Further Investigations on the Chemistry and Structure of Angustifoline and its Derivatives. Part 6.† New Evidence of Factors responsible for Basicity of α-Cyanoamines: Crystal and Molecular Structure of *N*-Cyanomethylangustifoline

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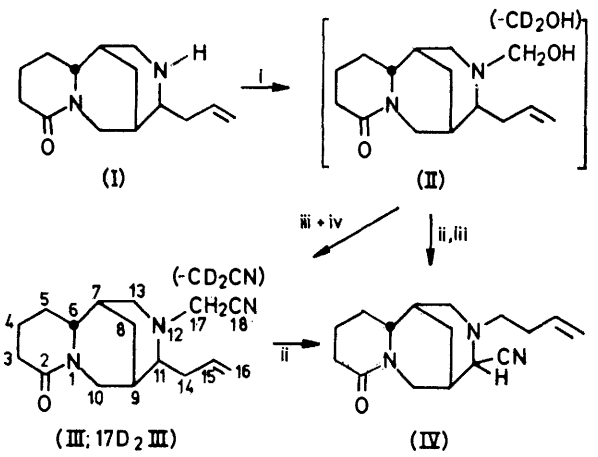
The crystal and molecular structure of *N*-cyanomethylangustifoline (III) has been determined from three-dimensional *X*-ray data by direct methods and refined by full-matrix least-squares calculations to a final *R* of 0.039 for 1 055 observed reflections. Crystals are monoclinic, a = 10.223(1), b = 9.416(1), c = 7.846 4(7) Å, β = 94.741(8)°, space group $P2_1$, and Z = 2.

The conformation of the cyanomethyl group was found to be the same as that preferred in solution. The lone pair at nitrogen N(12), bearing the cyanomethyl group, is *trans* to the nitrile group and *gauche* to the methylene hydrogen atoms. Possible factors stabilizing this conformation are discussed. Direct electrostatic interactions through space between the lone pair and ' acidic ' protons of the bridging methylene group may cause a greater decrease in the basicity of α-cyanoamines than that due to the inductive effect of the nitrile group.

There is a weak C–H · · · O=C intermolecular hydrogen bond [3.284(5) Å].

DURING our studies of the unusual intramolecular allyl rearrangement which takes place when the adduct (II) of angustifoline (I) and formaldehyde is treated with aqueous $NaBH_4$,[1] two isomeric α-cyanoamines (Scheme) were obtained in a similar manner by treating (II) with



SCHEME Reagents: i, $H_2CO(D_2CO)$; ii, H_2O; iii, KCN; iv, MeOH

KCN.[1] In anhydrous methanol (II) reacts with KCN as expected giving *N*-cyanomethylangustifoline (III) in high yield. In aqueous solution, however, the rearrangement of (II) under the influence of KCN gives rise to the formation of 11-cyanotetrahydrorhombipholine (IV).[1,2] In aqueous solutions (III) also is transformed in high yield into (IV).[1] Despite some similarities this reaction does not belong to the general category of [3,3] sigmatropic Claisen–Cope rearrangements, since there is some evidence that it proceeds by ionic dissociation and recombination, catalysed by the intramolecular effect of the lactam group. The hypothetical mechanism of this rearrangement will be discussed elsewhere.[1]

Both isomeric cyano-compounds, (III) and (IV), are very weak bases and, as can be seen from Table 1, their pK_a'(MCS) values ‡ are *ca.* 4—5 units lower than those of the parent amines. Additionally the pK_a'(MCS) and $\Delta pK_a'$(MCS) values of the two α-cyano-derivatives of lupanine (V) and (VI) [5,6] and of *N*-methyl- and *N*-isopropyl-piperidine (VII) and (VIII) [7] are listed in Table 1. In spite of the fact that in all these compounds the cyanomethyl group is α to the tertiary amino-group, its influence on the decrease of basicity of the parent amine is different. It is manifested by the drastic differences of $\Delta pK_a'$ values (see Table 1).

The highest $\Delta pK_a'$ values are for those α-cyanoamines [(III) and (VII)] in which the cyano- and amino-groups are separated by the methylene bridge $N–CH_2–CN$. The lowest values of $\Delta pK_a'$ are for (VI) and (VIII),

TABLE 1

Values of pK'(MCS) for some α-cyanoamines

Cpd. RCN	pK_a'(MCS) (R–H)	$\Delta pK_a'$ (MCS) *
(VII)	3.35 (8.60)	5.25
(III)	2.60 (7.05)	4.55
(IV)	3.10 (6.90)	3.80
(V)	5.05 (7.75)	2.70
(VIII)	6.50 (8.30)	1.80
(VI)	5.80 (7.55)	1.75

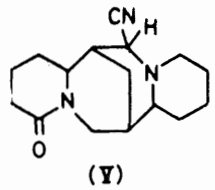
* pK'(RH) − pK'(RCN).

where the cyano- and amino-groups are linked by the disubstituted one-carbon-bridge: $-\overset{|}{\underset{|}{N}}-\overset{|}{\underset{|}{C}}-CN$. In (IV) and (V), where the nitrile and amino-groups are separated by a methine bridge, =N–CH–CN, the $\Delta pK_a'$ values are intermediate between those of the first group (*ca.* 5) and of the second (*ca.* 2).

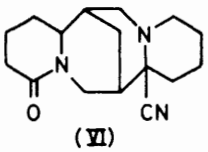
These drastic differences in the pK_a' values of α-cyanoamines are not in agreement with the results of Stevenson and Williamson [7b] and Soloway and Lip-

† Part 5, ref. 10.

‡ The pK_a'(MCS) are the pK_a values of bases and were determined by potentiometric titration of 3.5×10^{-3}M base solutions in a mixture of methylcellosolve (MCS) and water 80 : 20 w/w by use of a Radiometer automatic microtitration device. The principles of measurements were in accordance with Simon's procedure [4] and are described in detail in ref. 3.



