added to the residue, and the aqueous solution (pH 6–7) was extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and evaporated to afford 0.95 g (33%) of the diketopiperazine **20**, crystallized from ethanol: mp 171–173°; TLC (95% ethanol) R_f 0.55; mass spectrum *m/e* 290 (M^+), 291 ($M^+ + 1$); NMR δ 1.8–2.6 (m, 4 H), 3.34 (s, 2 H), 3.77 (s, 3 H), 3.7–4.0 (m, 1 H), 4.24 (d, 1 H, J = 13 Hz), 4.61 (s, 1 H), 4.90 (d, 1 H, J = 13 Hz), 6.43 (s, 1 H), 6.77 (d, 2 H, J = 7 Hz), 7.13 (d, 2 H, J = 7 Hz); ir (Nujol) 3380, 3300, 1670, 1650 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.0; H, 6.2; N, 9.6. Found: C, 61.9; H, 6.1; N, 9.6.

The aqueous layer was evaporated to dryness, and the residue (~2 g) was chromatographed on 150 g of silica gel using 3:1 1-propanol–water as the eluent to yield 1.6 g (54%) of the aminol **19**, crystallized from 95% ethanol: mp 206–208°; TLC (3:1 1-propanol–water, v/v, ninhydrin visualization) R_f 0.51; mass spectrum *m/e* 308 (M^+), 290 ($M^+ - H_2O$); NMR (D_2O) δ 1.6–2.2 (m, 4 H), 3.04 (d, 1 H, J = 13 Hz), 3.36 (d, 1 H, J = 13 Hz), 3.44–4.04 (m, 2 H), 3.64 (s, 3 H), 5.01 (s, 1 H), 5.25 (s, 1 H), 6.77 (d, 2 H, J = 9 Hz), 7.04 (d, 2 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.4; H, 6.5; N, 9.1. Found: C, 58.3; H, 6.5; N, 9.1.

Tabtoxinine-δ-lactam (1). A solution of the aminol **19** (200 mg, 0.65 mmol), anisole (400 mg, 3.7 mmol), and trifluoroacetic acid (5 ml) was heated at reflux for 44 hr under nitrogen. After cooling to room temperature, the excess trifluoroacetic acid was removed under reduced pressure, a solution (25 ml) of KH_2PO_4 (1 g) and K_2HPO_4 (1 g) was added to the residue, and the aqueous solution was extracted with chloroform. After again evaporating the aqueous layer to dryness, the resulting residue was digested in hot methanol. The hot methanolic mixture was filtered, and the filtrate evaporated to dryness. The residue thus obtained was chromatographed on silica gel (10 g) employing 3:1 1-propanol-water as the eluent to afford 0.080 g (66%) of (±)-tabtoxinine-δ-lactam (1). An analytical sample was obtained by dissolving the crude crystals in hot ethanol–water (1:1 v/v), allowing the solution to cool, and inducing crystal formation by the addition of acetone. Repetition of this procedure afforded the pure aminol 1: mp 234–236°; TLC (3:1 1-propanol–water, ninhydrin visualization) R_f (silica gel Camag) 0.15; mass spectrum *m/e* 170 ($M^+ - H_2O$, 8.98% RA, 0.37% TI), 159 ($M^+ - CH_2{=}NH$, 29.14% RA, 1.20% TI), 43 (100.00% RA, 4.12% TI); NMR (D_2O) δ 1.70–2.35 (m, 4 H), 3.07 (d, 1 H, J = 13 Hz), 3.38 (d, 1 H, J = 13 Hz), 3.81–4.12 (m, 1 H).

Anal. Calcd for $C_7H_{12}N_2O_4$: C, 44.7; H, 6.4; N, 14.9. Found: C, 44.8; H, 6.2; N, 14.6.

The R_f's of the synthetic and natural material were identical in three different systems: (1) silica gel G, 2:1 1-propanol–water, R_f 0.24 (lit.[10] R_f 0.24); (2) Whatman No. 1, 2:1 1-propanol–water, R_f 0.23 (lit.[10] R_f 0.23); (3) Whatman No. 1, 4:1 phenol–water, R_f 0.49 (lit.[10] R_f 0.48).

