146.3 °C (reported[5b] mp 146–147 °C); $[\alpha]^{20}_D$ −34.6° (*c* 0.940, $CHCl_3$).

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Registry No.—**1**, 61899-98-7; **4**, 564-24-9; **5**, 61899-99-8; **7**, 61900-00-3; **8**, 7712-68-7; **9**, 61900-01-4; **10**, 61900-02-5; **12**, 15524-81-9; **12** picrate, 61900-03-6; oxalyl chloride, 79-37-8.

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(17) The (+)-pulegone from which acid **8** was derived had $[\alpha]^{20}_D$ +22° (neat).

A Stereocontrolled Synthesis of (±)-Anhydronupharamine. The ^1H and ^{13}C Nuclear Magnetic Resonance of Piperidine Nuphar Alkaloids[1]

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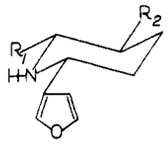
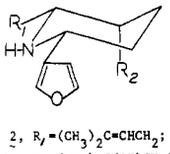
(±)-Anhydronupharamine is prepared in 11 steps starting from 6-methyl-5-hepten-2-one and proceeding through key intermediates *trans*-3-methyl-2-(3-methyl-2-butenyl)cyclopentanone, *trans*-6-(3-methyl-2-butenyl)-5-methyl-2-piperidone, and *trans*-2-(3-methyl-2-butenyl)-3-methyl-6-(3-furyl)-2,3,4,5-tetrahydropyridine. Stereocontrol is based on the greater stability of trans substituents in a 2,3-disubstituted cyclopentanone and the more favorable reduction of a C-2 substituted 2,3,4,5-tetrahydropyridine from the direction opposite the C-2 substituent. The ^1H and ^{13}C NMR characteristics of the various 3-furyl-substituted piperidines obtained in the course of synthesis are given and briefly discussed with regard to conformation.

The structures of (−)-anhydronupharamine (**1**) and (−)-nuphenine (**2**) exemplify the two stereochemical types of Nuphar piperidine alkaloids. The trans disposition of C-2 and C-3 hydrogen atoms in **1** similarly occurs in the Nuphar quinolizidine alkaloids where the carbons of the second ring might be considered constituted by those of the C-2 side chain in **1**. This trans arrangement appeared, until recently, to be the only one in the quinolizidine Nuphar alkaloids. However, the results of new isolation work show that the C-2 and C-3 cis arrangement of hydrogen atoms in **2** also presents itself in the C_{15} quinolizidine 1-*epi*-deoxynupharidine[2] and in some C_{30} thiaspiranes such as 1-*epi*,1′-*epi*-thiobinupharidine.[3] Regardless of the steric disposition of the C-2 and C-3 substituents, the 3-furyl group at C-6 always assumes an equatorial conformation and is cis to the C-2 substituent in the naturally occurring Nuphar piperidines and quinolizidines.



1, $R_1=(CH_3)_2C{=}CHCH_2$; $R_2=CH_3$
20, $R_1=R_2=H$
21, $R_1=CH_3$; $R_2=H$
28, $R_1=(CH_3)_2C(OH)CH_2CH_2$; $R_2=CH_3$

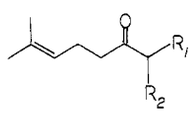


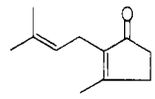
2, $R_1=(CH_3)_2C{=}CHCH_2$; $R_2=CH_3$
29, $R_1=(CH_3)_2C(OH)CH_2CH_2$; $R_2=CH_3$

We sought to prepare the piperidine Nuphar alkaloids by routes which would offer control over the C-2, C-3, and C-6 stereochemistry and which appeared to hold some promise for appropriate elaboration of the C-2 side chain in order that the route could be extended later to the Nuphar quinolizidines. We report here the synthesis[4] of (±)-anhydronupharamine by a route through which the stereocontrol of C-2 and C-3 substituents rests on the far greater stability of trans C-2, C-3 alkyl substituents in a cyclopentanone.[5] As results were to demonstrate, the basis for the C-2, C-6 cis arrangement of substituents is the more favorable reduction of a C-2 substituted 2,3,4,5-tetrahydropyridine from the side opposite the C-2 substituent. In addition we report on the results of the ^1H and ^{13}C NMR investigations of the stereochemistry of the new piperidine compounds which have arisen in the course of the synthesis.

Results and Discussion

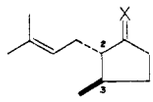
Synthesis. The cyclopentenone **6**, substituted by γ,γ-dimethylallyl and methyl groups at C-2 and C-3, was prepared by starting from the 6-methyl-5-hepten-2-one (**3**) and proceeding through **4** and **5** according to an established sequence[6] for preparing 2,3-disubstituted cyclopentenones. Thereafter the key intermediate cyclopentanone **7** possessing C-2 and C-3 trans substituents was prepared through lithium/liquid ammonia reduction of the cyclopentenone. None of the cis isomer





6

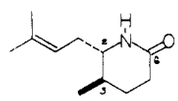
3, $R_1=R_2=H$
4, $R_1=COOCH_3$; $R_2=H$
5, $R_1=COOCH_3$; $R_2=CH_2COCH_3$



7, X=O
8, X=NOH

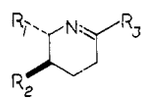
could be detected by ^1H NMR or GLC. The yields for these steps and all subsequent ones are given in the Experimental Section.

The conversion of ketone **7** to the oxime **8** with hydroxylamine hydrochloride in refluxing pyridine and subsequent Beckmann rearrangement of the oxime, by treatment of the latter with phosphorus pentachloride, achieved nitrogen incorporation in a six-membered lactam, **9,** in the desired position relative to C-2 and C-3 as indicated by the ^1H NMR. The trans disposition of substituents was largely preserved, but some loss of stereochemical integrity occurred in oxime formation. The presence of 8.5% of the cis oxime was detected by ^1H NMR observation of the C-3 methyl doublet which appeared at δ 0.82 ppm, while the methyl doublet from the predominant trans isomer appeared slightly downfield at δ 1.00 ppm. This cis isomer was carried through the remainder of the synthesis.



