[CONTRIBUTION FROM THE CHEMISTRY LABORATORIES OF LOYOLA UNIVERSITY]

An Investigation of the Mills–Nixon Effect in Pyridines

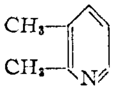
BY EDITH GODAR[1] AND RAYMOND P. MARIELLA[2]

RECEIVED AUGUST 27, 1956

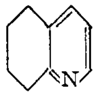
2,3-Lutidine (I), 6,7-dihydro-1,5-pyrindine (II), 6,7,8,9-tetrahydroquinoline (III) and 6,7,8,9-tetrahydro-5-cyclohepta[b]-pyridine (IV) were prepared, and the infrared spectra of the pure liquids and the ultraviolet absorption spectra in 1 *N* sulfuric acid, water, 95% ethanol and cyclohexane were recorded. The differences in the ultraviolet spectra were interpreted as showing the presence of ring strain on the pyridine nucleus. The infrared spectrum of IV gave evidence of steric hindrance of the 4-hydrogen of the pyridine ring. Nothing was found in any of the spectra which could be interpreted as bond fixation.

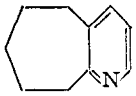
The significance of the Mills–Nixon effect has been the subject of a number of investigations in the past several years. Fieser and Lothrop[3] used the compounds studied by Mills and Nixon[4] and related compounds. On the basis of chemical studies, they concluded there was little basis for the theory of bond fixation as their results could also be explained by electrical effects. Recently Horning and Amstutz[5] reported on the study of the Mills–Nixon effect in a series of substituted pyridazines by means of their ultraviolet spectra. From calculations of the transition energies in these compounds and comparison with the corresponding hydrocarbons, they decided that the Mills–Nixon effect is not significant in these compounds.

In the present work it was decided to investigate the importance of the Mills–Nixon effect in a series of 2,3-disubstituted pyridines by means of their ultraviolet and infrared spectra. The compounds used for this purpose were 2,3-lutidine (I), 6,7-dihydro-1,5-pyrindine (II), 6,7,8,9-tetrahydroquinoline (III) and 6,7,8,9-tetrahydro-5-cyclohepta-[b]pyridine (IV).


I


II


III


IV

The ultraviolet spectra of these compounds have been obtained in four solvents of differing polarity: 1 *N* sulfuric acid, water, ethanol and cyclohexane. The infrared spectra of the pure liquids was obtained also.

Experimental

The 2,3-lutidine (I) was purchased from Matheson and purified by distillation in a Piros–Glover spinning band fractionating column at atmospheric pressure. The fraction used had a boiling point of 162°. The picrate of this compound melted at 186–187°. Elderfield reports a m.p. of 187–188°.[6]

6,7-Dihydro-1,5-pyrindine (II).—This compound was prepared by the procedure of Mariella[7] starting with cyclopentanone. The b.p. at atmospheric pressure was 199.5°. The equivalent weight by perchloric acid titration in glacial acetic acid was 120 (calcd. 119.6), m.p. of the picrate 180–181°.[8]

6,7,8,9-Tetrahydroquinoline (III).—This compound was prepared by the preceding procedure[7] starting with cyclohexanone. The b.p. was 222.2° at atmospheric pressure. The equivalent weight by perchloric acid titration was found 134.6 (calcd. 133.2). The picrate melted at 158–158.5°, reported[9] m.p. 158°.

6,7,8,9-Tetrahydro-3-cyano-5-cyclohepta[b]-2-pyridone (V).—To a two-liter three-necked flask (immersed in an ice–water cooling bath and fitted with a lubricated rubber sleeve and Hershberg stirrer, a condenser protected with a drying tube and an addition funnel and containing one liter of dry ether and 31.9 g. sodium metal) was added dropwise, over a period of 2 hr., a mixture of 151 g. of cycloheptanone and 100 g. of ethyl formate. When the addition was complete, the cooling bath was removed and the stirring continued for 1 hr., as the reaction mixture warmed up to room temperature. The reflux condenser was replaced for distillation and the bulk of the ether removed at atmospheric pressure and the remainder under reduced pressure. To the solid residue remaining in the flask were added 115 g. of cyanoacetamide dissolved in 750 ml. of water and a solution of 13.4 ml. of glacial acetic acid in 33 ml. of water, with enough piperidine to make the solution basic. The solution was refluxed for 2.5 hr. and then cooled in an ice-bath for 2 hr. After this time 200 ml. of water was added and enough glacial acetic acid to make the solution acidic. The solids were removed by filtration in a buchner funnel. It was washed several times with ice-water, then dried at 100° for 2 hr.

