were vacuum distilled from the residue. The remaining material was dissolved in 3 ml. of benzene and treated with 520 mg. (0.002 mole) of stannic chloride. After 1 hour at ordinary temperature, the mixture was diluted with ether and extracted successively with 2 *N* aqueous hydrochloric acid, 2 *N* aqueous potassium hydroxide and water. The remainder from the dried ($MgSO_4$) ether solution was recrystallized from a mixture of ethanol and water; yield 34 mg. (10%); infrared spectrum: 6.10 μ (carbonyl associated with NH); m.p. 250–252°.[32]

Anal. Calcd. for $C_{11}H_9NO$ (171.19): C, 77.17; H, 5.30. Found: C, 77.04; H, 5.66.

Diethyl α,α-di-(4-cyanoskatyl)-malonate was isolated from the mother liquors remaining after the crystallization of ethyl α-carboethoxy-β-(4-cyano-3-indole)-propionate[1] and was purified by recrystallization from acetone; m.p. 235–237°.

Anal. Calcd. for $C_{27}H_{24}N_2O_4$ (440.48): C, 69.22; H, 516; N, 11.96. Found: C, 69.10; H, 5.50: N, 11..97.

Methyl (4-Carbomethoxy-3-indole)-acetate.—To a solution of 200 mg. (0.001 mole) of 4-cyanogramine and 326 mg. (0.005 mole) of potassium cyanide in 25 ml. of methanol was added, in 4 portions at 15-minute intervals, 2.0 ml. (0.02 mole) of dimethyl sulfate. After 3 hours at ordinary temperature the solution was concentrated to a volume of 3 ml. Addition of water, followed by removal of a small quantity of resinous material, gave, at 0°, 135 mg. (74%) of (4-cyano-3-indolyl)-acetonitrile, m.p. 155–165°. Two recrystallizations from methanol left 100 mg. (55%), m.p. 163–165°.

A mixture of 258 mg. of the dinitrile prepared in this fashion and 2.7 ml. of 20% aqueous potassium hydroxide was maintained at reflux temperature for 24 hours. The cooled solution was clarified by filtration and acidified with 0.8 ml. of 12 *N* hydrochloric acid. The precipitate was collected by filtration, washed with water and dried; yield 305 mg. (98%), m.p. 247–249°.

The dicarboxylic acid was methylated in ether solution with diazomethane prepared from N-methyl-N-nitroso-N'-nitroguanidine. The product was recrystallized from a mixture of ether and petroleum ether (30–60°) to give 272 mg. (79%), m.p. 96–98°. The analytical sample was recrystallized from methanol; m.p. 100–101°.

Anal. Calcd. for $C_{13}H_{13}NO_4$ (247.26): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.61; H, 5.70; N, 5.64.

Acknowledgments.—The work was supported by grants from the National Science Foundation (NSF-G3684) and from the National Heart Institute of the United States Public Health Service (H-2205).

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(32) *Cf.* the preparation of this substance by the Fischer procedure from 1,2-cyclopentadione monophenylhydrazone: R. H. F. Manske, *Can. J. Research*, **4**, 501 (1931); J. Elkes, D. F. Elliott and B. A. Hems, *J. Chem. Soc.*, 624 (1944).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Studies of Hydrogen Bonding. III. Intramolecular Hydrogen Bonding in 3-Piperidinols

BY GILBERT HITE,[1] EDWARD E. SMISSMAN AND ROBERT WEST

RECEIVED JULY 20, 1959

The infrared spectra of *dl*-3-piperidinol and three substituted 3-piperidinols have been studied in the 3100–3800 cm.$^{-1}$ region. All of these compounds appear to form intramolecular hydrogen bonds of moderate strength from hydroxyl to nitrogen.

Intramolecular hydrogen bonds can form between diaxial *cis*-1,3-substituents on cyclohexane rings. Some examples are *cis*-1,3-cyclohexanediol[2] and various 3-substituted cyclohexanols in the steroid series.[3] Intramolecular hydrogen bonds might also form between *cis*-1,4-substituents on a cyclohexane ring, if the ring were to adopt the boat form. No examples are known of such transannular hydrogen bonds in cyclohexane compounds. However, Lyle has shown that intramolecular hydrogen bonding between hydroxyl and nitrogen takes place in 1-methyl-4-phenyl-2,2,6,6-tetramethyl-4-piperidinol, which must therefore exist in the boat form.[4] Other examples of 1,4-hydrogen bonding are known in highly substituted 4-piperidinols in the tropine series.[5]

This paper reports extension of these studies of intramolecular hydrogen bonding to *dl*-3-piperidinol and some substituted 3-piperidinols, using high-resolution infrared spectroscopy in the OH stretching region to detect hydrogen bond formation. Two additional substituted 4-piperidinols also have been studied.