9

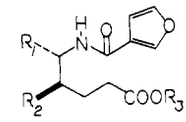
The major obstacle to the completion of the synthesis was the attachment of a 3-furyl group to the carbon present as the lactam carbonyl carbon in **9.** Alkylation of a lactam carbonyl carbon has been achieved through conversion of the lactam to a thioimidate ester followed by treatment of the latter with a lithium alkyl in the presence of diisopropylaluminum hydride (DIBAH).[7] Similarly the treatment of the *S*-methylthiolactim **10** with phenyllithium in the presence of DIBAH or diphenylmercury gave the imine **11** in yields up to 50%. The *O*-methyllactim **12** and phenyllithium also produced **11** in the



10, $R_1=R_2=H$; $R_3=SCH_3$
11, $R_1=R_2=H$; $R_3=C_6H_5$
12, $R_1=R_2=H$; $R_3=OCH_3$
13, $R_1=R_2=H$; $R_3=3$-furyl
14, $R_1=CH_3$; $R_2=H$; $R_3=OCH_3$
19, $R_1=CH_3$; $R_2=H$; $R_3=3$-furyl
23, $R_1=(CH_3)_2C=CHCH_2$; $R_2=CH_3$; $R_3=OCH_3$
26, $R_1=(CH_3)_2C=CHCH_2$; $R_2=CH_3$; $R_3=3$-furyl

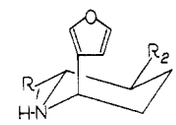
presence or absence of DIBAH, though in better yield when DIBAH was present.[8] However when 3-furyllithium and DIBAH or bis(3-furyl)mercury replaced the phenyl counterparts, the corresponding 3-furyl-substituted imine **13** was not obtained.

Since the direct attachment of the 3-furyl portion of the molecule seemed frustrated, the indirect incorporation of this group was attempted and achieved through N-acylation of an *O*-methyllactim with 3-furoyl chloride followed by decarboxylation and simultaneous nitrogen–carbon bond formation to reestablish the six-membered heterocyclic ring. Thus treatment of the *O*-methyllactims **12** and **14** with lithium hydride and 3-furoyl chloride produced the amido esters **15** and **16,** respectively,[9] which after ester hydrolysis and pyrolysis of the resulting amidocarboxylic acids, **17** and **18,** in the



15, $R_1=R_2=H$; $R_3=CH_3$
16, $R_1=R_3=CH_3$; $R_2=H$
17, $R_1=R_2=R_3=H$
18, $R_1=CH_3$; $R_2=R_3=H$
24, $R_1=(CH_3)_2C=CHCH_2$; $R_2=R_3=CH_3$
25, $R_1=(CH_3)_2C=CHCH_2$; $R_2=CH_3$; $R_3=H$

presence of calcium oxide gave the imines **13** and **19** in 52 and 60% yields, respectively, in the last step. Sodium borohydride reduction of **13** gave 2-(3-furyl)piperidine, **20,** while imine **19** led to a mixture of *cis*- (**21,** 91%) and *trans*-6-methyl-2-(3-furyl)piperidine (**22,** 9%). The sequence of transformations



22, $R_1=CH_3$; $R_2=H$
27, $R_1=(CH_3)_2C=CHCH_2$; $R_2=CH_3$

was applied thereafter to the lactam **9.** Conversion of the latter to the *O*-methyllactim **23,** N-acylation and ring opening to amido ester **24,** hydrolysis to the amido acid **25,** pyrolysis with calcium oxide to imine **26,** and reduction with sodium borohydride produced a mixture of piperidines. According to GLC analysis, this mixture consisted of 85% anhydronupharamine (**1**) and 15% of the stereoisomers nuphenine (**2**) and the 2,6-trans isomer, **27.** Each of the three was separated by elution chromatography and the samples of anhydronupharamine and nuphenine possessed chromatographic and spectrometric properties identical with those of the naturally occurring alkaloids.

^1H and ^{13}C NMR. (−)-Anhydronupharamine has been correlated[10] with (−)-nupharamine (**28**), which in turn has been correlated[11] with (−)-deoxynupharidine, whose stereochemistry is secure.[12] Therefore there is no question regarding the relative configuration of anhydronupharamine. The relative configurations of nuphenine[13] and the closely related tertiary alcohol 3-*epi*-nupharamine[14] (**29**) rest on the ^1H NMR spectra, which indicate the C-3 methyl groups are axial. The same spectra are consistent with the C-2 side chains being equatorial, though the axial disposition of these side chains is not necessarily ruled out. We have found that a comparison of the ^1H and ^{13}C NMR of the various 3-furyl-substituted piperidines has been useful in confirming and assigning conformation and configuration to the various 3-furyl-substituted piperidines.

The ^1H doublets exhibited by the C-3 methyls in anhydronupharamine, **1,** and the 2,6-trans isomer, **27,** are at nearly the same field strength (δ 0.91 and 0.89 ppm, respectively) and have the same coupling constants (6.0 Hz), but are upfield from and have slightly smaller coupling constants than the δ 0.98 ppm methyl doublet (J = 7.2 Hz) shown by nuphenine **2.** These ^1H NMR properties of the C-3 methyl-substituted piperidines parallel those of the corresponding quinolizidines where axial methyl groups, substituted at C-1 or C-3 in chair

Table I. ^{13}C Chemical Shift Values[a] of Selected Carbons in 3-Furyl-Substituted Piperidines

Compd	Substituted	Carbon no.[b] 2 (6)	3 (5)	4	5 (3)	6 (2)	CH_2	CH_3
	Piperidine[c]	47.7 (t)	27.5 (t)	26.1 (t)	27.5 (t)	47.7 (t)		
20	Mono	53.1 (d)	33.7 (t)	24.7 (t)[d]	25.9 (t)[d]	47.0 (t)		
21	Di	53.6 (d)	33.9 (t)[e]	24.9 (t)	33.2 (t)[e]	52.8 (d)		22.9
22	Di	46.9 (d)	31.0 (t)	20.0 (t)	33.0 (t)	45.5 (d)		21.3
1	Tri	53.8 (d)	34.7 (t)[f]	34.3 (t)[f]	35.9 (d)	64.1 (d)	32.4 (t)	18.2[g] (18.5) (q)[g]
2	Tri	54.4 (d)	28.6 (t)	33.2 (t)	30.7 (d)	60.5 (d)	32.6 (t)	11.8 (q)
27	Tri	43.6 (d)	29.4 (t)[h]	29.2 (t)[h]	35.6 (d)	57.2 (d)	32.3 (t)	18.2[i] (18.8) (q)[i]

[a] Given in parts per million from δ 0.0 ppm from Me_4Si with multiplicity in parentheses. [b] The carbon to which the 3-furyl group is attached is C-2 in the mono- and disubstituted piperidines but C-6 in the trisubstituted piperidines. The remaining carbons in the ring are numbered in sequence accordingly. [c] Values taken from ref 16. [d-i] Assignments may be interchanged where the same superscript letter appears.

form rings, appear downfield with slightly larger coupling constants than equatorial methyls.[15] Thus our analysis of the piperidines points to an equatorial C-3 methyl in anhydronupharamine and the 2,6-trans isomer, but an axial C-3 methyl in nuphenine.

