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CONFORMATION OF THE CARBONYL GROUP IN SECONDARY AMIDES*

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It is well known that the conformations adopted by peptide chains in enzymes and other systems have a large part to play in their reactivities. But, in these compounds intramolecular hydrogen bonds between the amino acid residues assist the formation of the particular conformation found. It would therefore be of fundamental interest to find whether the basic unit in them, viz., the corresponding simple amide carbonyl group, undisturbed by hydrogen bonding, has a preferred conformation. From the extensive work done on amides[1] it is known that simple aliphatic secondary amides, exist as a mixture of cis and trans isomers A and B, of which normally the trans isomer B is preponderant (Fig.I). But there is very little work to show whether there is a preferred conformer amongst the rotomers possible around the R_1-N-bond, when R_1 is a secondary carbon atom, as is largely found in the amino acid residues of peptides. For this purpose, a rigid skeleton as that

Fig. I

of the steroid molecule was chosen, and simple secondary amide groups were introduced at various positions in it, viz., at C_3, C_6, C_{11} and C_{17}, both in the α and β configurations. The conformations of these amides were then studied.

It has recently been shown by ORD[2], NMR[3] and IR[4] spectral studies that in the esters of the secondary hydroxyl groups of steroids, the ester carbonyl group, assumes a preferred conformation in which it nearly eclipses the secondary hydrogen atom concerned. We have now found that in such cases this secondary hydrogen atom undergoes a deshielding of about 0.2 ppm in the NMR spectra of the compound in benzene solution, compared to that in $CDCl_3$

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solution, as is shown in Table I. This is in agreement with the fact that this secondary hydrogen atom lies in the deshielding zone[5] of the carbonyl group, as could be seen from models.

TABLE I

Chemical shift in δ (ppm) of the C_6-H of -	in $CDCl_3$	in C_6H_6	Downfield shift in C_6H_6
1) 6β-acetoxycholestane	4.93	5.12	0.19
2) 6α-acetoxycholestane	4.65	4.92	0.27
--- of the C_{11}-H of -			
3) 11α-acetoxypregnane (m.p. 68-70° $(\alpha)_D$-37°	5.13	5.30	0.17

Since in the alcohols or methyl ethers of the alcohols, the secondary hydrogen atom shows an upfield shift in benzene by about 0.2 ppm, compared to that in $CDCl_3$ solution, the net deshielding of the carbonyl group on this hydrogen atom should be about 0.4 ppm.

With this parameter in hand, we now determined the spectra of the secondary amides of a number of steroid amines and the results are tabulated in Table II.

Amino groups were introduced at various positions in the steroid molecule, through known procedures, i.e. either through the ketone and oxime, or through the tosylate and azide and then by selective reduction. The primary amines were converted to the secondary amides with the appropriate acid anhydride. IR spectra of 6α- and 6β- acetamidocholestanes were taken in CCl_4 solution on a Perkin Elmer 221 spectrometer with grating and were found to have sharp absorptions at 3470 and 3435 cm^{-1} respectively (NH), and 1675 cm^{-1} (CO), showing thereby that there is no intermolecular hydrogen bonding between the carbonyl and NH groups.

The spectra of the corresponding amines show an upfield shift for the secondary hydrogen atom concerned of about 0.2 ppm in benzene, compared to that in $CDCl_3$ solution. Thus the amide carbonyl group also deshields the secondary hydrogen atom concerned and the magnitude of deshielding is very close to that of the ester carbonyl group. These results, thus, very similar to those in the esters, strongly suggest that the amide carbonyl group has the same preferred conformation as in the esters. It is noteworthy that in the simple cyclohexane molecule as well as in a long chain aliphatic molecule (2-heptylamine), the secondary amide group retains the same preferred conformation, as in the rigid steroid molecule. As the CH and NH show proton signals only at one place each, the molecules exist nearly completely in the same conformation.

Such a conformation of the carbonyl group would require the C-H bond

TABLE II

Chemical shift (δ ppm) of the C_3-H of -	in $CDCl_3$	in C_6H_6	Downfield shift in C_6H_6
4) 3β-acetamidocholestane	3.7	insoluble	---
5) 3α-acetamidocholestane	4.07	4.32	0.25
--of the C_6-H of -			
6) 6β-acetamidocholestane	4.05	4.3	0.25
7) 6α-acetamidocholestane	3.77	3.94	0.17
8) 6β-acetamido-3,5-cyclocholestane	4.42	4.68	0.26
9) 6α-acetamido-3,5-cyclo-cholestane	3.48	3.72	0.24
---of the C_{11}-H of -			
10) 11α-acetamidopregnane m.p. 240° $(\alpha)_D$ +17°	4.22	4.48	0.26
---of the C_{17}-H of -			
11) 17α-acetamido-5-androstene	4.03	4.23	0.20
--- of the -CH-NHCO-R, of -			
12) acetamidocyclohexane	3.75	3.95	0.20
13) propionamidocyclohexane, m.p.94°	3.71	3.93	0.22
14) benzamidocyclohexane	3.91	4.13	0.22
15) 2-acetamidoheptane B.P. 130°/6 m.m.	3.93	4.13	0.20

of the secondary hydrogen atom and the N-H bond from the amide nitrogen atom to be anti-parallel of nearly at 180° to each other and the methine hydrogen in the same plane as the amide carbonyl as in Fig. II. It is interesting to note that the NH signal in the amides of the steroids, of cyclohexane and even of 2-heptane showsup as a doublet J = 8 to 10 Hz, (clearly visible in CCl_4 solution). This doublet collapses to a singlet on irradiation at the resonance of the secondary hydrogen atom concerned showing thereby that the NH doublet is due to coupling with the secondary hydrogen atom on the carbon holding the amide[6,7]. These results would thus confirm the preferred conformation of the secondary amides on secondary carbon atoms as shown in Fig. II.

Fig. II

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7. It may be added that the Karplus equation (Ref. 6) originally calculated for vicinal CH-CH- proton couplings now appear to be applicable to vicinal CH-NH-proton couplings as well.

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