4-Alkylideneisoxazol-5-ones. Synthesis, Tautomerism, and Rearrangement to Pyrroles

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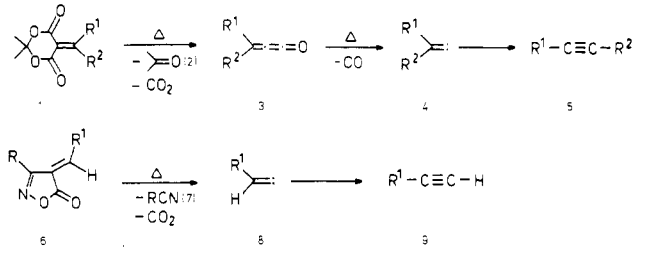
Received July 11, 1984

The synthesis of several 4-alkylidene- and 4-cycloalkylideneisoxazol-5-ones is described and their tautomerism is investigated by ^{13}C NMR, ^{1}H NMR, and IR spectroscopy. Through hydrogen shifts involving the exocyclic substituent (2-propylidene, cyclopentylidene, or 2-indanylidene) these compounds can exist in CH, NH, or OH forms (Scheme II). The CH form is favored in solvents of low polarity ($CDCl_3$) and in the absence of special enthalpic and conjugative effects stabilizing the NH form. The NH form is favored in polar solvents (Me_2SO), and its dominance is accentuated when the vinylic substituent is stabilized thermodynamically and conjugationally. The OH form is not observed directly, but the ionized O^- form is present in the morpholinium salts of **15**, **16**, and **17**. In the 2-propylidene derivative **12** only the CH form was spectroscopically detectable, but H/D exchange experiments on this and other isoxazolones showed that tautomerism does take place (**12** → **24**). The alkylideneisoxazolones rearrange to pyrrolecarboxylic acids on flash vacuum pyrolysis. Of two possible mechanisms, a vinylnitrene mechanism (Scheme IV) and a nitrile ylide mechanism (Scheme V), the former is shown to apply. The pyrrolecarboxylic acids often decarboxylate under the reaction conditions.

Two thermal methods for the synthesis of a variety of acetylenes have been developed in recent years: (i) flash vacuum pyrolysis of 2,2-dimethyl-5-methylidene-1,3-dioxane-4,6-diones (Meldrum's acid derivatives) (**1**), which



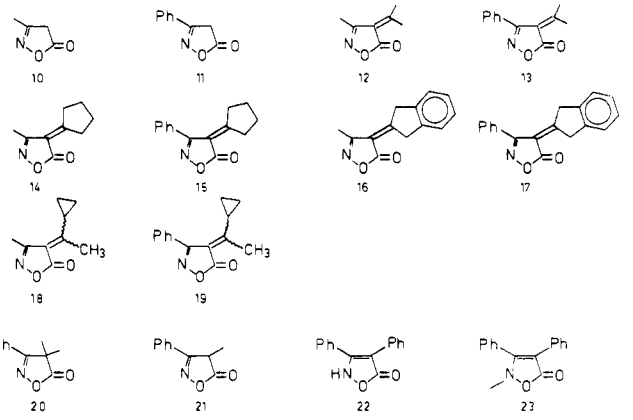
decompose to acetone (**2**), CO_2, and the methyleneketenes **3**,[2,3] and (ii) flash vacuum pyrolysis of 4-methylideneisoxazol-5(4*H*)-ones (**6**), which fragment to a nitrile (**7**), CO_2, and the vinylidenes **8**.[4,5]

Both methods are excellently suited for the production of aryl- and heteroarylacetylenes.[2,4] However, method i fails with aryl groups carrying *o*-CHR_2 substituents because of a tautomerization of the ketene **3** and recyclization to give a 2-naphthol derivative.[2,3] Method ii is not subject to this restriction, and (*o*-methylaryl)acetylenes are formed in good yields.[6] In this respect, the two methods complement each other.

Although dimethylacetylene, *tert*-butylacetylene, cyclononyne, and cyclooctyne can be formed from the corresponding Meldrum acid derivatives (**1**),[3,7] method i is severely limited as a synthetic method for alkylacetylenes because methyleneketenes **3** carrying one or two HCR_2 groups readily isomerize to vinylketenes.[3,8-10]

We now wish to report a study of alkylideneisoxazolones **12–17**. These compounds do not give rise to acetylenes on pyrolysis, or do so only to a very minor extent. Instead, the main products are pyrrolecarboxylic acids (**38**, **44**, and **47**) or the corresponding decarboxylated pyrroles (**29**, **39**, **45**, and **48**), all formed as a consequence of yet another tautomerization reaction.

Synthesis. 3-Methyl- (**10**) and 3-phenylisoxazol-5-(4*H*)-one (**11**) undergo condensation in position 4 with ketones under either acid[11] or base[12,13] catalysis. Also the use of 1 equiv of base in the form of the isoxazolone morpholinium salt has been employed.[14] The condensation products **12**[11] and **14–19** were prepared by a combination of these methods (see Experimental Section). The direct condensation of **11** with acetone has been reported to be unsuccessful;[15] however, we found that the desired product, **13**, is readily obtained in 69% yield by carrying out the reaction in the presence of an excess of PCl_5. The condensation with cyclopropyl methyl ketone was achieved by successive treatment with $TiCl_4$ and pyridine to give products **18** and **19** as *Z*/*E* mixtures. The latter method



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0022-3263/85/1950-2041$01.50/0

may be profitably applied in the preparation of other, difficultly accessible condensation products of isoxazolones with ketones.

Tautomerism. The subject of tautomerism of isoxazolones has been reviewed.[16] In general, 3- and/or 4-substituted isoxazol-5-ones may exist in CH, NH, or OH forms (Scheme I). Similarly, the methylidene derivatives **12–19** may also exist as CH, NH, or OH forms by virtue of a tautomerism involving the exocyclic substituents (Scheme II). An interconversion of the CH and OH forms could take place as a direct [1,5]-sigmatropic shift, whereas an interconversion of either the CH or OH form with the NH form is likely to proceed by intermolecular H transfer. As shown below, the OH forms have not actually been observed. However, some of the morpholinium salts of these compounds exist exclusively as the isoxazol-5-olates; these are designated O^- forms (see Scheme II).

We have investigated the tautomeric nature of the compounds **12–17** using IR, ^{13}C NMR (Table I), and ^1H NMR (Table II) spectroscopy. In order to provide a data base for ^{13}C NMR spectroscopy, compounds **10**, **11**, and **20–23** are also included. The assignment of the ^{13}C NMR spectra was aided by recording both $\{^1H\}$-decoupled and gated-decoupled spectra. A special numbering system (Scheme III) is used in order to number all carbon atoms in compounds **10–23** in a consistent manner.