The resonance of the proton attached to the 3-furyl bearing carbon appears in the region of δ 3.57–3.60 ppm as a doublet of doublets (J = 8.0–10.9 and 2.1–5.5 Hz) in the spectra of anhydronupharamine, nuphenine, and *cis*-2-(3-furyl)-6-methylpiperidine (**21**), while the corresponding resonance appears at lower field, δ 4.11 and 4.00, as a triplet (J = 4.0 Hz) in the spectra of the trans-2,6 compounds, **22** and **27**. The higher field doublet of doublet resonance indicates an axial proton (3-furyl equatorial) split by vicinal axial and equatorial protons, but the lower field triplet indicates an equatorial proton (3-furyl axial) split by vicinal axial and equatorial protons having equal coupling constants.

The ^1H resonance of the second carbinyl proton adjacent to nitrogen is less straightforward in providing useful stereochemical information. This proton appears as a quintet of doublets at 2.78 and 3.04 ppm, respectively, in the spectra of the *cis*- and *trans*-2-(3-furyl)-6-methylpiperidines. The splitting pattern is best rationalized for both spectra by the proton in question being axial and split by each of the three methyl protons and the vicinal axial proton by the same amount, 6.4 Hz, and split again by the vicinal equatorial proton by 2.3 Hz. The lower field shift value of this proton in the 2,6-trans isomer **22** would seem to reflect the conformation of the 3-furyl group. In the nuphenine case, the proton appears as a triplet of doublets (J = 7.4 and 2.2 Hz) at δ 2.77 ppm. The splitting with the vicinal C-3 equatorial proton is ambiguous regarding the question whether the C-2 proton is axial or equatorial. However the chemical shift value of the proton in question agrees with that of the corresponding proton in the cis-2,6 model compound **21**, and therefore suggests that the C-2 proton is axial and the side chain equatorial. In the case of anhydronupharamine and its trans-2,6 isomer **27**, the chemical shift value of the C-2 proton is anomalously low, occurring coincidentally with the allyl methylene in the δ 2.0–2.6 ppm region. This anomalous chemical shift is occurring only when an equatorial methyl group is attached to C-3, but the nature of the influence which this group has on the C-2 proton is not clear.

The ^{13}C chemical shifts, excluding the values for the 3-furyl, the vinyl, and the vinylmethyl carbons are given in Table I for the six 3-furyl-substituted piperidines. The chemical shifts excluded from Table I appear at the expected values.[17] Assignments were made with the assistance of ^1H off-resonance decoupled spectra and the chemical shift comparison within the series. Assignments for the ring carbons of the cis- and trans-2,6 model compounds **21** and **22** were given additional support by the agreement of observed chemical shifts with those calculated from parameters of Booth and Griffiths determined from a study of several methylpiperidines.[18] Carbons adjacent to nitrogen in all compounds except the mono-substituted piperidine were distinguished by ^1H single frequency decoupling experiments.

A comparison of the ^{13}C chemical shift values for the disubstituted piperidines **21** and **22** shows that all ring carbons, except C-5, are at higher field in **22** than in **21**. In addition the C-6 methyl group chemical shift values are very nearly the same, although the one for **22** is slightly higher, by 1.6 ppm. These observations, along with the ^1H NMR splitting patterns and chemical shift values for C-6, are consistent with the predominant conformer of the trans-2,6 isomer **22** being the one possessing an axial 3-furyl group and an equatorial methyl group. The axial–equatorial chemical shift increment for a C-1 or C-3 methyl group in quinolizidines is about 6 ppm. Assuming that this increment can be applied to the 2-methylpiperidine case and using the 1.6-ppm value of the methyl chemical shift difference in **21** and **22**, we estimate that the ratio of axial methyl conformer to axial 3-furyl conformer in the equilibrium mixture of the two is about 1:4.

The presence of the C-3 axial methyl in nuphenine is indicated by the lower chemical shift value of this group relative to the corresponding group in anhydronupharamine.[19] Also consistent with this stereochemistry is the observation that all ring carbon chemical shift values, except that for C-6, are lower for nuphenine than anhydronupharamine. Similarly in comparing **27** with **1**, both methyl chemical shift values are the same and the values for all ring carbons, except C-3, are lower in **27** than **1**. These observations are consistent with the C-3 methyl group in **27** being equatorial and the C-6 3-furyl group being axial.

Experimental Section

Spectra were determined as follows: infrared (IR) neat on a Perkin-Elmer 137 spectrometer; ^1H NMR in $CDCl_3$ solution in 5-mm tubes (1% Me_4Si; δ 0.00) on Varian A60 A and XL 100-15 spectrometers, the latter operating at 100 MHz in the FT absorption mode, lock being established on $CDCl_3$ (m, s, d, t, q, q′, and br refer to multiplet, singlet, doublet, triplet, quartet, quintet, and broad, respectively); ^{13}C NMR on a XL 100-15 spectrometer operating in the FT absorption mode at 25.2 MHz employing 8192 data points, using 5–69-mg samples in 5-mm tubes, the $CDCl_3$ also furnishing the secondary reference signal (77.2 ppm from Me_4Si at δ 0.0 ppm) and the deuterium resonance for field-frequency lock. Fully ^1H noise decoupled, selective ^1H decoupled, and ^1H off-resonance decoupled ^{13}C NMR spectra were obtained from 6 to 272 K transients, the number of transients for off-resonance decoupled spectra being at the higher end of the range. In all cases ^{13}C spectral widths were 5000 Hz and acquisition times were 0.8 s. Pulse angles for ^{13}C determinations ranged from 20 to 45 °C. Gas–liquid chromatography (GLC) is given as retention time (R_t) in minutes and was performed at the column temperature and flow rate or back pressure indicated on: a 5 ft × ¼ in. stainless steel column packed with 1.5% OV101 on 100/120 Chromo-

sorb G HP (column A); a 5 ft × ¼ in. stainless steel column packed with 20% SE 30 on 60/80 Chromosorb W (column B); 5 ft × ¼ in. stainless steel column packed with 10% Carbowax 20M on Chromosorb G (column C); 5 ft × ¼ in. stainless steel packed with 2% OV101 on 100/120 Chromosorb G HP (column D); 10 ft × ⅛ in. stainless steel column packed with 1.5% OV101 on 100/120 Chromosorb G (column E). Thin layer chromatography was performed on: A, Analtech precoated silica gel G (250-μm thickness) developed with hexane–ether (4:1), or with the solvent system indicated, and visualized with I_2 vapor; B, Merck Alumina (250-μm thickness) developed with hexane–ether (4:1) and visualized with Dragendorff–Munier reagent; C, Merck Alumina (250-μm thickness) developed with 5% EtOAc in benzene and visualized with Dragendorff–Munier reagent. Elemental analyses were performed by Galbraith Analytical Laboratories, Knoxville, Tenn.; melting points (mp) were taken on a Mel-temp apparatus and are uncorrected.

