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CONFIGURATION OF THE AMIDE BOND IN N-ACYLINDOLINES AND N-ACYLTETRAHYDROQUINOLINES*

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Abstract—The preferred configurations of the amide bond in N-acylindolines and N-acyltetrahydroquinolines are deduced from their NMR spectra.

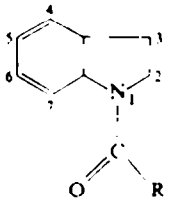
THE phenomenon of restricted rotation in various simple amides, including anilides has been the subject of several studies in the past, in which recently NMR spectroscopy is finding useful application.[1] In the case of amides carrying two different substituents on the nitrogen atom, two isomers are possible;[2] at room temperature, usually one or the other is more stable. NMR evidence has been presented recently to show that the preferred configuration of N-methylacetanilide is the one in which the CO group is oriented away from the benzene ring, in contrast to acetanilide which has the CO towards the aromatic ring.[3] The conditions under which the two isomers of an amide carrying two different substituents on the nitrogen atom can have separate existence have been discussed,[4] and a partial separation achieved by the same author in the case of N-mesitoyl-N-methylbenzyl amine.

At the time this work was started, there were no reports of a systematic study of the amide bond in N-acylindolines and N-acyltetrahydroquinolines.[5] Mclean[6] had recorded the spectra of a few simple N-acylindolines, but not made a detailed analysis. In Table 1, NMR spectra data are presented for some indolines and their N-acyl derivatives. In the NMR spectrum of N-acetylindoline the protons at positions 2 and 3 are seen as slightly broadened triplets ($J = 8{\cdot}5$ c/s; A_2X_2) at 3·07 and 3·95 ppm respectively; the downfield shift of the C-2 protons relative to their position in indoline is 0·68 ppm. The C-7 proton of N-acetylindoline is seen as a broad doublet (integration for nearly 1H; $J \sim 7$ c/s) at 8·22 ppm, its position in indoline being at 6·45 ppm. The considerable downfield shift of 1·77 ppm must be due to the field effect of the CO group and clearly indicates that I is the preferred configuration of N-acetylindoline[7] in $CDCl_3$ solution, and IA is contributing if at all insignificantly.

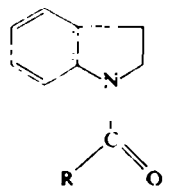
* Contribution No. 66 from CIBA Research Centre.

[1] M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.* **66**, 540 (1962).
[2] A. J. R. Bourn, D. G. Gillies and E. W. Randall, *Tetrahedron* **20**, 1811 (1964).
[3] B. F. Pedersen and B. Pedersen, *Tetrahedron Letters* 2995 (1965).
[4] A. Mannschreck, *Tetrahedron Letters* 1341 (1965).
[5] Tetrahydroquinoline and tetrahydroquinaldine refer to the 1,2,3,4-tetrahydro derivatives throughout this paper.
[6] Mclean, *Canad. J. Chem.* **38**, 2278 (1960).
[7] Alternately the spectrum can be interpreted in terms of a fast equilibrium of forms I and Ia with the weighted average in favour of I.

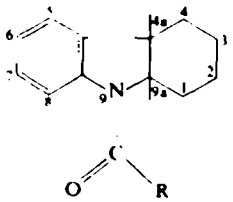
The magnitude of the downfield shift also implies full or nearly complete coplanarity of the amide and benzene planes.