(V)



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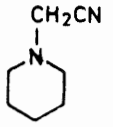

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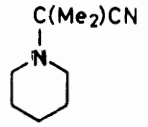


(VIII)

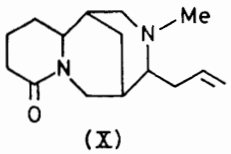
schitz,[8] who found that the decreased basicity of this group of compounds is caused only by the strong inductive effect of the cyano-group, transmitted through the C–C bonds. The classical inductive effect of the cyano-group, convincingly proved in the homologous series,[7,8] in the case of α-cyanoamines must be strongly modified by other factors.

From the data of Table 1 it seems that the spatial arrangement of both functional groups and the substituents at the methylene bridge is of decisive importance.

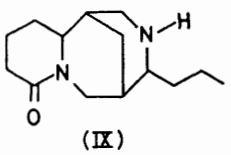
In order to elucidate this intriguing problem, *N*-cyanomethylangustifoline (III) was subjected to various spectroscopic and *X*-ray investigations.

RESULTS

Physicochemical Properties of (III) *and its Structure on the Basis of Spectroscopic Investigations.*—Figures 1 and 2 show fragments of the i.r. and n.m.r. spectra of (III) and of its dideuterio-derivative (17D_2III) [deuteriated at C(17)] in comparison with those of angustifoline (I), dihydroangustifoline (IX), and *N*-methylangustifoline (X).



(X)



(IX)

Figure 1 shows there are substantial differences between the spectra of (III) and (X) in the C–H stretching vibration region, and particularly in the region of the so-called *trans*-band (Bohlman's band [9]), which is shaded.

Complex spectroscopic analysis of angustifoline (I) seems to indicate the conformation of this molecule as being all-chair with the N(12)–H bond axial,[10] [see (I) in Figure 2]. A similar conformation for (III) must be rejected since the cyanomethyl substituent [replacing the N(12) hydrogen atoms in (I)] would be in an unfavourable axial position. From the four main conformers derived from (III) by the inversion of ring c and/or by inversion of nitrogen atom N(12),* only two seem to be reasonable [(IIIa) and (IIIb) in Figure 3].

From further considerations of the structure of (III), the rotamers resulting from rotation of the propenyl group at C(11) were neglected. Taking into account only the rotamers originating from rotation of the cyanomethyl-substituent around the N(12)–C(17) bond, three staggered rotamers might be derived from each of the two conformers (IIIa) and (IIIb). These are shown as Newman projections in Figure 3. This also shows the spatial arrangement of the substituents at C(11) and C(13), together with the number of C–H bonds antiperiplanar (C–H_{app}) to the lone pair at N(12). It can also be seen that only in two rotamers (IIIaγ) and (IIIbϕ) are none of the two C(17)–H bonds oriented antiperiplanar to the lone pair at N(12).

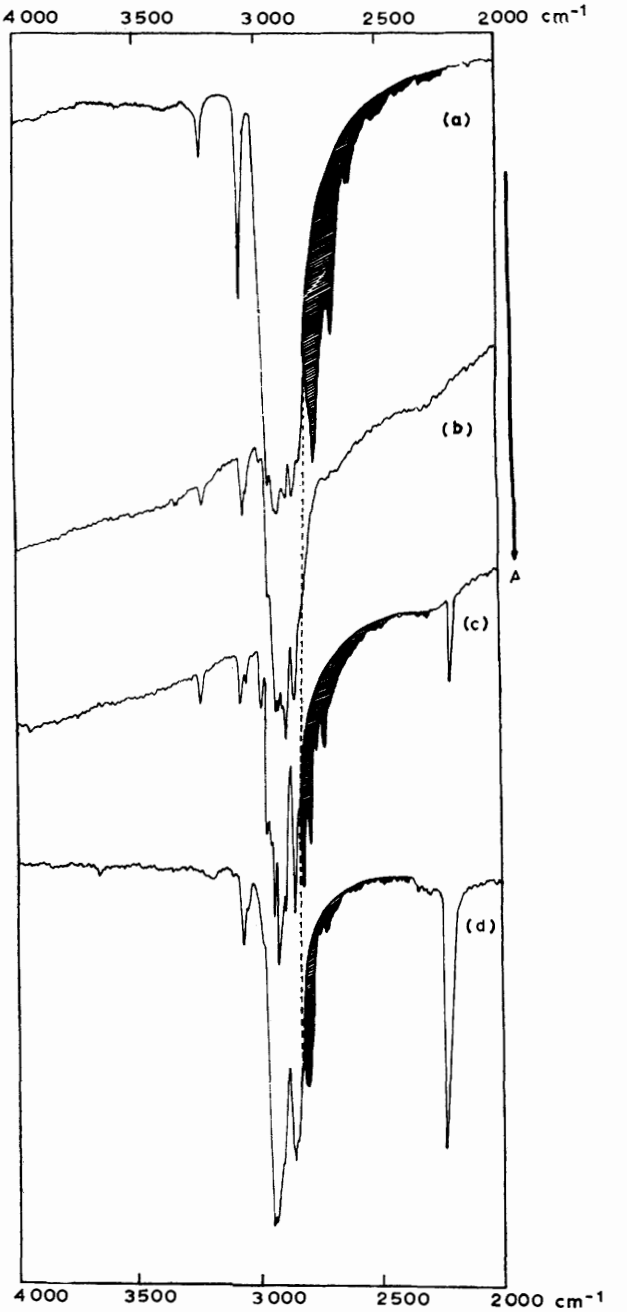


FIGURE 1 I.r. spectra (4 000 2 000 cm^{-1}) of a, (X); b, (I); c, (III) and its dideuterio-derivative (all Nujol); d, dideuterio-(III) in $CDCl_3$

* *X*-Ray studies on the structure of sparteine lactams have shown that the fragment of the molecule which contains the *trans*-quinolizidine system, *i.e.* rings A and B in (III), is quite rigid, and thus not very susceptible to conformational changes (see refs. 11—13).

