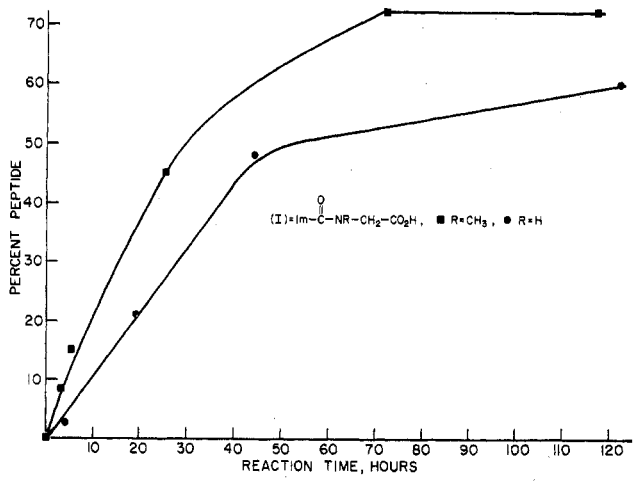
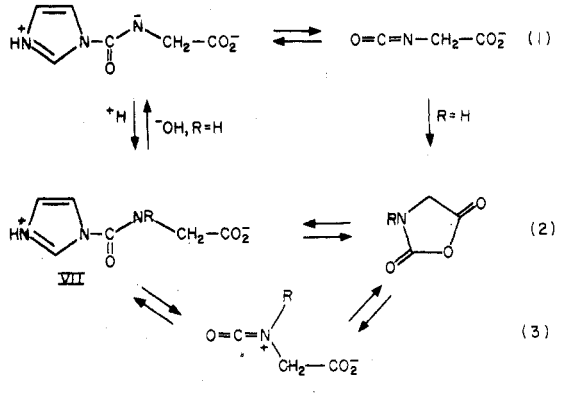


Figure 2. Plot of appearance of peptide as a function of time in the reaction of glycine and the reaction of sarcosine with carbonyldiimidazole in imidazole buffer.

seems the most probable route to the *N*-carboxyanhydride. The elimination–addition route (1) via the anionic zwitterion[4]



seems unlikely since glycine and sarcosine exhibit such similar behavior with respect to the disappearance of VII and to the appearance of peptide. Route 3, via the neutral zwitterionic isocyanate, seems unlikely on intuitive grounds and in light of the observation of Hegarty et al.[4] that the methyl analogue II, R = CH_3, hydrolyzes much slower than II, R = H. Again the similar behavior of glycine and sarcosine makes this route unlikely. The behavior of proline reflects the ring strain of its *N*-carboxyanhydride relative to that of most other amino acid *N*-carboxyanhydrides.[10]

This appears to be the first reported instance of an intramolecular acyl transfer reaction involving a carbamyl imidazole, and suggests that, despite Hegarty's work,[3,4] a careful study of the reaction of nucleophiles with carbamyl imidazoles at pH 7.0 is worthwhile.

Experimental Section

Sarcosine (98%, mp 208 °C) was purchased from Aldrich and purified by recrystallization from 3–4% aqueous ethanol. Glycine and proline were purchased from Calbiochem, *N,N'*-carbonyldiimidazole and imidazole from Sigma, and sarcosylglycine and prolylglycine from Vega-Fox-Biochemicals. Radioactive [α-^{14}C]glycine and [α-^{14}C]-proline were purchased from Schwarz. Radioactive [α-^{14}C]sarcosine was purchased from California Bionuclear Corp.

Paper electrophoresis was done on Whatman 3MM paper, using varsol as coolant, or using a Savant flat plate electrophoresis system. The buffers were I, 0.05 M formic acid adjusted to pH 2.7 with concentrated ammonium hydroxide; II, 0.03 M potassium phosphate, pH 7.1; III, 0.2 M lithium hydroxide adjusted to pH 4.5 with glacial acetic acid.

Paper chromatography was done in solvent system IV, isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2).

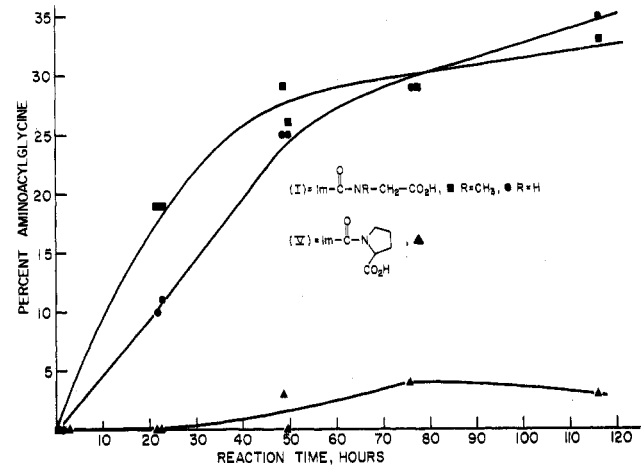


Figure 3. Plot of appearance of aminoacylglycine as a function of time in the reaction of glycine with I and VI.

