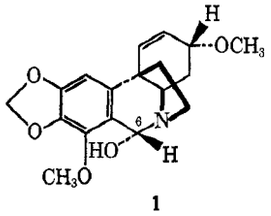
An X-ray crystallographic study of lycorenine methiodide has established the configuration of the C_7 hydroxyl group in the alkaloid to be that shown in **3**. A comparison of specific and molecular rotations of analogous alkaloids and their 7-oxo derivatives indicates that all alkaloids with the general structure **4** have an α-C_7 hydroxyl group. These data provide complete structures for oduline, nerinine, krigeine, unsevine, and krigenamine.

Amaryllidaceae alkaloids containing a benzylic hydroxyl group (as in **1**, **2**, and **4**) provide a number of



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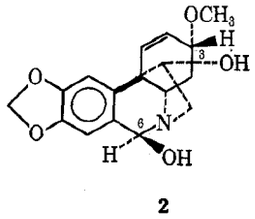

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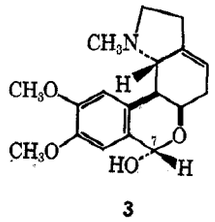
reactive compounds of chemical, biosynthetic, and spectroscopic interest.[2] Although the structures for many of these bases frequently have been assigned to the extent of the absolute configuration, the configuration of the benzylic hydroxyl group has been ignored in most representations. The structures of 6-hydroxybuphanidrine (**1**)[3] and 6-hydroxycrinamine (**2**)[4] have been determined by X-ray crystallographic techniques. No chemical methods exist for the assignment of con-



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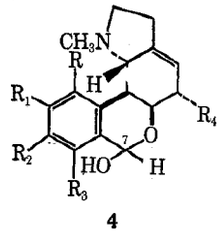

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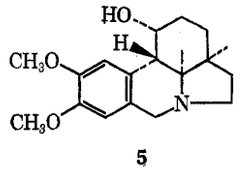

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(1) Supported by a research grant (HE-7503) from the National Institutes of Health, U. S. Public Health Service, and the Ames Laboratory of the U. S. Atomic Energy Commission, Contribution No. 3017.

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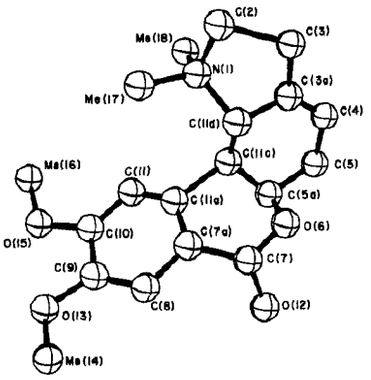

Figure 1.

figuration either at C_6 in **1** or **2**, or at C_7 in the "lycorenine type" alkaloids (**4**). Stereochemical assignment to the benzylic hydroxyl group frequently is complicated because **2** and haemanthidine (the C_3 epimer of **2**) exist *in solution* as an equilibrating mixture of C_6 epimers.[5]

There is no report that hemiacetal-type alkaloids (**3** and **4**) epimerize in solution at C_7 and it was of interest to determine the configuration of the hydroxyl group at this position in a representative alkaloid of this ring system. Lycorenine was chosen for study.

Experimental Section

Lycorenine methiodide was prepared by adding 1 ml of methyl iodide to a solution of 70 mg of lycorenine (mp 194–196°) in 4 ml of acetone. The reaction mixture was allowed to stand for 1 hr at room temperature. The product was filtered, washed with acetone, and recrystallized several times from ethanol to give colorless needles, mp 265° dec. Preliminary Weissenberg and precession photographs showed the $2/m\ 2/m\ 2/m$ Laue symmetry appropriate for the orthorhombic crystal class. A least-squares analysis of diffractometer-measured θ values gave a = 16.49 (1) Å, b = 8.25 (1) Å, c = 14.05 (1) Å. The systematic absences for $h00$ ($h = 2n + 1$), $0k0$ ($k = 2n + 1$), and $00l$ ($l = 2n + 1$) uniquely indicate the common space group $P2_12_12_1$ (D_2^4). Measured and calculated densities indicated four molecules per unit cell or one per asymmetric unit. A cubic crystal fragment of approximate dimensions 0.1 mm was selected for intensity work. The unique reflections ($2\theta \leq 70°$) were collected on a fully automated Hilger–Watts four-circle diffractometer using Zr-filtered Mo Kα (0.7107 Å) radiation. Of the 2425 reflections measured, 1890 were judged observed after background, Lorentz, and polarization corrections. No absorption corrections were made.