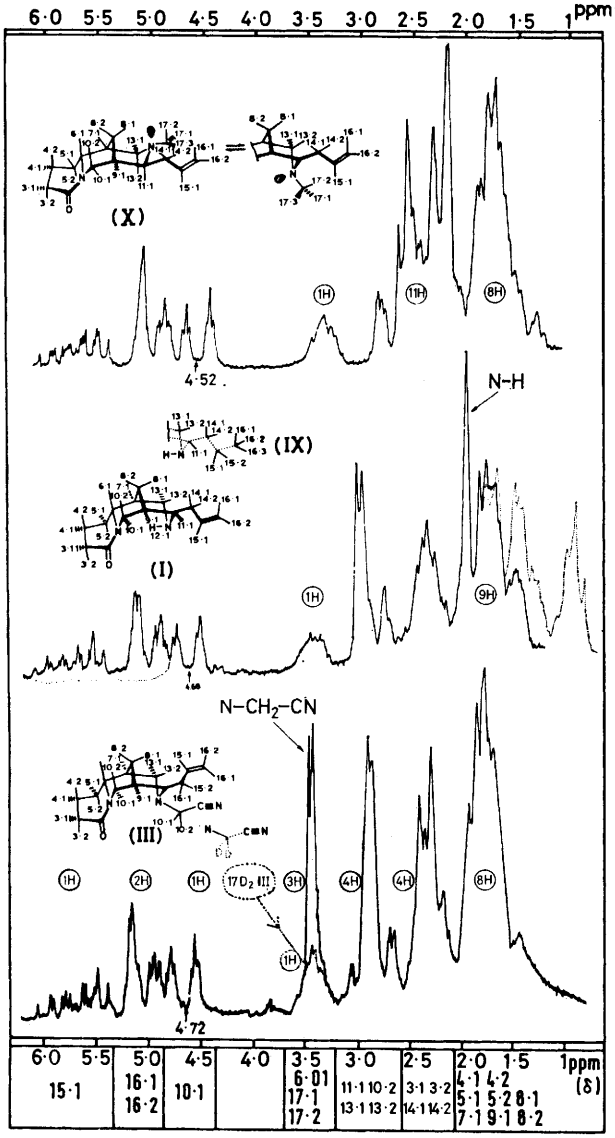


FIGURE 2 ^{1}H N.m.r. spectra ($CDCl_3$) of *N*-methylangustifoline (X), angustifoline (I), dihydroangustifoline (IX), *N*-cyanomethylangustifoline (III), and 17,17-dideuterio-*N*-cyanomethylangustifoline ($17D_2$III)

In the i.r. spectrum of (III), there is a distinct *trans*-band whose structure and intensity is the same as in the i.r. spectrum of the dideuteriated derivative of (III). In addition, in the latter spectrum the $\nu(C-D_2)$ band at *ca.* 2 000 cm^{-1} does not appear (Figure 1). From this it may be concluded that of the six rotamers shown in Figure 3, only two may actually exist, *i.e.* (IIIaγ) and/or (IIIbϕ), in which both geminal C(17)–H bonds are gauche with respect to the lone pair at N(12) and which therefore have no possibility of contributing towards *trans*-band formation.

Comparison of the spectrum of (III) with that of its deuterio-derivative shows that the absorption bands derived from the C(17) hydrogen and deuterium are located at 2 960 and 2 220 cm^{-1} respectively. The stretching vibrations of these bonds are thus shifted towards shorter wavelengths when compared with expected values. This fact additionally supports the conclusion, drawn from inspection of the *trans*-band, that the spatial arrangement of the C(17)–H bonds should be *gauche* and not *anti* with respect to the lone pair at N(12), and may therefore correspond to the (IIIaγ) and/or (IIIbϕ) rotamers (see Figure 3).

The *trans*-band in the i.r. spectrum of (III) for chloroform solution appears to be less intense and simpler than that for (III) in the solid state (see Figure 1d and c).

Comparison of the ^{1}H n.m.r. spectra of (III) and its deuterio-derivative enables us to localize the signals of both geminal protons at δ 3.5 p.p.m. The chemical shift of this signal and the lack of geminal coupling is in agreement with the existence of both the (IIIaγ) and (IIIbϕ) rotamers, and against that of the remaining four rotamers.

In conclusion, the i.r. and ^{1}H n.m.r. spectral analysis of (III) and its deuterio-analogue limits the number of possible rotamers to two, *i.e.* (IIIaγ) and (IIIbϕ).

Further substantial progress in the structural investigations of (III) was achieved by means of *X*-ray analysis.

X-Ray Results.—Final positional parameters are given in Table 2. A list of observed and calculated structure factors and thermal parameters is included in Supplementary Publication No. SUP 22509 (15 pp., 1 microfiche).*

The structural and conformational features of (III) are illustrated in Figure 4. Relevant bond distances, angles,

TABLE 2

Final fractional co-ordinates for non-hydrogen atoms ($\times 10^4$) and probable hydrogen atoms positions ($\times 10^3$)

	x	*y*	*z*
N(1)	8 092(2)	4 144(5)	3 904(3)
C(2)	7 590(4)	5 460(5)	3 647(5)
C(3)	7 621(5)	6 106(6)	1 891(6)
C(4)	8 661(4)	5 531(6)	836(5)
C(5)	8 596(4)	3 918(6)	881(5)
C(6)	8 893(3)	3 395(5)	2 706(4)
C(7)	8 771(3)	1 769(5)	2 855(4)
C(8)	9 051(3)	1 312(5)	4 705(5)
C(9)	7 991(4)	1 960 [a]	5 703(4)
C(10)	8 101(4)	3 572(6)	5 650(4)
C(11)	6 620(8)	1 403(5)	5 047(4)
N(12)	6 412(2)	1 654(5)	3 194(3)
C(13)	7 459(3)	1 150(5)	2 190(4)
C(14)	6 400(3)	−144(5)	5 600(4)
C(15)	6 626(4)	−330(5)	7 483(4)
C(16)	7 430(5)	−1 239(6)	8 261(5)
C(17)	7 113(3)	1 322(5)	2 430(4)
C(18)	4 888(3)	−187(6)	1 913(4)
N(19)	4 731(4)	−1 328(6)	1 464(4)
O	7 106(3)	6 115(5)	4 785(4)
H(31)	748	717	190
H(32)	654	567	118
H(41)	959	611	137
H(42)	846	593	−41
H(51)	931	337	26
H(52)	763	356	41
H(61)	991	362	308
H(71)	948	145	216
H(81)	905	24	472
H(82)	988	164	511
H(91)	824	160	702
H(101)	730	400	619
H(102)	890	406	637
H(111)	593	212	576
H(131)	718	163	96
H(132)	749	−2	217
H(141)	691	−80	494
H(142)	549	−47	517
H(151)	610	37	827
H(161)	764	−144	955
H(162)	771	−194	771
H(171)	503	183	125
H(172)	443	163	328

[a] Co-ordinate fixed in polar space group $P2_1$.