The yield was 119.8 g. (47.3%). The crude material was decolorized by two treatments with activated charcoal, then recrystallized from glacial acetic acid. The m.p. was 247–250°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: N, 14.83. Found: N, 14.89.

6,7,8,9-Tetrahydro-5-cyclohepta(b)-2-pyridone-3-carboxylic Acid (VI).—Sixty grams of V was dissolved in 500 ml. of concentrated hydrochloric acid and refluxed for 5 hr. The solution was poured over 500 g. of ice and stirred. The precipitate was filtered and washed several times with ice-water. It was dried in a forced draft oven for 2 hr. at 100°. The yield was 51.8 g. (75%). After several recrystallizations from ethanol the compound melted at 245–248°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: N, 6.76. Found; N, 6.76.

6,7,8,9-Tetrahydro-5-cyclohepta(b)pyridine-2-ol (VII).—Twenty grams of VI was heated to 350° under a cold finger. The yield was 15.6 g. (99%). The black crystalline product was purified by decolorizing with several small portions of activated charcoal and two recrystallizations from ethanol. The m.p. was 194–194.5°.

Anal. Calcd. for $C_{10}H_{13}NO$: N, 8.58. Found: N, 8.35.

6,7,8,9-Tetrahydro-2-chloro-5-cyclohepta(b)pyridine (VIII).—Twenty-five and seven-tenths grams of VII was dissolved in 30 ml. of phosphorus oxychloride, heated to reflux and 37 g. of phosphorus pentachloride added over a 45-minute period through the condenser. The temperature was raised to 160° and the solution refluxed 1 hr. The phosphorus oxychloride was removed under vacuum and the residue poured over ice. The solution was made alkaline and steam distilled. The yield was 14.0 g. (55%). After recrystallization from ethanol the m.p. was 69–69.5°.

Anal. Calcd. for $C_{10}H_{12}ClN$: N, 7.70. Found: N, 7.64.

---

(1) Taken in part from the M.S. Thesis of Edith Godar.

(2) To whom inquiries should be sent.

(3) L. F. Fieser and W. C. Lothrop, THIS JOURNAL, **58**, 2050 (1936); **59**, 945 (1937).

(4) W. H. Mills and I. G. Nixon, *J. Chem. Soc.*, 2510 (1939).

(5) R. H. Horning and E. D. Amstutz, *J. Org. Chem.*, **20**, 1069 (1955).

(6) J. Finkelstein and R. C. Elderfield, *ibid.*, **4**, 365 (1939).

(7) R. P. Mariella, THIS JOURNAL, **69**, 2620 (1947).

(8) W. C. Thompson, *ibid.*, **53**, 3160 (1931), reports a b.p. of 199° at 750 mm. and a m.p. of 181–182° for the picrate.

(9) V. Prelog and S. Szpilvogel, *Helv. Chim. Acta*, **28**, 1684 (1945).

6,7,8,9-Tetrahydro-5-cyclohepta(b)pyridine (IV).—To a solution of 9.96 g. of VIII in 100 ml. of absolute ethanol was added 2.0 ml. of concentrated hydrochloric acid and 0.9 g. of catalyst (10% Pd-on-charcoal). The mixture was put in a Parr bomb and hydrogen added. The hydrogen uptake rose rapidly to the theoretical value and then stopped. The catalyst was filtered off immediately and the bulk of the ethanol removed by vacuum distillation. The remainder of the ethanol was removed by heating under an infrared lamp.

The free base was obtained by making the aqueous solution of the hydrochloride alkaline with potassium hydroxide and extracting with ethyl ether. The ether solution was dried over potassium hydroxide, the ether allowed to evaporate and the amine again dried; b.p. at atmospheric pressure 238°; equivalent weight calcd. 147.2, found 148; m.p. of picrate 131–132°, reported[10] m.p. 130–131.5°.

Procedure for Determination of Ultraviolet Spectra.—All samples were redistilled immediately before use. The concentrations of the final solutions ranged from 6.6 to 17.8 mg./l. The solvents used were 1 *N* sulfuric acid, water, ethanol and cyclohexane. All data were obtained by use of a Beckman DU, using 1.0-cm. matched quartz cells (Figs. 1 to 4).