Electrophoretograms of radioactive samples were treated as described earlier.

Acknowledgment. This work was supported by NSF Grant MPS 73-08792.

Registry No.—I (R = CH_3), 59643-40-2; I (R = H), 59643-41-3; VI, 59643-42-4; carbonyldiimidazole, 530-62-1; glycine, 56-40-6; sarcosine, 107-97-1; proline, 147-85-3.

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The Structures of Staphigine and Staphirine. Two Novel Bisditerpene Alkaloids from *Delphinium staphisagria*

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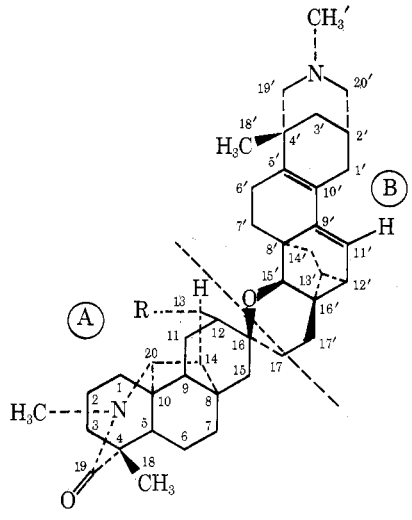
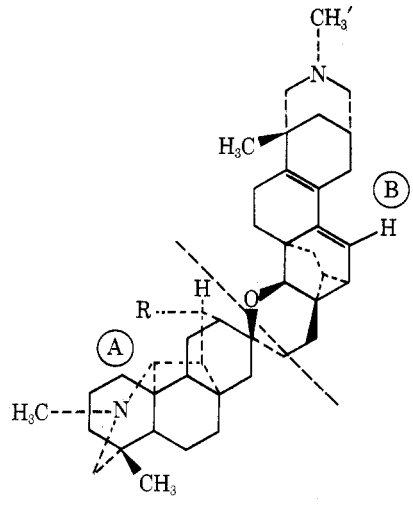
Received March 12, 1976

We wish to report the structures of staphigine (1) and staphirine (2), two new bisditerpene alkaloids isolated from the mother liquors of *Delphinium staphisagria*. ^{13}C and ^{1}H NMR spectroscopy played a major role in the determination of these structures. These alkaloids are unusual in containing a lactam moiety in addition to many of the uncommon features of the staphisine skeleton (3).[1]

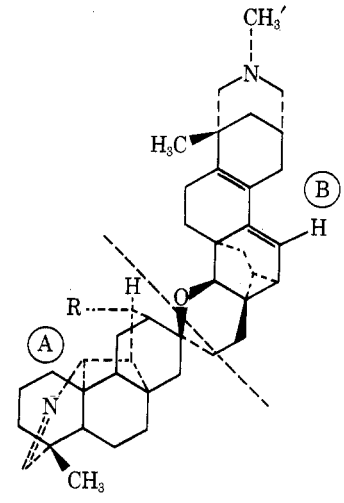
The mother liquors accumulated during the isolation of delphinine from the seeds of *D. staphisagria* were found to contain a relatively large amorphous fraction of alkaloids.[2] From these mother liquors, we have recently isolated three new bisditerpene alkaloids, staphidine (4), staphinine (5), and



1, R = OCH_3 staphigine
2, R = H staphirine



3, R = OCH_3 staphisine
4, R = H staphidine



5, R = OCH_3 staphinine
6, R = H staphimine

staphimine (6), and determined their structures by the successful application of ^{13}C and ^1H NMR spectroscopy.[3] In addition, we have isolated, by chromatography and crystallization, two new lactam-containing bisditerpene alkaloids designated as staphigine ($C_{43}H_{58}N_2O_3$) and staphirine ($C_{42}H_{56}N_2O_2$).[4]

Table I. ^1H NMR Chemical Shifts of Staphigine (1), Staphirine (2), Staphisine (3), Staphidine (4), Staphinine (5), and Staphimine (6)[a]

Carbon	1	2	3	4	5	6
-C-CH_3^{18}	1.12	1.12	0.91	0.91	1.00	1.00
-C-$CH_3^{18'}$	0.94	0.94	0.91	0.91	0.94	0.94
N-CH_3'	2.13	2.13	2.13	2.13	2.13	2.13
N-CH_3	2.98	2.92	2.27	2.21		
O-CH_3	3.30		3.30		3.30	
-C=CH-	5.85	5.85	5.85	5.85	5.85	5.85
-N=CH-					7.30	7.30

[a] ^1H NMR spectra were determined in $CDCl_3$ and shifts are given on the δ scale relative to Me_4Si.

