3 drops of pyridine; the mixture was cooled to −78°. It was warmed to 25° and then distilled at atmospheric pressure to give 2.8 g of the iminooxazoline as a colorless liquid: bp 103–104°; $n^{25}D$ 1.3168; $\lambda_{max}^{cyclohexane}$ 230 mμ (ε 3800); infrared spectrum, 5.80 and 3.03 μ. The ^{19}F nmr spectrum showed singlets at +77.2 (6 F), +81.7 (3 F), and +118.5 ppm (2 F) from CCl_3F. The ^1H nmr spectrum showed a broad singlet at τ 0.84.

Anal. Calcd for $C_7HF_{11}N_2O$: C, 24.87; H, 0.30; F, 61.82; N, 8.29. Found: C, 24.94; H, 0.65; F, 61.47; N, 8.53.

5-Imino-2,2-bis(chlorodifluoromethyl)-4-trifluoromethyl-3-oxazoline.—α-Iminotrifluoropropionitrile, 6.1 g (0.05 mol), was added dropwise to 25 g (0.12 mol) of stirred 1,3-dichlorotetrafluoroacetone containing 0.05 ml of pyridine; the mixture was cooled to 0°. Distillation of this gave 9.2 g (57%) of the iminooxazoline as a colorless liquid: bp 84–85° (100 mm); $n^{25}D$ 1.3814; $\lambda_{max}^{cyclohexane}$ 237 mμ (ε 4740); infrared spectrum, 5.80 and 3.02 μ. The ^{19}F nmr spectrum showed an A_2B_2 pattern (four principal peaks) centered at about +61.2 ppm (4 F) and a singlet at +69.2 ppm (3 F). The ^1H nmr spectrum showed a broad singlet at τ 0.74.

Anal. Calcd for $C_6HCl_2F_7N_2O$: C, 22.45; H, 0.31; Cl, 22.09; F, 41.43; N, 8.73. Found: C, 22.79; H, 0.62; Cl, 22.90; F, 41.16; N, 8.80.

4-Amino-2,5-dicyano-2,5-bis(trifluoromethyl)-3-imidazoline (10).—Triethylamine (0.5 ml) was added dropwise over 2 min to a solution of 14.0 g (0.115 mol) of α-iminotrifluoropropionitrile in 15 ml of benzene. An exothermic reaction occurred, and a gas (CF_3CN) was evolved. The reaction mixture was cooled to keep the temperature between 30 and 40°. After 30 min, the solid that formed was filtered off and washed with benzene to give 2.9 g of an off-white solid. Sublimation at 130° (1.0 mm), recrystallization from benzene, and resublimation gave 1.3 g (12.5%) of 4-amino-2,5-dicyano-2,5-bis(trifluoromethyl)-3-imidazoline as a white crystalline solid, mp 187–190° (with some decomposition). The infrared spectrum showed bands at 2.94, 3.02, 3.15 and 6.20 (NH and NH_2), 4.44 (C≡N), and 5.86 μ (C=N). The ^{19}F nmr spectrum in acetone indicated the presence of two isomers. The major isomer (88%) showed a pair of quartets (J = 2.7 Hz) of equal area centered at +76.1 and +81.9 ppm from CCl_3F. (This is probably the isomer with the CF_3 groups on the same side of the ring.) The minor isomer (12%) showed two singlets of equal area at +76.3 and +82.0 ppm. The ^1H nmr spectrum in $(CD_3)_2CO$ showed broad absorptions at τ 2.38 (NH_2) and 3.13 (NH).

Anal. Calcd for $C_7H_3F_6N_5$: C, 31.01; H, 1.11; F, 42.05; N, 25.83; mol wt, 271. Found: C, 31.31; H, 1.21; F, 41.79; N, 25.83; mol wt, 272.

Registry No.—**2a** (R_f = CF_3), 17244-08-5; **2b** (R_f = CF_3), 17244-09-6; **2a** (R_f = C_2F_5), 17244-10-9; **2b** (R_f = C_2F_5), 17244-11-0; **2a** (R_f = $CF_3CF_2CF_2$–), 17244-12-1; **2b** (R_f = $CF_3CF_2CF_2$–), 17244-13-2; **3**, 17244-18-7; **8**, 17244-19-8; **9**, 17244-14-3; $C_7HF_{11}N_2O$, 17244-15-4; $C_6HCl_2F_7N_2O$, 17244-16-5; **10** (CF_3 groups *cis*), 17244-17-6; **10** (CF_3 groups *trans*), 17244-47-2.