The iodine position was determined from the three-dimensional Patterson synthesis, and the 24 nonhydrogen atom positions were revealed in the subsequent iodine-phase electron density synthesis.[6] Full-matrix least-squares refinements in which all atomic positions and anisotropic thermal parameters were varied reduced the discrepancy index to its present minimum of 0.088 for the observed reflections.[7,8] The estimated standard deviations as given by the variance-covariance matrix from least-squares refinements are ±0.01 Å for bond lengths and ±2.0° for bond angles.[9] A computer-generated drawing (less the iodine atom) is given in Figure 1.[10] Table I lists the final atomic fractional coordinates. All bond distances and angles agree well within generally accepted values. No abnormally short intermolecular contacts were found. As can be seen from the final X-ray model the benzylic hydroxyl lies below the plane of the aromatic and dihydropyran rings. The absolute configuration depicted is derived from the chemical conversion of lycorenine to α-dihydropluviine (**5**), the absolute configuration of which is known.[11,12]

TABLE I

FINAL ATOMIC COORDINATES[a]

Atom	x/a	y/b	z/c
1	0.3432 (1)	−0.1512 (1)	0.5310 (1)
2	0.3996 (1)	−0.1228 (2)	0.6312 (1)
3	0.4151 (1)	0.0634 (2)	0.6162 (1)
3a	0.3907 (1)	0.1176 (2)	0.5153 (1)
4	0.3794 (1)	0.2745 (2)	0.4871 (1)
5	0.3515 (1)	0.3090 (2)	0.3878 (1)
5a	0.3496 (1)	0.1638 (2)	0.3247 (1)
6	0.4340 (1)	0.1292 (1)	0.2972 (1)
7	0.4433 (1)	0.0000 (2)	0.2269 (1)
7a	0.3743 (1)	−0.1229 (2)	0.2285 (1)
8	0.3830 (1)	−0.2457 (2)	0.1570 (1)
9	0.3228 (1)	−0.3695 (2)	0.1551 (1)
10	0.2551 (1)	−0.3569 (2)	0.2190 (1)
11	0.2538 (1)	−0.2385 (2)	0.2877 (1)
11a	0.3204 (1)	−0.1245 (1)	0.2936 (1)
11c	0.3162 (1)	0.1240 (2)	0.3734 (1)
11d	0.3707 (1)	−0.0246 (2)	0.4577 (1)
Me(16)	0.1333 (1)	−0.4853 (3)	0.2720 (1)
O(15)	0.2007 (1)	−0.4764 (1)	0.2058 (1)
Me(14)	0.3966 (1)	−0.5243 (3)	0.0366 (1)
O(13)	0.3212 (1)	−0.4884 (1)	0.0904 (1)
Me(17)	0.2549 (1)	−0.1183 (2)	0.5607 (1)
Me(18)	0.3471 (1)	−0.3276 (2)	0.5002 (1)
O(12)	0.4450 (1)	0.09842 (2)	0.1376 (1)

[a] The error in the least significant digit, as estimated by the inverse least-squares matrix, is given in parentheses.

Discussion

The X-ray study confirms the structure assigned to lycorenine by chemical means and specifically locates the benzylic hydroxyl group. Optical rotations at 589 nm for lycorenine (**3**), homolycorine (**3**, >C=O at C_7), and deoxylycorenine (**3**, >CH_2 at C_7) provide a basis for the assignment of the benzylic hydroxyl group in oduline, nerinine, krigeine, krigenamine, and unsevine.[2] Homolycorine and deoxylycorenine show comparable rotations at 589 nm. Introduction of the α-C_7 hydroxyl group (as in **3**) increases the specific rotation in a positive direction by almost 70°. Comparable dextrorotatory shifts are found in all other alkaloids possessing this ring system. From these

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(8) Listings of structure factors will appear immediately following this article in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfilm.

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TABLE II
SPECIFIC AND MOLECULAR ROTATIONS OF LYCORENINE, HOMOLYCORINE, AND ANALOGOUS ALKALOIDS

Compd	No.	Registry no.	Structure R	R1	R2	R3	R4	C7	[α]D (solvent), deg	Δα[D], deg	MD, deg	Δ[M]D, deg
Deoxylycorenine	3	13255-14-6						CH_2	+95 (EtOH)	57	+288	282
Lycorenine[a]	3	477-19-0						CHOH	+152 (EtOH)	67	+570	202
Homolycorine	3	477-20-3						C=O	+85 (EtOH)		+368	
Deoxykrigenamine	4	32247-13-5	CH_3O	O_2CH_2		H	H	CH_2	+123 (EtOH)	87	+385	315
Krigenamine	4	1165-00-0	CH_3O	O_2CH_2		H	H	CHOH	+210 ($CHCl_3$)	103	+695	325
Oxokrigenamine	4	1165-01-0	CH_3O	O_2CH_2		H	H	C=O	+117 ($CHCl_3$)		+370	
Oduline	4	477-18-9	H	O_2CH_2		H	H	CHOH	+239 ($CHCl_3$)	99	+720	300
Masonine	4	568-40-1	H	O_2CH_2		H	H	C=O	+140 ($CHCl_3$)		+420	
Krigeine	4	905-37-3	CH_3O	O_2CH_2		H	OH	CHOH	+234 ($CHCl_3$)	72	+813	254
Neronine	4	1167-58-4	CH_3O	O_2CH_2		H	OH	C=O	+162 ($CHCl_3$)		+559	
Nerinine	4	481-44-7	H	OCH_3	OCH_3	OCH_3	H	CHOH	+155 ($CHCl_3$)	83	+538	293
Albomaculine	4	668-63-3	H	OCH_3	OCH_3	OCH_3	H	C=O	+72 ($CHCl_3$)		+225	
Unsevine	4	4838-99-7	H	O_2CH_2		H	OCH_3	CHOH	+170 ($CHCl_3$)	69	+564	231
Nivaline	4	568-40-1	H	O_2CH_2		H	OCH_3	C=O	+101 ($CHCl_3$)		+333	