Methyl 7-Methyl-3-oxo-6-octenoate (4). To a suspension of 38 g of NaH (1.58 mol) in 250 mL of dry ether under N_2 was added 142.75 g of dimethyl carbonate (1.58 mol), the resulting mixture was heated to reflux, and 100 g of 6-methyl-5-hepten-2-one (0.79 mol) (purchased from the Aldrich Chemical Co.) was added over 5 h to the heated mixture. The mixture was heated to reflux another 2 h, cooled to 25 °C, and poured onto crushed ice containing 99 mL of acetic acid. The ether solution was separated, washed with dilute aqueous $NaHCO_3$ and dried ($MgSO_4$). Removal of the ether at reduced pressure left an oil which was distilled to give 112 g of **4** (77%): bp 84–85 °C (0.5 mm); IR (neat) 1742 ($COOCH_3$), 1715 cm^{-1} (RCOR); ^1H NMR δ 5.08 (m, 1 H, C-6 H), 3.70 (s, OCH_3), 3.41 (s, 2 H, C-2 H), 2.00–2.83 (m, 4 H, C-4 and C-5 H), 1.65 (d, J = 1.2 Hz, 3 H, CH_3), 1.60 (s, 3 H, CH_3); GLC (column A, 125 °C, back pressure 16 psi) R_t 6.9; TLC (A) R_f 0.39. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.77. Found: C, 65.30; H, 8.87.

4-Carbomethoxy-9-methyl-8-decene-2,5-dione (5). To a stirred suspension of 5.72 g of NaH (0.237 mol) in 300 mL of ether under N_2 was added dropwise a solution of 44 g of **4** (0.237 mol) in 100 mL of ether. The resulting slurry was stirred until no effervescence was observed. Ether (200 mL) was added to facilitate stirring, the slurry was cooled to −25 °C, and a solution of 32.7 g of bromoacetone (0.238 mol) in 50 mL of ether was added with vigorous stirring. The mixture was heated to reflux for 30 min, cooled to 25 °C, and poured into crushed ice. The pH was adjusted to 5 with 25% aqueous H_2SO_4, the ether solution was separated, and the aqueous phase was extracted repeatedly with ether. The extracts were combined with the ether solution and the resulting solution was dried ($MgSO_4$). Removal of the ether at reduced pressure yielded 51 g of **5** (94%), 46 g of which was used in the next step without further purification and 1 g of which was distilled by short-path distillation to afford **5**: bp 104–106 °C (0.1 mm); IR (neat) 1742 ($COOCH_3$), 1720 (RCOR), 1715 cm^{-1} (RCOR); ^1H NMR δ 5.08 (m, 1 H, C-6 H), 4.00 (t, 1 H, C-2 H), 3.69 (s, 3 H, OCH_3), 3.50–2.00 (m, 6 H, C-4, C-5, and C-2 H), 2.14 (s, 3 H, CH_3), 1.65 (d, 3 H, CH_3), 1.60 (d, 3 H, CH_3); GLC (column B, 175 °C, 60 ml/min) R_t 9.4; GLC (column A, 150 °C, back pressure 18 psi) R_t 11.2; TLC (A) R_f 0.16. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.96; H, 8.40. Found: C, 65.05; H, 8.50.

3-Methyl-2-(3-methyl-2-butenyl)-2-cyclopentenone (6). A solution of 50 g of **5** in 800 mL of 3% aqueous NaOH was stirred at 70 ± 2 °C for 3 h and thereafter cooled to 25 °C. The pH was adjusted to 4.0 with 25% aqueous H_2SO_4 and the liberated ketone was extracted repeatedly with 100 mL of ether. The combined extracts were washed with brine and dried ($MgSO_4$). Removal of the ether at reduced pressure and distillation of the residue gave 28 g of **6** (78%): bp 76–77 °C (0.2 mm); IR (neat) 1691 (RCOR), 1640 cm^{-1} (C=C); ^1H NMR δ 5.05 (m, 1 H, C-7 H), 2.86 (d, 2 H, C-6 H), 2.44 (m, 4 H, C-4 and C-5 H), 2.03 (s, 3 H, CH_3), 1.66 (s, 6 H, C-9 and C-10 H); GLC (column B, 175 °C, 60 ml/min) R_t 3.9; GLC (column C, 210 °C, 60 ml/min) R_t 13.3; GLC (column A, 125 °C, back pressure 16 psi) R_t 9.3; TLC (A) R_f 0.19. Anal. Calcd for $C_{11}H_{16}O$: C, 80.42; H, 9.83. Found: C, 78.46; H, 9.92.

***trans*-3-Methyl-2-(3-methyl-2-butenyl)cyclopentanone (7).** A solution of 5 g of **6** in 50 mL of ether was added to 400 mL of liquid NH_3 in a flask at −78 °C. Small pieces of lithium wire totaling 1.7 g (0.24 g atom) were added over a period of 3 min with vigorous stirring. The blue reaction mixture was stirred an additional 10 min, solid NH_4Cl was added, vigorous stirring was continued for 15 min, and to the resulting white slurry was added slowly 100 mL of water. The flask was removed from the cooling bath and kept at 35–40 °C until the bulk of the NH_3 had evaporated. The ether layer was separated, the aqueous layer was extracted repeatedly with ether, and the combined extract and original ether layer was dried ($MgSO_4$). Removal of the ether at reduced pressure gave an oil which was distilled to yield 3.7 g of **7** (73%): bp 83–84 °C (3.5 mm); IR (neat) 1740 cm^{-1} (RCOR); ^1H NMR δ 5.08 (m, 1 H, C-7 H), 1.25–2.50 (m, 8 H, $(C)_3CH$ and $(C)_2CH_2$), 1.62 (d, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.11 (d, 3 H, C-3 CH_3); GLC (column B, 170 °C, 60 ml/min) R_t 2.8; GLC (column A, 125 °C, back pressure 15 psi) R_t 5.0; TLC (A) R_f 0.52. Anal. Calcd for $C_{11}H_{18}O$: C, 79.44, H, 10.93. Found: C, 79.25; H, 10.84.