Registry No.—**1**, 56599-17-8; **6a**, 56599-18-9; **6b**, 56599-19-0; **7b**, 56599-20-3; **8b**, 56599-21-4; **9a**, 56599-22-5; **9b**, 56599-23-6; **13**, 2207-52-5; **14**, 100-26-5; **15a**, 56599-24-7; **15b**, 56650-75-0; **16a**, 56599-25-8; **16a** HCl, 56599-26-9; **16b**, 56599-27-0; **17**, 56650-76-1; **18**, 56599-29-1; **19**, 56599-29-2; **20**, 56599-30-5; trichloroacetyl chloride, 76-02-8; anisyl alcohol, 105-13-5; 2,4-dimethoxybenzyl alcohol, 7314-44-5; ozone, 10028-15-6; *m*-chloroperbenzoic acid, 937-14-4.

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(8) Solvent evaporations were carried out in vacuo using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared (ir) spectra were measured on a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian T-60 spectrometer; peak positions are given as δ values in $CDCl_3$ (unless otherwise noted) downfield from tetramethylsilane as internal standard, expect that sodium trimethylsilylpropanesulfonate was used as internal standard in aqueous solutions. Mass spectra were obtained on an AEI MS-12 and high-resolution mass spectra were obtained on a CEC 21-110B spectrometer. Gas chromatography was performed on a Varian 90-P chromatograph. Thin layer chromatography (TLC) was performed on plates utilizing Camag D-5 silica gel unless otherwise specified. E. Merck silica gel 60 was employed for column chromatography. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.
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(10) Referred to as compound "282" in ref 2 and later shown to be identical with tabtoxinine-δ-lactam (1): ref 1.

General Methods of Alkaloid Synthesis. XI. Total Synthesis of the Sceletium Alkaloid A-4 and an Improved Synthesis of (±)-Mesembrine

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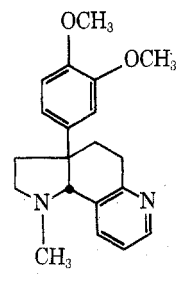
An efficient total synthesis of the pharmacologically interesting alkaloid Sceletium A-4 (1) is presented together with an improved synthesis of mesembrine (3). Key steps in these syntheses utilize the acid-promoted rearrangement of cyclopropylimine 9 to 2-pyrroline 10 and acid-catalyzed annelation of this intermediate with methyl vinyl ketone or methyl 5-oxohept-6-enoate.

Interest in the so-called Mesembrine alkaloids[3] has been renewed with the discovery[4–7] of several new bases found in various *Sceletium* species. Extracts of these plants are used by the natives of Southwest Africa in the preparation of a pharmacologically interesting drug known as "Channa" or "Koegoed". Since nearly all of the alkaloids from these plants which have been isolated thus far are not available in sufficient quantity for biological evaluation, we have been actively pursuing a program of total synthesis.[8,9] Of particular interest in the present study are the pyridine alkaloids Sceletium A-4 (1) and its seco analog tortuosamine (2).[6,7] These two substances represent completely new structural types and differ from the more common Mesembrine alkaloids such as mesembrine itself (3) by the interesting addition of a fused pyridine ring.



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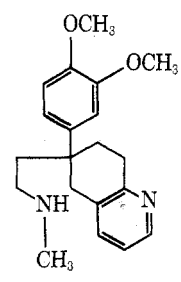

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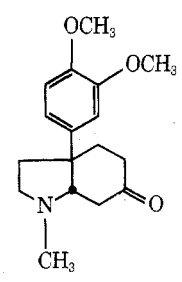

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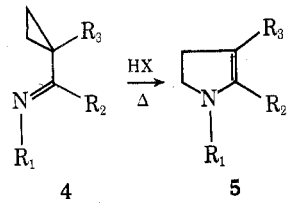
Our synthetic planning was dictated by two fundamental considerations. The first of these involves the previously demonstrated[8,9] utility of the acid-catalyzed rearrangement of cyclopropylimines (4) to 2-pyrrolines (5) and the annelation of these as well as other endocyclic enamines with methyl vinyl ketone or analogs thereof as effective methods for the generation of cis-fused[10] hydroindolones or hydroquinolones (6) common to a whole host of otherwise superficially unrelated alkaloid families. Secondly, from