Conformations of Alkylpiperidine Amides

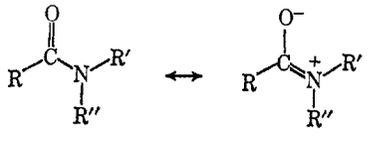
ROY A. JOHNSON

Biochemical Research Division, The Upjohn Company, Kalamazoo, Michigan 49001

Received December 8, 1967

The nuclear magnetic resonance signals of the C-2 and C-6 protons of a series of alkylpiperidine benzamides coalesce at a temperature lower than that for the same protons in similar alkylpiperidine acetamides. This leads to the conclusion that the energy barrier to rotation about the C—N amide bonds is lower in the benzamides than in the acetamides as a result of increased steric interactions between the phenyl ring and the C-2 and C-6 substituents in the planar benzamide conformation. Such steric interactions between the amide and C-2 and C-6 alkyl substituents in both acetamides and benzamides are sufficient to cause conformational bias in the piperidine ring, resulting in the preference for axial configurations for the alkyl groups. These examples are a special case of the general concept of $A^{(1,3)}$ strain. The piperidine-containing molecule 3-benzoyl-3-azabicyclo[3.3.1]nonane has been found to have a chair–chair conformation. The nmr spectrum of 1-benzoyl-*trans*-decahydroquinoline shows no variation with temperature change, suggesting that the amide group in this molecule has no preferred conformation.

Our interest in the behavior of the benzamides of azacycloalkanes in biological systems raised the question of what the conformation of the amide functional group will be in these molecules at physiological temperatures. Simple amides, such as dimethylformamide, have been shown by nmr spectroscopy to have a preferred conformation at room temperature.[1] This conformation results from an energy minimum due to overlap of the π-electron orbitals of the carbonyl with the orbital of the lone pair of electrons on the nitrogen. This preferred conformation is the one in which the O=C—N bonds lie in a plane. The familiar resonance



forms also may be used to illustrate this conformation. One type of evidence that such a preferred conformation exists in dimethylformamide is the presence of two distinct signals for the $-CH_3$ protons in the nmr spectrum of this compound when taken at room temperature.[1] The different environments in which the methyl groups are found in this conformation result in the observation of the two nmr signals. When the nmr spectrum is taken at increasingly higher temperatures, the two methyl signals are seen to coalesce into a single signal. This effect is attributed to an increase in the rate of rotation around the C—N amide bond as the temperature is raised until the environments of the two methyl groups become equivalent as detectable by nmr spectroscopy. Others have enlarged upon the initial experiments,[2] have determined relative ratios of the two possible conformations when R′ ≠ R″,[3] have studied solvent effects on "*cis*" and "*trans*" forms,[3] and have examined similar effects in various types of amides.[4]

(1) (a) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955); (b) H. S. Gutowsky and C. H. Holm, *ibid.*, **25**, 1228 (1956).

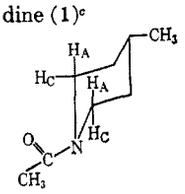
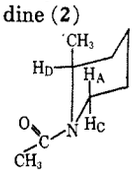
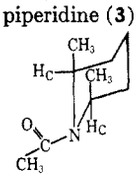
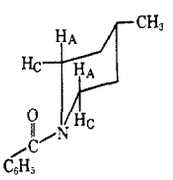
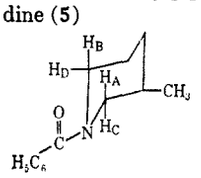
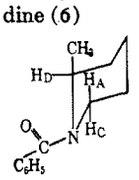
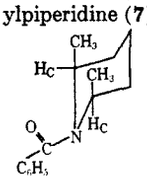
(2) M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962).

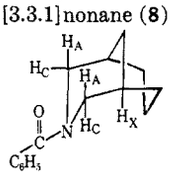
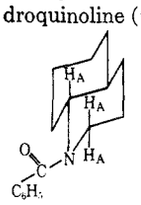
(3) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **85**, 3728 (1963).

(4) (a) R. M. Moriarty and J. M. Kliegman, *J. Org. Chem.*, **31**, 3007 (1966); (b) D. M. Lynch and W. Cole, *ibid.*, **31**, 3337 (1966); (c) T. H. Siddall, III, *ibid.*, **31**, 3719 (1966); (d) K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683 (1967); (e) J. P. Chupp and J. F. Olin, *J. Org. Chem.*, **32**, 2297 (1967); (f) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967).

