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THE IR SPECTRA, THE NIR SPECTRA AND THE CONFORMATION OF SOME BASIC AMIDES

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Abstract—The NH stretching region in a series of basic primary and secondary amides have been examined, discussed and some norms, which allow a distinction between inter and intramolecular hydrogen bonds have been drawn. Basic amide molecules are found to be strongly associated in chloroform, but far less in dichloromethane solution.

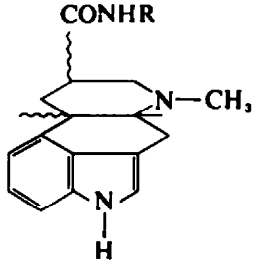
When certain steric conditions are satisfied, a strong intramolecular N—H . . . N bond can be formed and it is detected by the appearance of a strong and broad band at ca. 3220 cm^{-1} (dichloromethane solution), by a shift of the amide I band (1660 instead of 1675 cm^{-1}) and by an absorption band in the NIR at 1·980 μ.

By determining the extent of the intramolecular hydrogen bond the conformation of 1-methyl-4-phenylisonipecotamide, tetrahydro-3-quinolinecarboxamides, hexahydronicotamides and β-N-piperidinopropionamides has been ascertained.

The energy of the intramolecular N—H . . . N hydrogen bond has been valued to be about 1 kcal/mole.

INTRODUCTION

IN THE former paper[1] we presented the IR-spectra of the four dihydrolysergamides



(8α,10β; 8β,10β; 8α,10α; 8β,10α) and their N-ethyl derivatives (R = C_2H_5). The following observations were made:

(i) The two primary amides (8β,10α; 8α,10β), to which an equatorial conformation was later assigned, show, in chloroform solution, beside the usual 3520 and 3410 cm^{-1} bands (NH stretching modes of a free primary amide group) some strong[2] absorption bands at ca. 3480, 3330 and 3180 cm^{-1} (Table 1). These bands, in solutions (0·06 to 0·015 molar) are slightly affected by dilution and are no longer present in dichloromethane solution.

The homologous N-ethylamides, beside the expected[2] 3460 cm^{-1} band (NH stretching mode of a free secondary amide group), show a strong and broad band at about 3340 cm^{-1}, which is likewise little affected by dilution, but is practically absent in dichloromethane solution.

[1] L. Bernardi and W. Barbieri, *Tetrahedron* **21**, 2523 (1965).
[2] L. J. Bellamy. *The infrared spectra of complex molecules* p. 206. Methuen, London (1958).

(ii) The two primary amides (8α,10α; 8β,10β), to which an axial conformation was assigned (conformation which *a priori* allows the formation of an intramolecular N—H . . . N bond), show either in chloroform or dichloromethane solution a sharp band at ca. 3480 cm^{-1} and a strong broad band at about 3220 cm^{-1}, both bands being concentration-independent.

The homologous N-ethylamides show in chloroform and in dichloromethane strong broad bands at about 3220 cm^{-1}.

TABLE 1

Amide	Absorption bands (cm^{-1}) $CHCl_3$ 0·03 mole	CH_2Cl_2 0·03 mole
Equatorial dihydrolysergamides and other non-bonded basic amides.		
Primary	3520 (s; sh)	3520 (s; sh)
	3410 (s; sh)	3410 (s; sh)
	3480 (ms; sh)	
	3320 (m; br)	
	3180 (w; br)	
Secondary	3460 (s; sh)	3460 (s; sh)
	3350 (s; br)	
Axial dihydrolysergamides and other intramolecularly bonded basic amides		
Primary	3480 (s; sh)	3480 (s; sh)
	3220 (s; br)	3220 (s; br)
Secondary	3220 (s; br)	3220 (s; br)

s = strong; ms = medium-strong; m = medium; w = weak; sh = sharp; br = broad.

The published material[2] concerning the NH stretching region of the IR spectra is of limited value in interpreting these complex spectra. It is known[2] that alkylcarboxamides present, in chloroform solution, beside the two bands due to the free NH_2 (ca. 3520 and 3410 cm^{-1}), up to four further (weaker and broader) bands at 3498, 3345, 3300 and 3181 cm^{-1}. These bands, called association bands, are usually assigned to the NH stretching modes of the amide groups present in associate polymeric forms. Apparently these association bands should be similar to those present in the spectra of equatorial dihydrolysergamides (observation i); the problem, however, is more complex since, as observed experimentally, in the case of an alkylcarboxamide such as valeramide, butyramide or chloroacetamide the association bands are strongly concentration-dependent. It can be seen in Fig. 1 that, even at 0·06 molar concentration, valeramide shows very weak association bands in chloroform.

The different behaviour of the dihydrolysergamides therefore, are either due to a plurality of conformations which allow the presence of some intramolecular bond[3] or can be ascribed to the presence in these molecules of a basic centre. In other words in valeramide the association proceeds by way of weak N—H . . . O=C hydrogen bonds,[2] whereas in the case of basic amides a much stronger N—H . . . N bond is

[3] Actual construction of models reveals that, for instance, in the case of 8α,10β-dihydrolysergamide six conformations, including four boat conformations, are possible and for some of these an intramolecular hydrogen bond is possible.

possible and therefore even in dilute solution these amides can be present in associate form.

The IR spectra of basic amides

To test the hypothesis, model basic primary and secondary amides were prepared and examined: the significant part of their spectra is reported in Figs. 1 and 2.

The spectra of γ-diethylaminobutyramide (I) and ε-dimethylaminocaproamide (II)

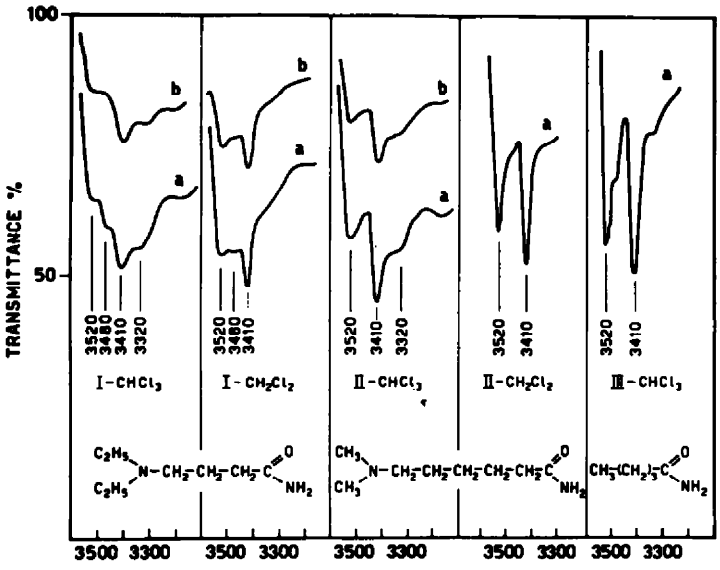


FIG. 1. Spectra of γ-diethylaminobutyramide (I); ε-dimethylaminocaproamide (II) and valeramide (III).
a = 0·06 M solution; b = 0·03 M solution

(Fig. 1) in chloroform carry a strong resemblance to the spectra of the dihydrolysergamides 8β,10α and 8α,10β and differ from the spectra of valeramide (III) inasmuch as the association bands are less affected by dilution, whereas they are very sensitive to change of solvent[4] (dichloromethane).