Previous investigations using UV,[17,18] IR,[17–19] and ^1H NMR spectroscopy[18–21] have demonstrated that simple 3- and/or 4-substituted isoxazol-5-ones tend to exist in the CH form in solvents of low polarity ($CDCl_3$). Depending on substituents, the NH form may become more or less pronounced in solvents capable to supporting hydrogen bonds (e.g., $(CD_3)_2SO$). In strongly basic media (pyridine, piperidine, and aqueous NaOH) the OH form and the ionized O^- form also enter the equilibrium.[20–21] A detailed ^{13}C NMR study of 3-(phenoxymethyl)isoxazol-5-one in pyridine solution revealed the presence of 15 ± 3% CH, 10 ± 5% NH, 10 ± 8% OH, and 65 ± 8% O^- forms.[22]

Whereas compound **10** has been detected only in the CH form,[17–19] mixtures of CH and NH forms are observed for **11** in $(CD_3)_2SO$, and for **21** even in $CDCl_3$ solution[18–20] (Table I). The CH forms are readily distinguished from the NH or OH forms by the position, coupling constant, and multiplicity of C-4 in the ^{13}C NMR spectra (Table I). A distinction between NH and OH forms cannot easily be made on the basis of ^{13}C NMR alone, but the facts that only one form other than CH is observed and that this form shows a strong carbonyl absorption in the IR (Table I) demonstrate that the unknown species is the NH and not the OH form.

A previous report[23] on the OH form of **11** cannot be substantiated. Rather, the data reported, allegedly for the OH form in $CHCl_3$ solution, agree with our data for the NH form in $(CD_3)_2SO$ solution as presented in Table I.

In agreement with a conclusion based on IR spectroscopy,[17] compound **22** exists exclusively in the NH form shown in $CDCl_3$ solution; no signal due to a carbon atom carrying a directly bonded proton could be detected in the ^{13}C NMR spectrum (Table I). The increased stability of **22**-NH vis-à-vis **21**-NH can be ascribed to a gain in conjugation.

The ^{13}C and ^1H NMR spectra of the 4-alkylideneisoxazolones **12–17** can now be assigned (Table I and II, respectively). The CH and NH forms are readily distinguished by the appearance of a vinylic carbon (C-8) in the ^{13}C NMR spectrum, split into a doublet in the gated-decoupled spectrum, and a corresponding vinylic hydrogen (H-8) in the ^1H NMR spectrum of the NH form. The IR spectra of **16** and **17** in dimethyl sulfoxide solution (only one tautomer detectable by NMR) clearly demonstrate the presence of the NH rather than the OH forms. In agreement with the literature,[17–20] the carbonyl bands of the CH forms are at higher wavenumber than those for the NH forms (e.g., ca. 1800 cm^{-1} for **11**-CH; 1720 cm^{-1} for **11**-NH). Similarly, **16** and **17** exhibit strong C=O bands at 1720–1730 cm^{-1} in dimethyl sulfoxide solution. In the ^1H NMR spectra, the NH protons appear as broad signals at 8–10 ppm.

The large chemical shift of C-6 in the CH forms of **12–17** (171–186 ppm) deserves comment. Such high values are, in fact, characteristic of planar, conjugated ketones,[24] and the increase by ca. 13 ppm on going from **12** to **14** or from **13** to **15** can be accounted for as the combined effect of alkylation and ring formation.[24]

It will be seen from an inspection of Tables I and II that the tendency to tautomerize to the NH form increases in the series **12–17**. **12** and **13** have only been observed in the CH forms (also the case in $(CD_3)_2SO$ solution (spectra not shown), in which they are only sparingly soluble). **14**, **15**, **16**, and **17** exist in the NH forms to an extent of 6%, 30%, ca. 100%, and 100%, respectively, in $(CD_3)_2SO$ solution, and **17** even exists as 85% NH form in $CDCl_3$ solution. This trend, too, is readily understood because an endocyclic double bond in a five-membered ring is thermodynamically preferred over an exocyclic one. In contrast, a 2-propylidene substituent is preferred over a 2-propenyl substituent.[25] Moreover, the increased conjugation on going from the CH to the NH forms of **16** and **17** confers additional stability to these tautomers.

The trend from CH form (**12** and **13**) to NH form (**16** and **17**) is reflected in the solubilities and ease of sublimation of these compounds: **12** is only slightly soluble in dimethyl sulfoxide, **16** and **17** are very soluble, and **14** and **15** are intermediate. The opposite trend is observed for solubilities in chloroform. Again, the CH compounds **12** and **13** are easily sublimable; the NH compounds **16** and **17** sublime with extreme difficulty.

An OH form has not been directly detected in any of the compounds studied. However, the morpholinium salts of **15**,[14] **16**, and **17** are devoid of C=O bands in the IR and thus are entirely ionized. The ^{13}C and ^1H NMR spectra of the morpholinium salt of **16** are given in Tables I and II and are best interpreted in terms of the O^- forms. Whereas the vinylic proton H-8 in **16**-NH appears at 7.21 ppm, the corresponding signal for **16**-O^- is displaced to higher field (6.60 ppm) due to an increased electron density at C-8, arising from conjugation with the isoxazol-5-olate system. In the ^{13}C NMR spectrum the signals for C-4 and

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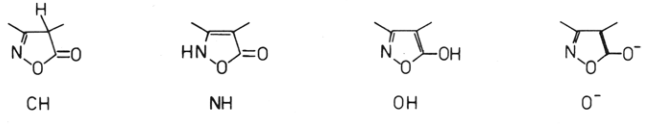
Table I. ^{13}C NMR Data,[a,b] Infrared Data, and Equilibrium Composition of Isoxazolones