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF AMIDES OF ALKYLPIPERIDINES

Compound	Sample temp, °C	Chemical shift in cps, multiplicity,[a] J in cps (protons coupled[b]) H_A	H_B	H_C	H_D	H_{CH_3}
1-Acetyl-4-methylpiperidine (1)[c] 	36	154, t, 182, t, } −13 (*gem*) 13 (aa)		230, bd, −13 (*gem*) 274, bd, −13 (*gem*)		
	70[d]	172[e]		252[e]		
	120	176,[e] t		252,[e] d		
1-Acetyl-2-methylpiperidine (2) 	37	174		262	262	69, d, 6.5
	100[f]	175, st, −13 (*gem*) 13 (aa) 4 (ae)		240, bd, −13 (*gem*)	270, m, 6.5 (CH_3)	69, d, 6.5
1-Acetyl-*cis*-2,6-dimethylpiperidine (3) 	37			264, m, 7 (CH_3)		70, d, 7
1-Benzoyl-4-methylpiperidine (4) 	−20	166, st, −13 (*gem*) 179, st, 12 (aa) 3 (ae)		225, bd, −13 (*gem*) 285, bd, −13 (*gem*)		57, d, 5
	12[g]	173		225, s 285, s		
	35[h]	173, bt, −13 (*gem*)		252		
	60	172, st, −13 (*gem*) 12 (aa) 3 (ae)		250, bd, −13 (*gem*)		
1-Benzoyl-3-methylpiperidine (5) 	−20	146, m 159, m		220, d, −13 (*gem*) 278, d, −13 (*gem*)		48, d, 5.5 59, d, 5.5
	15[g]	163, m		220, d, −13 (*gem*) 278, d, −13 (*gem*)		53, s
	35[h]	154, q, −13 (*gem*) 10 (aa)	174, o, −13 (*gem*) 10 or 12 (aa) 4 (ae)	244, s	244, s	52, d, 6
	60	154, q, −13 (*gem*) 10 (aa)	174, o, −13 (*gem*) 10 or 12 (aa) 4 (ae)	244, bd, −13 (*gem*)	244, bd, −13 (*gem*)	52, d, 6
1-Benzoyl-2-methylpiperidine (6) 	−40	179, t, −13 (*gem*) 190, t, 12 (aa)		215, bd, −13 (*gem*) 278, bd, −13 (*gem*)	242, bd, 6.5 (CH_3) 306, bd, 6.5 (CH_3)	71, d, 6.5 77.5, d, 6.5
	−15[g]	182, s		210, m 272, m	245, m 300, m	74, d, 7
	0[h]	180, t, 12		255		
	37	178, st, −13.5 (*gem*) 11 (aa) 4 (ae)		241, bd, −13.5 (*gem*)	272, m, 6.5 (CH_3)	72, d, 6.5
1-Benzoyl-*cis*-2,6-dimethylpiperidine (7) 	−40			240, m, 7 (CH_3) 298, m, 7 (CH_3)		72, d, 7 83, d, 7
	−20[h]			266		78, d, 7
	37			269, m, 7 (CH_3)		76, d, 7

Compound	Sample temp, °C	Chemical shift in cps, multiplicity,[a] J in cps (protons coupled[b]) H_A	H_B	H_C	H_D	H_{CH_3}
3-Benzoyl-3-azabicyclo-[3.3.1]nonane (8) 	10	184, d, −13 (*gem*) 4 (ae)		227, d, −13 (*gem*)		
	34[d]	190, s		289, d, −13 (*gem*) 227, d, −13 (*gem*)		
	60[h]	189, t, −13 (*gem*)		289, d, −13 (*gem*) 251 (very broad)		
1-Benzoyl-*trans*-decahydroquinoline (9) 	−20	203, m				
	37	203, m				
	120[i]	203, m				

[a] s = singlet, d = doublet, t = triplet, q = quartet, st = sextet, o = octet, m = multiplet, bd = broad doublet, bt = broad triplet. The descriptions st and o refer to six- or eight-line patterns only and do not indicate equal spacing between lines. [b] *gem* = geminal coupling, aa = axial–axial coupling, ae = axial–equatorial coupling. Signs of coupling constants have been assumed. [c] Ref 4b. [d] Approximate temperature of coalescence of peaks. [e] Estimated from Figure 2, ref 4b. [f] Neat. [g] Temperature (±2.5°) of coalescence of axial proton signals. See ref 7. [h] Temperature (±2.5°) of coalescence of equatorial proton signals. See ref 7. [i] In dimethylformamide-d_7 solution.