Staphigine, mp 225–227 °C, $[\alpha]^{25}D$-116° (*c* 2.0, benzene), shows absorption at λ_{max} (EtOH) 267 nm (ϵ 17 200) in agreement with a transoid heteroannular conjugated diene system. The ir spectrum shows absorption at 1720 (conjugated diene), 1650 (lactam ring), 1101 and 1062 cm^{-1} (ether linkage). The mass spectrum exhibits a molecular ion peak at *m/e* 650 corresponding to the molecular formula $C_{43}H_{58}N_2O_3$.[4] The ^1H NMR spectrum reveals the presence of two angular methyl groups (δ 0.94 and 1.12), two *N*-methyl groups (δ 2.13 and 2.98), a methoxyl group (δ 3.30), and a vinyl proton (δ 5.85). Staphirine, mp 222–225 °C, $[\alpha]^{25}D$-126° (*c* 0.5, benzene), showed ir and uv spectra which are very similar to those of staphigine. The ^1H NMR spectrum was also identical in all respects with that of staphigine except for the absence of a methoxyl singlet at δ 3.30 (Table I). The above data indicate that staphigine (1) and staphirine (2) are similar to each other and are closely related to the known staphisine-type alkaloids staphisine (3), staphidine (4), staphinine (5), and staphimine (6).[3]

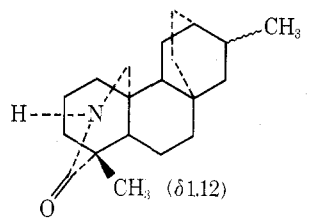
Further correlation of staphigine (1) and staphirine (2) with known alkaloids 3–6 and atisine derivative 7 was made

Table II. Carbon-13 Chemical Shifts of Staphigine (1), Staphirine (2), Staphisine (3), Staphidine (4), Staphinine (5), and Staphimine (6)

Carbon	1	2	3	4	5	6
C-4	44.6 (s)	44.7 (s)	34.2 (s)	34.2 (s)	41.5 (s)	41.5 (s)
C-8	38.4 (s)	38.7 (s)	37.4 (s)	37.6 (s)	38.1 (s)	38.3 (s)
C-10	44.6 (s)	44.3 (s)	46.0 (s)	45.5 (s)	44.3 (s)	43.7 (s)
C-13	90.3 (d)		89.4 (d)		91.2 (d)	
C-16	72.2 (s)	73.5 (s)	72.2 (s)	73.6 (s)	72.3 (s)	73.8 (s)
C-19	175.1 (s)	175.0 (s)	60.7 (t)	60.4 (t)	168.1 (d)	167.6 (d)
C-20	72.9 (d)	77.0 (d)	74.4 (d)	77.0 (d)	73.1 (d)	75.8 (d)
N-CH_3	46.9 (q)	46.9 (q)	43.9 (q)	43.5 (q)		
C-OCH_3	57.0 (q)		57.8 (q)		56.4 (q)	
C-4′	34.5 (s)	34.5 (s)	34.5 (s)	34.4 (s)	34.4 (s)	34.5 (s)
C-5′[a]	135.6 (s)	136.1 (s)	135.6 (s)	135.6 (s)	135.5 (s)	135.7 (s)
C-8′	41.8 (s)	41.9 (s)	41.8 (s)	41.6 (s)	41.6 (s)	41.6 (s)
C-9′[a]	128.2 (s)	128.1 (s)	127.6 (s)	127.7 (s)	127.7 (s)	127.9 (s)
C-10′[a]	136.1 (s)	136.4 (s)	135.6 (s)	135.8 (s)	135.5 (s)	135.7 (s)
C-11′	113.7 (d)	113.1 (d)	112.9 (d)	112.7 (d)	112.9 (d)	113.3 (d)
C-15′	78.5 (d)	78.1 (d)	78.1 (d)	77.6 (d)	78.5 (d)	77.9 (d)
C-16′	29.7 (s)	29.4 (s)	29.5 (s)	29.3 (s)	29.5 (s)	29.4 (s)
C-19′[b]	62.5 (t)	62.7 (t)	62.5 (t)	62.4 (t)	62.5 (t)	62.3 (t)
C-20′[b]	64.7 (t)	64.8 (t)	64.7 (t)	64.5 (t)	64.7 (t)	64.4 (t)
N-CH_3'	46.4 (q)	46.6 (q)	46.6 (q)	46.3 (q)	46.3 (q)	46.4 (q)

[a,b] These assignments may be interchanged.

through a study of their ^1H NMR spectra (Table I). The absorption at δ 2.13 in these alkaloids in comparison with that of compounds **3–6** is assigned to the *N*-methyl group in the B unit of the molecule. This result establishes the presence of a lactam ring in the A unit of the molecule. These data also indicate that the exceptionally low field absorptions at δ 2.98 and 2.92 in staphigine and staphirine, respectively, are accommodated by the *N*-methyl group of the lactam ring. The downfield methyl singlet at δ 1.12 is also in perfect agreement with the value for the methyl singlet of the atisine lactam derivative **7**.[5]