I: R = Me, ph
II: R = H



IA: R = Me, ph
IIA: R = H



III: R = Me
IV: R = OMe

TABLE 1

Compound	Chemical shifts (ppm) of protons at				
	C-3	C-2	C-7	C-4,C-5,C-6	Others
Indoline	2·78 (m)	3·27 (m)	6·45 (d; J ~ 7 c/s)	6·60–7·20	NH-3·53
N-Acetyl-indoline	3·07 (t; J 8·5 c/s)	3·95 (t; J 8·5 c/s)	8·22 (d; J ~ 7 c/s)	6·75–7·50	N-acetyl-2·13
N-Formyl-indoline	3·07 (t; J 8·5 c/s)	4·02 (t; J 8·5 c/s)	8·05 (broad d; J ~ 9 c/s 25% of 1H)	6·67–7·50	Formyl H-8·47 (25%) 8·89 (75%)
N-thioacetyl-indoline	3·08 (t; J ~ 8 c/s)	4·23 (minor t; J ~ 8 c/s) 4·55 (major t; J ~ 8 c/s)	9·50 (broad d; 33% of 1H	6·90–7·50	Thioacetyl-2·77 (33%) 2·95 (67%)
N-acetyl-3,3-dimethyl-indoline		3·77 (s)	8·18 (broad d; J ~ 7 c/s)	6·92–7·35	*gem* dimethyl 1·32 N-acetyl-2·20
N-Benzoyl-3,3-dimethyl-indoline		3·80 (s)	~7·6	6·90–7·25	*gem* dimethyl-1·30 Benzoyl-7·25-7·60
5-Acetyl-indoline	3·03 c/s (t; J 8 c/s)	3·69 (t; J 8 c/s)	6·50 (d; J 9 c/s)	7·60–7·83	NH-4·42 C-acetyl-2·38
N,5-diacetylin-doline	3·17 (t; J 8 c/s)	4·10 (t; J 8 c/s)	8·13 (broad d; J 9 c/s)	7·67–7·90	C-acetyl-2·52 N-acetyl-2·23

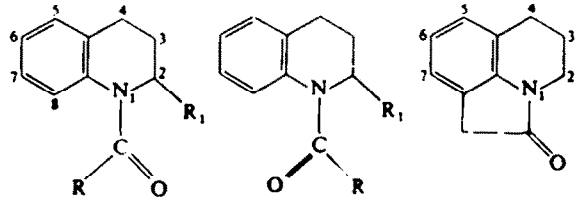
s-singlet; d-doublet; t-triplet; m-multiplet.

In all the N-acetyl or benzoyl indolines studied, NMR spectra indicated that the CO group was preferentially oriented towards the phenyl ring. In contrast to these, the spectrum of N-formylindoline showed two species to be present; the signal of the downfield aromatic hydrogen integrated only for about 25% of 1 proton, indicating that IIA was the predominant configuration. The formyl proton gave rise to two signals, a minor one at 8·47 ppm for II and the major one at 8·89 ppm from IIA

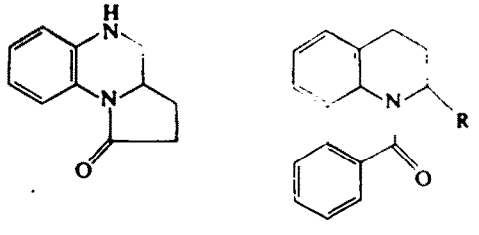
in which it experiences considerable deshielding.[8] The spectrum of N-thioacetylindoline[8] likewise indicated that the preferred configuration is the one in which the thiocarbonyl group is oriented towards the hetero ring.

N-Acylhexahydrocarbazoles are special cases of N-acylindolines; the NMR spectra of N-carbomethoxy-4a-methylhexahydrocarbazole and N-carbethoxyhexahydrocarbazole[9] show that the CO group is preferentially oriented towards the phenyl ring. We have studied in addition, N-acetyl (III) and N-carbomethoxy (IV)-*cis*-hexahydrocarbazoles and find in their NMR spectra nearly one full aromatic proton, evidently the one at C-8, shifted downfield by about 1·3 and 1·05 ppm respectively. In III the acetyl methyl appeared as a sharp singlet at 3·25 ppm and in IV, the carbomethoxy Me group as a sharp singlet at 3·80 ppm. In neither case was there evidence of a second species being present. In general the signals from the hydroaromatic protons appeared blurred and this may be due to slow inversion of the *cis* fused cyclohexane ring. In kopsine, an alkaloid containing a N-carbomethoxyhexahydro carbazole chromophore, the CO group is turned away from the benzene ring by intramolecular hydrogen bonding with a OH group and hence the C-8 proton does not appear separated from the rest of the aromatic hydrogens.[9]

The NMR spectra of some tetrahydroquinolines and their N-acyl derivatives have been examined[10] in relation to the flexibility of the tetrahydropyridine ring. The multiplicity of the signals of the heterocyclic protons in tetrahydroquinoline and its N-acyl derivative was best explained by postulating rapid inversion. We have repeated and amplified the earlier study, mainly to derive the preferred configuration of the amide bond, and incidentally to look into the conformation of the Me group in some N-acyltetrahydroquinaldines. Our NMR data are summarized in Tables 2 and 3.