The above method of determining amide conformations appeared suitable to satisfy our desire for a qualitative measure of the conformational mobility of the benzamides of azacycloalkanes at physiological temperatures. A description of the nmr spectrum of 1-acetyl-4-methylpiperidine (1)[4b] (see Table I) suggested that a series of benzamides of alkylpiperidines would be useful for nmr study. In the high temperature (120°) spectrum of 1, signals for the C-2 and C-6 protons are observed at approximately 176 (axial) and 252 cps (equatorial) downfield from TMS and have splitting patterns which are characteristic. At 36°, however, the rate of rotation around the C—N amide bond has decreased so that the two axial and the two equatorial protons each are in different magnetic environments and give signals at 154 and 182 cps (axial) and at 230 and 274 cps (equatorial), while retaining the splitting constants observed at high temperature. The temperature at which these signals coalesce is approximately 70°.[4b] From this it may be concluded that rotation around the C—N amide bond in 1 is relatively slow and that the planar amide conformation is more important near physiological temperatures. For a similar study of conformations in the benzamides of azacycloalkanes, we have prepared a series of 1-benzoylalkylpiperidines and have obtained their nmr spectra at various temperatures.[5] The nmr data of interest for these compounds are compiled in Table I. Several conclusions of interest concerning the conformations of both the amide groups and the alkylpiperidine rings are reached in the following discussion.

First, it is important to relate the temperature of nmr signal coalescence to changes in the energy barrier to amide rotation as the former will be used to compare the amide conformations in different molecules. The energy barrier to rotation around the C—N amide bond is the result of the difference in energy between the highest energy nonplanar conformation and the energy minimum of the preferred planar conformation. Consequently, any effect which will raise or lower the energy level of either of these conformations will change the energy barrier to rotation. As an example, if increased steric interactions are introduced into the planar conformation of an amide, the energy level of the conformation will be raised, but the energy barrier to rotation will be smaller. In such a case, the coalescence of the nmr signals will be expected at a lower temperature.

With the above in mind, it is interesting to speculate on whether the planar conformation will be found to be more or less preferred in the benzamides than in the acetamides. Qualitatively, steric interactions between the phenyl group and the equatorial hydrogens at C-2 and C-6 are greatly increased in the benzamides. Furthermore, these interactions become greatest when the amide and the phenyl groups are coplanar, *i.e.*, cross-conjugated in the planar conformation.[6] These steric interactions may be judged as severe by examination of Dreiding model. Relief of these interactions requires rotation around either the C—N amide bond or the phenyl–carbonyl bond, resulting in loss of the resonance energy gained through orbital overlap. It seems probable, then, that the planar conformation will be less preferred in the benzamides than in the acetamides. This prediction is supported by the temperatures at which signals are observed to coalesce in the spectra of the benzamides. The coalescence temperatures[7] range from approximately 35° in 1-benzoyl-4-methylpiperidine (4) and 1-benzoyl-3-methylpiperidine (5) to $<-10°$ in 1-benzoyl-2-methylpiperidine (6) and 1-benzoyl-*cis*-2,6-dimethylpiperidine (7). These temper-

(5) Following completion of this work we have found the nmr spectrum of 1-benzoyl-4-*t*-butylpiperidine given in the Experimental Section of a paper by H. O. House, B. A. Tefertiller, and C. G. Pitts, *J. Org. Chem.*, **31**, 1073 (1966).

(6) For the resonance energy of the component parts of this cross-conjugated system, see G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, pp 86–114.

(7) The higher temperatures at which the signals of the equatorial (C-2 and C-6) protons coalesce than do those of the axial protons is related to the greater separation of the signals for these protons at lower temperatures.[1b]

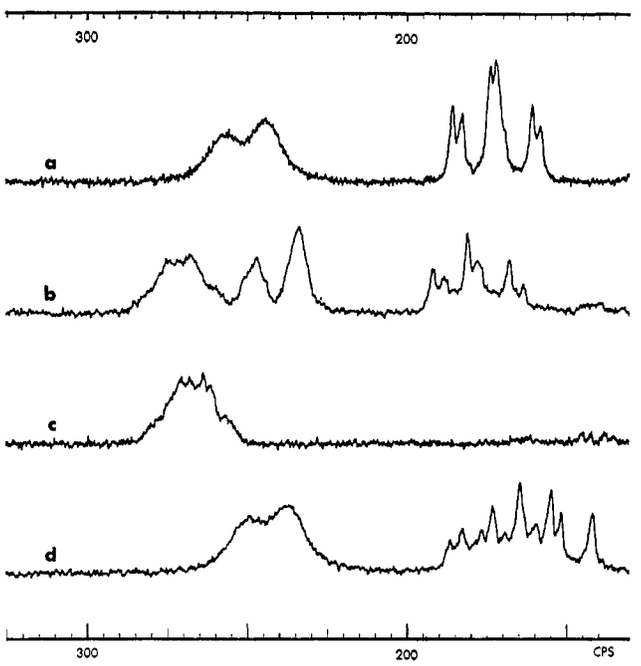
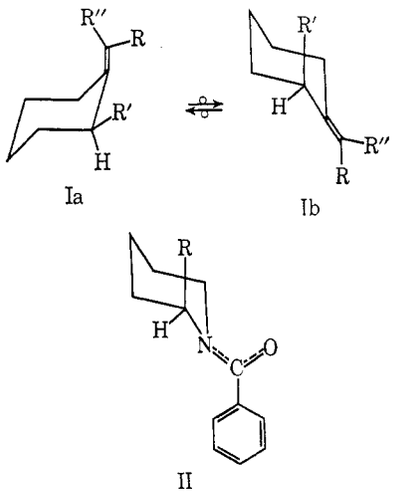