***trans*-3-Methyl-2-(3-methyl-2-butenyl)cyclopentanone Oxime (8).** A solution of 2.5 g of hydroxylamine hydrochloride (0.035 mol) in 10 mL of 50% EtOH was added to a solution of 5 g of **7** in 10 mL of pyridine. The mixture was heated to reflux for 15 min, cooled to 25 °C, and the reaction flask was evacuated at 60 °C to form an oil which was treated with 50-mL portions of ether. The combined ether solution was dried ($MgSO_4$) and the ether was removed at reduced pressure to give an oil which when distilled afforded 5.3 g of **8** (98%): bp 90–91 °C (0.2 mm); IR (neat) 3300 (OH), 1670 cm^{-1} (C=N); ^1H NMR δ 5.20 (m, 1 H, C-7 H); 1.16–3.00 (m, 8 H, $(C)_3CH$ and $(C)_2CH_2$), 1.66 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.01 (d, 3 H, CH_3); GLC (column A, 150 °C, back pressure 17 psi) R_t 5.6; TLC (A) R_f 0.37. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.86; H, 10.58; N, 7.72. Found: C, 72.92; H, 10.50; N, 7.73.

***trans*-6-(3-Methyl-2-butenyl)-5-methyl-2-piperidone (9).** A 6.9-g quantity of PCl_5 (0.032 mol) was added to 4 g of **8** (0.022 mol) in ether and the resulting slurry was stirred at 25 °C for 20 h. The reaction flask was evacuated at 25 °C to obtain an oil which was dissolved in 150 mL of CH_2Cl_2 and the resulting solution was poured onto crushed ice containing 100 mL of 10 N NaOH. The mixture was stirred and additional NaOH was added to pH 10–12. The phases were separated and the aqueous phase was extracted repeatedly with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to obtain an oil which was chromatographed on silica gel (grade 62) using hexane–ether–methanol (80:15:5) to obtain 2.6 g of **9** (65%): IR (neat) 1645 cm^{-1} (amide); ^1H NMR δ 5.11 (m, 1 H, C-8 H), 3.75 (m, 1 H, C-6 H), 1.16–2.66 (m, 7 H, $(C)_3CH$ and $(C)_2CH_2$), 1.68 (d, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.03 (d, 3 H, CH_3); GLC (column A, 175 °C, back pressure, 18 psi) R_t 5.8; TLC (A, hexane–ether–methanol, 80:15:5) (A) R_f 0.20. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.86; H, 10.58; N, 7.72. Found: C, 72.69; H, 10.64; N, 7.80.

***trans*-2-(3-Methyl-2-butenyl)-3-methyl-6-methoxy-2,3,4,5-tetrahydropyridine (23).** To a mixture of 2 g of **9** (0.011 mol) and 0.344 g of dimethyl sulfate (0.0027 mol) at 80 °C was added dropwise over a period of 15 min 1.049 g (0.79 mL, 0.0083 mol) of dimethyl sulfate. The resulting mixture was kept at 80 °C 3 h, 2.5 mL of benzene was added, and then the mixture was cooled to 25 °C. A solution of 0.493 g of NaOH (0.012 mol) in 1 mL of water was slowly added with stirring; thereupon the temperature rose to 55 °C. The mixture was stirred at 55–60 °C for 15 min. After cooling, the two phases were separated. The aqueous phase was extracted repeatedly with benzene, the combined extracts were dried ($MgSO_4$), the benzene was distilled off at 760 mm, and the residue was distilled. The fraction collected at 45–46 °C (0.1 mm) consisted of 1.48 g of **23** (69%): IR (neat) 1680 (C=N), 1210 cm^{-1} (OCH_3); ^1H NMR δ 5.27 (m, 1 H, C-8 H), 3.62 (s, 3 H, OCH_3), 2.83–3.57 (m, 1 H, C-6 H), 1.17–2.55 (m, 7 H, $(C)_3CH$ and $(C)_2CH_2$), 1.72 (d, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 1.00 (d, 3 H, CH_3); GLC (column A, 150 °C, back pressure 18 psi) R_t 3.4. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.77; H, 10.85; N, 7.17. Found: C, 73.55; H, 10.93; N, 7.23.

Methyl *erythro*-5-(3-Furamido)-4,8-dimethyl-7-nonenoate (24). A solution of 1.0 g of **23** (0.0051 mol) in 12 mL of THF was added to a suspension of 0.035 g of LiH (0.005 mol) in 10 mL of THF under N_2. After the mixture had been heated to reflux for 3 h and cooled to 25 °C, a solution of 0.668 g of 3-furoyl chloride (0.0051 mol) in 12 mL of THF was added and the mixture was stirred for 7 days at 25 °C. A 12-mL quantity of 6 N aqueous HCl was added slowly with stirring. After continued stirring for 15 min, the mixture was extracted repeatedly with CH_2Cl_2. The combined extracts were dried ($MgSO_4$ and $NaHCO_3$) and the solvent was removed at reduced pressure to obtain an oil which was chromatographed on Alumina (activity 1) with ether and thereby was afforded 0.74 g of oily **24** (47%): ir (neat) 3300 (NH), 3120 (furan CH), 1735 ($COOCH_3$), 1630 (CONH), 871 cm^{-1} (furan); ^1H NMR δ 7.88 (m, 1 H, 3-furyl α-H), 7.36 (m, 1 H, 3-furyl α-H), 6.58 (m, 1 H, 3-furyl β-H), 5.85 (d, 1 H, NH), 5.10 (m, 1 H, C-7 H), 3.96 (m, 1 H, C-5 H), 3.64 (s, 3 H, OCH_3), 1.00–2.60 (m, 7 H, $(C)_3CH$ and $(C)_2CH_2$), 1.65 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 0.91 (d, 3 H, C-4 CH_3); GLC (column A, 200 °C, back pressure 20 psi) R_t 15.6; TLC (A, ether) R_f 0.73. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.41; H, 8.21; N, 4.55. Found: C, 66.16; H, 8.08; N, 4.30.