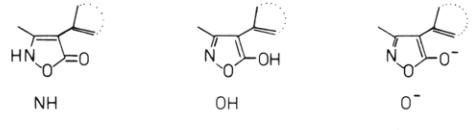
compd	solv	δ C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18	J_{C_4H},[c] Hz	IR($\nu_{C=O}$),[d] cm^{-1}	amt in equilib,[e] %
									CH Form											
10	$CDCl_3$	164.4	36.3	175.6				13.5										137.0 (t)	1797[f,g]	100
11	$CDCl_3$	163.0	34.0	174.6				127.6	129.1	126.5	132.1							139.9 (t)	1807,[g,h] 1800 (KBr)	100
11	$(CD_3)_2SO$	164.7	34.6	176.2				127.8	129.0	126.5	131.7								1801[g]	42
20	$CDCl_3$	169.6	45.7	181.7	22.9			127.5	129.1	126.8	131.6								1803[g,h]	
21	$CDCl_3$	167.2	39.5	178.8	14.5													135.3 (d)	1800[h]	70
12	$CDCl_3$	158.2	117.1	168.7	171.3	24.4	22.5	15.9											1755 (KBr)	100
13	$CDCl_3$	161.8	116.9	168.8	173.0	25.6	22.9	130.0	128.7	128.3	130.1								1750 (KBr)	100
14	$CDCl_3$	158.8	114.5	169.1	182.7	35.0	34.9	14.6				25.5	24.9						1760 (KBr)	100
14	$(CD_3)_2SO$	159.5	113.7	169.0	184.5	35.0	34.8	14.3				25.2	24.8							94
15	$(CD_3)_2SO$	162.2	112.9	168.7	186.0	36.2	35.3	129.1	128.7	128.5	130.3	25.2	24.6						1760 (KBr)	70
17	$CDCl_3$	161.8	115.7	168.8	[185.0]	41.7	41.5													15
									NH Form											
11	$(CD_3)_2SO$	164.1	79.7	172.6				127.8	129.0	126.5	131.1							183.7 (d)	1720	58
21	$CDCl_3$	161.6	99.0	174.4	7.6													6.8 (q)	1735[h]	30
22	$CDCl_3$	161.1	102.3	172.0														0	1690, 1680 (KBr)[h]	100
23	$CDCl_3$	163.6	103.5	169.5															1762 (KBr)	
14	$(CD_3)_2SO$	158.1	94.0	169.8	132.0	[33.5]	123.7	11.9				22.4	[32.0]							6
15	$(CD_3)_2SO$	159.8	95.4	170.0		[33.9]						22.7	[32.2]							30
16	$(CD_3)_2SO$	158.2	93.5	169.5	137.2	39.5	123.7	12.3				145.0	141.8	120.0	126.3	123.5	123.2		1720	~100
17	$CDCl_3$	160.3	99.2	171.5	[134.4]	40.0	[126.4]		[128.4]	[129.1]	131.3			120.8	[127.5]	124.6	123.3		1705, 1685	85
17	$(CD_3)_2SO$	159.8	94.6	169.8	136.0	39.8	[126.2]	128.0	129.0	128.6	131.0	144.6	141.8	120.2	126.3	124.0	123.2		1730	100
									OH (O^-) Form											
16[i]	$(CD_3)_2SO$	158.0	83.6	175.1	143.6	39.8	113.8	14.2				147.4	140.6	125.9	125.9	122.6	120.7		absent[j]	100

[a] Spectra were run at 25.16 MHz. Concentrations 0.3–2.7 mol/L. Assignments from gated-decoupled spectra. Shifts in brackets denote uncertain assignments. [b] For numbering system, see Scheme III. [c] $^1J_{C_4H_4}$ in **10**, **11**, and **21**-CH. $^2J_{C_4CH_3}$ in **21**-NH. Multiplicities given in parentheses. [d] Carbonyl band in IR spectrum in same solvent as used for ^{13}C NMR unless otherwise indicated. [e] Composition of tautomeric mixture determined from integrated ^1H NMR spectra (Table II) and qualitatively confirmed by the ^{13}C NMR intensities. [f] Reference 18. [g] Reference 19. [h] Reference 17. [i] As morpholinium salt. [j] C=N at 1630 cm^{-1}.

Scheme I



Scheme II



Scheme III

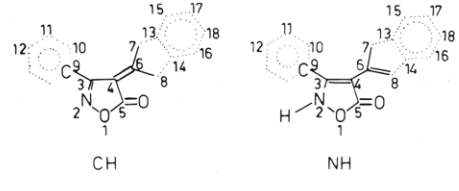


Table II. ^{1}H NMR Data and Equilibrium Composition of Isoxazolones[a]

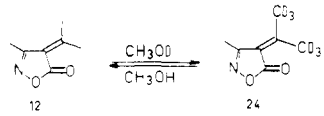
compd	solv	δ H-2	H-4	H-7	H-8	H-9	H-10	H-11,12	H-13,14	H-15 to H-18	amt in equilib, %
					CH Form						
11[b]	$CDCl_3$		3.80 s				7.68 m	7.50 m			100
11[b]	$(CD_3)_2SO$		4.31 s				7.75 m	7.50 m			42
12	$CDCl_3$			[2.24] s	2.36 s	[2.19] s					100
13	$CDCl_3$			1.92 s	2.55 s			7.46 m			100
14	$CDCl_3$			2.81 t	2.94 t	2.21 s			1.79 m		100
14	$(CD_3)_2SO$			2.95 m		2.26 s			1.80 m		94[c]
15	$(CD_3)_2SO$			2.29 t	3.02 t			7.52 s	1.64 m		70
17	$CDCl_3$			3.73 m	4.53 m						15
					NH Form						
11[b]	$(CD_3)_2SO$	12.63 br	5.72 s				7.75 m	7.50 m			58
14	$(CD_3)_2SO$				6.05 t	2.21 s					6[c]
15	$(CD_3)_2SO$			[2.14] m	6.12 t		[7.52] s				30
16	$(CD_3)_2SO$	9.84 br		3.71 s	7.21 s	2.37 s				7.20 m	~100
17	$(CD_3)_2SO$	8.16 br		3.40 s				7.45 s		7.25 m	85
17	$(CD_3)_2SO$	10.36 br		3.36 s	[7.17] s			7.61 s		7.12 m	100
					O$^-$ Form						
16[d]	$(CD_3)_2SO$			3.63 s	6.60 s	2.15				6.7–7.3 m	100

[a] Spectra were run at 100 MHz. Multiplicities (first order) are indicated. Brackets denote uncertain assignment; br = broad (NH). [b] See also ref 19 and 20. [c] At 90 °C 14 exists exclusively in the CH form in $(CD_3)_2SO$. [d] As morpholinium salt.

C-8 are shifted to higher fields for the same reason. The ^{1}H NMR spectrum of the morpholinium salt of **15** in $CDCl_3$ solution has been previously interpreted in terms of the isoxazol-5-olate structure.[14]

To conclude this section, the tautomeric behavior of the alkylideneisoxazolones **12–17** parallels that of the simpler 3- and/or 4-substituted isoxazolones. Polar solvents, enthalpic effects, and increased conjugation favor the NH forms. Strongly basic solvents (morpholinium salts) favor the O$^-$ forms.