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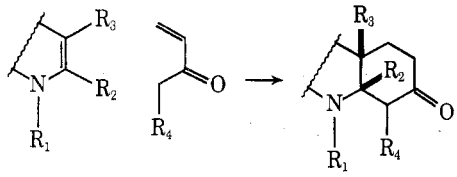

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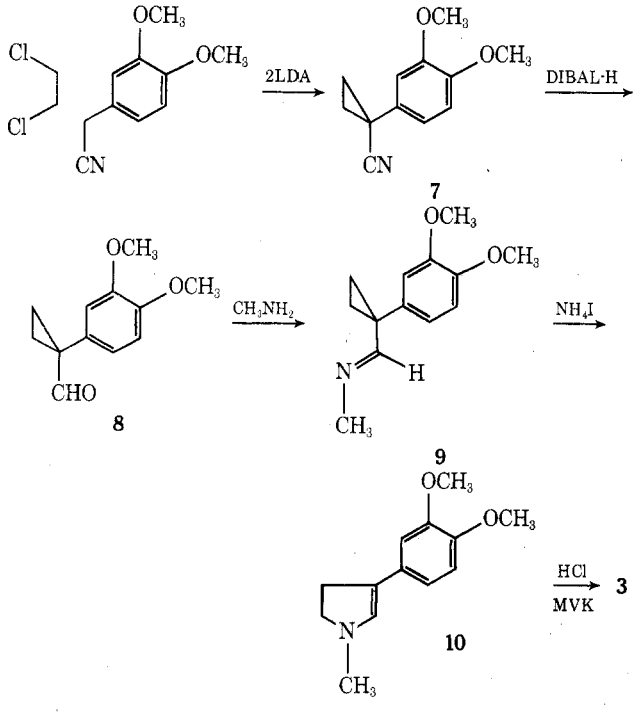
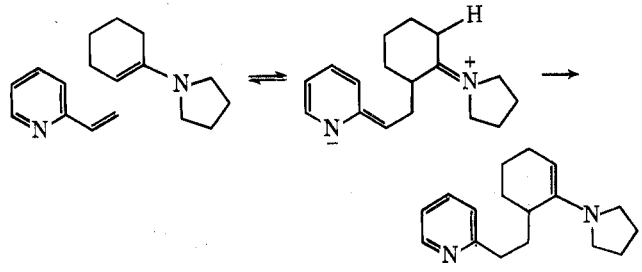
what we know about the probable mode of biosynthesis of these substances,[6] there appears to be a very distinct possibility that dihydropyridone 14 might also be a natural product—a possibility sufficiently attractive to prompt us to employ an appropriate intermediate (12) capable of transformation into this substance.

The synthesis of the required 2-pyrroline (10) was executed by methods described previously[8,9] with the very important difference that the cyclopropanation of 3,4-dimethoxybenzyl cyanide was improved dramatically by employing ethylene dichloride as the alkylating agent and lithium diisopropylamide (LDA) as the base instead of ethylene dibromide and lithium amide. In this fashion almost pure cyclopropane 7 was obtained without need for further purification. Selective reduction of this nitrile to the corresponding aldehyde (8) employing diisobutylaluminum hydride (DIBAL-H) and subsequent imine formation proceeded smoothly as did the ammonium iodide induced re-