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978 Index issue.

and torsional angles are listed in Table 3. Those in the ring system agree well with these previously noted in lupanine [11] and in lupanine hydrochloride dihydrate.[12] In the cyanomethyl group, however, the C(17)–C(18) sp^3–sp^2 bond is significantly longer than in other similar compounds: C(sp^3)–C(sp) bond lengths range from 1.446(4) to 1.478(10) Å, mean 1.459 Å.[14] The possible factors responsible for this lengthening will be discussed (see later).

All three rings in the molecule have chair conformations although that for ring A is highly distorted owing to the that of an ideal chair and a sofa in which carbon atom C(4) is outside the plane of the other five atoms.

The interaction of the unshared electron-pair orbital of N(1) with the π orbital of the C(2)=O bond causes the shortening of the N(1)–C(2) and lengthening of the C(2)=O bond. Similar observations for ring A were made in lupanine derivatives.[11–13]

The second nitrogen atom in the ring system, N(12), and its three substituents, C(11), C(13), and C(17), form a flattened pyramid with its apex axial relative to ring C.

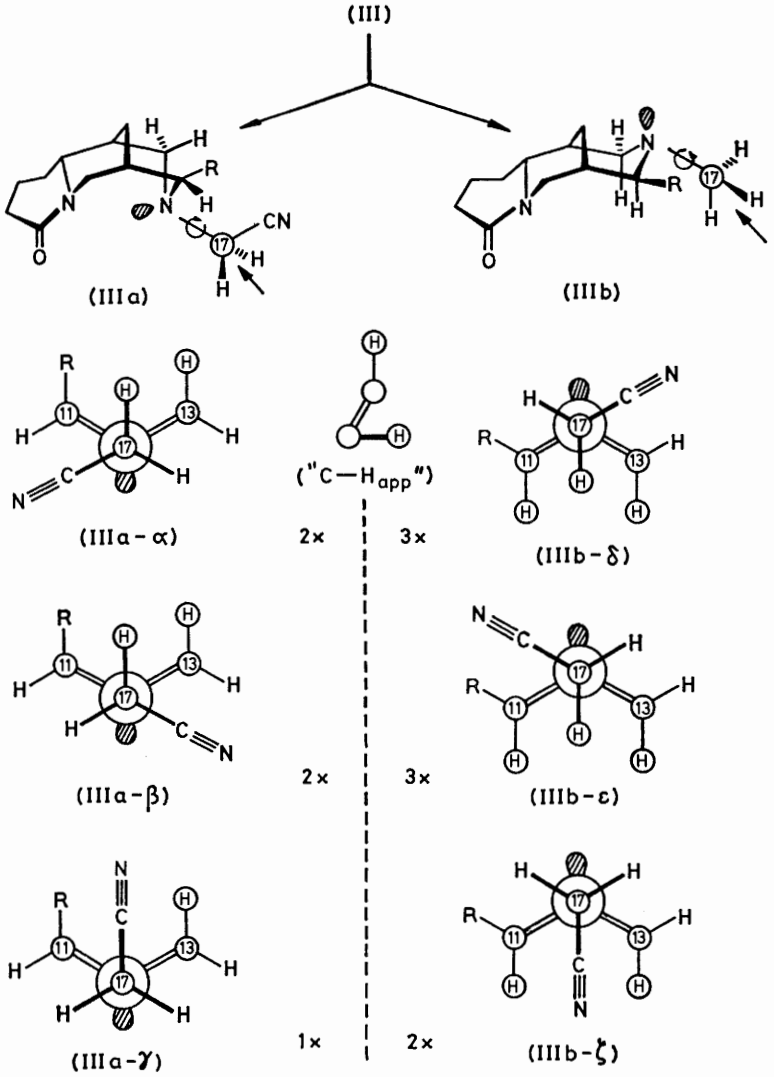


FIGURE 3 Possible rotamers of (III)

presence of the lactam group. The sum (355.6°) of the three angles at N(1) indicates that it adopts an almost planar configuration.

Within the lactam portion of the molecule the four atoms N(1), C(2), C(3), and O are coplanar. The best least-squares plane through these atoms makes an angle of 6° with that defined by N(1) and its three substituents C(2), C(6), and C(10). Atom N(1) deviates by 0.218 Å from the plane formed by atoms C(2), C(3), C(5), and C(6), while C(4) is out of this plane by −0.696 Å. The conformation of ring A can thus be described as being intermediate between

The sum of the bond angles around N(12) is 343.9° indicating that the hybridization of the nitrogen atom is intermediate between sp^2 and sp^3. The cyanomethyl group at N(12) is attached equatorially. The torsion angle C(11)–N(12)–C(17)–C(18) (−85°) describes the position of the unshared electron pair as being quasi-*gauche* with respect to both geminal hydrogen atoms at C(17), and quasi-*anti* with respect to the C(17)–C(18) bond.