The spectra of the homologous monoethylamides IV and V[5] (Fig. 2) show, in chloroform, beside the 3460 cm^{-1} band (secondary amide), a strong border band at 3340 cm^{-1}, scarcely affected by dilution but almost absent in dichloromethane. Similar spectral behaviour is shown by the monoethylamides of dihydrolysergic acid 8β,10α and 8α,10β.[6]

[4] In one case (II) the association bands disappear in dichloromethane; in another case (I), some weak association bands (particularly the 3480 cm^{-1} band) are still present even in dilute solution and this means probably that I is in part intramolecularly hydrogen bonded, via a 7 member ring (v.i.).

[5] Compounds I, II, IV and V were obtained by treatment of the corresponding acid chlorides with ammonia viz. ethylamine. ε-Dimethylaminocaproic acid was prepared by reductive alkylation (formaldehyde and hydrogen with a Pd catalyst) of ε-aminocaproic acid.

[6] It is interesting to note that the spectrum of a chloroform solution containing ethylvaleramide and ethylpiperidine in a 1:1 molar ratio presents a strong band at about 3350 cm^{-1} (Fig. 2). This band is not present in dichloromethane solution.

It can, therefore, be concluded that not only (equatorial) dihydrolysergamides but, in general, basic amide molecules are associated even in fairly dilute (chloroform) solutions: the N—H . . . N bond is stronger that the N—H . . . O=C bond and the association bands are stronger[7] and less affected by dilution. A better dissociating solvent, however, breaks down these bonds and the spectra of a 0·06 molar dichloromethane solution of these basic amides show the same known features as the spectra

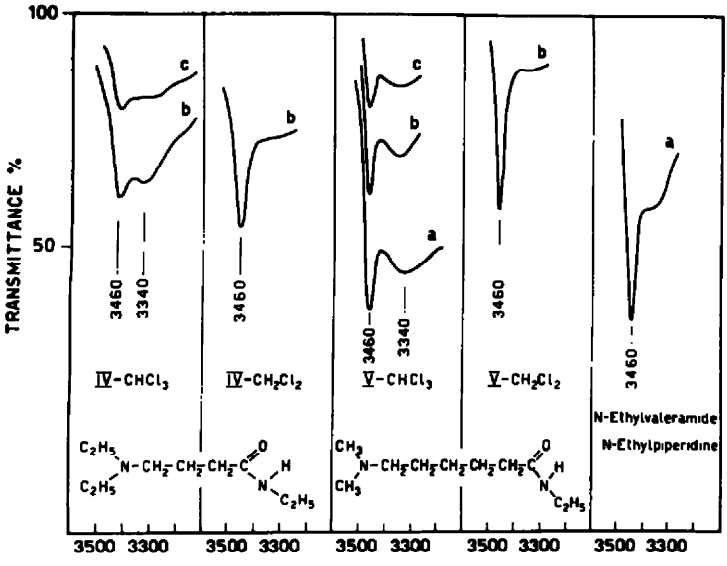


FIG. 2. Spectra of N-ethyl-γ-diethylaminobutyramide (IV); N-ethyl-ε-dimethylaminocaproamide (V) and 1:1 mixture of N-ethylvaleramide and N-ethylpiperidine in $CHCl_3$. a = 0·08 M solution; b = 0·06 M solution; c = 0·03 M solution

of non-basic amides. The first group of observations (i), concerning the equatorial dihydrolysergamides are therefore interpreted and explained by the presence in the amide molecule of a basic centre.

The spectra of β-N-piperidinopropionamide (VI) and N'-ethyl-β-piperidinopropionamide (VII)[8] (Fig. 3) provide the solution to the spectra of axial amides.

The spectrum of VI shows in chloroform and in dichloromethane[9] strong sharp bands at 3480 cm^{-1} and strong broad bands at about 3220 cm^{-1}, both sets of bands being concentration-independent. The spectrum of VII in dichloromethane[10] presents a medium, sharp band at 3460 cm^{-1} (free NH of a secondary amide) and a larger band at about 3210 cm^{-1}, both bands being concentration-independent.

[7] There is also some band shift, but it is difficult to determine it, because the bands are broad and partly overlapping.

[8] For the synthesis of VI and VII, β-chloropropionyl chloride was made to react with ammonia viz. ethylamine and the resulting β-chloropropionamide and N-ethyl-β-chloropropionamide were next treated with piperidine in tetrahydrofuran.

[9] Only one spectrum is reported for sake of simplicity (dichloromethane).

[10] In chloroform solution there is also present a concentration-dependent band due to an intermolecular bond, absent, as usual, in dichloromethane solution.

The features of these spectra are similar to those of axial dihydrolysergamides (observation ii of the introduction). These bands, which are concentration independent and unaffected by the nature of the solvent, depend on the existence of an intramolecular hydrogen bond between the H of the amide group and the tertiary nitrogen.

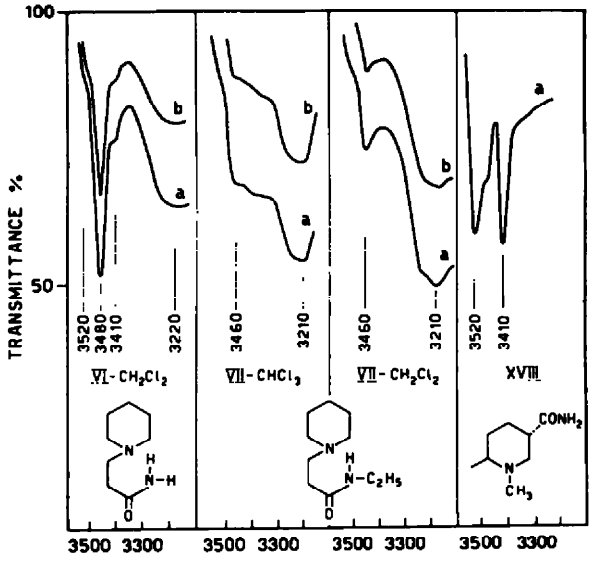
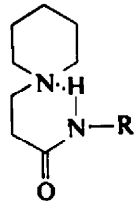


FIG. 3. Spectra of β-N-piperidinopropionamide (VI), N′-ethyl-β-N-piperidinopropionamide (VII) and *trans*-1,6-dimethylhexahydronicotamide (XVIII).
a = 0·06 Msolution; b = 0·03 M solution

In the case of VI and VII this means that these molecules exist in solution largely in a *coiled* intramolecularly bonded form.[11–13]



Since the prominent and sometimes sole band in secondary axial dihydrolysergamides[1] and in N′-ethyl-β-N-piperidinopropionamide (VII) is the broad[14] band at about 3220 cm^{-1}, this must be assigned to the intramolecularly hydrogen bonded NH

[11] The presence in the spectrum of VII of a band at ca. 3460 cm^{-1} due to a free NH (secondary) shows that some of the molecules are in a stretched (uncoiled) form.