***erythro*-5-(3-Furamido)-4,8-dimethyl-7-nonenoic Acid (25).** A suspension of 0.75 g of **24** in 20 mL of 5% aqueous KOH was heated to reflux for 2 h. The mixture was cooled to 5 °C, the pH was adjusted to 2 with 6 N aqueous HCl, and the mixture was extracted with four 50-mL portions of methyl isobutyl ketone (MIBK). The combined

MIBK extracts were washed with 25 mL of brine, dried ($MgSO_4$), and the MIBK was removed at reduced pressure to afford an oily residue, which was dried over P_2O_5 at 60 °C (0.5 mm) to produce 0.70 g of **25** (98%): IR (neat) 3318 (NH), 3122 (furan CH), 1710 (COOH), 1630 (CONH), 872 cm^{-1} (furan); ^1H NMR δ 7.88 (m, 1 H, 3-furyl α-H), 7.36 (m, 1 H, 3-furyl α-H), 6.58 (m, 1 H 3-furyl β-H), 5.85 (d, 1 H, NH), 5.10 (m, 1 H, C-7 H), 3.96 (m, 1 H, C-5 H), 1.00–2.60 (m, 7 H, $(C)_3CH$ and $(C)_2CH_2$), 1.65 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 0.91 (d, 3 H, C-4 CH_3). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.45; H, 7.91; N, 4.77. Found: C, 65.52; H, 7.97; N, 4.87.

***trans*-2-(3-Methyl-2-butenyl)-3-methyl-*cis*-6-(3-furyl)piperidine (1).** A 0.5-g quantity of **25** was mixed thoroughly with 0.5 g of CaO and placed in a Pyrex tube fitted with a side arm which projected far into an Erlenmeyer flask cooled at 0 °C. The Pyrex tube was heated by the gentle application of a microburner flame until the enamine distilled. To the enamine in 20 mL of absolute ethanol was added 240 mg of $NaBH_4$ under N_2 and the resulting mixture was stirred 5 h at 25 °C. The solvent was removed at reduced pressure, the residue was dissolved in 25 mL of CH_2Cl_2, 5 mL of H_2O was added, the two phase system was stirred for 10 min, the phases separated, the aqueous extracted repeatedly with CH_2Cl_2, and all CH_2Cl_2 solutions combined and dried. Removal of the CH_2Cl_2 at reduced pressure afforded 225 mg of oil (57%) which according to GLC (column A, 150 °C, back pressure 17 psi) contained 85% **1** (R_t 13.2 min) and 15% of a mixture of what later proved to be **2** and **27** (R_t 14.8). A 140-mg portion of this oil was chromatographed on neutral Alumina (4% H_2O) in a 8 × 1 cm column packed in C_6H_6. Elution with the following solvents in the specified quantities produced the fractions and milligram amounts indicated in parentheses: 1 mL C_6H_6, Al (6); 70 mL C_6H_6, A2 (123); 30 mL C_6H_6, A3 (8); 30 mL CH_2Cl_2–C_6H_6 (1:1), A4 (3). Fraction A1, a brown oil, was the only one which was Dragendorff inactive and was discarded. Fraction A2 was chromatographed on neutral Alumina (3% H_2O) by eluting with 5% ether–hexane in the following amounts, constituting the fractions indicated in parentheses: 50 mL (B1), 100 drops (B2), 36 mL (B3), 30 mL (B4), 20 mL (B5), 220 mL (B6). Fractions B7 and B8 were eluted with 60 mL of chloroform each. Combined fractions B1–B3 consisted of a total of 12 mg of UV active but Dragendorff inactive material and were discarded. Combined fractions B4–B6 consisted of a total of 79 mg of pure **1**. Fraction B7 consisted of a 2-mg mixture of **1** and **2** and B8 consisted of a 16-mg mixture of **1** and **27**. The GLC (column A, 150 °C, back pressure 17 psi), the TLC (B and C), IR (CCl_4), ^1H NMR, and ^{13}C NMR of **1** were identical with those of (−)-anhydronupharamine and are as follows: GLC R_t 13.2; TLC (B) R_f 0.80; TLC (C) R_f 0.54; IR (CCl_4) 2770 (Bohlmann bands), 873 cm^{-1} (3-furyl); ^1H NMR δ 7.27–7.35 (3-furyl α-H), 6.36 (apparent t, J = 1.4 Hz, 1 H, 3-furyl β-H), 5.12 (t, J = 6 Hz, 1 H, CH=C), 3.57 (dd, J = 10.0 and 2.1 Hz, 1 H, C-6 ax H), 1.96–2.52 (m, 3 H), 1.70 (s, CH_3 C(C)=C), 1.64 (s, CH_3 C(C)=C), 0.91 (d, J = 6.0 Hz, 3 H, C-3 CH_3); ^{13}C NMR, see Table 1; GLC (column E, 185 °C) R_t 10.15.

***cis*-2-(3-Methyl-2-butenyl)-3-methyl-*cis*-6-(3-furyl)piperidine (2).** Fraction B7 was chromatographed on neutral Alumina (4% H_2O) in a 0.6 × 24 cm column packed in hexane. Elution with 5% ether in hexane in 25-, 15-, and 40-mL volumes yielded fractions C1 (0 mg), C2 (1 mg), and C3 (0.5 mg). Fraction C2 contained pure **2**: TLC (B) R_f 0.82; TLC (C) R_f 0.50; GLC (column A, 150 °C, back pressure 17 psi) R_t 14.8; GLC (column E, 185 °C) R_t 11.04; ^1H NMR δ 7.28–7.36 (3-furyl α-H), 6.41 (apparent t, 1 H, 3-furyl β-H), 5.12 (t, J = 7 Hz, 1 H, C=CH), 3.60 (dd, J = 5.0 and 8.0 Hz, 1 H, C-6 H), 2.77 (td, J = 7.4 and 2.2 Hz, 1 H, C-2 H), 2.05 (br t, J = 7.4 Hz, 2 H, CH_2C=C), 1.63 (s, $CH_3C(C)$=C), 1.71 (d, J = 0.5 Hz, $CH_3C(C)$=C), 0.98 (d, J = 7.2 Hz, 3 H, C-3 CH_3), and whose TLC, GLC, and ^1H NMR were identical with those of naturally occurring (−)-nuphenine.