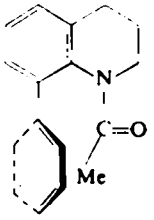


V VI VII

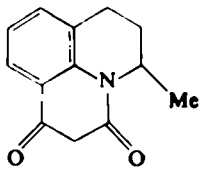


VIII IX: R = H
X: R = Me

[8] A detailed study of the NMR spectrum of this compound is presented elsewhere.
[9] T. R. Govindachari, B. R. Pai, S. Rajappa, N. Viswanathan, W. G. Kump, K. Nagarajan and H. Schmid, *Helv. Chim. Acta* **45**, 1146 (1962).
[10] H. Booth, *J. Chem. Soc.* 1841 (1964).



XI



XII

The NMR spectra of N-acyltetrahydroquinolines show that the C-8 proton is not separated from the other aromatic protons and hence indicate that the preferred configuration of the amide bond is as in V and not as in VI. A rigid model for the latter structure is the tricyclic compound VIII in which the C-8 proton appears as a doublet at 8·43 ppm compared to 7·14 ppm for the other aromatic protons.[11] The configuration assignment is supported by the fact that in the spectra of N-acetyltetrahydroquinoline and lilolidone (VII), the protons at C-2 have approximately the same chemical shifts. In VII, the CO group is rigidly oriented towards C-2. Further, the chemical shifts of the C-2 protons in N-benzoyltetrahydroquinoline and the tetracyclic compound IX[12] are approximately the same. The slightly larger chemical shift of the latter is accounted for by the increased aromaticity in IX due to the phenanthridone system. The approximate triplet, quintet, triplet signals due respectively to the protons at C-2, C-3 and C-4 are due to rapid inversion of the tetrahydropyridine half-chair;[10] this would account for the relatively small field effect (about 0·6–0·9 ppm) of the CO group on the C-2 protons. N-Thioacetyltetrahydroquinoline also has the thiocarbonyl group oriented away from the benzene ring; as is to be expected,[13] the CS group has a larger field effect on the C-2 protons than the CO group. The NMR spectrum of N-acetyl-8-phenyltetrahydroquinoline (XI) is noteworthy in several respects. The abnormally low chemical shift (1·43 ppm) of the N-acetyl Me group suggests that (i) the CO group is oriented away from the benzo ring; (ii) the Me group is held over the "hole" in the ph group at position 8, and (iii) the diphenyl system is twisted as shown. In addition, the signals of the protons at C-2, C-3 and C-4 have lost their usual triplet-quintet-triplet structure; instead enormous multiplicity is now observed, indicating a slow inversion of the half-chair. This is particularly borne out by the fact that one of the C-2 hydrogens, presumably the equatorial one, in the plane of the CO group, is seen as a multiplet at 4·7 ppm and the other at 3·03 ppm. The large chemical shift of the former would be consistent with this analysis.[14]

The NMR spectra of N-acyltetrahydroquinaldines again show that the preferred configuration of the amide bond is as in V. This is further supported by the fact that the chemical shifts of the C-2 proton in N-benzoyltetrahydroquinaldine, tetracyclic compound X[12] and tricyclic compound XII are nearly similar. The somewhat larger chemical shift in X is to be attributed to its aromaticity and in XII to the effect of the solvent. The data in Table 3 further show that unlike in the case of tetrahydroquinoline and its N-acyl derivatives, the C-3 protons of tetrahydroquinaldine and its

[11] E. C. Taylor and A. McKillup, *J. Am. Chem. Soc.* **87**, 1984 (1965).
[12] K. Nagarajan and P. M. Pillai, paper to be published
[13] R. H. Martin, N. Defay, F. Geerts-Evrard, P. H. Given, J. R. Jones and R. W. Wedel, *Tetrahedron* **21**, 1833, (1965).
[14] F. Bohlmann and D. Schumann, *Tetrahedron Letters* 2435 (1965).