[12] The CO band of VI appears at 1665 cm^{-1} both in chloroform and in the solid state and this confirms that the bond is intramolecular.

[13] α-Aminoacetamides could be likewise intramolecularly hydrogen bonded by closing a five member ring: the distinctive spectra of these compounds will be the subject of a later report.

[14] Intramolecular hydrogen bonds give rise to *broad* association bands, as in the case, for instance, of 3-aminoalcohols.[15]

[15] M. St. C. Flett, *Spectrochimica Acta* 10, 27 (1957).

mode. Consequently, of the two bands (3480 and 3220 cm^{-1}) present in the spectra of primary axial dihydrolysergamides and β-N-piperidinopropionamide (VI), the broad one at ca. 3220 cm^{-1} should be ascribed to the intramolecularly hydrogen bonded NH mode. The sharp band at ca. 3480 cm^{-1} is ascribed to the NH stretching mode of the second hydrogen atom which is not involved in the intramolecular hydrogen bond. Since hydrogen bonding, as well as substitution, makes the amide nitrogen more electronegative, the NH stretching frequency of this (unbonded) hydrogen atom should be close to the one of a secondary amide (about 3460 cm^{-1}), as is actually the case.[16]

At this point the features of the IR-spectra of basic amides both inter- and intramolecularly bonded, are sufficiently clear, but as a further check, two epimeric amides, whose conformation though fixed could be determined and would, therefore, clearly show either intermolecular or intramolecular bonds were examined. For this purpose *cis*- and *trans*-6-*t*-butylhexahydronicotamide was synthesized. Since the conformation of the t-butyl group is always equatorial[18] the conformation of the amide group becomes fixed, either equatorial in the *trans* epimer (only intermolecular bonds feasible) or axial in the *cis* isomer (intramolecular bonds feasible).[19]

Catalytic reduction (PtO_2) of 6-t-butylnicotamide[20] afforded *cis*-6-t-butylhexahydronicotamide (VIII)[21] from which, by epimerization with potassium t-butoxide in t-butanol, the *trans* derivative (IX) can be obtained.

The IR spectrum of the *cis*-isomer (VIII), clearly shows the 3480 and 3220 cm^{-1} bands, assigned to the intramolecularly bonded amide group[23] (Fig. 4).

Similarly, the spectrum of the *trans*-isomer (IX) clearly depicts the equatorial conformation of the amide group for which an intramolecular bond is impossible.[24]

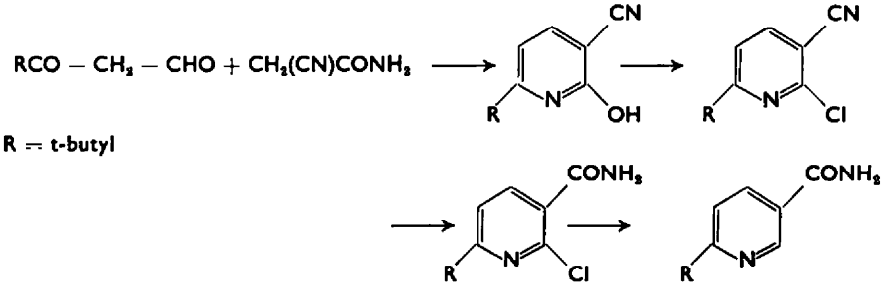
[16] Davies[17] has examined the IR spectra of concentrate solutions of acetamide (intermolecular bonds) and has assigned a similar band to the antisymmetric stretching mode of a bonded NH.

[17] M. Davies and H. E. Hallam, *Trans. Faraday Soc.* **47**, 1170 (1951).

[18] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* **77**, 5562 (1956).

[19] Unless of course the piperidine ring assumes a boat conformation. The spectra, however, are clear-cut and therefore the objection can be disregarded.

[20] 6-t-Butylnicotamide was obtained according to the following scheme:



[21] Catalytic reduction of 4-t-butylbenzoic acid has been shown[22] to give *cis*-4-t-butylhexahydrobenzoic acid; by analogy the *cis* axial configuration should be assigned to VIII. Moreover equilibration of VIII gives proponderantly IX; VIII must therefore be the less stable (*cis*, axial) isomer.

[22] E. A. Cavel, N. B. Chapman and M. D. Johnson, *J. Chem. Soc.* 2637 (1962).

[23] Two shoulders (3520 and 3410 cm^{-1}), corresponding to the NH modes of a free NH_2, can be noted in the spectrum of VIII and this means that the amide group is not 100% hydrogen bonded. The same fact,[1] but on a larger scale, was previously observed with 1-methyldihydrolysergamide-II and similarly interpreted.

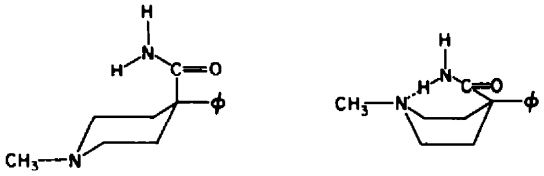
[24] The position of the CO band in chloroform (1660 cm^{-1} for VIII and 1675 cm^{-1} for IX) confirms the above assigned configurations.

The conformation of some piperidinecarboxamides

As a logical extension of this work, the IR spectra of some piperidinecarboxamides having a non-rigid conformation were investigated.