Experimental

Materials.—Reagent grade *dl*-3-piperidinol and 1-methyl-4-piperidinol were used as obtained from the Aldrich Chemical Co. The *dl*-1-methyl-3-piperidinol was a commercial sample obtained from Dr. J. Cannon. It was purified by repeated fractional distillation under vacuum. The preparation of *dl*-1-methyl-3-benzoyl-3-piperidinol and *dl*-1-methyl-4-benzoyl-4-piperidinol is described in a previous publication.[6] *dl*-1-Methyl-3-phenyl-3-piperidinol was prepared from a sample of 1-methylpiperidone hydrochloride hydrate kindly supplied by Dr. R. Lyle. To 785 mg. (5.0 millimoles) of anhydrous bromobenzene dissolved in 50 ml. of anhydrous ether was added 122 mg. (5 millimoles) of ether-washed, dried magnesium turnings. After refluxing for 3 hours 35–40 ml. of the ether was removed and replaced with 60 ml. of anhydrous benzene. To this refluxing mixture was added 250 mg. (1.5 millimoles) of 1-methyl-3-piperidone hydrochloride monohydrate. The solvent was removed after refluxing for 3 hours. The dry solid was treated with 15 ml. of 5% hydrochloric acid. The solution was made basic and extracted with purified petroleum ether, b.p. 35°. The petroleum ether extracts were dried over sodium sulfate, treated with carbon, and filtered through sintered glass to give, after removal of the solvent, a colorless oil, 140 mg. (0.73 millimole, 49% yield), which was microdistilled in a sublimation apparatus at reduced pressure.

The methiodide salt was prepared and recrystallized from ethanol–ether, m.p. 238–239° dec. (lit.[7] m.p. 239.5–240.5°).

(1) Former Parke–Davis and Co. fellow in the Department of Pharmaceutical Chemistry.

(2) L. P. Kuhn, THIS JOURNAL, **74**, 2492 (1952).

(3) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

(4) R. E. Lyle, *J. Org. Chem.*, **22**, 1286 (1957).

(5) B. L. Zenitz, C. M. Martini, M. Prinzar and F. C. Nachod, THIS JOURNAL, **74**, 5564 (1952); S. M. Archer, private communication.

(6) E. E. Smissman and G. Hite, THIS JOURNAL, **81**, 1201 (1959).

(7) S. M. McElvain and J. F. Vozza, *ibid*, **71**, 896 (1949).

Spectra.—The infrared spectra of the compounds in the region 3100–3800 cm.$^{-1}$ were determined in carbon tetrachloride solution using a Perkin–Elmer model 112 single-beam double-pass spectrometer with a lithium fluoride prism, standardized against water and ammonia vapor, at a constant slit width of 85 μ. Frequencies are believed to be accurate to ± 2 cm.$^{-1}$ for sharp bands. Each compound was examined at two concentrations below 0.01 M except *dl*-3-piperidinol which was studied only as a saturated solution, about 0.002 M. The band positions and relative peak heights were independent of concentration, showing that none of the absorption bands was due to intermolecular hydrogen bonds. Observed spectral bands are listed in Table I and some representative curves are shown in Fig. 1.

Discussion

1-Methyl-4-piperidinol, *dl*-3-piperidinol and *dl*-1-methyl-3-piperidinol all have as a common feature of their infrared spectra a narrow band near 3620 cm.$^{-1}$ (Table I, Fig. 1). This frequency is near that of the free O–H vibration for cyclohexanol, 3621 cm.$^{-1}$, and for other secondary and tertiary alcohols.[2] Both from its position and its appearance it can be assigned to the free O–H vibration of the piperidinols.

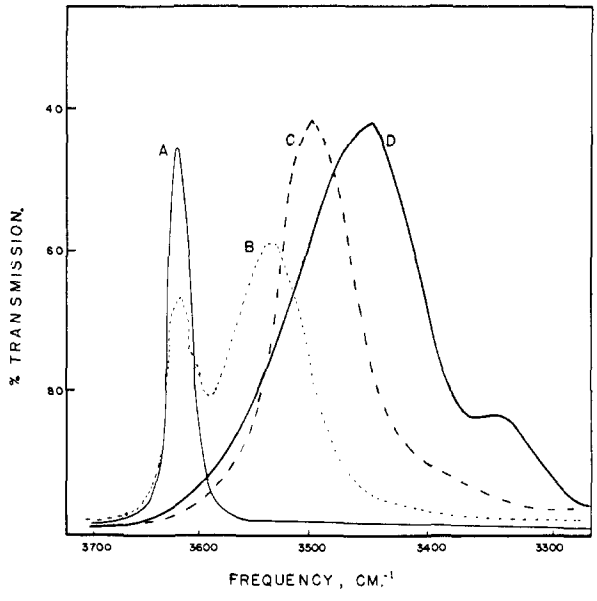


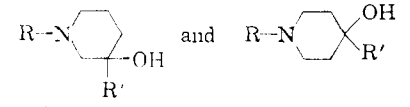
Fig. 1.—Infrared spectra in the hydroxyl region for some piperidinols, 0.01 M in carbon tetrachloride: A, 1-methyl-4-piperidinol; B, *dl*-1-methyl-3-piperidinol; C, *dl*-1-methyl-3-phenyl-3-piperidinol; D, *dl*-1-methyl-3-benzoyl-3-piperidinol.