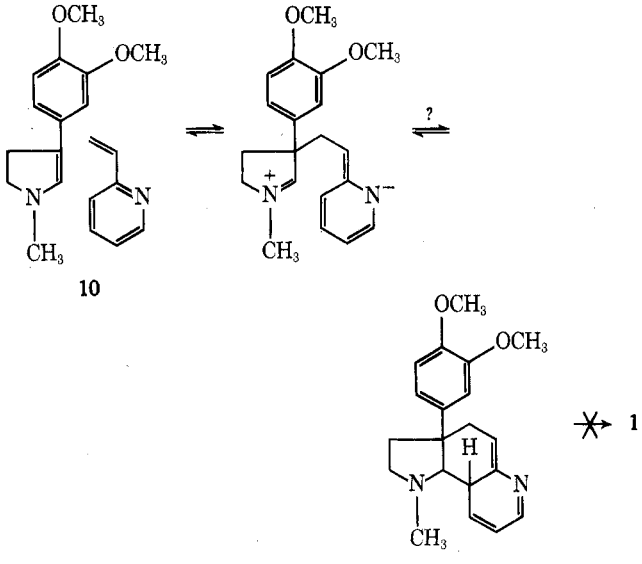


arrangement of cyclopropylimine 9 to the required 2-pyrroline 10. Annelation of this intermediate with methyl vinyl ketone (MVK) employing the improved HCl-catalyzed procedure[9,11] provided racemic mesembrine (3) in vastly improved overall yield.

With substantial supplies of endocyclic enamine 10 available, we were now in a position to employ this important synthon in the synthesis of Sceletium A-4. In principle, this could be accomplished in a single step[12] by annelation with 2-vinylpyridine. This prospect appeared rather attractive, since it had been demonstrated previously[14] that *exo*cyclic enamines do react with 2-vinylpyridine in the manner outlined below. Thus, there appeared to be

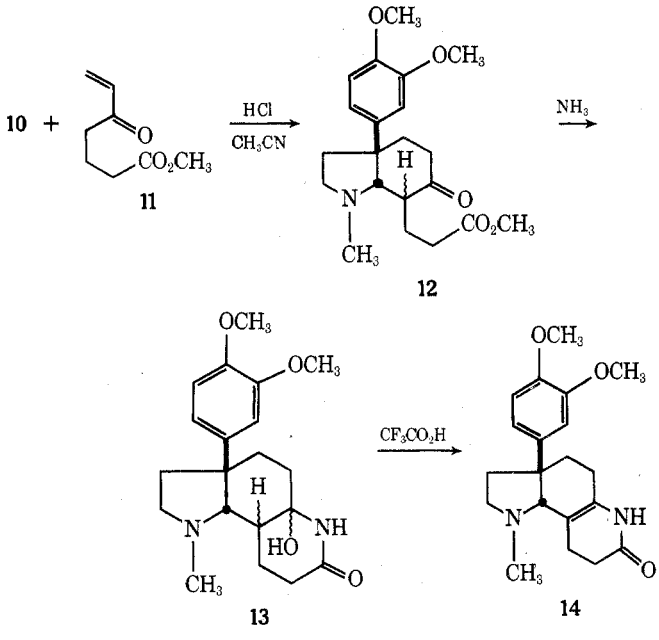


ample precedence for the Michael addition step. However, in the case of *endo*cyclic enamine 10, after the initial Michael addition the proton transfer step is constitutionally impossible, thus rendering annelation a feasible possibility. Unfortunately, we have been unable to effect this desirable transformation under a variety of conditions.