The spectra of 1-methyl-1,4,5,6-tetrahydronicotamide[25] and 1-methyl-1,2,5,6-tetrahydronicotamide[26] which cannot form, for steric reasons an intramolecular bond, do in fact present only the 3520 and 3410 cm^{-1} bands (free NH_2).[27]

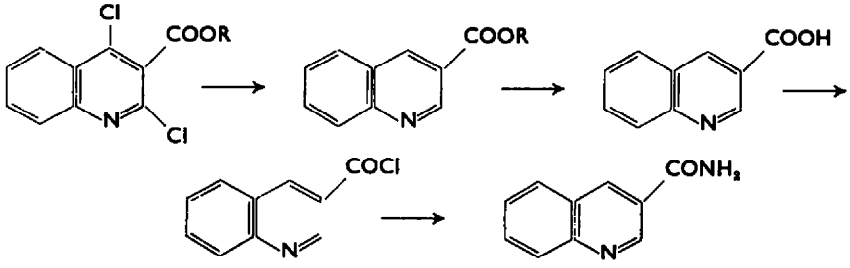
1-Methyl-4-phenylisonipecotamide (X),[28] for which an axial conformation of the amide group can be assumed, can have either a chair or (less probable) a boat conformation:



The boat conformation does not preclude an intramolecular N—H . . . N hydrogen bond (via a 7 member ring), but, since the IR spectrum (in CH_2Cl_2) presents only the two bands (3520 and 3410 cm^{-1}) of a free primary amide, this conformation can be excluded.[29]

The spectra of 1,2,3,4-tetrahydro-3-quinolinecarboxamide (XI) and 1-methyl-1,2,3,4-tetrahydro-3-quinolinecarboxamide (XII) in CH_2Cl_2[33] (Fig. 4) show, although in reduced measure, the association bands previously[1] observed and related to an

[25] M. Marty, M. Viscontini and P. Karrer, *Helv. Chim. Acta* **39**, 1451 (1956).
[26] G. Thuillier, P. Rumpf, H. Nakajima and J. Thuillier, *C.R. Acad. Sci., Paris* **244**, 1792 (1957).
[27] Since the spectra present only the usual two bands of a primary amide they are not reported here.
[28] Obtained by hydrolysis of 1-methyl-4-phenyl-4-cyanopiperidine.
[29] It is known[30–32] that 4-hydroxypiperidines do not present intramolecular bonds and therefore in these cases also, the piperidine ring has a chair-like conformation.
[30] R. E. Lyle, *J. Org. Chem.* **22**, 1286 (1957).
[31] G. Hite, E. E. Smissman and R. West, *J. Amer. Chem. Soc.* **82**, 1207 (1960).
[32] H. O. House, H. C. Müller, C. G. Pitt and P. P. Wickham, *J. Org. Chem.* **28**, 2407 (1963).
[33] 3-Quinolinecarboxamide was prepared from ethyl 2,4-dichloro-3-quinolinecarbonate[34] according to the following scheme:



3-Quinolinecarboxamide was reduced (H_2/Ni Raney) to give XI. The synthesis of XII was achieved by treatment of 3-quinolinecarboxamide with methyl iodide followed by hydrogenation (H_2/PtO_2) of the resulting quaternary salt.
[34] M. F. Grundon, M. J. McCorkingdale and M. N. Rodger, *J. Chem. Soc.* 4289 (1955).

intramolecular hydrogen bond and this means that the amide group is partly in a *quasi*-axial conformation.[35]

When the piperidine ring is completely free as it is in the case of hexahydronicotamides the axial conformation of the amide group becomes preponderant. In effect the spectra of hexahydronicotamide[36] (XIII) and 1-methylhexahydronicotamide[37]

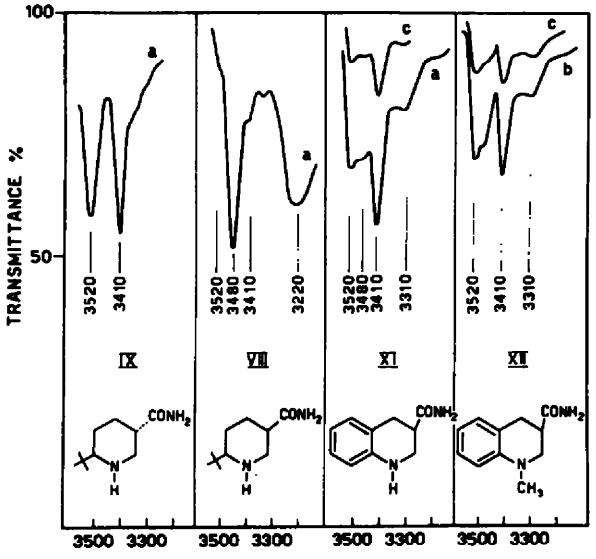


FIG. 4. Spectra of dichloromethane solution of *trans*-6-t-butylhexahydronicotamide (IX); *cis*-6-t-butylhexahydronicotamide (VIII); 1,2,3,4-tetrahydro-3-quinoline-carboxamide (XI); 1-methyl-1,2,3,4-tetrahydro-3-quinolinecarboxamide (XII). a = 0·06 M solution; b = 0·03 M solution; c = 0·015 M solution

(XIV) show strong intramolecular bonds and the same can be said of the spectra of N′-ethylhexahydronicotamide (XV) and N′-ethyl-1-methylhexahydronicotamide (XVI)[38] (Fig. 5).

The spectrum of XVI in carbon tetrachloride shows that in this solvent XVI exists (Fig. 5) almost completely as the axial hydrogen bonded conformation; hydrogen bond breaking solvents such as dichloromethane clearly reduce the extent of this axial conformation.[40]

The spectra (Fig. 5) also show that the 1-methylderivatives (XIV and XVI) are more intramolecularly bonded than the unmethylated ones (XIII and XV)[41],

[35] We suppose the conformation of tetrahydroquinolines be very similar to the one of cyclohexene.
[36] H. Fox, *J. Org. Chem.* **17**, 542 (1952).
[37] P. Karrer and F. J. Stare, *Helv. Chim. Acta* **20**, 418 (1937).
[38] Hydrogenation of N-ethylnicotamide[39] in presence of PtO_2 gave XV, likewise hydrogenation of N-ethylnicotamide methiodide afforded XVI.
[39] T. S. Work, *J. Chem. Soc.* 429 (1942).
[40] The CO mode of XIII and XIV in chloroform occurs at 1662 cm^{-1} and this also is a good indication that these compounds are largely intramolecular bonded.[1]
[41] The 3520 and 3410 cm^{-1} bands (free NH_2) are stronger in XIII than in XIV. Similarly the 3480 cm^{-1} band (free secondary NH) is stronger in XV.

as is to be expected since in the former case the nitrogen atom must be more nucleophilic.[42]

The energy of the intramolecular bond

In the hexahydronicotamides the conformation supporting an axial group is favoured since the free-energy difference between the axial and the equatorial forms is partly neutralized by the energy of formation of the intramolecular hydrogen bond.