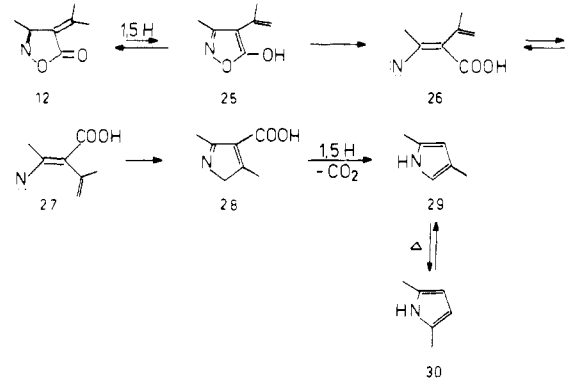
H/D Exchange. Although only one tautomer (the CH form) of **12** was spectroscopically detectable, this compound does tautomerize, as shown by deuterium exchange experiments. The six protons of the 2-propylidene side chain exchange slowly in neutral D_2O solution, and in CH_3OD solution with a half-life of 16 h, giving **24**, as monitored by ^{1}H NMR spectroscopy.



Compounds **14**, **15**, and **16** similarly undergo exchange of H-7 and H-8 (see Scheme III) in $(CD_3)_2SO$–CD_3OD solution with half-lives of 16, 25, and 60 min, respectively. It was shown by ^{1}H NMR spectroscopy that in each individual compound, the exchange rates for H-7 and H-8 are identical. The "slowness" of compound **12** may be ascribed to the presence of only minute concentrations of the NH and/or OH tautomers in the equilibrium. The slowness of compound **16**, as compared with **14** and **15**, may be similarly ascribed to the low concentration of the CH form. **14** and **15** exist in both CH and NH forms in $(CD_3)_2SO$ solution, and the exchange rates demonstrate that the two forms interconvert relative rapidly. The possibility that low concentrations of the OH forms are also involved in the exchange reactions remains open.

Pyrolysis. In contrast to 4-(arylmethylidene)isoxazol-5(4*H*)-ones,[4,5] no acetonitrile was formed on flash vacuum pyrolysis of **12** at 550–700 °C (5×10^{-4} torr). Instead, the pyrolysis product consisted of CO_2 and a ca. 45:55 mixture of the dimethylpyrroles **29** and **30**. The decomposition of **12** was complete at 700 °C, and at higher temperatures smaller amounts of other isomeric dimethylpyrroles were formed as well. Control experiments demonstrated that **29** and **30** interconvert at elevated temperatures (vide infra), and almost identical mixtures were formed from both at 850–975 °C, with only minor amounts of the other isomers being present.

Scheme IV



A mechanism for the formation of **29** and **30** is given in Scheme IV. It is suggested that **12** interconverts with the OH form **25** in the gas phase at low pressure. This tautomer will be kinetically favored over the NH form under these conditions because it is generated in a direct [1,5]-sigmatropic shift. Cleavage of the weak N–O bond in **25** gives the nitrene **26** and is rotamer **27**, the latter cyclizing to the 2*H*-pyrrole **28**. A [1,5]-hydrogeh shift and decarboxylation of **28** give **29**, which interconverts with **30** via [1,5] shifts of H and CH_3. There is precedence for the thermal interconversion of pyrroles by substituent migration.[26a] It has also been found in many examples that the temperatures required to bring about a certain secondary rearrangement reaction, e.g., substituent migration in a pyrrole, are subject to chemical activation in the system studied. Hence, the temperatures required to bring about such reactions in "control experiments", where chemical activation is absent, may be much higher.[26] This explains the observation that fully interconverted mixtures of **29** and **30** are formed from **12** at 550–700 °C, although

(26) (a) Wentrup, C. *Top. Curr. Chem.* **1976**, *62*, 238–239. (b) Wentrup, C. *React. Intermed. (Plenum)* **1980**, *1*, 263–319.

Scheme V

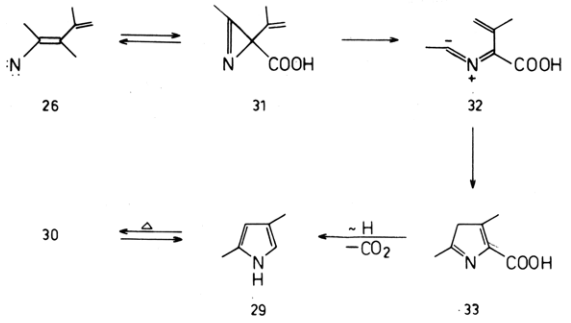


Table III. Products of Pyrolysis of 14

temp, °C[a]	rel yield[b] 14	38	39
500	0.6	1	0
560	0.3	1	0
600	0	1	1
800	0	1	3.7

[a] Pressure, 5×10^{-4} torr. [b] By ^{1}H NMR spectroscopy.

such interconversion of the pure pyrroles is complete only at ca. 850 °C.

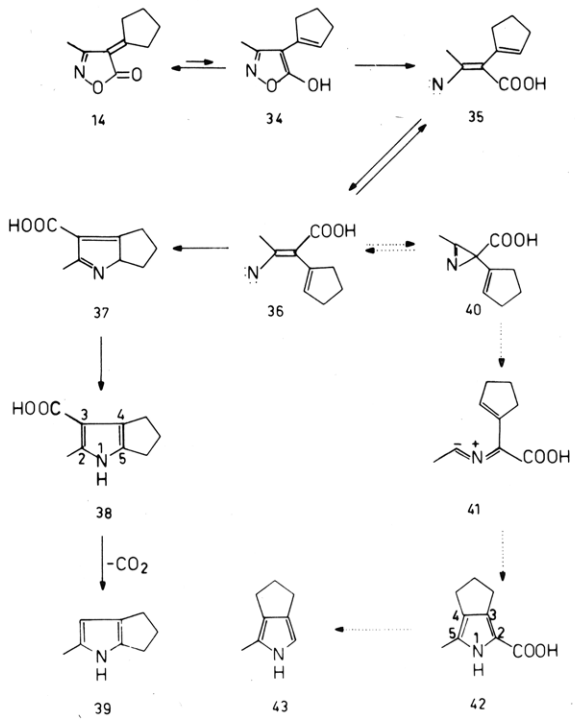
There is also precedence for the ring opening of isoxazoles, including 5-alkoxyisoxazoles,[27] to vinylnitrenes and recyclization of the latter to 2*H*-azirines.[28] 3-Vinyl-2*H*-azirines in turn ring open to dienylnitrenes that cyclize to 2*H*-pyrroles.[28]

An alternative to the mechanism shown in Scheme IV needs to be considered, namely C–C bond cleavage of the 2*H*-azirine **31** (Scheme V) to give the nitrile ylide **32**. Although nitrene formation is the normal event, several instances of thermal nitrile ylide formation from 2*H*-azirines have been reported.[28,29] Recyclization of ylide **32** to 3*H*-pyrrole **33** followed by decarboxylation would give **29**, viz., the same product as obtained in Scheme IV.