The Newman projection (Figure 5) shows the spatial arrangement of the substituents at N(12) and C(17) and, in addition, at C(11) and C(13). The conformation about

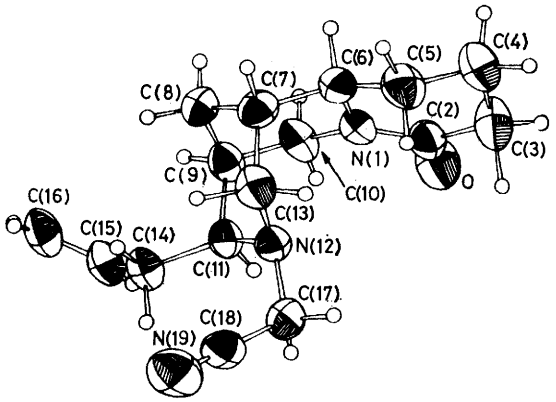


FIGURE 4 A perspective view of the molecule with thermal vibration ellipsoids scaled to 50% probability and hydrogen atoms drawn as spheres on an arbitrary scale

the C(17)–N(12) bond deviates from an ideal staggered arrangement by *ca.* 25°.

Two nitrogen atoms, N(1) and N(12), are separated by 2.933(5) Å, which is somewhat less than the sum of the van der Waals radii (3·0 Å).

Figure 6 is a packing diagram viewed along [001]. A close C–H · · · O intermolecular interaction (H · · · O 2.32 Å) was found between a hydrogen atom of the cyanomethyl group and the oxygen atom of the lactam group of the molecule at $1 - x$, $y - \frac{1}{2}$, $1 - z$. The C–H · · · O angle is 152° and C · · · O distance 3.284(5) Å. This may represent a weak intermolecular hydrogen bond since the C–H bond in the cyanomethyl group is highly polarized by adjacent electron-withdrawing substituents.[14c]

TABLE 3

Molecular geometry of (III)

(*a*) Bond distances (Å)

N(1)–C(2)	1.349	N(1)–C(10)	1.472
C(2)–O	1.223	C(7)–C(13)	1.516
C(2)–C(3)	1.509	C(9)–C(11)	1.545
C(3)–C(4)	1.501	N(12)–C(13)	1.460
C(4)–C(5)	1.520	N(12)–C(11)	1.471
C(5)–C(6)	1.521	C(11)–C(14)	1.542
C(6)–N(1)	1.476	C(14)–C(15)	1.487
C(6)–C(7)	1.542	C(15)–C(16)	1.303
C(7)–C(8)	1.519	N(12)–C(17)	1.445
C(8)–C(9)	1.517	C(17)–C(18)	1.490
C(9)–C(10)	1.523	C(18)–N(19)	1.138

(*b*) Bond angles (°)

C(6)–N(1)–C(2)	124.5	C(7)–C(8)–C(9)	107.1
N(1)–C(2)–C(3)	118.1	C(13)–C(7)–C(8)	108.2
C(2)–C(3)–C(4)	115.3	C(8)–C(9)–C(11)	111.0
C(3)–C(4)–C(5)	108.3	C(7)–C(13)–N(12)	110.9
C(4)–C(5)–C(6)	109.8	C(9)–C(11)–N(12)	109.1
C(5)–C(6)–N(1)	111.5	C(11)–N(12)–C(13)	115.4
N(1)–C(2)–O	121.7	C(11)–N(12)–C(17)	115.3
C(6)–N(1)–C(10)	117.2	N(12)–C(17)–C(18)	115.8
N(1)–C(10)–C(9)	113.3	C(17)–C(18)–N(19)	177.6
C(10)–C(9)–C(8)	109.2	N(12)–C(11)–C(14)	114.7
N(1)–C(6)–C(7)	112.0	C(11)–C(14)–C(15)	112.1
C(6)–C(7)–C(8)	110.1	C(14)–C(15)–C(16)	125.7

(*c*) Torsion angles (°)

C(6)–N(1)–C(2)–C(3)	12	C(7)–C(8)–C(9)–C(10)	−64
N(1)–C(2)–C(3)–C(4)	−24	C(13)–C(7)–C(8)–C(9)	−63
C(2)–C(3)–C(4)–C(5)	49	C(7)–C(8)–C(9)–C(11)	62
C(3)–C(4)–C(5)–C(6)	−62	C(8)–C(9)–C(11)–N(12)	−54
C(4)–C(5)–C(6)–N(1)	50	C(9)–C(11)–N(12)–C(13)	51
C(5)–C(6)–N(1)–C(2)	−26	N(12)–C(13)–C(7)–C(8)	60
C(7)–C(6)–N(1)–C(10)	42	C(11)–N(12)–C(13)–C(7)	−55
N(1)–C(6)–C(7)–C(8)	−52	C(14)–C(11)–N(12)–C(17)	59
C(6)–N(1)–C(10)–C(9)	−43	C(11)–N(12)–C(17)–C(18)	−85
N(1)–C(10)–C(9)–C(8)	54	C(15)–C(14)–C(11)–N(12)	180
C(6)–C(7)–C(8)–C(9)	64	C(11)–C(14)–C(15)–C(16)	−125

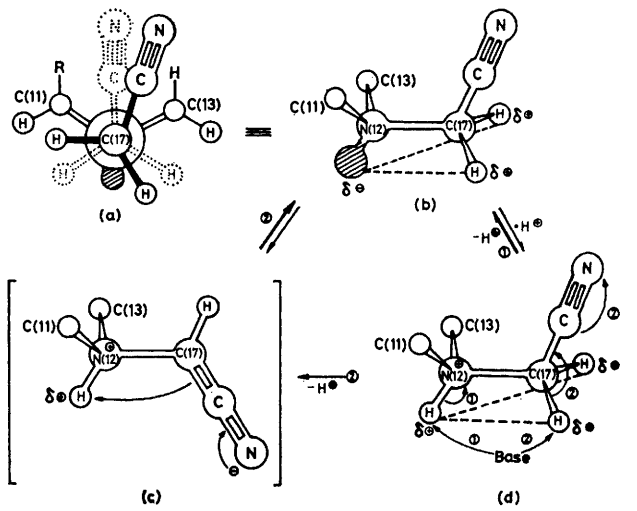


FIGURE 5 Newman projections showing the spatial arrangements of substituents at N(12), C(17), and at C(11) and C(13) in (III)

The remaining intermolecular contacts correspond to van der Waals interactions, the shortest being between C(17) of the reference molecule (Table 2) and C(16) of the molecule at $1 - x$, $\frac{1}{2} + y$, $1 - z$.