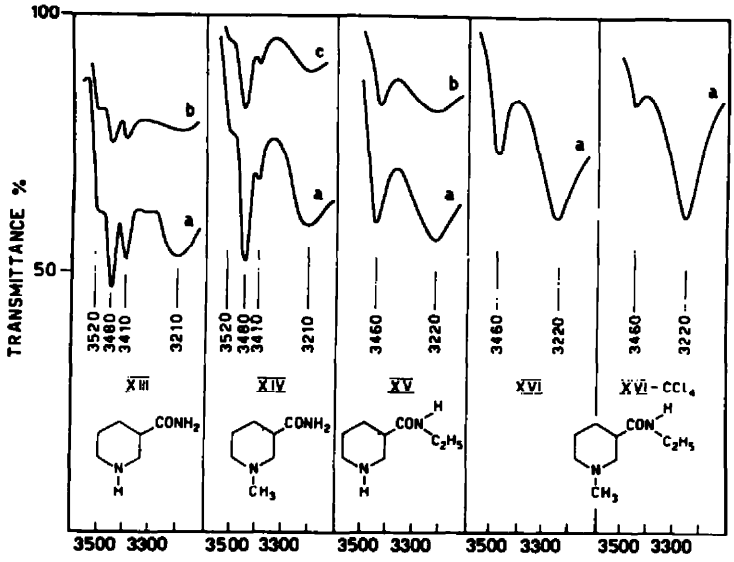
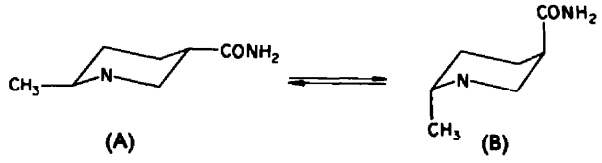


FIG. 5. Spectra of dichloromethane solutions of hexahydronicotamide (XIII); 1-methylhexahydronicotamide (XIV); N'-ethylhexahydronicotamide (XV) and N'-ethyl-1-methylhexahydronicotamide (XVI).
a = 0·06 M solution; b = 0·03 M solution; c = 0·015 M solution

In order to calculate the energy of this bond, which should average 2–4 kcal/mole,[45] the spectra of *trans*-6-methylhexahydronicotamide (XVII) and *trans*-1,6-dimethylhexahydronicotamide (XVIII) were examined.

Two conformations (A and B) are possible for these compounds and the



[42] It is known that in nonaqueous solvents[43] tertiary amines are more basic than secondary amines as expected from the inductive effect.[44]

[43] In aqueous solvents, owing to solvation effects, the order of basicity is reversed: p*K*'s of XIII is 8·79; p*K*'s of XIV is 7·86.

[44] L. N. Fergurson, *The modern structural theory of organic chemistry* p. 292. Prentice-Hall, Englewoods Cliffs, N.J. (1963).

[45] See Ref. 44, p. 128.

free-energy difference $\Delta F(A\text{-}B)$ can be calculated:

$$\Delta F(A\text{-}B) = \Delta F_{CH_3} - \Delta F_{CONH_2} + H$$

where H is the unknown energy of the hydrogen bond; $-\Delta F_{CH_3}$ and $-\Delta F_{CONH_2}$ are the experimental free-energy differences between equatorial and axial substituent. Only $-\Delta F_{CH_3}$ is known (1·8 kcal/mole[46]), but $-\Delta F_{CONH_2}$ is estimated to be equivalent to $-\Delta F_{COOC_2H_5}$ (1·2 kcal/mole[47]). However, the C_3 axial substituent in a piperidine ring interacts with the C_5 (axial) hydrogen atom and with the nitrogen lone pair, whereas an axial substituent in a cyclohexane ring (for whom the value $-\Delta F_{COOC_2H_5} =$ 1·2 kcal/mole has been determined) interacts instead with *two* hydrogen atoms. At present the question of the steric requirements of the nitrogen lone pair is still under discussion but it is generally understood that in aprotic solvents they are far lower than those of the hydrogen atom[48,49] and perhaps negligible.[50,51]

The practical value of $-\Delta F_{CONH_2}$ in our case in therefore probably somewhat over $1{\cdot}2/2 = 0{\cdot}6$ kcal/mole and we feel justified in adopting a value of $0{\cdot}9 \pm 0{\cdot}3$ kcal/mole, keeping in mind that the lower figure is more probable. Accordingly, we obtain:

$$\Delta F(A\text{-}B) = -1{\cdot}8 - 0{\cdot}9 + H = -2{\cdot}7 + H$$

It can be calculated from the formula $\Delta F = -RT \ln K$ that for H=O the equilibrium is 98% in favour of conformation A, whereas for, say, $H = 2{\cdot}7$, $\Delta F(A\text{-}B) = 0$ and the ratio A/B becomes equal to 1. Had the value of H been as high as expected (2–4 kcal/mole), the presence of conformation B should have been easily detected in the spectra of *trans*-6-methylhexahydronicotamide.

Catalytic reduction of 6-methylnicotamide[52] affords the expected *cis*-6-methylhexahydronicotamide[53] (XIX), which by treatment with potassium t-butoxide in t-butanol gives *trans*-6-methylhexahydronicotamide (XVII) which may be isolated by

[46] See Ref. 44 p. 240.

[47] E. Eliel, H. Haubenstoock and R. V. Acharya, *J. Amer. Chem. Soc.* **83**, 2351 (1961).

[48] N. W. J. Pumphrey and M. J. T. Robinson, *Chem. & Ind.* 1903 (1963).

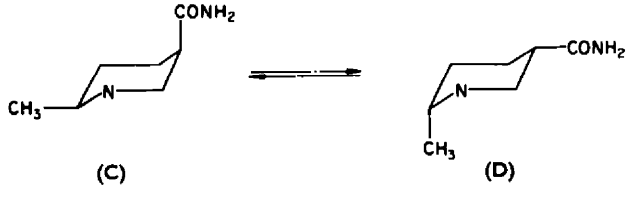
[49] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones and A. R. Katritzky, *Proc. Chem. Soc.* 257 (1964).

[50] T. A. Claxton, *Chem. & Ind.* 1713 (1964).

[51] N. L. Allinger, J. G. D. Carpenter and F. M. Karkowski, *Tetrahedron Letters* No **45**, 3345 (1964).

[52] P. A. Plattner, W. Keller and A. Boller, *Helv. Chim. Acta* **37**, 1379 (1954).