A distinction between the two mechanisms is possible by using the cyclopentylideneisoxazolone **14**. On pyrolysis of this compound, both dihydrocyclopentapyrrolecarboxylic acid and the corresponding decarboxylated derivative could be isolated. At mild temperatures (500–560 °C) only the starting material **14** and the carboxylic acid were obtained; at higher temperatures (600–800 °C) progressive decarboxylation took place (Table III). Two isomeric carboxylic acids, **38** and **42**, can be envisaged, depending on whether the nitrene (**35** → **36** → **37** → **38**) or nitrile ylide (**36** → **40** → **41** → **42**) mechanism is operating, as illustrated in Scheme VI.

In the event, a single isomer was isolated, the ^{13}C NMR spectrum of which is best in agreement with structure **38**. The ^{13}C NMR chemical shifts of substituted pyrrolecarboxylic acid derivatives can be calculated with good accuracy by using literature data.[30a] The calculated shifts (Table IV) are seen to agree quite well with experiment for structure **38**. In addition, the decarboxylated pyrrole was shown by ^{1}H NMR spectroscopy to have the structure **39** (derived from **38**) rather than **43** (derived from **42**). The

Scheme VI



Scheme VII

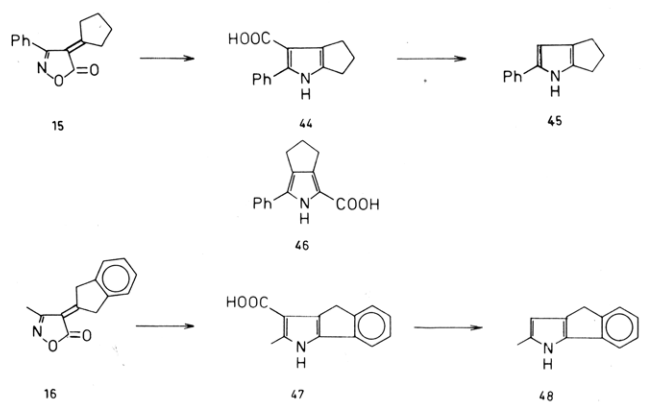


Table IV. Observed and Calculated ^{13}C NMR Chemical Shifts in Dihydrocyclopentapyrrolecarboxylic Acids[a]

compd		δ C-2	C-3	C-4	C-5
38[b]	exptl	137.4	107.0	126.9	133.1
38	calcd	135	110	126	130
42	calcd	117	133	129	131
44[c]	exptl	136.1	107.6	129.5	133.2
44	calcd	137	108	126	130
46	calcd	118	130	123–127	135

[a] Calculations based on additive increments for methyl and ester groups from ref 30a. Experimental spectra in $(CD_3)_2SO$ solution at 25.16 MHz. [b] Additional signals: δ 13.4 (CH_3), 24.7 (CH_2), 26.2 (CH_2), 28.1 (CH_2). [c] Additional signals: δ 24.9 (CH_2), 26.6 (CH_2), 28.2 (CH_2), 126.9 (phenyl para), 127.6, 128.8, 138.7 (phenyl C-1).

single ring proton resonates at 5.46 ppm, close to the value of 5.6 ppm for 2,3,5-trimethylpyrrole. This value is incompatible with structure **43**, which, by analogy with 2,3,4-trimethylpyrrole,[30b] would be expected to show a resonance near 6.5 ppm. Moreover, the ring proton at 5.46 ppm exhibits an allylic coupling of 0.7 Hz with the methyl group at C-2. Thus, the methyl group appears as a doublet, but the single proton resonance has a complex multiplicity because it also couples allylically with the NH proton. This

(27) Nishiwaki, T. *Synthesis* **1975**, *20*.
(28) Wentrup, C. *Adv. Heterocycl. Chem.* **1981**, *28*, 231–251.
(29) Wendling, L. A.; Bergman, R. G. *J. Org. Chem.* **1976**, *41*, 831. Demoulin, A.; Gorissen, H.; Hesbain-Frisque, A. M.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 4409.
(30) (a) Abraham, R. J.; Lapper, R. D.; Smith, K. M.; Unsworth, J. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1004. See also: Martin, L. L.; Chang, C.-J.; Floss, H. G.; Mabe, J. A.; Hagaman, E. W.; Wenkert, E. *J. Am. Chem. Soc.* **1972**, *94*, 8942. (b) Roomi, M. W.; Dugas, H. *Can. J. Chem.* **1970**, *48*, 2303. (c) Gronowitz, S.; Hörnfeldt, A.-B.; Gestblon, B.; Hoffman, R. A. *Ark. Kemi* **1961**, *18*, 133.

is normal for pyrroles.[31] The latter coupling is removed on N-deuteration, thus transforming the single proton resonance into a quartet. Spin-decoupling experiments confirmed the relationship between the methyl group and the single proton. The observed coupling constant of 0.7 Hz, together with the ^{13}C NMR spectrum, uniquely identifies the compound as 4,5-dihydro-2-methylcyclopenta-[*b*]pyrrole (**39**).[30b-c]

The phenyl-substituted isoxazolone **15** reacted in a manner entirely analogous to that of **14**, giving the pyrrolecarboxylic acid **44** at temperatures between 500 and 700 °C and the decarboxylated pyrrole **45** above 700 °C (Scheme VII and Table IV).

The indanylidene derivatives **16** and **17** exist essentially in the NH forms and sublime with extreme difficulty. Accordingly, vacuum pyrolyses are not easily performed. Nevertheless, small amounts of products were isolated following pyrolyses of **16** and tentatively assigned the structures **47** and **48** on the basis of NMR spectra of the mixture. In particular, compound **48** again shows an allylic coupling of 0.6 Hz between the methyl group and the single proton (H-3) at 5.83 ppm, as well as a coupling of 1.7 Hz between H-1 and H-3.

Conclusion

4-Alkylidene- and 4-cycloalkylideneisoxazol-5-ones can exist in CH and/or NH tautomeric forms, depending on the nature of the substituents and the solvent. A morpholinium salt of the OH tautomer has also been observed. Due to the tautomeric equilibria, these isoxazolones do not undergo thermal fragmentation to nitriles, CO_2, vinylidenes, and acetylenes[32] but instead react like other substituted isoxazoles by ring opening to dienylnitrenes and recyclization to pyrroles (Scheme IV and VI). Pyrrole formation does not take place via C–C bond cleavage in 2*H*-azirines in these systems (Schemes V and VI).