Figure 1.—Nmr spectra of 1-benzoylalkylpiperidines in $CDCl_3$ at 60°: (a) 1-benzoyl-4-methylpiperidine (**4**); (b) 1-benzoyl-2-methylpiperidine (**6**); (c) 1-benzoyl-*cis*-2,6-dimethylpiperidine (**7**); (d) 1-benzoyl-3-methylpiperidine (**5**).

atures are significantly lower than the 70° coalescence temperature observed for 1-acetyl-4-methylpiperidine (**1**).[4b] From this it is concluded that the energy barrier to rotation about the C—N amide bond in the benzamides is lower than in similar acetamides. With respect to physiological systems, it may be expected that this increased conformational freedom will allow the benzamides to assume a particular conformation, such as may be required by enzymatic systems, more easily than the acetamides with the exception of the planar conformation. Any bearing that this will have on reaction rates, etc., will then follow accordingly.

A methyl substituent on the piperidine ring is expected[4b] to bias the conformational equilibrium associated with ring inversion so that the methyl group will, on the average, have an equatorial configuration. However, the methyl substituents of 1-benzoyl-2-methylpiperidine (**6**) and 1-benzoyl-*cis*-2,6-dimethylpiperidine (**7**) must be assigned axial configurations when the nmr signals for the C-2 and C-6 protons of these compounds are examined. In all of the amides studied here, the axial protons at C-2 and C-6 of the piperidine ring give signals in the range of 140–190 cps, while the equatorial proton signals are found between 215 and 300 cps. The splitting patterns and constants for these signals are consistent with this assignment. Portions of the nmr spectra of compounds **4**–**7** showing the signals of the C-2 and C-6 protons are illustrated in Figures 1 and 2. For example, the signal centered at 178 cps in the spectrum of 1-benzoyl-2-methylpiperidine (**6**, see Figure 1) is a six-line pattern having a geminal coupling (J = −13.5 cps), an axial–axial coupling (J = 11 cps), and an axial–equatorial coupling (J = 4 cps). These couplings require assignment of an axial configuration to this secondary proton (H_A in **6**). Coupled with H_A is the signal of equatorial proton H_C at 241 cps (J_{gem} = −13.5 cps). Remaining downfield at 272 cps is the signal for proton H_D, which shows, in its outline, coupling (J = 6.5 cps) with the adjacent methyl group. The position and width of this signal compared with that of axial proton H_A leaves little doubt that H_D has an equatorial configuration.[8] The methyl groups therefore must be in the axial positions in compounds **6** and **7**. A Dreiding model of **6** reveals that a methyl group in an equatorial configuration at C-2 prevents rotation of the C—N amide bond owing to steric overlap of the phenyl and methyl groups when the amide approaches a planar conformation. This steric interaction can be relieved by inversion of the ring, which places the methyl group in an axial configuration. The present examples are closely related to a general type of stereochemical interaction, which has been defined as $A^{(1,3)}$ strain.[9] The concept of $A^{(1,3)}$ strain recognizes that steric interactions will exist between substituents on the 1 and 3 positions of allylic and pseudo-allylic systems. When such a system is part of a cyclic molecule, such as I, relief of the strain occurs by conformational inversion of the ring. If partial double-bond character is ascribed the C—N amide bond, as in II, then the present examples represent a type of pseudo-allylic system.[9] While inversion of piperidines **6** and **7** relieves $A^{(1,3)}$ strain, the total steric interaction between the benzamide group and the adjacent C-2 and C-6 positions in these molecules remains larger than in those compounds having no C-2 or C-6 substituents. Evidence supporting this is seen in the lower temperatures at which the signals for the C-2 and C-6 protons of **6** and **7** coalesce when compared with compounds **4** and **5**. This again must result from a lower energy barrier to rotation, reflecting an increase in the energy minimum of the planar amide conformation due to the increased steric interactions found in this conformation.