[53] The spectrum of the NH region of compound XIX is not reported because it is almost identical to the one of VIII (Fig. 4). Two conformations, C and D, are possible for compound XIX, but it would be impossible to determine the extent of conformation D from the intensities of the 3520 and 3410 cm^{-1} bands (free NH_2) because, as we have already shown,[1] these bands could be due



either to an equatorial amide group (conformation D) or to an incompletely bonded axial amide. For this reason the study of this equilibrium was not attempted; however, the IR spectrum of XIX does not present appreciable bands due to a free NH_2 (3520 and 3410 cm^{-1}): very little D is therefore present.

crystallization. The IR spectrum[54] of XVII shows only the bands due to an equatorial amide, and therefore, it must be concluded that very little of form B is present. On the other hand the IR spectrum of *trans*-1,6-dimethylhexahydronicotamide (XVIII) (Fig. 3)[55] shows a weak but distinct shoulder, at about 3480 cm^{-1}, unaffected by dilution, usually assigned to an axial amide; the content of form B can be estimated (v.i.) to be not over 8%. The value of the energy of the intramolecular hydrogen bond in *trans*-1,6-dimethylhexahydronicotamide in dichloromethane solution can thus be calculated to be less than 1·25 kcal/mole.[56]

In order to check this result, an estimate of the axial content in 1-methylhexahydronicotamide and related substances was obtained. A whole series of mixture of *cis*- and *trans*-6-t-butylhexahydronicotamide with varying concentrations of each isomer were examined as 0·05 molar solutions (dichloromethane) and the NH stretching modes recorded. Three sharp bands (3520, 3480 and 3410 cm^{-1}) were taken into consideration. By direct comparison of the spectra and by means of graphic interpolation, the axial content of 1-methylhexahydronicotamide in dichloromethane was estimated as being 68 ± 3%, the axial content of hexahydronicotamide 48 ± 3% and the axial content of *trans*-1,6-dimethylhexahydronicotamide 7 ± 1%.[57,58]

From the first of these values the energy of the hydrogen bond in 1-methylhexahydronicotamide was calculated: a value of H = 1·35 was found,[60] which is in good agreement with the one previously determined.[61]

Near-infrared spectra

In order to check the results previously reported the NIR spectra of a group of primary basic amides up to 2·2 μ have been examined in chloroform solution. According to Goddu[62] two bands, corresponding to the first overtone, should be present at about 1·5 μ and a third band, possibly due to a combination of the NH stretching vibration at 2·82 μ and the amide II deformation band at 6·4 μ, should be present at about 2 μ. We examined 19 compounds (Table 2) and found the expected bands; only the 2 μ band being the most intense of the three will be discussed.

Compounds 1–8 are either neutral amides or basic amides that cannot present intramolecular hydrogen bonds and all of them absorb at about 1·959 μ. Compounds 9–13 absorb at about 1·980 μ and since we have already shown that in these compounds

[54] On account of solubility, the spectrum was performed in tetrachloroethane solution and it is not reported since it is identical with that of *trans*-6-t-butylhexahydronicotamide (IX) (Fig. 4).

[55] We examined this compound because 1-methylderivatives (the nitrogen atom being more nucleophilic) present a stronger intramolecular hydrogen bond.

[56] 92% of more stable isomer at equilibrium, requires a $\Delta F = -1{\cdot}45$ and therefore $-1{\cdot}45 = -2{\cdot}7 + H$; $H = 1{\cdot}25$.

[57] We must of course assume that the extinction coefficients of the 3520 and 3410 cm^{-1} (free NH_2) and 3480 cm^{-1} (bonded NH_2) bands are the same for either 1-methylhexahydronicotamide and its 6-alkyl derivatives.

[58] In the same way the percentage of axial amide in the crude equilibrium mixture of VIII and IX was found to be 34 ± 3%. Formerly[59] we had found that the highly strained dihydrolysergamides afforded equilibrium mixtures having a 28–30% content of axial isomer.

[59] L. Bernardi and W. Barbieri, *Gazz. Chin. Ital.* **95**, 375 (1965).

[60] At equilibrium, a 32% of the more stable isomer requires $\Delta F = +0{\cdot}45$ and since $\Delta F = H - 0{\cdot}9$, it results $H = 1{\cdot}35$

[61] The same value has been reported[45] for the N—H . . . N (intermolecular) bond in NH_3.

[62] R. F. Goddu, *Near infrared spectrophotometry. Advances in analytical chemistry and instrumentation* Vol. 1; p. 384. Interscience, New York (1960).

one NH_2-hydrogen is involved in a strong intramolecular bond we can assign the 1·980 μ band to an intramolecularly bonded amide group. Moreover, compounds such as 1-methyldihydrolysergamide-II (19) which is incompletely bonded,[1] or 1-methyllysergamide (18) which is in part bonded,[1] present 2 bands, at about 1·960 and

Table 2. NIR bands of primary amides in the 2 μ range
(0·1 molar solutions in chloroform)

No.	Amide	λ Max μ	
1	Butyramide	1·959	
2	Valeramide	1·959	
3	Chloroacetamide	1·967	
4	*e*-Dimethylaminocaproamide	1·958	
5	*trans*-6-Methylhexahydronicotamide	1·958	
6	*trans*-6-t-Butylhexahydronicotamide	1·959	
7	1-Methyldihydrolysergamide-I	1·959	
8	1-Methyldihydroisolysergamide-II	1·959	
9	β-N-Piperidinopropionamide		1·978
10	*cis*-6-Methylhexahydronicotamide		1·980
11	*cis*-6-t-Butylhexahydronicotamide		1·979
12	1-Methyldihydroisolysergamide-I		1·980
13	1-Methylisolysergamide		1·978
14	Hexahydronicotamide	1·958 (s)	1·980 (m)
15	1-Methylhexahydronicotamide	1·958 (ms)	1·980 (s)
16	1,2,3,4-Tetrahydro-3-quinolinecarboxamide	1·958 (s)	1·979 (w)
17	1-Methyl-1,2,3,4-tetrahydro-3-quinolinecarboxamide	1·958 (s)	1·979 (w)
18	1-Methyllysergamide	1·962 (s)	1·978 (ms)
19	1-Methyldihydrolysergamide-II	1·958 (m)	1·981 (s)

1·980 μ. Similar behaviour is presented by compounds 14–17 in which the piperidine ring, being flexible, allows the amide group to assume an axial, intramolecularly bonded conformation and since the 1·96 μ band does not interfere with the 1·98 μ band, the latter band may be quantitatively estimated.

In order to calculate the percentage of axial form in 1-methylhexahydronicotamide, the extinction coefficient at 1·958 μ and 1·98 μ of *cis*- viz. *trans*-6-methylhexahydronicotamide and 1-methylhexahydronicotamide (Table 3) was determined. Based the

Table 3

Compound	ε λ 1·958 μ	ε λ 1·980 μ
trans-6-Methylhexahydronicotamide	1·2	0
cis-6-Methylhexahydronicotamide	0·25	0·92
1-Methylhexahydronicotamide	0·40[a]	0·65

[a] The value has been corrected for the absorbance of the 1·98 μ band at 1·958 μ.

assumption that these similar compounds have comparable extinction coefficients, an axial content of 0·65/0·92 = 0·70, was calculated and is in good agreement with the value previously found. The 1·958 μ band can also be used, although with minor reliability, to determine the amount of free amide group (equatorial) if use is made of a value of ε corrected for the residual absorption of the 1·98 μ band at 1·958 μ. Such

corrected value being 0·4 the percentage of equatorial form is 0·4/1·2 = 0·33, still in good agreement with the previous values.