***trans*-2-(3-Methyl-2-butenyl)-3-methyl-*trans*-6-(3-furyl)piperidine (27).** Fractions A3 and B8 were combined (24 mg) and chromatographed on neutral Alumina (4% H_2O) in a 1 × 10 cm column. Elution with 5% ether–hexane was carried out in the following volumes constituting the fractions indicated in parentheses: 100 mL (D1), 150 mL (D2), 100 mL (D3). Fraction D4 was eluted with 100 mL of $CHCl_3$. Fraction D2 contained 5 mg of pure **27**: TLC (B) R_f 0.39; GLC (column E, 185 °C) R_t 11.34; IR (CCl_4) 873 cm^{-1} (3-furyl); ^1H NMR δ 7.22–7.46 (m, 2 H, 3-furyl α-H), 6.28 (m, 1 H, 3-furyl α-H), 5.12 (apparent t, J = 7.2 Hz, 1 H, CH=C), 4.11 (t, J = 4 Hz, 1 H, C-6 H), 1.72 (s, CH_3 C(C)=C), 1.66 (s, $CH_3C(C)$=C), 0.89 (d, J = 6.0 Hz, 3 H, C-3 CH_3); ^{13}C NMR, see Table I.

Nuphenine and (−)-Anhydronupharamine. These two alkaloids had been isolated in these laboratories from *N. luteum* subsp. *variegatum* and *N. japonicum*, respectively, and were purified by elution chromatography on Alumina immediately before comparison with synthetic samples. Optical rotations, ^1H NMR, and IR of these samples agreed with those reported earlier for (−)-nuphenine (**2**) and (−)-anhydronupharamine (**1**). The ^{13}C NMR of these two compounds are reported in Table I.

5-(3-Furamido)pentanoic Acid (17). Procedure A. A suspension of 500 mg of methyl 5-(3-furamido)pentanoate, **15**,[9] in 10 mL of 2.25% aqueous KOH was heated to reflux for 2 h, during which time solution resulted. The mixture was cooled to 25 °C over the course of 1 h, the pH was adjusted to 2.0 with 25% aqueous H_2SO_4, and the mixture was repeatedly extracted with 50-mL quantities of methyl isobutyl ketone. The combined extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure to obtain an oil which was dissolved in 25 mL of ether. From this solution crystals were formed on inducement. Drying these crystals at 40 °C at reduced pressure gave 400 mg of **17** (85%): mp 118–119 °C.

Procedure B. To a solution of 5 g of 5-aminopentanoic acid (0.04 mol) in 150 mL of H_2O was added 250 mL of methyl isobutyl ketone (MIBK) and the pH of the mixture was adjusted to 8.5 with 10% aqueous KOH. A 6.68-g sample of 3-furoyl chloride (0.05 mol) in 75 mL of MIBK was added in one portion with vigorous stirring. As the pH dropped it was adjusted to 8.0–8.5 by dropwise addition of 10% aqueous KOH. The reaction mixture was stirred until the pH remained constant (about 1.5 h), at which point the pH was adjusted to 2.0 with 25% H_2SO_4 and two phases were separated. The aqueous phase was extracted repeatedly with MIBK and all the MIBK extracts and solutions were combined and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave an oil which, in the manner described in procedure A above, was transformed to 8.7 g of crystalline **17** (97%): mp 118–119 °C; IR (KBr) 3340 (NH), 1700 (COOH), 1620 (CONH), 875 cm^{-1} (3-furyl); ^1H NMR (Me_2SO-d_6) δ 8.15 (m, 2 H, 3-furyl α-H and COOH), 7.70 (m, 1 H, 3-furyl α-H), 6.85 (m, 1 H, 3-furyl β-H), 3.32 (m, 2 H, C-5 H), 2.25 (m, 2 H, C-2 H), 1.52 (m, 4 H, C-3 and C-4 H). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.85; H, 6.22; N, 6.63. Found: C, 57.00; H, 6.46; N, 6.56.

2-(3-Furyl)piperidine (20). A 1.5-g sample of **17** was mixed thoroughly with 1.5 g of CaO and the mixture was heated as described above in the preparation of **1**. The resulting distillate was collected in 25 mL of 10% aqueous HCl, the pyrolysis tube was rinsed with $CHCl_3$, and the solid residue was extracted with $CHCl_3$. The aqueous HCl solution and the combined $CHCl_3$ solutions were added to a separatory funnel. After shaking, the $CHCl_3$ layer was discarded, the aqueous layer was cooled to 5 °C, mixed with ether, and basified to pH 10 with 20% NaOH. The aqueous phase was extracted repeatedly and all ether extracts were combined and dried ($MgSO_4$). Removal of the ether at reduced pressure gave 550 mg of brown oily **13** (52%): GLC (column A, 150 °C, back pressure 12 psi) R_t 3.1. A 500-mg portion of **13** in 5 mL of dry EtOH under N_2 was mixed with 250 mg of $NaBH_4$ and the resulting heterogeneous mixture was stirred at 25 °C for 5 h. The EtOH was removed at reduced pressure, the residue was suspended in ether, water was added to the suspension, and the layers were separated. The aqueous layer was extracted with ether and all ether extracts were combined and dried ($MgSO_4$). Removal of the ether at reduced pressure gave 432 mg of brown oily **20** (85%): GLC (column A, 150 °C, back pressure 12 psi) R_t 2.1; IR 2920, 2840 (CH), 870 cm^{-1} (3-furyl); ^1H NMR δ 7.35 (m, 2 H, 3-furyl α-H), 6.45 (m, 1 H, 3-furyl β-H), 2.50–3.80 (m, C-2 and C-6 H), 1.75 (6 H, m, C-3, C-4, and C-5 H); ^{13}C NMR is given in Table I. Anal. Calcd for $C_9H_{14}NOCl$: C, 57.60; H, 7.52; N, 7.37. Found: C, 57.49; H, 7.71; N, 7.37.

5-(3-Furamido)hexanoic Acid (18). A suspension of 300 mg of methyl 5-(3-furamido)hexanoate[9] in 6 mL of 2.25% aqueous KOH was treated as **15** in the preparation of **17** (procedure A) described above. In that manner was obtained 242 mg of **18** (80%): mp 112–113 °C; IR (KBr) 3300 (NH), 1700 (COOH), 1630 (CONH), 875 cm^{-1} (3-furyl); ^1H NMR (Me_2SO-d_6) δ 8.31 (s, 1 H, COOH), 7.83 (m, 2 H, 3-furyl α-H), 6.97 (m, 1 H, 3-furyl β-H), 3.8–4.3 (m, 1 H, C-5 H), 2.00–2.45 (m, 2 H, C-2 H). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 56.85; H, 6.72; N, 6.21. Found: C, 58.52; H, 6.77; N, 6.47.