It now was of interest to determine if there is sufficient $A^{(1,3)}$ strain[9] in 2-substituted piperidine acet-

(8) An alternative conformation of amides **6**, **7**, **2**, and **3**, having equatorial methyl groups at C-2 and C-6 and an axial benzoyl group (through inversion of the nitrogen), has been suggested. Shielding of the resulting axial C-2 and C-6 protons by the benzoyl group is suggested to cause a change in the relative positions of the C-2 and C-6 axial and equatorial nmr signals. Such an argument requires that both axial protons be shifted downfield, a situation which is not observed for compound **6** (discussed above) and is not consistent with the splittings and positions of signals in the spectra of the other amides (see Figures 1 and 2).

(9) F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, **87**, 5492 (1965).

amides to result in a preference for axial configurations for the 2 substituent. Accordingly, the readily available derivatives, 1-acetyl-2-methylpiperidine (2) and 1-acetyl-2,6-*cis*-dimethylpiperidine (3), were prepared. The nmr spectra of these compounds are included in Table I and show that in each case the preferred conformation of the ring is the one having the methyl substituents in an axial configuration.

The piperidine amides may have "*cis*" and "*trans*" forms in the planar conformation if the piperidine ring is unsymmetrically substituted. When these substituents come into steric interaction with the amide group, as in benzamide 6, it is possible that one of the forms will be preferred over the other. One might then expect to see differences in the sizes of the two signals of a particular proton in the low-temperature nmr spectrum. Of the present compounds, benzamide 6 would be most likely to show a preference for one of the two possible amide forms. The most distinctive signals in the spectrum of 6 are those of the equatorial protons at C-2 and C-6. At high temperature, these appear at 241 (geminal splitting and therefore the secondary proton) and 272 cps (tertiary). At low temperature, two pairs of signals having a shape identical with the high-temperature signals are seen in the spectrum of 6. The two pairs are nearly equal in size, showing that equal populations of the "*cis*" and "*trans*" forms of the planar amide are present in 6. The ratio was not noticeably changed by further cooling of the nmr sample solution.

The different environments at low temperatures cause two signals for each of the C-2 and C-6 protons. Similarly, the methyl groups at these positions give two signals at low temperature. Separation between these signals is 6.5 cps in the case of 6 and 11 cps in the case of 7. It was surprising to find a separation of the same magnitude (11 cps) between the pair of methyl signals in the low-temperature spectrum of the 3-methyl derivative (5) since now the methyl group is further removed from the site of nonequivalence in the molecule and shielding effects should be reduced. The possibility that axial and equatorial methyl signals are being observed owing to slow ring inversion seems unlikely since a similar effect is absent in the 4-methyl derivative.

Finally, we have examined the amide conformations in two other molecules containing the piperidine ring, namely, 3-benzoyl-3-azabicyclo[3.3.1]nonane (8) and 1-benzoyl-*trans*-decahydroquinoline (9). In the former (8), coalescense of the nmr signals is observed at a higher temperature than in the piperidine benzamides, suggesting a lower energy minimum for the planar conformation of the amide in this molecule. Alternatively, slight steric interactions between the amide benzene ring and the *endo* C-7 hydrogen may raise slightly the energy barrier to rotation. Such interaction is possible since it may be concluded from the coupling constants of the C-2 and C-4 protons that the piperidine ring of 8 is in a chair conformation. These coupling constants (J_{AX} and/or J_{BX} = 4 cps, J_{AB} = −13 cps) may be compared with those reported[10] for the chair form of 3-azabicyclo[3.3.1]nonane hydrochloride (J_{AX} = 2.2, J_{BX} = 0–2, J_{AB} = −12.8 cps) and contrasted with those for the boat form in the methiodide

(10) R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Commun.*, 356 (1965).