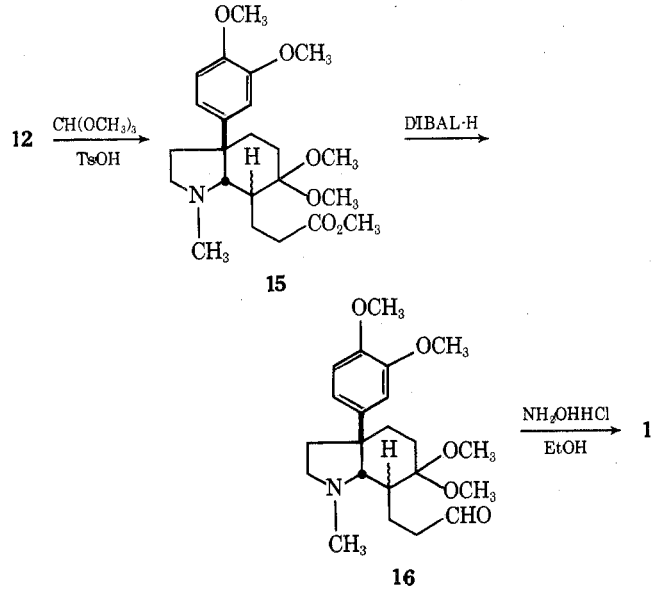


In contrast to this disappointing result, annelation of the hydrochloride salt of 10 with enone 11[15] in refluxing acetonitrile provided hydroindolone 12 as a readily separated and interconvertible mixture of epimers at C-3. The assignment of cis stereochemistry to the ring fusion is based on *all* previous annelations of this type[10] and ultimately on the success of the synthesis. Treatment of this epimeric mixture with ammonia in methanol smoothly transformed it into the isomeric carbinolamides (13) which, without purification, was dehydrated in neat CF_3CO_2H to dihydropyridone 14, thus completing the first synthesis of the basic nucleus of Sceletium A-4. The possibility mentioned above that this substance might also be a naturally occurring alkaloid is presently under investigation.[16]

Completion of the synthesis of Sceletium A-4 itself required adjustment of the oxidation state of the ester side chain in 12 to an aldehyde. This was accomplished in high yield by protection of the ketone as its dimethyl acetal (15)



and selective reduction of the ester with DIBAL-H. We had originally envisaged hydrolysis of the acetal back to the ketone, since it had been demonstrated previously[17] that 1,5-dicarbonyl systems can be converted to pyridines by treatment with hydroxylamine. We were pleasantly surprised to discover that the hydrolysis step was unnecessary—treatment of acetal **16** with hydroxylamine hydrochloride in re-



fluxing ethanol gave Sceletium A-4 directly identical in all respects with the natural product.[18]

Experimental Section

Infrared spectra were obtained on a Beckman IR-8 spectrometer. ^{1}H NMR spectra were secured from a Varian A-56/60 spectrometer in $CDCl_3$ using trimethylsilane as internal standard. Mass spectra were recorded on a Consolidated Electrodynamics Corp. 21-110 high-resolution instrument. Melting points and boiling points are uncorrected.

1-(3,4-Dimethoxyphenyl)cyclopropanecarbonitrile (7). Improved Procedure. To a cold solution of diisopropylamine (67.2 ml, 0.476 mol) in 700 ml of dry THF under N_2 was added an equivalent amount of *n*-butyllithium in hexane. The solution was stirred at 0° for 0.5 hr and then cooled to −76°. Dry hexamethylphosphoramide (88 ml, 0.515 mol) was added dropwise followed by 30 g (0.17 mol) of (3,4-dimethoxyphenyl)acetonitrile in 150 ml of THF after which the temperature was allowed to rise to −20° and 1,2-dichloroethane (70 ml, 0.89 mol) was added slowly. After addition was complete the mixture was cooled again to −76° and stirred overnight, allowing the temperature to rise slowly to 25°. The solvents were removed under reduced pressure and 200 ml of H_2O added cautiously to the residue. The mixture was extracted with benzene and washed with water (4 × 20 ml) and the solvent was removed in vacuo, leaving a dark mass which was sublimed (100°, 0.07 mm) providing 29.6 g (86%) of pure nitrile **7**.

Hydroindolone 12. The hydrochloride salt (290 mg, 1.33 mmol) of pyrroline **10** and methyl 5-oxohept-6-enoate (**11**, 625 mg, 4 mmol) were dissolved in 25 ml of dry acetonitrile and the mixture was refluxed for 24 hr, after which the solvent was removed under reduced pressure and the residue dissolved in benzene and extracted with dilute hydrochloric acid. The aqueous phase was neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2. After drying over Na_2SO_4 the solvent was removed and the residue chromatographed on neutral alumina (activity III) using ethyl acetate as eluent. Hydroindolone **12** (270 mg, 54%) was obtained as an oil: ir (neat) 1735, 1710 cm^{-1}; ^{1}H NMR major singlets at δ 6.9 (3 H), 3.93 (6 H), 3.68 (3 H), and 3.43 (3 H); mass spectrum *m/e* 375 (M^+), 344 ($M - OCH_3$), 302 ($M - C_3H_6O_2$), 219.