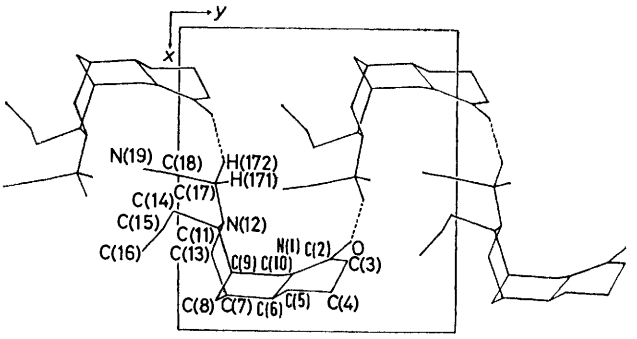


FIGURE 6 Packing diagram for (III) viewed along [001]

DISCUSSION

From the structural arrangement of the substituents at N(12), [(a) in Figure 5] one might expect that the lone pair at N(12) would interact with antibonding orbitals of the C(13)–H and C(11)–C(14) bonds, and to the same extent with the antibonding orbital of the C(17)–C(18) bond.[15] This type of interaction with both geminal C(17)–H bonds, however, is not possible.

This provides a satisfactory explanation for the complete lack of the C–D *trans*-band in the dideuteriated derivative of (III). In the i.r. spectrum the bands due to νC(17)–H and νC(17)–D occur at 2 960 and 2 220 cm^{-1}, respectively [the latter band is overlapped by a γ(C≡N) absorption]. A complete lack of absorption near 2 000 cm^{-1} in the i.r. spectrum of the dideuterio-derivative of (III) in the solid state and in solution unequivocally indicates that the conformation around the N(12)–C(17) bond in solid state does not change when (III) is dissolved in chloroform. This means that the repulsive forces

between the R and C≡N groups (Figure 5a) in the solid state, which are probably responsible for the deformation (*ca.* 25°) from the ideal staggered conformation around the N(12)–C(17) bond, are not strong enough to overcome some stabilizing forces which favour this conformation.

An attempt was made to specify these forces on the basis of *X*-ray and spectroscopic (i.r. and n.m.r.) results.

The lengthening of the C(17)–C(18) bond and simultaneous shortening of the N(12)–C(17) bond (see Table 3) indicate that there is in fact a donation of electrons from the unshared electron pair into an antibonding orbital of the C(17)–C(18) C(sp^3)–C(sp) bond.

The interaction of the lone electron pair with the antibonding orbitals of the neighbouring C–H_{app} bonds was already postulated by Hamlow [16] to explain the origin of the so-called *trans* band (Bohlman band) in the i.r. spectra of quinolizidine and other cyclic amines.

Recently, this type of interaction was forseen by Bellamy [15] for other antiplanar bonds, including C–C_{app} bonds. Our *X*-ray results have confirmed Bellamy's suggestion and have given evidence for the existence of the interaction of the lone pair at N(12) with the antibonding orbital of C(17)–$C(18)_{app}$. The relatively low precision of the *X*-ray measurements for C–H bond lengths, however, meant that it was not possible to confirm this type of interaction of a lone pair at N(12) and the C(13)–H_{app} bond in (III).

The i.r. spectra indicate unequivocally that this interaction is present, and it must be quite strong because the *trans* band in the i.r. spectra of crystalline (III) (Figure 1c) is more intense than the *trans* band caused by the stretching vibration of the single C–H_{app} bond.[9,13]

This interaction, however, seems to be insufficiently strong to stabilize conformation (a) of Figure 5. It was suggested therefore that the preference for this conformation may also be due to a direct electrostatic (through space) attraction between both geminal hydrogen atoms at C(17) and the lone pair at N(12).

This is consistent with the well-known acidic properties of the α-carbon hydrogen atoms in nitriles and with the localization of the νC(17)–H band at *ca.* 3 000 cm^{-1} in the i.r. spectrum of (III).

This kind of interaction (through space), shown schematically in projection (b) of Figure 5, provides a satisfactory explanation for the very weak basicity of α-cyanoamines of that type, since it hinders the protonation of the nitrogen as well as facilitating the dissociation of the proton from the protonated cation (Figure 5d). The latter process may occur by means of two mechanisms: dissociation of the proton from the N^+–H group, leading directly to the formation of the neutral form (Figure 5b), or by dissociation of one of the protons from the C(17) CH_2 group, leading at first to formation of the zwitterion (Figure 5c), and then to the neutral form (Figure 5b).

Since the deprotonation mechanism (Figure 5) cannot be taken into account in the case of 11-cyano-α-isolupanine (VI) and *N*-cyanoisopropylpiperidine (VIII) with regard to the absence of protons at the carbon atom bridging the cyano- and amino-groups, the decrease of the basicity of (VIII) and (VI) is mainly due to the presence of the electron-accepting cyano-group (classical inductive effect), and is manifested by relatively low values of $\Delta pK_a'$ (1.80 and 1.75).