***cis*- and *trans*-6-Methyl-2-(3-furyl)piperidine (21 and 22).** A mixture containing 440 mg of **18** and 440 mg of CaO was treated as described above in the preparation of **1**. In this manner was obtained 191 mg of a light brown oily **19** (60%): GLC (column A, 150 °C, back pressure 16 psi) R_t 3.1. A 185-mg portion of **19** in 3 mL of dry EtOH under N_2 was mixed with 185 mg of $NaBH_4$ and the resulting suspension was treated as described above in the preparation of **1**. Thereby was obtained 150 mg of a light brown oily mixture of **21** and **22** (80%), GLC (column A, 150 °C, back pressure 16 psi), R_t 2.4 (91% **21**) and 3.1 (9% **22**), which was chromatographed on a neutral alumina (activity 2) column (1 × 11 cm) eluted with CH_2Cl_2, in 20 (E1), 7 (E2) and 170 mL (E3) fractions and with $CHCl_3$ in 75 (E4) and 100 mL (E5) fractions. Fraction E3, 69 mg, contained **21**: GLC (column E, 150 °C) R_t 5.27; TLC (Alumina, twice developed, once with CH_2Cl_2 then

$CHCl_3$) R_f 0.38; IR (CCl_4) 2778 (Bohlmann bands), 873 cm^{-1} (3-furyl); ^1H NMR δ 7.31 (m, 2 H, 3-furyl α-H), 6.36 (m, 1 , 3-furyl β-H), 3.60 (dd, J = 10.4 and 3.0 Hz, 1 H, C-2 H), 2.78 (q'd, 1 H, C-6 H), 1.05 (d, J , 6.6 Hz, 3 H, C-2 CH_3); ^{13}C NMR, see Table I; high-resolution MS, obsd/calcd mass (formula) 165.1151/165.1152 ($C_{10}H_{15}NO$).

Fraction E4 was chromatographed on a 1 × 11 cm column of neutral fractions and a 30-ml $CHCl_3$ fraction (F4). Fraction F4 was chromatographed on a 0.7 × 2-cm column of neutral Alumina (activity 2) with 150 mL of CH_2Cl_2 (G1) and two 75-mL portions of $CHCl_3$–CH_2Cl_2 (1:9) (G2 and G3). Fractions F3 (3 mg) and G3 (7 mg) were combined and consisted of pure **22**: GLC (column E, 150 °C) R_t 6.06; TLC (Alumina, twice developed, once with CH_2Cl_2 and then $CHCl_3$) R_f 0.31; IR (CCl_4) 2718 (very weak Bohlmann bands), 873 cm^{-1} (3-furyl); ^1H NMR δ 7.24–7.44 (m, 2 H, 3-furyl α-H), 6.36 (m, 1 H, 3-furyl β-H), 4.10 (t, J = 4 Hz, 1 H, C-2 H), 3.04 (q'd, J = 7.0 and 2.2 Hz, 1 H, C-6 H), 1.11 (d, J = 6.0 Hz, 3 H, C-6 CH_3); ^{13}C NMR, see Table I; high-resolution MS, obsd/calcd mass (formula) 165.1173/165.1152 ($C_{10}H_{15}NO$).

Registry No.—**1**, 61949-86-8; **2**, 61949-87-9; **3**, 110-93-0; **4**, 53067-23-5; **5**, 61900-43-4; **6**, 61900-44-5; **7**, 61900-45-6; **8**, 61900-46-7; **9**, 61900-47-8; **13**, 61900-48-9; **15**, 61586-90-1; **17**, 61900-30-9; **18**, 61900-31-0; **19**, 61900-32-1; **20**, 61900-33-2; **21**, 61900-34-3; **22**, 61900-35-4; **23**, 61900-36-5; **24**, 61900-37-6; **25**, 61900-38-7; **27**, 61949-85-7; dimethyl carbonate, 616-38-6; hydroxylamine HCl, 5470-11-1; dimethyl sulfate, 77-78-1; 3-furoyl chloride, 26214-65-3; 5-aminopentanoic acid, 660-88-8; 5-(3-furamido)hexanoate, 61900-39-8; (−)-nuphenine, 4850-01-5; (−)-anhydronupharamine, 4849-88-1.

References and Notes

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(19) Our ^{13}C NMR resonance assignments for anhydronupharamine agree with those of another study [S. Yasuda, M. Hanaoka, and Y. Arata, *Chem. Pharm. Bull.*, **24**, 2521 (1976)] which we became aware of after this paper had been submitted for publication.

A Carbon-13 Nuclear Magnetic Resonance Study of Thiol Esters

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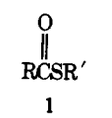
The ^{13}C NMR chemical shifts for each of the carbons of a number of simple thiol esters have been measured in Me_2SO-d_6 and $CDCl_3$ and the results related to known chemical properties of the thiol ester function. In general the chemical shift of the thiol ester carbonyl carbon occurs some 15–20 ppm further downfield than that found for all other carboxylic acid derivatives reported to date. The carbon α to the carbonyl function in thiol esters is also shifted downfield by about 10 ppm relative to the α carbon in acids, oxygen esters, or amides. The effect of carbon group and halogen substituents on thiol ester chemical shifts has been analyzed. A solvent study on β-hydroxy thiol esters shows that the carbonyl carbon is shielded in Me_2SO-d_6 relative to $CDCl_3$, which may be attributed to intramolecular hydrogen bonding in the latter solvent. Carbon-13 chemical shift changes resulting from conversion of mercaptans to thiol ester derivatives indicate relatively little difference between *S-tert*-butyl and other types of *S*-alkyl thiol esters in contrast to results obtained previously with *tert*-butyl oxygen esters.

The thiol ester group **1** is the ester function of choice in condensation and acyl transfer reactions occurring in biochemical systems.[1] In contrast to (oxygen) esters or amides, relatively little is known about the electronic structure of this group. As a result of our interest in the chemistry and properties of thiol esters, we have undertaken a ^{13}C NMR study of this class of compounds. A search of the literature has not produced any general ^{13}C NMR studies on the thiol ester function.[2] We have thus obtained natural abundance ^{13}C NMR spectra for some 30 different compounds. These results are discussed in connection with ^{13}C NMR data available for other carbonyl derivatives.[3,4] Substituent effects of the thiol ester group are analyzed and the effect of structure on thiol ester chemical shifts has been examined. Finally, we have focused attention on the relationship of these ^{13}C NMR results to the chemistry and biological properties of the thiol ester function.



1

Experimental Section

Spectra. The ^{13}C NMR spectra were obtained on ca. 20–25% (w/v) solutions in $DCCl_3$ or Me_2SO-d_6 using a Varian CFT-20 spectrometer