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on Varian XL 100 and JEOL FX 100 instruments at 100 and 25.16 MHz, respectively; for some ^1H NMR spectra a Varian T60 instrument was also used. IR spectra were recorded on a Beckman 18A or Perkin-Elmer 281 instrument and mass spectra on a Varian MAT CH7a or 711 instrument. Gas chromatography was performed on a Perkin-Elmer 900 instrument equipped with a Spectra Physics Integration–Computer Autolab System I and using a poly(propylene glycol) capillary column (Ucon LB 550 X) at 100 °C, He as carrier gas, and a flame ionization detector. The pyrolysis apparatus employed a 2 × 30 cm quartz tube, a Heraeus ROK 3/30 tubular oven, and a Leybold–Heraeus oil diffusion pump with a pumping capacity of 25–30 $L \cdot s^{-1}$ and an ultimate vacuum of 10^{-4} torr. Further details have been published.[33] Melting points are uncorrected.

4-(2-Propylidene)-3-phenylisoxazol-5(4*H*)-one (13). PCl_5 (4.16 g, 0.02 mol) was added to 15 mL of dry acetone with stirring under N_2. After the exothermic reaction had subsided, 1.61 g (0.01 mol) 3-phenylisoxazol-5(4*H*)-one (**11**) in 75 mL of $CHCl_3$ was added. After the mixture was stirred for 24 h at room temperature, the precipitate was filtered and recrystallized from acetone to give 1.38 g (69%): mp 139–140 °C (sublimes 125 °C) (lit.[15b] mp 136 °C). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.59; H, 5.48; N, 6.93.

4-Cyclopentylidene-3-methylisoxazol-5(4*H*)-one (14). A mixture of the morpholinium salt of 3-methylisoxazol-5-one[18] (7.36 g, 0.04 mol) and cyclopentanone (6.72 g, 0.08 mol) in 40 mL of dry tetrahydrofuran was stirred at room temperature. The mixture turned orange-brown within 10 min, and after 24 h the solvent was removed in vacuo. Ethanol (20 mL) and water (10 mL) were added, the ethanol was distilled in vacuo, and the resulting precipitate was filtered and washed with water to give 1.65 g (25%) of white needles: mp 101.5–103 °C (lit.[34] mp 93 °C). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.49; H, 6.60; N, 8.44.

4-Cyclopentylidene-3-phenylisoxazol-5(4*H*)-one (15). A mixture of 3-phenylisoxazolone (16.1 g, 0.1 mol), cyclopentanone (8.4 g, 0.1 mol), and piperidine (1 mL) in 200 mL of ethanol was refluxed for 1.5 h. The solvent was removed in vacuo and the resulting product (9.1 g, 40% crude) recrystallized three times from methanol to give 6.4 g (28%) of light pink crystals, turning brown in the air: mp 161 °C (lit.[13] mp 158–159 °C; lit.[14] mp 157–158 °C). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.89; H, 5.74; N, 6.16.

Morpholinium 4-(2-Indanylidene)-3-methylisoxazol-5-olate. The morpholinium salt of 3-methylisoxazolone[18] (9.2 g, 0.05 mol) in 200 mL of ethanol was added to a solution of 2-indanone (6.6 g, 0.05 mol) in 150 mL of ethanol, and the mixture was allowed to stand at room temperature. The product crystallized as colorless needles after 1 h and after 15 h was filtered and washed with $CHCl_3$ to give 12.13 g (81%): mp 174–196 °C (dec above 162 °C). Anal. Calcd for $C_{17}H_{20}N_3O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.71; H, 6.58; N, 9.35.

4-(2-Indenyl)-3-methylisoxazol-5(2*H*)-one (NH Form of 16). The aforementioned morpholinium salt (6.0 g, 0.02 mol) was stirred with 40 mL of 2 N HCl (0.08 mol) for 10 min. The product was filtered, washed with $CHCl_3$, and dried in vacuo over silica gel to give 4.13 g (98%) of long colorless needles, which turned light green on the surface through the influence of light: mp 187–196 °C (dec above 178 °C). Anal. Calcd for $C_{13}H_{10}NO_2$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.40; H, 5.05; N, 6.66.

4-(2-Indenyl)-3-phenylisoxazol-5(2*H*)-one (NH Form of 17). A mixture of 3-phenylisoxazol-5(4*H*)-one (2.25 g, 0.014 mol), 2-indanone (1.85 g, 0.014 mol), and 20 drops of piperidine in 45 mL of dry ethanol was refluxed under N_2 for 1.5 h. The solvent was removed in vacuo and the resulting product recrystallized from 10% aqueous ethanol to give 1.85 g (48%) of bright lemon yellow crystals, turing green through the influence of light: mp 148–155 °C (lit.[35] mp 144–145 °C). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.58; H, 4.87; N, 5.10.

(*E*)- and (*Z*)-4-(1-Cyclopropylethylidene)-3-phenylisoxazol-5(4*H*)-one (19). $TiCl_4$ (5.5 mL) in 12.5 mL of CCl_4 was added dropwise at 0 °C to a mixture of dry tetrahydrofuran (20 mL) and dry dioxane (80 mL). Cyclopropyl methyl ketone (2.1 g, 0.025 mol) and 3-phenylisoxazol-5(4*H*)-one (4.025 g, 0.025 mol) were then added, and this was followed by the dropwise addition of 8 mL of dry pyridine in 17.5 mL of dioxane. The brown color of the mixture changed to reddish brown. The reaction was slightly exothermic and the temperature rose momentarily to +10 °C. The mixture was then allowed to stir for 15 h at room temperature, hydrolyzed with 25 mL of H_2O, and extracted with three 25-mL portions of ether. The combined organic phase was washed with 25 mL of saturated NaCl solution, 25 mL of $NaHCO_3$ solution, and 25 mL of NaCl solution and dried over $MgSO_4$. After filtration and distillation of the solvent the brown solid thus obtained (4.71 g, 75% crude yield) was recrystallized three times from ethanol to give 2.78 g (50%) of colorless crystals: mp 88.5–110 °C; IR (KBr) 1745 (s), 1590 (s) cm^{-1}; mass spectrum, *m/z* 227 (M^+, 55), 182 (74), 77 (100). The product consisted of a mixture of *E* and *Z* isomers in a ratio of 58:42 as determined from the ^1H NMR spectrum. The isomers can be separated by fractional crystallization from methanol or ethanol, in which the *Z* isomer is more soluble. ^1H NMR ($CDCl_3$): *E* isomer, δ 1.00 (m, 4 H, cyclopropyl), 2.15 (s, 3 H, CH_3), 1.87 (m, 1 H, cyclopropyl), 7.45 and 7.46 (m, 5 H, Ar); *Z* isomer, δ 1.23 (m, 4 H, cyclopropyl),

(31) Gossauer, A. "Die Chemie der Pyrrole"; Springer: Berlin, 1974; pp 79–84.