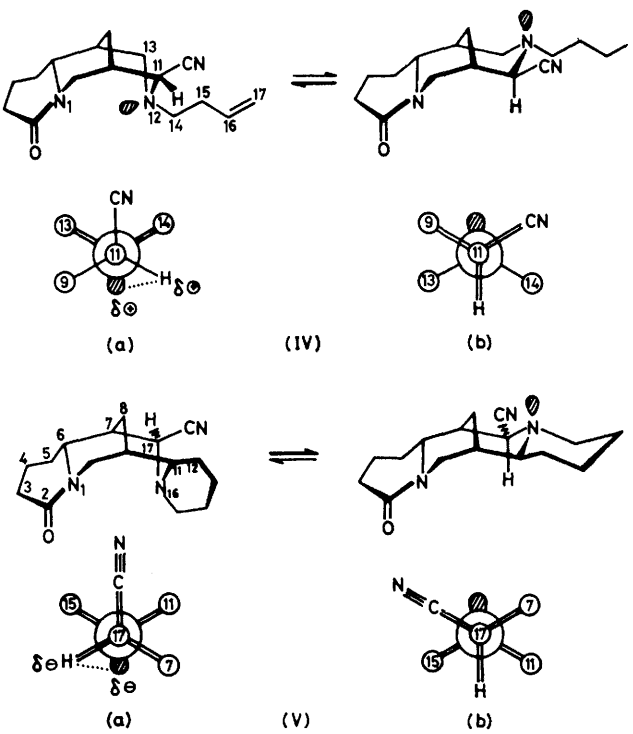


FIGURE 7 Conformations and Newman projections for (IV) and (V)

In the case of (IV) and (V), there is one hydrogen atom attached to the carbon bridging cyano- and amino-groups and hence direct interactions between this hydrogen atom and the unshared electron pair may occur. These interactions, however, would depend on the conformation and should in general be weaker since only one hydrogen atom might be engaged in such an interaction. The $\Delta pK_a'$ values for (IV) and (V) are in agreement with this hypothesis (3.80 and 2.70).

The relatively large differences in the basicity of these two compounds originate probably from the different dynamic conformational equilibria of (IV) and (V) (Figure 7).

In both cases spectroscopic investigations have established that the predominant conformations, (IVa) and (Vb), are mainly responsible for the properties of (IV) and (V). The Newman projections of these two conformers show that only in (IVa) may direct electrostatic interactions between the lone pair at N(12) and the proton of the bridging methine group be expected. [The conformations of (IVa) and (Vb) were determined mainly by analysis of the *trans*-bands in their i.r. spectra and those of their deuteriated derivatives (ref. 10).]

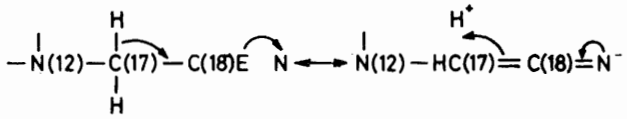
As a result, the pK_a'(MCS) value of (IV) is lower by 2 units than that of (V), and only 0.5 units greater than

that of (III); (V) is a weaker base than (VI) by only 0.75 units. It can be supposed that if the conformational equilibrium (Va)⇌(Vb) were entirely moved towards the form (Vb), the pK_a' value of (V) would still be closer to that of (VI).

The pK_a' and ΔpK_a' values of *N*-cyanomethylpiperidine (VII) and *N*-cyanoisopropylpiperidine (VIII) are very similar to corresponding values for *N*-cyanomethylangustifoline (III) and 11-cyanoisolupanine (VI), respectively (see Table 1).

Conclusions.—The classical inductive effect of the cyano-group decreases the basicity of α-cyanoamines by *ca.* 1.8 units of pK_a'(MCS). It is the difference between pK_a'(MCS) of the parent amine (R–H) and that of α-cyanoamines having no hydrogen atoms at the bridging carbon [(VI) and (VIII) in Table 1]. Further decrease of the basicity of α-cyanoamines is attributed to the direct (through space) electrostatic interactions between the cisoidal lone-pair at the nitrogen atom and one or two hydrogen atoms attached to the methine or methylene group. This effect does not occur in α-cyanoamines with no hydrogen atoms attached to the carbon bridge.

Great differences in the pK_a values of α-cyanoamines (with or without hydrogen atoms at the bridging carbon atom) were first observed by Marxer,[7a] who suggested that the decrease of basicity of α-cyanoamines was caused not only by an inductive effect, but also by hyperconjugation (below). *X*-Ray analysis of (III) has



not confirmed this hypothesis. If hyperconjugation participated in the structure of the N–CH_2–CN group, the C(17)–C(18) bond would be shorter in comparison with the normal C(sp_3)–C(sp) bond, whereas the data of Table 3 show that this bond is distinctly longer.

Since in the preferred conformation of α-cyanoamines of the type =N–CH_2–CN the lone pair is antiperiplanar to the nitrile group, there exist optimal conditions for electrostatic interactions between the two geminal hydrogen atoms of the methylene bridge and the lone pair. The decrease of basicity attributed to this effect may reach the value of 3.5 pK_a'(MCS), which, together with the classical inductive effect (1.80), may give the value of ΔpK_a'(MCS) *ca.* 5.0.

In α-cyanoamines with the methine bridge =N–CH–CN the occurrence of electrostatic interactions between the lone pair at nitrogen and the acidic hydrogen atom depends on the preferred conformation. If the electrostatic interactions are operating [(IV) and (Va) in Figure 7], the decrease of basicity may reach 2 pK_a'(MCS) units and the ΔpK_a'(MCS) value may be of the order of 4. In cases when the conformation excludes electrostatic interactions [(IVb) and (Vb)] the ΔpK_a'(MCS) value depends on the inductive effect only, and its value is therefore *ca.* 2.

If α-cyanoamines with a methine bridge form a mixture of different conformers, then, depending on the dynamic conformational equilibrium, the additional effect decreasing the basicity will be shown by the pK_a'(MCS) values in the range 0 to 2 units, the total ΔpK_a'(MCS) value being in the range 2 to 4.

It would be expected that the ΔpK_a' values characteristic of β-, γ-, and δ-cyanoamines (3.10, 1.56, and 0.82) [3b] would also be influenced by two effects: the classical inductive effect, and direct electrostatic interactions between the acidic hydrogen atoms at the carbon atom α to the nitrile group, and the lone pair at the nitrogen atom. Determination of the approximate contribution of these two factors is not at present possible, because pK_a' (and ΔpK_a') values are not known for β-, γ-, and δ-cyanoamines having no hydrogen atoms at the α-carbon atom.