TABLE 2. NMR DATA OF TETRAHYDROQUINOLINES AND THEIR N-ACYL DERIVATIVES

Compound	Chemical shifts (ppm) of protons at				
	C-2	C-3	C-4	C-5 to C-8	Others
Tetrahydroquinoline	3·07 (t; J 5·5 c/s)	1·77 (m)	2·63 (t; J 6·5 c/s)	6·17–7·10 (m)	NH-3·53
N-formyltetrahydroquinoline	3·67 (t; J 6·1 c/s)	1·80 (q; J 6·1 c/s)	2·70 (t; J 6·1 c/s)	6·67–7·20 (unresolved m)	Formyl H-8·68
N-Acetyltetrahydroquinoline	3·80 (t; J 6·5 c/s)	4·93 (q; J 6·5 c/s)	2·72 (t; J 6 c/s)	6·90–7·50 (unresolved m)	Me-2·20
Lilolidone (VII)	3·73 (t; J ~ 6 c/s)	2·03 (q; J ~ 6 c/s)	2·78 (t; J ~ 6 c/s)	6·9–7·20 (C-5, C-6, C-7 H)	C-8 CH_2-3·50
N-Benzoyltetrahydroquinoline	3·93 (t; J 6·5 c/s)	2·03 (q; J 6·5 c/s)	2·85 (t; J 6·5 c/s)	6·67–7·25 (m)	PhCO-7·25–7·50
Compound IX	4·27 (t; J ~ 6 c/s)	2·05 (q; J ~ 6 c/s)	2·93 (t; J ~ 6 c/s)	7·0–8·67 (m; all aromatic H)	
N-Thioacetyltetrahydroquinoline	4·38 (t; J 6·5 c/s)	2·05 (q; J 6·5 c/s)	2·73 (t; J 6·5 c/s)	7·23 (broad s)	Me-2·72
N-acetyl-6-methoxytetrahydroquinoline	3·78 (t; J 6·5 c/s)	1·93 (q; J 6·5 c/s)	2·70 (t; J 6·5 c/s)	6·6–7·4 (m)	COMe-2·18 OMe-3·78
N-Acetyl-8-phenyl-1,2,3,4-tetrahydroquinoline (XI)	4·7 (H_a; m) ~3·03 (H_e; m)	Multiplet at	1·50 2·82	7·1 7·5 (m)	Me-1·43

q; quintet; s, d, t, m as in Table 1.

N-acyl derivatives are differentiated. This has been interpreted as being indicative of slow inversion.[10] Tetrahydroquinaldine itself would be expected to have the Me group in the equatorial conformation; the multiplicity of the axial C-2 proton signal in the 60 Mc spectrum, although not analyzed fully, would support this deduction. But in the case of N-acyltetrahydroquinaldines, the considerable chemical shift of their C-2 proton (1·6–1·7 ppm) relative to tetrahydroquinaldine would be consistent only with the assignment of an equatorial conformation to it.[14] The signal due to this proton is generally seen as a sextet with a J value of about 6·5–7·0 c/s and could be explained by a simple first order treatment, involving nearly equal couplings of the C-2 proton with the methyl and the C-3 hydrogens.[15] Models indicate unfavourable interaction between the Me group in the equatorial conformation with the CO group in V. This interaction can be visualized as being about equivalent to that between the 1–3 diaxial hydrogen atoms in a cyclohexane chair[16] and may suffice to push the Me group into an axial conformation.

Decoupling experiments carried out at 100 Mc on tetrahydroquinaldine and its N-acetyl derivative support the deductions from their 60 Mc NMR spectra. The 100 Mc $CDCl_3$ spectrum of tetrahydroquinaldine in the presence of D_2O shows 11–12 lines from the methine proton, centred at around 3·25 ppm. When the solution is irradiated to remove the Me coupling (J 6 c/s), a doublet of doublet (all the 4 lines of equal intensity) with J values of 8 and 3 c/s is revealed, indicating an axial disposition for the C-2 proton. The signals due to the methine proton could be expected to consist of 16 lines, but with the observed coupling constants of 8, 6 and 3 c/s, it is likely that adjacent pairs of the ten inner lines may be actually seen as single lines, thus giving rise to an apparent multiplicity of eleven lines. The observed relative intensities of the eleven lines are in rough agreement with the theoretical values. The 100 Mc NMR spectrum of N-acetyltetrahydroquinaldine shows the C-2 proton as a clean sextet at 4·76 ppm with a spacing of 7 c/s, which reduces to a triplet (J = 7 c/s) when the Me region is irradiated. Equal values[15] for the coupling of the C-2 hydrogen atom with its two neighbours at C-3 would agree with the assignment of equatorial conformation to this proton.

N-Thioacetyltetrahydroquinaldine likewise has the CS oriented towards the hetero ring, with the hydrogen at C-2 in the equatorial position. The downfield shift of this proton relative to its position in tetrahydroquinaldine is about 2·6 ppm and deserves special mention.