1-Methyl-4-piperidinol shows no band in the OH region at lower frequency, indicating that all of the OH groups in this substance are non-bonded at low concentrations. This conclusion is in agreement with the work of Lyle who established that the 1-methyl-4-phenyl-4-piperidinol does not exhibit intramolecular hydrogen bonding, although the corresponding 2,2,6,6-tetramethyl derivative does.

The compound 1-methyl-4-benzoyl-4-piperidinol shows, in addition to a sharp band at 3601 cm.$^{-1}$ assigned to the free O–H vibration, a broad band at 3467 cm.$^{-1}$. We believe that the lower frequency band results from hydrogen bonding of the hydroxyl hydrogen to the neighboring carbonyl group, rather than to the nitrogen across the ring. Our evidence is that the OH spectrum observed for the piperidinol compound is virtually identical with that of 1-benzoyl-1-cyclohexanol, the analogous compound containing no nitrogen atom (similar bands observed at 3601 and 3470 cm.$^{-1}$).

TABLE I

INFRARED ABSORPTION BANDS OF *dl*-3- AND 4-PIPERIDINOLS



R	Substd. position	R'	ν, cm.$^{-1}$	Assignment
H	3	H	3617	Free O—H
			3539	O—H···N
			3370w	N—H
CH_3	3	H	3623	Free O—H
			3539	O—H···N
CH_3	3	C_6H_5	3496	O—H···N
CH_3	3	C_6H_5CO	3455	O—H···O
			3340w	O—H···N ?
CH_3	4	H	3620	Free O—H
CH_3	4	C_6H_5CO	3601	Free O—H
			3467	O—H···O

dl-1-Methyl-3-piperidinol and *dl*-3-piperidinol both have broad absorption bands at 3539 cm.$^{-1}$ in addition to the free OH band. The 3539 cm.$^{-1}$ band can be attributed to intramolecular hydrogen bonding between the hydroxyl and the basic nitrogen atom. Both bonded and non-bonded forms are present at equilibrium in solutions of these two compounds.

In order for intramolecular hydrogen bonding to take place in *dl*-3-piperidinol and *dl*-1-methyl-3-piperidinol, the OH group must adopt the less favorable axial conformation (I, where R = H).

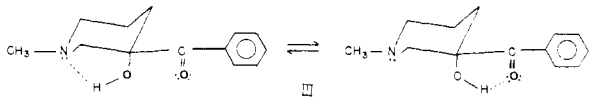
Steric repulsion of the hydroxyl group by the 5-axial hydrogen is apparently sufficient to maintain an equilibrium population of molecules in the non-bonded OH-equatorial conformation, II. The preferred conformation in *dl*-1-methyl 3-phenyl-3-piperidinol, on the other hand, would be I (R = C_6H_5), the one with the bulky phenyl group in the equatorial position and the hydroxyl group axial. In agreement with this argument, the phenyl-substituted compound shows only a single broad band at 3495 cm.$^{-1}$, indicating that the concentration of non-bonded molecules is too small to be detected by our method.

The shifts, $\Delta\nu$, on going from the free to the hydrogen-bonded absorption bands in *dl*-3-piperidinol and *dl*-1-methyl-3-piperidinol are only about 80 cm^{-1}. Adopting the usual correlation of $\Delta\nu$ with ΔH for the hydrogen-bonding reaction,[8] this shift corresponds to a remarkably weak hydrogen bond in view of the strongly basic character of the piperidinol nitrogen. As a comparison case, $\Delta\nu$ for the intermolecular hydrogen bonding of cyclohexanol to N-methylpiperidine was observed to be 290

(8) R. F. Badger, *J. Chem. Phys.*, **8**, 288 (1940); R. F. Badger and S. H. Bauer, *ibid.*, **5**, 839 (1937).

cm.$^{-1}$, nearly four times as great a shift as that for the intramolecular hydrogen bond in the 3-piperidinols. Molecular models suggest reasons why the O—H . . . N hydrogen bond may be unusually weak in 3-piperidinols. Some distortion of the ring would be necessary for the hydroxyl hydrogen to come within effective bonding distance of the nitrogen atom. Moreover, the hydrogen bond in 3-piperidinols must be strongly angular, a factor which is known to lead to weakening of hydrogen bonds.[3,9]

Finally, the compound *dl*-1-methyl-3-benzoyl-3-piperidinol (III) will be considered. This com-



III

pound, like its 4-substituted isomer discussed above has a strong broad absorption band at 3455 cm.$^{-1}$, attributable to intramolecular hydrogen bonding to carbonyl oxygen. However, unlike the 4-substituted compound and 1-benzoylcyclohexanol, compound III has a weak shoulder near 3350 cm.$^{-1}$ but no free hydroxyl band near 3620 cm.$^{-1}$.