Carbinolamide 13. The keto ester **12** (227 mg, 0.605 mmol) was dissolved in dry methanol (5 ml) and placed in a pressure vessel at −78°. Approximately 5 ml of liquid NH_3 was condensed into the vessel, which was then sealed and allowed to warm to room temperature and the contents stirred magnetically until homogeneous. After 18 hr, the vessel was again cooled to −78°, opened, and allowed to warm up very slowly. Excess NH_3 and methanol were evaporated, leaving a yellow foam (230 mg, 100%). TLC (silica gel, CH_3OH) indicated that a minimum of three diastereomers were present. The foam crystallized from benzene–pentane as a white solid (mp 110–116°, with softening at 105°): ir (CH_2Cl_2) 1665 cm^{-1}; ^{1}H NMR δ 6.95 (m, 3 H), 3.86 (s, 6 H), the rest of the spectrum integrates to 19 H; mass spectrum *m/e* 360 (M^+), 342 ($M - H_2O$), 327, 251, 221, 219.

Dihydropyridone 14. The mixture of isomeric carbinolamides (**13**, 1.68 g, 4.67 mmol) was cooled in an ice bath and 15 ml of CF_3CO_2H was added slowly. The solution was stirred under N_2 at room temperature for 4.5 hr and the CF_3CO_2H removed in vacuo. The residue was dissolved in CH_2Cl_2 and extracted four times with 1 *N* HCl. Neutralization of the combined aqueous extracts with solid $NaHCO_3$ and extraction with CH_2Cl_2 provided 1.27 g (79%) of pure dihydropyridone **14** as a pale yellow oil: ir ($CHCl_3$) 3420, 1675, 1588, and 1511 cm^{-1}; ^{1}H NMR δ 7.52 (s, 1 H), 6.80 (s, 3 H), 3.92 (s, 6 H), 2.5 (s, 3 H); mass spectrum, calcd, 342.1943; found, 342.1972.

Acetal 15. Hydroindolone **12** (479 mg, 1.28 mmol) was dissolved in 4 ml of dry methanol containing 2 ml of trimethyl orthoformate and 342 mg (1.8 mmol) of *p*-toluenesulfonic acid and the resultant dark red solution stirred overnight. After addition of solid $NaHCO_3$, 15 ml of water was added and the solution extracted with benzene. Removal of the solvent in vacuo left 488 mg (90%) of essentially pure acetal: ir (neat) 1738, 1110, 1040 cm^{-1}; ^{1}H NMR δ 6.6–7.0 (m, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.54 (s, 3 H), 3.18 (s, 3 H), 3.12 (s, 3 H), 2.33 (s, 3 H); mass spectrum, calcd, 421; found, 390 ($M - CH_3O$).

Aldehyde 16. To a cooled (Dry Ice–acetone) solution of 298 mg (0.71 mmol) of acetal **15** in 20 ml of toluene was added slowly a pentane solution of diisobutylaluminum hydride (0.75 mmol). After stirring for 1 hr, 15 ml of a pH 2 sulfuric acid solution was carefully added and the mixture stirred for 0.5 hr. Methylene chloride was added and the mixture was neutralized with solid $NaHCO_3$ and extracted three times with methylene chloride. Removal of the solvent left 258 mg (92%) of crude aldehyde which was sufficiently pure for use in the next step: ir (neat) 1726, 1110, 1040 cm^{-1}; ^{1}H NMR δ 9.44 (t, 1 H), 6.5–7.0 (m, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.27 (s, 3 H), 3.22 (s, 3 H), 2.77 (s, 3 H).

(±)-Sceletium A-4 (1). A solution of 110 mg (0.28 mmol) of aldehyde **16** and hydroxylamine hydrochloride (70 mg, 1 mmol) in 4 ml of ethanol was refluxed under N_2 for 2 days. The solution was then made basic with 2 *N* NaOH and the ethanol removed in vacuo. Additional water was added and the solution extracted with methylene chloride. After removal of the solvent the crude product was chromatographed on neutral alumina (activity III) using benzene–chloroform (70:30) as eluent. In this manner 50 mg (55%) of pure Sceletium A-4 was obtained which could be recrystallized from ethyl acetate, mp 149–151°. The ir, ^{1}H NMR, and mass spectra were identical with those of the natural product as was the TLC behavior in several solvents; mass spectrum calcd for $C_{20}H_{24}N_2O_2$, 324.1837; found, 324.1828.