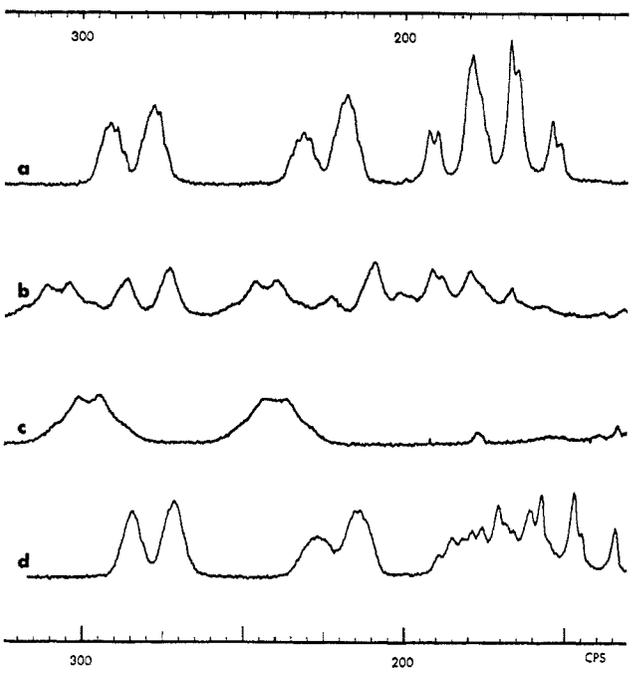


Figure 2.—Nmr spectra of 1-benzoylalkylpiperidines in $CDCl_3$ at low temperatures: (a) 1-benzoyl-4-methylpiperidine (4) at −20°; (b) 1-benzoyl-2-methylpiperidine (6) at −40°; (c) 1-benzoyl-*cis*-2,6-dimethylpiperidine (7) at −40°; (d) 1-benzoyl-3-methylpiperidine (5) at −20°.

of the same compound (J_{AX} = 10.3, J_{BX} = 2.1, J_{AB} = −13.5 cps). The nmr spectrum of 1-benzoyl-*trans*-decahydroquinoline shows no temperature dependence between −20 and 120°. The carbon (C-8a) α to the nitrogen of this molecule has an equatorial substituent which cannot be displaced to an axial configuration by inversion since the molecule is rigid. As a result steric interactions of this substituent with the benzamide cannot be relieved and rotation about the C—N amide bond probably will be prevented. A planar amide conformation therefore will be unlikely. The probable lack of a preferred amide conformation in 9 is reflected in the absence of temperature dependence in the nmr spectrum.

Experimental Section

The nmr spectra were determined at 60 Mc with a Varian Model A-60A spectrometer, using tetramethylsilane as an internal standard. The temperature ranges were calibrated using the peak separations of ethylene glycol and methanol.

Preparation of Acetamides.—The acetamides were prepared by standard methods using the addition of acetyl chloride to the piperidine in the presence of triethylamine and were purified by distillation. **1-Acetyl-2-methylpiperidine** (2) was a colorless liquid, bp 55–56° (0.15 mm) [lit.[3] bp 86.5–87.5° (3.5 mm)]. **1-Acetyl-*cis*-2,6-dimethylpiperidine** (3) was a very light yellow liquid, bp 92–95° (1 mm). A solution of 3 in ether was washed with dilute aqueous HCl and with 5% aqueous sodium bicarbonate, dried, concentrated, and redistilled: bp 62–63° (0.15 mm); n_D 1.4785.

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.91; H, 11.05; N, 8.97.

Preparation of Benzamides.—The benzamides were prepared by the Schotten–Baumann method. They were purified by distillation or recrystallization. **1-Benzoyl-4-methylpiperidine** (4) was recrystallized from acetone–Skellysolve B and had mp 83–85° (lit.[11] mp 83.5–84°). **1-Benzoyl-3-methylpiperidine** (5) was a colorless oil: bp 115–117° (0.13 mm); $n^{25}D$ 1.5421.

(11) N. J. Leonard and Z. W. Wicks, *J. Amer. Chem. Soc.*, **68**, 2402 (1946).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.24; H, 8.56; N, 6.65.

1-Benzoyl-2-methylpiperidine (6) was obtained as crystals from Skellysolve B: mp 46–49° (lit.[12] solid mp 44–45°). **1-Benzoyl-*cis*-2,6-dimethylpiperidine** (7) was obtained as crystals from benzoylation of commercially available (Eastman) 2,6-dimethylpiperidine and had mp 109–111° (lit.[13] mp 110°). **3-Benzoyl-3-azabicyclo[3.3.1]nonane** (8) was obtained as colorless crystals, mp 86–88°.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.31; H, 8.47; N, 6.01.

(12) H. Bunzel, *Chem. Ber.*, **22**, 1053 (1889).

(13) R. K. Hill, T. H. Chan, and J. A. Joule, *Tetrahedron*, **21**, 147 (1965).

(+)-**1-Benzoyl-*trans*-decahydroquinoline** (9) has been described elsewhere.[14]

Registry No.—**1**, 17037-65-9; **2**, 17037-66-0; **3**, 17037-67-1; **4**, 17037-68-2; **5**, 17037-69-3; **6**, 17037-70-6; **7**, 17037-71-7; **8**, 17037-72-8; **9**, 17037-73-9.

Acknowledgment.—The author wishes to thank Dr. B. Vernon Cheney, Dr. Jackson B. Hester, Dr. Gunther S. Fonken, and Dr. George Slomp for many helpful comments and suggestions concerning this study.

(14) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3207 (1968).