(9) L. Hunter, in W. Klyne, edit., "Progress in Stereochemistry," Vol. I, Academic Press, Inc., New York, N. Y., p. 224.

It therefore seems probable that molecules with hydrogen bonds both to carbonyl oxygen and to nitrogen are present in solutions of *dl*-1-methyl-3-benzoyl-3-piperidinol. The O—H . . . N absorption band would be expected to be shifted to lower frequency than in the other 3-piperidinols, because of the acid-strengthening effect of the benzoyl group on the hydroxyl hydrogen. This absorption band may lie at about the same frequency as the O—H . . . O band, or may cause the shoulder at 3350 cm.$^{-1}$.[10] Hydrogen bonding interaction between hydroxyl and nitrogen in III previously was predicted[7] from optical rotatory dispersion studies. Compound III, as the pure *d*-isomer, shows no inversion in the sign of the Cotton effect in going from aqueous acidic solution to octane solution, while the analogous *l*-α-halogenated ketone (III with chlorine in place of hydroxyl) shows a reversal in sign of the Cotton effect in going from one solvent to another.

Acknowledgment.—The authors wish to thank Parke–Davis and Co. for partial support of this research.

(10) The shoulder might also be the first overtone of the carbonyl stretching vibration at 1665 cm.$^{-1}$.

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[CONTRIBUTION FROM THE PIONEERING RESEARCH LABORATORY, TEXTILE FIBERS DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO., INC.]

Synthesis and Polymerization of Atom-bridged Bicyclic Lactams

BY H. K. HALL, JR.

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The polymerizabilities of a variety of atom-bridged bicyclic lactams were studied and compared with expectation based on conformational analysis. Agreement was good, supporting the idea that H–H crowding is the major factor causing polymerization of these compounds. An attempt to prepare a lactam possessing a nitrogen atom at the bridgehead, but free of H–H crowding, namely 1-azabicyclo[3:3:1]nonan-2-one (XXII), led only to the corresponding polyamide. This is the first case in which polymer is favored over monomer in the bicyclo[3:3:1]nonane system and emphasizes the reluctance of the amide link to deviate from coplanarity.

Introduction

Polymerization is a powerful method for detecting conformational strains in cyclic compounds.[1] The merit of this method is that it provides direct experimental measurement of the equilibrium between cyclic monomer and linear polymer, and does not require an indirect assessment of various contributions to the strain.

In earlier work the polymerizabilities of a variety of monocyclic and bicyclic compounds were examined. The present article expands the study to other atom-bridged bicyclic lactams.

Synthesis of Lactams.—Most of the required lactams were prepared by Beckmann rearrangements from bicyclic ketones which had been prepared by previous investigators. The rearrangements were carried out by the addition of benzenesulfonyl chloride to a solution or suspension of the oxime in concentrated alkali.[2] The pertinent details are given in the Experimental section. The ketones and lactams are listed for the most part in Table I.

(1) H. K. Hall, Jr., THIS JOURNAL, **80**, 6412 (1958).

(2) M. Gates and S. P. Malchick, *ibid.*, **79**, 5546 (1957).

A few remarks are pertinent. The rearrangements of bicycloheptanone and bicyclooctanone oximes (and the polymerization of the resulting lactams) have been described in three Swiss patents.[3] We have been unable to duplicate these claims.

2-Azabicyclo[3:2:1]octan-3-one (II) was the only lactam not obtained in apparently stereochemically pure form. Bicycloheptanone oxime occurs as an oily mixture of *syn* and *anti* isomers which on rearrangement gave a mixture of isomeric lactams which we were unable to separate. There were indications of other isomers in the preparation of IV and VI (variable m.p. of oxime, only partial crystallization of lactam), but in these cases a pure crystalline isomer could be obtained.[2]

The lactam structures given in Table I are based on the assumption that the migrating group is that which forms the stablest carbonium ion. In nortricyclanone oxime, the cyclopropane ring is assumed to migrate.[4]

(3) Swiss Patents 270,546 (1951); 280,367 (1952) and 287,863 (1953) to Inventa AG, Lucerne.

(4) W. D. Burrows and R. H. Eastman, THIS JOURNAL, **79**, 3756 (1957).