(32) In all the pyrolyses of **12**, **14**, **15**, and **16**, at most, traces of acetonitrile or benzonitrile were formed. The formation of vinylidenes **8** and acetylenes **9** can, therefore, at most, represent a very minor reaction channel. The isolation of a trace of dodecahydrotriphenylene, formally the trimer of cyclohexyne, after pyrolysis of **14** at 800 °C is described in another context.[10]

(33) Wentrup, C.; Damerius, A.; Reichen, W. *J. Org. Chem.* **1978**, *43*, 2037. Lân, N. M.; Wentrup, C. *Helv. Chim. Acta* **1976**, *59*, 2068.

(34) Braunholtz, J. T.; Freeman, P. F. H. Brit. Pat. 1 074 803; *Chem. Abstr.* **1968**, *68*, P68973*d*.

(35) Brooker, L. G. S.; Webster, F. G. *Brit. Pat.* 988 627; *Chem. Abstr.* **1965**, *63*, 7151.

1.44 (s, 3 H, CH_3), 3.90 (m, 1 H, cyclopropyl), 7.49 (s, 5 H, Ar). Anal. Calcd for $C_{14}H_{13}NO_2$ (*E*/*Z* mixture): C, 73.99; H, 5.76; N, 6.16. Found: C, 73.79; H, 5.68; N, 6.18.

(*E*)- and (*Z*)-4-(1-Cyclopropylethylidene)-3-methylisoxazol-5(4*H*)-one (18). (a) This product was obtained from 3-methylisoxazol-5(4*H*)-one (1.0 g, 0.01 mol) in the same manner as described for **19** above: yield 0.50 g (30%) of colorless crystals; mp 122–124 °C; IR (KBr) 1745 (s), 1610 (s), 1450 (m), 1415 (m) cm^{-1}; mass spectrum, *m*/*z* 165 (M^+, 36), 79 (100). The product showed only one spot by thin-layer chromatography although it was an *E*/*Z* mixture (85:15) as determined from the ^1H NMR spectrum. *E* isomer, ^1H NMR ($CDCl_3$): δ 1.19–1.27 (m, 5 H, cyclopropyl), 2.13 (s, 3 H, 3-CH_3), 2.45 (s, 3 H, 8-CH_3); *Z* isomer, δ 1.93 (s, 3 H, 3-CH_3), 2.37 (s, 3 H, 7-CH_2), 2.42 (m, 4 H, cyclopropyl), 3.82 (m, 1 H, cyclopropyl). Anal. Calcd for $C_9H_{11}NO_2$ *E*/*Z* mixture): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.61; H, 6.83; N, 8.14.

(b) A mixture of 0.99 g (0.010 mol) of 3-methylisoxazol-5-(4*H*)-one and 0.84 g (0.010 mol) of cyclopropyl methyl ketone in 50 mL of dry ether was treated with HCl gas for 50 min and then stirred for 4 h. After the solvent was removed in vacuo, the resulting oil was triturated with CCl_4 and the solid so obtained recrystallized from ethyl acetate to give a product identical with that described under method a but in variable yield (0–30%). Hence, method a is to be preferred.

4-([$^2H_6$]Isopropylidene)-3-methylisoxazol-5-(4*H*)-one (24). 4-Isopropylidene-3-methylisoxazol-5(4*H*)-one[11] (**12**) (2.00 g, 0.0144 mol) was dissolved in 50 mL of CH_3OD and 3 mL of $CDCl_3$ and allowed to stand for 3 weeks at room temperature. The solvent was removed in vacuo and the solid sublimed at 80–90 °C (0.1–1 torr) to give 1.85 g (89%) of **24** as white needles: mp 123 °C; IR (KBr) 1745 (s), 1615 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s); mass spectrum, *m*/*z* 145 (M^+, 93). Anal. Calcd for $C_7H_3D_6NO_2$: C, 57.91; H (D), 10.40; N, 9.65. Found: C, 57.57; H, 10.78; N, 9.93.

Pyrolysis of 12 to Dimethylpyrroles 29 and 30. Flash vacuum pyrolysis (see General section) of **12** at 550–700 °C (5 × 10^{-4} torr) gave a liquid product which by GC, GC–MS, and ^1H NMR comparison with authentic samples[36] was shown to consist of a mixture of 2,4-dimethylpyrrole (**29**) and 2,5-dimethylpyrrole (**30**) (ratio 45:55 at 650 °C, insensitive to pyrolysis temperature). 2,4-Dimethylpyrrole: ^1H NMR (CCl_4) δ 2.02 (s, 3 H, 4-CH_3), 2.13 (s, 3 H, 2-CH_3), 5.70 (m, 1 H, H-3), 6.32 (m, 1 H, H-5), 7.67 (br, 1 H, NH). 2,5-Dimethylpyrrole: ^1H NMR (CCl_4) δ 2.00 (s, 6 H, CH_3), 5.73 (d, *J* = 2.5 Hz, 2 H, H-3 and H-4), 7.18 (br, 1 H, NH). At temperatures above 700 °C small amounts of other products were formed as well, indicated by GC–MS to be dimethylpyrroles, but these were not investigated further.

Separate pyrolyses of each of the pyrroles **29** and **30** showed that these interconvert, starting at 650 °C, and at temperatures of 850 °C and above small amounts of the other isomeric dimethylpyrroles were also detected by GC–MS. The pyrolyses of **29** gave the following ratios of **29** and **30**: at 750 °C, 94:6; at 800 °C, 67:33; at 850 °C, 64.33; at 975 °C, 44:35. The pyrolyses of **30** gave the following ratios of **29** and **30**: at 750 °C, 13:87; at 850 °C, 39:51; at 975 °C, 42:37.