EXPERIMENTAL

I.r. spectra were determined on Unicam SP 200 G or Perkin-Elmer 181 instruments by use of 0.1 mm NaCl cells and a sample concentration of 0.2M in $CDCl_3$. ^{1}H N.m.r. spectra were measured with Varian A 60 and 80 MHz Tesla BC 487 A spectrometers with tetramethylsilane as internal reference. Mass spectra were recorded on a JEOL JMS D 100 mass spectrometer.

Some of the spectra were recorded for Nujol suspensions. Elemental analyses were performed on a Perkin-Elmer 240 analyser.

Preparations.—Angustifoline (I). This was isolated from Lupinus angustifoline seeds according to the method of ref. 17.

N-*Methylangustifoline* (X). This was obtained from (I) by treatment with methyl iodide.[1]

11-*Cyano-tetrahydrorhombifoline* (IV). This was obtained by treating (I) with formaldehyde and potassium cyanide in aqueous solution,[1] and had spectroscopic properties (i.r., n.m.r., and m.s.) identical with those of the compound obtained in the fragmentation reaction of 13-tosyloxylupanine.[2] Previously [2] (IV) was supposed to be an oil, but we obtained crystals, which after recrystallization from light petroleum had m.p. 102 °C; pK_a(MCS) 3.1; $[\alpha]_D^{20}$ 100.4° (EtOH). When aqueous solutions of (III) are set aside at room temperature for *ca.* 20 h, (IV) can be extracted from the solution with diethyl ether in *ca.* 90% yield; it is probable that (III) is transformed immediately into (IV) although it dissolves very slowly.

N-*Cyanomethylangustifoline* (III). (I) (200 mg) was dissolved in benzene (10 ml) and heated for 10 min for azeotropic removal of traces of water. Paraformaldehyde (*ca.* 100 mg) was then added, the mixture set aside for 3 h, and benzene evaporated under reduced pressure. The residue was dissolved in methanol (10 ml), potassium cyanide (400 mg) was added, and the mixture stirred (3 h) at room temperature. Methanol was evaporated from the filtered solution and the residue dissolved in diethyl ether. The ethereal solution was dried (KOH) and concentrated. The residue (130 mg) was recrystallized from benzene–light petroleum; m.p. 95—97 °C; $[\alpha]_D^{20}$ 63.5° (EtOH); pK_a(MCS) 2.60; *m/e* 273 (M^+) (Found: C, 70.2; H, 8.25; N, 15.25. Calc. for $C_{16}H_{23}N_3O$: C, 70.39; H, 8.49; N, 15.39). For i.r. and n.m.r. spectra, see Figures 1 and 2. The deuteriated derivative (*m/e* 275) was obtained similarly but by use of deuteriated paraformaldehyde.

17-*Cyanolupanine*. This was obtained from lupanine (XII) through the anhydronium salt of 17-hydroxylupanine on reaction with potassium cyanide.[6]

11-*Cyanolupanine* (VI). This was prepared from lupanine (XII) by reaction of Δ^{11}-dehydrolupanine cation with potassium cyanide.[5]

N-*Cyanomethylpiperidine* (VII) *and* N-*Cyanoisopropylpiperidine* (VIII). These were prepared according to the methods of ref. 7. Their properties were identical with those reported previously: pK_a(H_2O) (VII) 4.15, (VIII) 9.15; pK_a(MCS) (VII) 3.35, (VIII) 6.50.

X-*Ray Measurements*.—Suitable crystals were grown from diethyl ether–light petroleum by slow evaporation. The crystal selected for analysis was 0.15 × 0.20 × 0.30 mm. Retigraph and precession photographs showed monoclinic symmetry.

Diffraction data were collected by use of a Syntex $P2_1$ automatic four-circle diffractometer graphite monochromated with Cu-K_a radiation. Accurate unit-cell parameters were determined by least-squares from the adjusted angular settings of 15 reflections.[18]

Crystal data. $C_{16}H_{23}N_3O$, M = 273.38. Monoclinic, a = 10.223(1), b = 9.416(1), c = 7.846 4(7) Å, β = 94.741(8)°, u = 752.7(1) Å^3, D_m = 1.21 (by flotation), Z = 2, D_c = 1.21 g cm^{-3}. Space group $P2_1$ or $P2_1/m$ from systematic absences ($0k0$ for $k = 2n$); the former shown to be correct by subsequent successful analysis. Cu-K_α radiation, λ = 1.541 8 Å; δ(Cu-K_α) = 6.2 cm^{-1}.

Intensity measurements were carried out in the θ—2θ mode up to $2\theta_{max.}$ 115°, with variable scan speed 2.5 to 29.3° min^{-1}. Of 1 103 reflections, 1 055 having intensities $I > 1.96\ \sigma(I)$ were used in the structure refinement. Corrections for Lorentz and polarization effects were applied, but not for absorption or extinction.

Structure determination. The structure was solved straightforwardly by MULTAN. An E map revealed twenty possible atom positions of which eighteen were found to be ultimately correct. After full-matrix least-squares refinement these positions were used to phase a difference Fourier synthesis which indicated two remaining atom positions. With these atoms in the model R was 0.13. Four cycles of full-matrix least-squares calculations carried out with isotropic thermal parameters reduced R to 0.11 and then, with anisotropic thermal parameters, to 0.087. All hydrogen atoms were located on two successive difference-Fourier synthesis by means of nineteen-point electron-density interpolation. Full-matrix least-squares refinement was carried out using varying positional and thermal parameters of non-hydrogen atoms; hydrogen atoms were included as fixed contributions each with isotropic temperature factor B one unit greater than that of the atom to which it was bonded. Initially statistical weights, $w = 1/\sigma_F^2$, were used, but in the last three cycles of refinement the weighting scheme applied was: $w = F_o^2/a^2$ if $F_o \leqslant a$, $w = 1$ if $a < F_o < b$, and $w = b^2/F_o^2$ if $F_o \geqslant b$, where a = 2.8 and b = 10. The quantity minimized in the least-squares calculations was $\Sigma\ w(F_o - F_c)^2$. The final R was 0.039 for observed reflections only.

All calculations were performed on a NOVA minicomputer using original or locally modified (by M. Jaskólski) Syntex XTL programs.

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