[a] Registry number for methiodide, 32367-48-9.

comparisons (see Table II) it is most probable that the C_7 hydroxyl groups of oduline, nerinine, krigeine, unsevine, and krigenamine have α configurations as well.

A Synthesis of 4-Azaoxindole

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The condensation product of ethyl cyanoacetate and 2-chloro-3-nitropyridine (**1**) was converted by reduction, cyclization, and acid hydrolysis into 4-azaoxindole (**4**). A study of the dibenzyl-4-azaoxindole derivatives **5**, **9**, and **13** was made to evaluate the type and extent of the tautomerism possible with this system. Rapid autoxidation of the 3-benzyl-4-azaoxindole (**11**) to the dioxindole **14** was observed. The presence of virtual coupling in the nmr spectrum of **4** was noted.

Azaindoles have attracted considerable interest in view of their potential relationship to pharmacologically important indoles, *e.g.*, serotonin, and a review of azaindoles has recently appeared.[1]

Azaoxindoles, on the other hand, are virtually unknown, with only the preparation of 7-azaoxindole[2,3] and 3,3-dimethyl-7-azaoxindole[4] and unsuccessful attempts at 5-azaoxindole[5] and 4-azaoxindole[6] preparation being described.

Our earlier interest in azaindole chemistry[7] and our current interest in arylations with 2-chloro-3-nitropyridine motivated us to make a contribution to this area. We describe now the synthesis of the previously undescribed 4-azaoxindole and some of its chemistry.

The arylation of ethyl cyanoacetate by 2-chloro-3-nitropyridine was described by Willette.[6] The resulting product, for which we favor the tautomeric structure **1** on the basis of infrared evidence (a very strong CN stretching and the ester C=O at 1628 cm^{-1}), could be reduced in our hands in excellent yield by hydrogenation in ethanol over 10% palladium on carbon at 50 psi and room temperature. Reflux of the product **2** in xylene effected ring closure to the 3-cyano-4-azaoxindole **3**. Some of the interesting chemistry of this new system was evident with this first member, for it is amphoteric. In fact, **3** is best purified by precipitation, from a solution of aqueous sodium hydroxide, with a stream of carbon dioxide. Reflux of **3** in concentrated hydrochloric acid converted it to the unsubstituted 4-azaoxindole **4** (Scheme I), which is shown in the principle tautomeric form **4a** based on the nmr evidence (2-proton singlet at δ 3.6). This is a very easily enolizable compound and uv evidence suggests the presence of the tautomer **4b** in protic solvents [λ max 359 mμ (ε 2070)]. In order to explore this interesting tautomerism we decided to prepare and obtain the physical data on alkyl derivatives of assignable structure, where the alkylation had blocked or restricted the tautomeric possibilities. Benzyl was chosen as the alkyl group for the study and as **4** has three acidic protons, we attempted the synthesis of as many dibenzyl compounds as possible. Reaction of **4** (see Scheme I) with 2 equiv of sodium hydride and benzyl chloride in dimethylformamide yielded a dibenzyl compound **5**. From the nmr spectrum of **5** (4-proton singlet at δ 3.30, a low-field exchangeable proton) it seemed that both benzyl groups were bound to carbon. Thus the only tautomerism available to **5** is normal amide enolization. There was no spectral evidence of this and therefore the spectral data for **5** can be taken as being representative of the pure oxindole tautomer **4a**. Benzylation of the 3-cyano-4-azaoxindole **3** yielded a monobenzyl compound **6**, whose nmr spectrum showed that the benzyl group was attached to a heteroatom, not to carbon (2-proton singlet at δ 5.72). Reaction of **6** under benzylating conditions yielded a dibenzyl-3-cyano-4-azaoxindole **7**, which no longer had an exchangeable proton in its nmr spectrum and where both benzyl groups were attached to heteroatoms (2-proton singlets at δ 5.72 and 5.09).

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