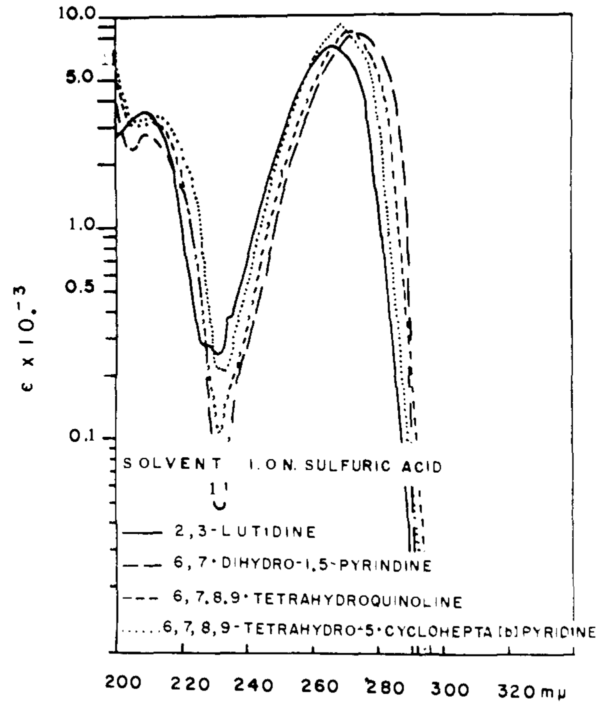


Fig. 1.

Procedure for Determination of Infrared Spectra.—All samples were redistilled immediately before use. The instrument was a Perkin-Elmer model 21 (Fig. 5).

X-Ray powder diffraction patterns of the picrates of I, II, III and IV were determined and are of value in future analytical work (Fig. 6).

Discussion of Ultraviolet Spectra

The data presented in Table I indicate that the wave length of maximum absorption of each of the four compounds tends to occur in the same order in the different solvents. That is, in every solvent used, the dimethyl compound (2,3-lutidine) absorbs at the shortest wave length, with the IV, III and II showing maximum absorption at successively higher wave lengths.

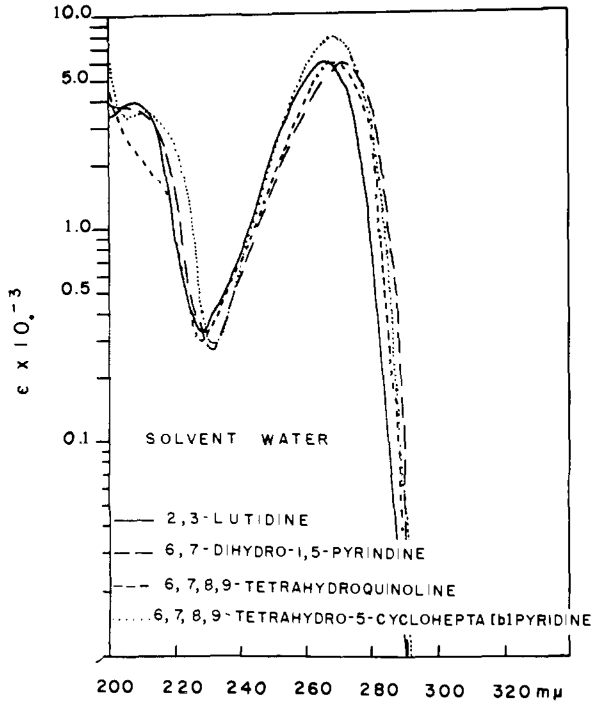


Fig. 2.