EXPERIMENTAL

(with Dr. Severina Coda)

M.ps are uncorrected. All the compounds reported furnished satisfactory IR spectra.

γ-Diethylaminobutyramide (I). A suspension of γ-diethylaminobutyric acid[63] (2 g) in THF (25 ml) and $SOCl_2$ (7 ml) was refluxed for 15 min. The solvent was removed by distillation *in vacuo* and the residue was treated with ammonia and crushed ice. The mixture was extracted with benzene and the extracts were chromatographed on alumina giving on elution with benzene–CH_2Cl_2 1:1, 0·8 g of I, light brown oil. (Found: N, 17·3. $C_8H_{18}N_2O$ requires: N, 17·7%.)

N-*Ethyl-γ-diethylaminobutyramide* (IV). Treatment of crude γ-diethylaminobutyryl chloride (see prep. I) with ethylamine, followed by chromatography on alumina afforded IV (55% yield), light tan oil. (Found: N, 15·2. $C_{10}H_{22}N_2O$ requires: N, 15·0%.)

ε-Dimethylaminocaproamide (II). Hydrogenation of ε-aminocaproic acid (Fluka; 9 g) in water (200 ml) with 40% formaldehyde (13 g) in presence of Pd–C catalyst (9 g) gave *ε-dimethylaminocaproic acid*, m.p. 64–66° (from acetone–petr. ether) (7·1 g). (Found: C, 54·0; H, 10·5. $C_8H_{17}NO_2.H_2O$ requires; C, 54·2; H, 10·8%) which was treated in THF (100 ml) with $SOCl_2$ (20 ml) at reflux temp for 30 min. Elimination of the solvent *in vacuo*, followed by treatment with ammonia and crushed ice afforded II, m.p. 70–72° (70% yield). (Found: N, 17·5. $C_8H_{18}N_2O$ requires: N, 17·7%.)

N-*Ethyl-ε-dimethylaminocaproamide* (V). The preparation of V followed the same procedure adopted for II. The product was purified by chromatography on alumina. Elution with benzene–CH_2Cl_2 1:1 gave V, brown oil. (Found: N, 14·7. $C_{10}H_{22}N_2O$ requires: N, 15·0%.)

β-N-Piperidinopropionamide (VI). β-Chloropropionamide was prepared by treating at 0° an ether solution of β-chloropropionyl chloride with an excess NH_4OH aq 40% yield, m.p. 101–102° (lit.[64] m.p. 102°). β-Chloropropionamide (4 g) was treated in THF (50 ml) with piperidine (8 ml) at reflux temp for 90 min. The solvent was removed *in vacuo* and the residue basified and extracted with ethyl acetate. Elimination of the solvent and crystallization from acetone–petr. ether gave VI (3 g), m.p. 86–88°. (Found: N, 17·6. $C_8H_{16}N_2O$ requires: N, 17·9%.)

N′-*Ethyl-β-N-piperidinopropionamide* (VII). β-Chloropropionyl chloride (Eastman, 5 g) was added, with stirring at 0° to ethylamine (1·7 g) in water (12 ml) containing one equiv. NaOH. After 12 hr the solution was extracted at pH 10 with ethyl acetate and the organic layer next washed with dil. HCl and water. The solvent was evaporated *in vacuo* and the residue crystallized from ether–petr.ether to yield N-*ethyl-β-chloropropionamide* (3 g) m.p. 68–70°. (Found: N, 10·5. $C_5H_{10}ClNO$ requires: N, 10·3%.) This was dissolved in THF (20 ml) and treated with piperidine (10 ml) at reflux temp for 2 hr. The solvent was removed by distillation; the residue basified and extracted with ethyl acetate. Evaporation of the solvent and distillation of the residue *in vacuo* gave VII (1·8 g), b.p. 110°/1 mm. (Found: C, 65·0; H, 11·1. $C_{10}H_{20}N_2O$ requires: C, 65·2; H, 10·9%.)

1-*Methyl-4-phenylisonipecotamide* (X). 1-Methyl-4-phenyl-4-cyanopiperidine[65] (1·5 g) dissolved at 0° in H_2SO_4 (20 ml) and left overnight at room temp. The solution was poured on crushed ice and made alkaline with conc. NaOH aq. A white solid separated which was crystallized from CH_2Cl_2–Et_2O m.p. 126–128° (lit.[66] m.p. 125°).

cis-6-t-*Butylnipecotamide* (VIII). Methyl t-butyl ketone was condensed with ethyl formate and the resulting hydroxymethylene ketone was condensed with cyanacetamide to give 3-*cyano-6-t-butylpyridone-2* according to the procedure reported[67] for the preparation of 3-cyano-6-isobutylpyridone-2, (80% yield) m.p. 203–206°. (Found: C, 68·1; H, 6·8. $C_{10}H_{12}N_2O$ requires: C, 68·1; H, 6·8%.) 3-Cyano-6-t-butylpyridone-2 (6·8 g) in chlorobenzene (50 ml) was treated at reflux for 5 hr with $POCl_3$ (2·5 ml) and PCl_5 (10 g). The solvent was distilled *in vacuo* and the residue was poured on ice and basified. The precipitate was collected, dried and distilled to give 2-*chloro-3-cyano-6-t-butylpyridine* (6 g), b.p. 100°/0·5 mm, m.p. 57–59°. (Found: C, 61·3; H, 5·8. $C_{10}H_{11}ClN_2$ requires: C, 61·7; H, 5·7%.)

[63] F. F. Blicke, W. B. Wright and M. F. Zienty, *J. Amer. Chem. Soc.* **63**, 2488 (1941).
[64] C. C. Price and J. Zomlefer, *J. Org. Chem.* **14**, 210 (1949).
[65] O. Eisleb, *Ber. Dtsch. Chem. Ges.* **74**, 1433 (1941).
[66] E. Walton and M. B. Green, *J. Chem. Soc.* 315 (1945).
[67] R. P. Mariella, *J. Amer. Chem. Soc.* **69**, 2670 (1947).