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Registry No.—1, 56782-26-4; 3, 6023-73-0; 7, 20802-15-7; 10 HCl, 56744-06-0; 11, 34990-33-5; 12, 56744-07-1; 13, 56744-08-2; 14, 56744-09-3; 15, 56744-10-6; 16, 56744-11-7; (3,4-dimethoxyphenyl)acetonitrile, 93-17-4; 1,2-dichloroethane, 107-06-2.

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(2) Fellow of the National Research Council, Canada, 1973–present.
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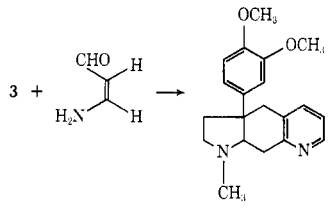

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(16) In collaboration with Professor A. Wiechers of the University of Pretoria, Pretoria, South Africa.
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(18) We are indebted to Professor Jeffs of Duke University for providing us with this data and a sample of Sceletium A-4.

A Convenient Synthesis of 2,3′-Imino-1-(β-D-lyxofuranosyl)uracil and Its Derivatives Using Azide Ion

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To exploit azide chemistry in the nucleoside area, a variety of derivatives of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil were synthesized as substrates for the reaction of azide ion. These contain 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-5-bromouracil (**1b**), 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (**1c**) and its 5′-chloro-5′-deoxy analog (**1e**), and analogous 2,2′-anhydro nucleoside with 5′-*O*-trityl and 3′-*O*-mesyl substituents (**1d**). These anhydro nucleosides as well as the known 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**1a**) with in situ generated ammonium azide gave 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**3a**), its 5-bromo (**3b**) and 5′-*O*-trityl analog (**3c**). An analogous anhydro nucleoside with the 5′-azido group (**3e**) was obtained from 5′-chloro-5′-deoxy-2′,3′-di-*O*-tosyluridine (**4**). **3a** and **3c** were deprotected to 2,3′-imino-1-(β-D-lyxofuranosyl)uracil (**3d**). **3a** was derived to its 2′-*O*-acetyl (**5**) and 4-thioxo analogs (**6**). In contrast, 2,2′-anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (**7**) with the same reagent afforded 1-(2′-azido-2′-deoxy-5′-*O*-trityl-β-D-ribofuranosyl)uracil (**9**), which was converted to the 3′-*O*-mesyl derivative (**10**) for the NMR measurement.

Introduction of an azide group followed by reductive cleavage has long been one of the standard methods for the syntheses of amino sugars and amino sugar nucleosides, while the use of other aspects of an azide reaction for the alterations of nucleosides is notably missing; an azide is known to have multiple reactivity leading to a nitrene, imine, and/or triazole depending upon reaction conditions and the character of a substrate.[1] Hence, our recent concern has been turned to exploitation of intramolecular nucleophilic reactions by an azide group in the nucleoside field, which would occur with or without decomposition of the introduced nitrogen chain. This paper describes a facile, selective, one-step synthesis of the derivatives of 2,3′-imino-1-(β-D-lyxofuranosyl)uracil (**3d**, Scheme II) from readily available 2,2′-anhydrouracil arabinosides.

Moffatt et al.[2] have shown that the reaction of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (i) with lithium azide gives 2′-azido-2′-deoxyuridine (iii), while Hirata[3] obtained 2,2′-anhydro-1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)-uracil (iv) from 2,2′-anhydro-1-(3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (ii) and sodium azide (Scheme I). For the latter reaction an azidonium intermediate (v) has been proposed by Fox and coworkers[4] without any direct evidence. The proposed intermediate (v) was, however, interesting to us, since it suggested eventual synthesis of a compound with a "down" 2′,3′-imino function under appropriate conditions.

Scheme I