Pyrolysis of 14 to 4,5-Dihydro-2-methylcyclopenta[*b*]pyrrole-3-carboxylic Acid (38) and 4,5-Dihydro-2-methylcyclopenta[*b*]pyrrole (39). **14** (200 mg, 1.21 mmol) was sublimed at 85 °C and pyrolyzed at 600 °C (5 × 10^{-4} torr). The products were condensed on a cold finger at −196 °C and, after the end of the pyrolysis, dissolved in warm (60 °C) toluene and then evaporated to dryness. The solid was dissolved in dilute $NaHCO_3$ solution and extracted with ethyl acetate to give **39** (62 mg, 41%): mp 109–112 °C (sublimes >105 °C); ^1H NMR ((CD_3)$_2$SO) δ 2.1–2.7 (m, 6 H), 2.16 (d, *J* = 0.7 Hz, 3 H, CH_3), 5.46 (m, 1 H, H-3). On addition of D_2O the latter signal simplified to a quartet, *J* = 0.7 Hz; spin decoupling of this signal transformed the CH_3 signal at δ 2.16 to a singlet. High-resolution mass spectrum, *m*/*z* 121.0889 (calcd for $^{12}C_8H_{11}N$, 121.08915).

The alkaline solution above was acidified with dilute HCl and extracted with toluene, and the extract was diluted with petroleum ether (bp 40–60 °C), causing precipitation of the acid **38** (80 mg, 39%): mp 208 °C (sublimes >185 °C); IR (KBr) 3300 (s), 2930 (m, br), 2850 (m), 2800–2400 (m, br), 1630 (s), 1600 (m) cm^{-1}; ^1H NMR ((CD_3)$_2$SO) δ 2.1–2.5 (m, 6 H), 2.16 (s, 3 H, CH_3), 10.0 (s, 1 H, COOH); ^{13}C NMR, see Table IV; high-resolution mass spectrum, *m*/*z* 165.0784 (calcd for $^{12}C_9H_{11}NO_2$, 165.07898).

The results of pyrolyses at other temperature are indicated in Table III.

4,5-Dihydro-2-phenylcyclopenta[*b*]pyrrole-3-carboxylic Acid (44). **15** (500 mg, 2.2 mmol) was sublimed at 145 °C and pyrolyzed at 500 °C (3 × 10^{-4} torr). The product was rinsed from the cold finger with hot toluene and recrystallized from toluene to give 142 mg (28%): mp 195–199 °C with gas evolution. Thin-layer chromatography showed only one spot: IR (KBr) 3380 (s), 3050 (w), 2980 (m), 2870 (m), 2680 (br), 2580 (br), 1655 (s), 1610 (m), 1600 (m), 1520 (m), 1490 (m), 1465 (s), 1435 (s), 1300 (s), 1140 (s) cm^{-1}; ^1H NMR (1:1 $CDCl_3$–(CD_3)$_2$SO 1:1) δ 2.2–3.0 (m, 6 H), 7.3 (m, 3 H, Ar), 7.6 (m, 2 H, Ar), 10.8 (s, 1 H, COOH); ^{13}C NMR, see Table IV; high-resolution mass spectrum, *m*/*z* 227.0938 (calcd for $^{12}C_{14}H_{13}NO_2$, 227.09463). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.22; H, 5.85; N, 6.09.

4,5-Dihydro-2-phenylcyclopenta[*b*]pyrrole (45). **15** (1.0 g, 4.4 mmol) was sublimed at 158 °C and pyrolyzed at 850 °C. The solid pyrolysis product (0.65 g) was recrystallized from ether–petroleum ether to give 0.20 g (25%) of **45**: mp 116–118 °C; IR (KBr) 3380 (s), 2940 (s), 2840, (s), 1600 (s), 1510 (s), 1440 (s), 750 (s) cm^{-1}; ^1H NMR (CCl_4) δ 1.8 (m, 2 H), 2.6 (m, 4 H), 6.3 (d, *J* ≃ 2 Hz, 1 H, H-3; coupling with NH removed on addition of D_2O), 7.0–7.5 (m, 5 H, Ar); high-resolution mass spectrum, *m*/*z* 183.1044 (calcd for $^{12}C_{13}H_{13}N$, 183.104799).

Pyrolysis of 16. This compound sublimed with extreme difficulty at 150 °C (10^{-4} torr) so that only very little pyrolysis product was isolable. From 200 mg of **16** was obtained 20 mg of product after pyrolysis at 700 °C during 3 h. The ^1H NMR spectrum is interpreted as a 1:3 mixture of **47** and **48**. **48**: ^1H NMR ((CD_3)$_2$SO) δ 2.28 (d, *J* = 0.6 Hz, 3 H, CH_3; collapses to singlet on decoupling of the proton at δ 5.82), 3.32 (s, 2 H, CH_2), 5.82 (m, 1 H, H-3; collapses to doublet, *J* = 1.7 Hz, on irradiation of the CH_3 signal at δ 2.28; collapses to quartet, *J* = 0.6 Hz, on addition of D_2O); ^{13}C NMR ((CD_3)$_2$SO) δ 13.6 (CH_3), 30.2 (CH_2), 102.3 (C-3), 115.0, 121.6, 124.8, 126.2, 128.1, 131.5, 135.6, 136.0, 145.7; high-resolution mass spectrum, *m*/*z* 169.0884 (calcd for $^{12}C_{12}H_{11}N$, 169.08915).

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (Grant We 774/7-1). We are indebted to U. Stutz, F. Bosold, and D. Laqua for technical assistance with much of the experimental work.

Registry No. **10**·morpholine, 67823-26-1; **11**, 1076-59-1; **12**, 17975-59-6; **13**, 41837-01-8; **14**, 17975-64-3; **15**, 36771-30-9; **16**, 96151-73-4; **16**·morpholine, 96151-74-5; **16** (NH form), 96151-75-6; **17** (NH form), 96151-76-7; (*E*)-**18**, 96151-79-0; (*Z*)-**18**, 96151-80-3; (*E*)-**19**, 96151-77-8; (*Z*)-**19**, 96151-78-9; **24**, 96164-24-8; **29**, 625-82-1; **30**, 625-84-3; **38**, 96151-81-4; **39**, 92705-53-8; **44**, 96151-82-5; **45**, 79379-48-9; **47**, 96151-83-6; **48**, 96151-84-7; Me_2CO, 67-64-1; cyclopentanone, 120-92-3; 2-indanone, 615-13-4; cyclopropyl methyl ketone, 765-43-5.

Supplementary Material Available: Infrared and mass spectra of **13**–**17** (2 pages). Ordering information is given on any current masthead page.

(36) 3,4-Dimethylpyrrole: Nagarkatti, J. P.; Ashley, K. R. *Synthesis* **1974**, 186. 2,5-Dimethylpyrrole: Aldrich Chemical Co.