In conclusion it would appear that in general the CO group of N-acyl indolines and tetrahydroquinolines would preferentially be oriented away from the benzene ring as is the case with N-methylacetanilide,[3] provided steric or hydrogen bonding[9] effects are not operative. Thus N-formylindoline has the preferred configuration IIA, but in N-acetyl or benzoylindolines, as well as in N-acylhexahydrocarbazoles, the interaction of the C-7 proton wth the CO substituents may be sufficiently severe to favour structure I. In N-thioacetylindoline, apparently the interaction of the C-7 proton with sulphur is more severe[17] than that with the Me group. In N-acyltetrahydroquinolines and tetrahydroquinaldines, the flexibility of the tetrahydropyridine

[14] The e–e and e–a couplings are of course on the larger side.

[16] B. Rickborn, *J. Am. Chem. Soc.* **84**, 2201 (1962).

[17] In this case the preferred configuration is also solvent dependent; this will be discussed in a forthcoming publication.

TABLE 3. NMR DATA OF TETRAHYDROQUINALDINES AND THEIR N-ACYL DERIVATIVES

Compound	Chemical shifts (ppm) of protons at					
	C-2	C-3	C-4	C-5 to C-8	CH_3 at C-2	Others
Tetrahydro-quinaldine (+D_2O)	3·17 (m > 10)	1·17–1·67 (m) 1·47–2·17 (m)	2·5–2·83 (m)	6·17–7·1 (m)	1·0 (d; J 6·2 c/s)	
N-Acetyltetra-hydroquinaldine	4·78 (se; J ~ 7 c/s)	1·1–1·67 (m) 2·0–2·33 (m)	2·33–2·7 (m)	7·15 (broad s)	1·1 (d; J 6·5 c/s)	COMe-2·12
N-Thioacetyltetra-hydroquinaldine	5·80 (se; J ~ 6·5 c/s)	~1·25–1·70 (m) ~2·25–2·60 (m)	~2·5–2·80 (m)	7·1–7·3	1·17 (d; J 6·5 c/s)	COMe-2·63
Compound XII*	5·42	2·33	3·0–3·6	H at C-8: 8·25 Others: 7·4–8·0	2·55	
N-Benzoyl-tetra-hydroquinaldine	4·85 (se; J ~ 6·5 c/s)	~1·3–2·00 (m) ~2·0–2·60 (m)	2·77 (t; J 6·5 c/s)	6·5–7·5 (all aromatic)	1·24 (d; J 6·5 c/s)	
Compound X	5·25–5·75 (m)	1·80–2·22 (m)	2·83–3·50 (m)	7·0–8·7 (all aromatic)	1·34 (d; J 7 c/s)	
6-Methyltetra-hydroquinaldine	3·23 (m)	1·17–2·0 (m)	2·3–2·85 (m)	6·1–6·85 (m)	1·07 (d; J 6 c/s)	Me at C-6 2·15
N-Acetyl-6-methyltetra-hydroquinaldine	4·88 (se; J 6·5 c/s)	1·1–1·75 (m) 2·0–2·5 (m)	2·3–2·8 (m)	7·03 (broad s)	1·1 (d; J 6·5 c/s)	Me at C-6 2·12 COMe-2·32
N-Benzoyl-6-methyltetra-hydroquinaldine	4·83 (se; J 6·5 c/s)	1·2–1·8 (m) 2·0–2·6 (m)	2·72 (t; J ~ 6·5 c/s)	6·3–7·5 (all aromatic)	1·22 (d; J 6·5 c/s)	Me at C-6 2·21

* in CF_3CO_2H; resolution was poor

se, sextet; s, d, t, m as in Table 1.

ring allows the R group to avoid unfavourable interactions with the C-8 proton of structure V. This is not possible in the case of N-acyl indolines, where the hetero ring is relatively rigid. In the diphenyl derivative XI, the repulsion between the π electrons of the phenyl ring at C-8 and of the CO group may drive the latter to take the orientation shown; the twisting of the ph group out of plane with the other aromatic ring would accommodate the Me group.[18]

EXPERIMENTAL

NMR spectra were recorded for $CDCl_3$ solns at 41° (probe temp) using a Varian A-60 spectrometer. Chemical shifts are in ppm from TMS internal standard. The compounds used in the study were commercially available or made by known procedures. Pure distilled liquids or recrystallized solids were utilized.

We express our thanks to Professor T. R. Govindachari for his interest in this work, Dr. S. Rajappa for some helpful suggestions and to Dr. S. Selvavinayakam and his associates as well as to Drs. Zürcher and Stuber for the spectra.

[18] During the course of this work, we learnt from Dr. A. Mannschreck of the University of Heidelberg, Germany, that he has reached essentially the same conclusions regarding 1-mesitoylindolines and 1-mesitoyltetrahydroquinolines. We are grateful to him for the communication.