2-Chloro-3-cyano-6-t-butylpyridine (5 g) was treated in MeOH (50 ml) with 20% NaOH aq (6 ml) and 30% H_2O_2 (9 ml). After 24 hr the solution was diluted with water and the resulting *2-chloro-6-t-butylnicotamide* (4 g), m.p. 142° (Found: C, 56·5: H, 6·4; $C_{10}H_{13}ClN_2O$ requires: C, 56·5; H, 6·2%) was hydrogenated in presence of 10% Pd–C catalyst (1 g) and one equivalent triethylamine to give *6-t-butylnicotamide* (80% yield), m.p. 178°. (Found: C, 67·7; H, 8·0. $C_{10}H_{14}N_2O$ requires: C, 67·4; H, 7·9%.) Hydrogenation of 6-t-butylnicotamide (2·5 g) in EtOH (70 ml) at room temp and 150 atm. in presence of PtO_2 (1·5 g) gave cis-*6-t-butylnipecotamide* (VIII: 1·6 g), m.p. 135–137°. (Found: C, 65·1; H, 10·9. $C_{10}H_{20}N_2O$ requires: C, 65·1; H, 10·9%.)

trans-*6-t-Butylnipecotamide* (IX). A solution of VIII (0·8 g) in t-BuOH (40 ml) containing BuOK (0·8 g) was refluxed for 2 hr to give a mixture of VIII and IX from which *trans*-6-t-butylnipecotamide (IX) was secured by chromatography on alumina followed by crystallization from H_2O, m.p. 154–157°. (Found: C, 65·1; H, 11·0. $C_{10}H_{20}N_2O$ requires: C, 65·1; H, 10·9%.)

1,2,3,4-*Tetrahydro-3-quinolinecarboxamide* (XI). Ethyl 2,4-dicloro-3-quinolinecarbonate[84] (11 g) and AcONa (7·2 g) were dissolved in EtOH (600 ml) and hydrogenated at room temp and atm press. in presence of 10% Pd–C catalyst (3·3 g). When the adsorption of H_2 was over, the solution was filtered and evaporated. The residue (mostly ethyl 1,2-dihydro-3-quinolinecarbonate) was dissolved in acetic acid (60 ml) and CrO_3 (13 g) in H_2O (40 ml) was slowly added. The mixture was heated at 90° for 30 min to complete the reaction, cooled, diluted with H_2O and neutralized with NaOH aq. Ethyl 3-quinolinecarbonate (5·5 g), m.p. 64–65° lit.[68] m.p. 65°) was hydrolysed with NaOH aq to 3-quinolinecarboxylic acid which by treatment with $SOCl_2$ and NH_3 afforded the known 3-quinolinecarboxamide, m.p. 200° (lit.[69] m.p. 198–199°). Reduction of 3-quinolinecarboxamide (0·7 g) in EtOH (50 ml) at 140 atm. and 130°, in presence of Raney Ni (1 g) gave XI (0·5 g), m.p. 119–121°, λ_{max} 250 and 300 mμ (EtOH). (Found: C, 68·2; H, 7·1. $C_{10}H_{12}N_2O$ requires: C, 68·2; H, 6·9%.)

1-*Methyl*-1,2,3,4-*tetrahydro-3-quinolinecarboxamide* (XII). 3-Quinolinecarboxamide (0·6 g) in MeOH (6 ml) was treated with MeI (0·9 ml) at reflux temp for 15 hr; *3-quinolinecarboxamide iodomethylate* (0·8 g), m.p. 272–277° (Found: N, 8·8. $C_{11}H_{13}INO$ requires: N, 8·9%) was hydrogenated in EtOH (300 ml) at 4 atm. in presence of PtO_2 (0·3 g). After elimination of the solvent the residue was basified and extracted with ether. The solvent was distilled off and the residue was crystallized from aqueous MeOH to give XII (0·3 g) m.p. 131°. (Found: C, 69·2; H, 7·3. $C_{11}H_{14}N_2O$ requires: C, 69·4; H, 7·4%.)

N'-*Ethylnipecotamide* (XV). N-Ethylnicotamide (5 g) in 0·5 N HCl (60 ml) was hydrogenated at 70° and 60 atm. in presence of PtO_2 (0·5 g). The solution was basified and extracted with chloroform which was then evaporated *in vacuo*. The residue was chromatographed on alumina and, on elution with $CHCl_3$, XVI was obtained (3 g), yellow oil; picrate, m.p. 168–170° (EtOH–Et_2O). (Found: N, 18·2. $C_9H_{18}N_2O.C_6H_3N_3O_7$ requires: N, 18·2%.)

N'-*Ethyl*-1-*methylnipecotamide* (XVI). N-Ethylnicotamide (5 g) in MeOH (20 ml) was refluxed for 20 hr with MeI (4 ml). The solvent was evaporated and the residue repeatedly washed with ether. The hygroscopic solid was dissolved in water (150 ml) and hydrogenated at 70° and 80 atm. in presence of PtO_2 (2 g). The solution basified and extracted with ether; evaporation of the solvent left XVII (4 g) as an oil that later crystallized, m.p. 54–57° (ether–petr. ether). (Found: N, 16·4. $C_9H_{18}N_2O$ requires: 16·5%.)

cis-6-*Methylnipecotamide* (XIX). 6-Methylnicotamide (7 g) in MeOH (200 ml) was hydrogenated at 130 atm. and 80° in presence of PtO_2 (7 g). The solvent was distilled off and the residue chromatographed on 100 g alumina. Elution with $CHCl_3$ and crystallization from Me_2CO–Et_2O gave XIX (5 g), m.p. 110–114°. (Found: C, 59·0; H, 10·1. $C_7H_{14}N_2O$ requires: C, 59·1; H, 9·9%.)

trans-6-*Methylnipecotamide* (XVII). Potassium (60 mg) was dissolved in t-BuOH (10 ml), XIX (0·5 g) was added and the solution refluxed 24 hr. After elimination of the solvent the residue was crystallized from MeOH to give XVIII (0·3 g), m.p. 178–181°. (Found: C, 59·1, H, 9·9. $C_7H_{14}N_2O$ requires: C, 59·1; H, 9·9%.)

trans-1,6-*Dimethylnipecotamide* (XVIII). *trans*-6-Methylnipecotamide (XVIII; 150 mg) in MeOH (20 ml) containing 40% formaldehyde (0·26 ml) and 10% Pd–C catalyst (0·3 g) was hydrogenated at room temp and atm. press. After removal of the solvent the residue was crystallized from Me_2CO to give XVIII (100 mg), m.p. 173–175° (mixed m.p. with XVII, 145°–160°). (Found: C, 61·5; H, 10·6. $C_8H_{16}N_2O$ requires: C, 61·5; H, 10·3%.)

[68] W. Borsche and R. Manteuffel, *Liebigs Ann.* **526**, 22 (1936).
[69] W. H. Mills and W. H. Watson, *J. Chem. Soc.* **97**, 745 (1910).

cis-1,6-*Dimethylnipecotamide*. This was obtained from XIX, as reported for XVIII, m.p. 94–96°. (Found: C, 61·7; H, 10·4. $C_8H_{16}N_2O$ requires: C, 61·5; H, 10·3%.)

IR-spectra. The IR spectra were obtained with the apparatus previously[1] described.

NIR infra-red spectra. The spectra were recorded on an Optica CF_4 spectrometer fitted with a PbS cell. Samples were prepared as 0·1 molar solutions in $CHCl_3$ and examined in 1 cm quartz cells.

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