D-Homoannulation of 5α-Pregnane-3β,20β-diol 3-Acetate with Phosphorus Pentabromide

R. T. LI[1] AND Y. SATO

Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

Received March 12, 1968

3β-Acetoxy-17aα-bromo-17α-methyl-D-homo-5α-androstane (IIa) and its 17aβ-bromo epimer (IIIa) were obtained when 3β-acetoxy-5α-pregnan-20β-ol (I) was treated with phosphorus pentabromide. The 17α-methyl-D-homo structure was established by the synthesis of 17α-methyl-D-homo-5α-androstan-3β-ol (IVa). The assignment of the 17aα and 17aβ configurations for bromo compounds IIa and IIIa were based on spectral studies.

In the course of our studies on the synthesis of steroidal alkaloids, the need for the preparation of 3β-acetoxy-20α-bromo-5α-pregnane arose. This was sought by the treatment of 3β-acetoxy-5α-pregnan-20β-ol (I) with phosphorus pentabromide in chloroform in the presence of calcium carbonate. Two bromo compounds, IIa and IIIa, were obtained with yields of 32 and 6.8% respectively. Initially the two bromo compounds were assumed to be the epimeric 3β-acetoxy-20α- and -20β-bromo-5α-pregnanes with the major product IIa (acetate, mp 166–170°, $[\alpha]^{20}D$ −20.5°; alcohol, mp 170–175°, $[\alpha]^{20}D$ −15.3°) being assigned the α orientation and the minor product IIIa (acetate, mp 130–131°, $[\alpha]^{20}D$ +9.6°; alcohol, mp 184.5–186°, $[\alpha]^{20}D$ +10.9°) being assigned the opposite β orientation. This assignment is based on the fact that halogenation of alcohols by phosphorus pentahalides usually proceeds by a SN2 mechanism leading predominantly to inversion of configuration.[2,3]

An attempt to prepare the Grignard of IIa in an exploratory run using methyl iodide as an initiator[4a] resulted in a product which appeared to be derived from a coupling reaction.[5] To explore this route further as an approach to the synthesis of sterols (*e.g.*, cholestanol), IIa was treated with isohexylmagnesium bromide. The product to our mild surprise analyzed for the formulation $C_{21}H_{36}O$ (mol wt 304) and was subsequently ascribed the D-homo structure IVa. It was found also that the lithium aluminum hydride reduction of IIa led to IVa as well and that catalytic reduction over Raney nickel afforded the acetate IVb. See Scheme I.

The original assumption of IVa being perhaps 5α-pregnan-3β-ol resulting from the functional exchange[4b] of the 20α-bromo derivative with isohexylmagnesium bromide followed by hydrolytic cleavage was discarded in favor of the D-homo compound when the physical constants (melting point and rotation) of IVa and its derivatives (3-acetate, IVb, and 3-oxo, IVc) were not in agreement with those of authentic 5α-pregnan-3β-ol and its derivatives.[6,7] In addition the nmr data were more consonant with a D-homo product rather than a normal steroid. The proton resonance of an unperturbed C-18 methyl in 5α,14α steroids is observed at 0.692 ppm while that of the C-19 methyl is seen at 0.792 ppm.[8] Upon ring-D expansion, however, the former (C-18) has been observed to shift downfield to 0.792 ppm.[8,9] This is in harmony with compound IVa which displays a strong resonance peak (integrated for six protons) at 0.81 ppm for the C-18 and C-19 protons. Furthermore, it was considered mechanistically more probable for the D-homo rearrangement to occur earlier in the treatment with phosphorus pentabromide rather than during the reductive phase from IIa to IVa. It seems reasonable to assume that the rearrangement occurs through a C-20β ester–halide complex in a concerted process with the preferential migration of the C-16,17 bond to afford a product bearing a C-17α (equatorial) methyl function. This is comparable in manner with 5α-pregnane-3β,20β-diol 3-acetate 20-tosylate which un-

(1) Visiting Fellow, 1966–1968.

(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 392.

(3) G. Adam and K. Schreiber, *Tetrahedron*, **22**, 3581 (1966).

(4) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954: (a) p 38; (b) p 1060.

(5) A solution of CH_3I (0.34 g, 0.0024 mol) in 5 ml of ether was added to magnesium (0.41 g). As the reaction started, a mixture of compound IIa (1.0 g, 0.0024 mol) and CH_3I (1.36 g, 0.0096 mol) in 20 ml of ether was added dropwise and the mixture was refluxed for 3 hr. After hydrolysis with dilute H_2SO_4, the product isolated showed mol wt 318 in the mass spectrum.

(6) L. Ruzicka, M. W. Goldberg, and E. Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939).

(7) L. Ruzicka, P. Meister, and V. Prelog, *ibid.*, **30**, 867 (1947).

(8) R. F. Zürcher, *ibid.*, **46**, 2054 (1963).

(9) N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc Chem. Soc.*, 214 (1961).