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The comparison of carbon-13 chemical shifts of these two new staphisine-type bisditerpene alkaloids was made with known alkaloids **3–6** to establish the presence of a lactam ring and their complete structures **1** and **2** (Table II). Assignment of the resonances to individual carbon atoms was achieved by using conventional techniques, chemical shift theory, and direct analysis of nonprotonated carbon centers.[6]

The pattern of carbon-13 chemical shifts in these new alkaloids is very similar to that of the known alkaloids **3–6.** The chemical shifts of C-4′, C-5′, C-8′, C-9′, C-10′, C-11′, C-15′, C-16′, C-19′, C-20′, and N-CH_3′ carbons in staphigine and staphirine are similar to those of compounds **3–6,** suggesting that the B unit is staphigine and staphirine is identical with that in compounds **3–6.**

The presence of the carbonyl group (singlets at 175.1 and 175.0 ppm),[7] and the lack of the *N*-methylene carbon resonance at 60.7 and 60.4 ppm in staphigine and staphirine when compared to **3** and **4**, indicate that the carbonyl carbon is present as a part of the lactam moiety in staphigine and staphirine. The downfield shifts (10.4 and 10.5 ppm) of the C-4 carbon and the upfield shift (1.5 ppm) of the C-20 carbon in **1** and **2** relative to **3** and **4**, respectively, are due to the presence of the lactam ring in the A unit. The lactam moiety in unit A was also confirmed on the basis of an *N*-methyl singlet at δ 2.13 in the ^1H NMR spectrum and the constant carbon-13 chemical shifts shown by C-19′, C-20′, and N-CH_3′ carbons of staphigine and staphirine in comparison with the known alkaloids **3–6** (Tables I and II). Based on the arguments presented here, we assign structures **1** and **2** for staphigine and staphirine, respectively.[8]

Staphigine and staphirine occur in extremely small amounts in the seeds of *D. staphisagria* in comparison with staphisine (**3**) and staphidine (**4**). These lactam alkaloids do not appear to be artifacts which arise by oxidation of compounds **3** and **4**, respectively, during isolation. All of these alkaloids (**1–6**) are closely related in structure and occur as methoxyl and demethoxyl pairs in *D. staphisagria.*

Experimental Section

Carbon-13 spectra were determined at 25.03 MHz in the Fourier mode using a JEOL-PFT-100 spectrometer in conjunction with an EC-100-20K memory computer. The spectrometer features a deuterium lock system, a JNM-SD-HC random noise (2500 Hz bandwidth) proton decoupler, and JNM-DP-1 digital pulse programmer. Spectra of the compounds were determined in deuteriochloroform solutions (which also provided the lock signal) with 5% Me_4Si added as internal reference. All samples were contained in precision ground 10-mm o.d. tubes. The spectrometer was used in the crosscoil configuration. On the average, a 12-μs pulse, corresponding to an approximate tilt angle of 45°, was employed. For the average spectral width of 5000 Hz the delay between pulses was 3 s. Acquisition times averaged 2–8 over 8K data points for concentrations of the order of 0.1–0.5 M. For of-resonance spectra this time was 8–32 h.

Acknowledgment. We thank Mr. Courtney Pape for providing the carbon-13 NMR spectra needed for this investigation. We acknowledge with pleasure a National Science Foundation matching grant to the department for purchase of the ^{13}C NMR spectrometer. We are grateful to the late Dr. Lyman C. Craig and to Dr. William C. Agosta of the Rockefeller University for generous supplies of the mother liquors of *D. staphisagria.*

Registry No.—**1,** 59588-13-5; **2,** 59588-14-6; **3,** 36575-56-4; **4,** 59588-15-7; **5,** 59588-19-1; **6,** 59588-18-0.

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(8) We were unable to carry out any transformation of compounds **1** and **2** to **3** and **4**, respectively, owing to the unstability of **1** and **2** toward various reagents (e.g., $LiAlH_4$, $NaBH_4$, etc.).

2*H*-Benzo[*b*]thiete 1,1-Dioxide

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Received March 19, 1976

In 1967 the synthesis of 2*H*-benzo[*b*]thiete 1,1-dioxide (benzothiete sulfone) was reported in very low yield from 7-thiabicyclo[4.2.0]-1(6)-octene 7,7-dioxide.[1] Recently, the method described in our earlier report has been improved to provide benzothiete sulfone in a higher overall yield.[2] This report describes a different synthesis of the sulfone (in still higher yield) and some of its chemical properties. Scheme I illustrates this new synthesis.

Scheme I