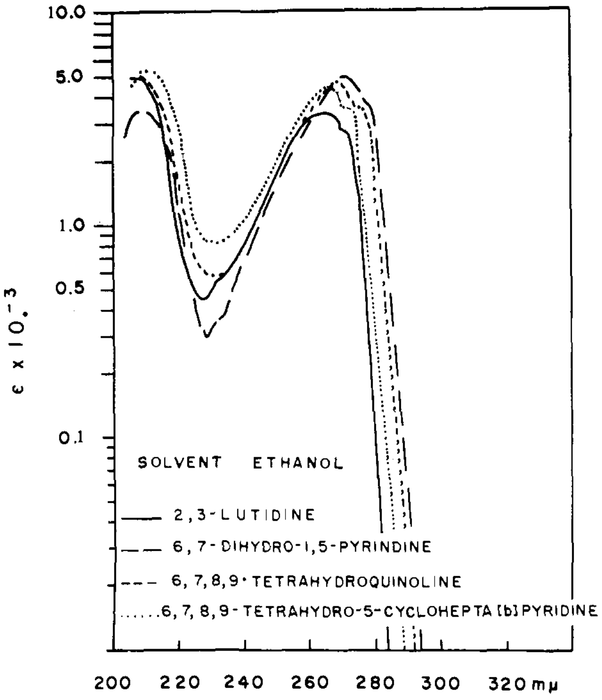


Fig. 3.

The intensity at λ_{max} seems to show more correlation with the compound than with the solvent. III has the second highest intensity in all four solvents. The dimethyl compound has the lowest intensity in three of the solvents, and in the fourth one, water, the intensity is so close to that of the II that they may be considered equal. IV has the highest intensity in water and sulfuric acid and II shows higher intensity than the other compounds in the non-polar solvents ethanol and cyclohexane.

---

(10) V. Prelog and W. Hinden, *Helv. Chim. Acta.*, **27**, 1854 (1944).

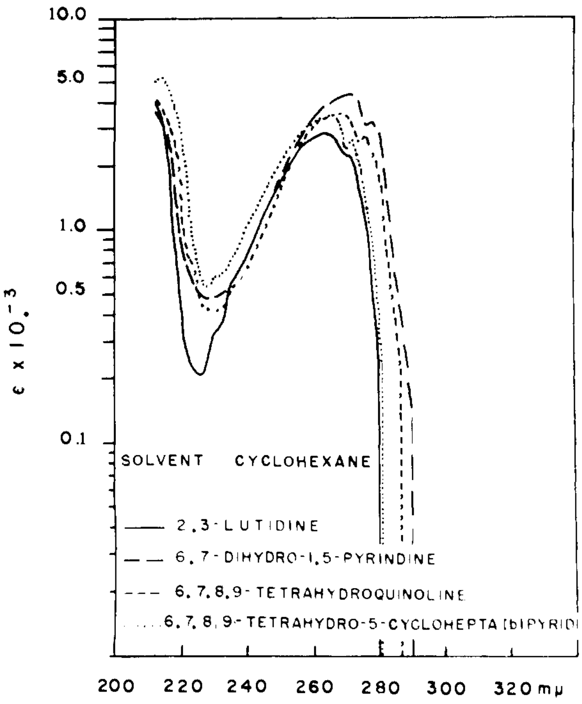


Fig. 4.

There do not seem to be any data here which would indicate bond fixation. If there were any bond fixation, it would be expected that the compound containing the cyclopentano-ring would be more similar to the compound containing the cyclohexano-ring than the latter would be to the other compounds. As can be seen from the data of Table I, there are more differences between these two compounds than there are between III and IV, or between IV and I.

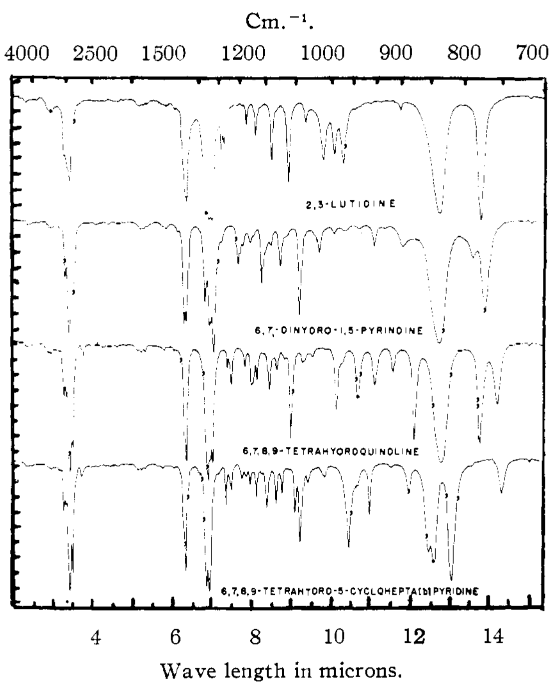


Fig. 5.

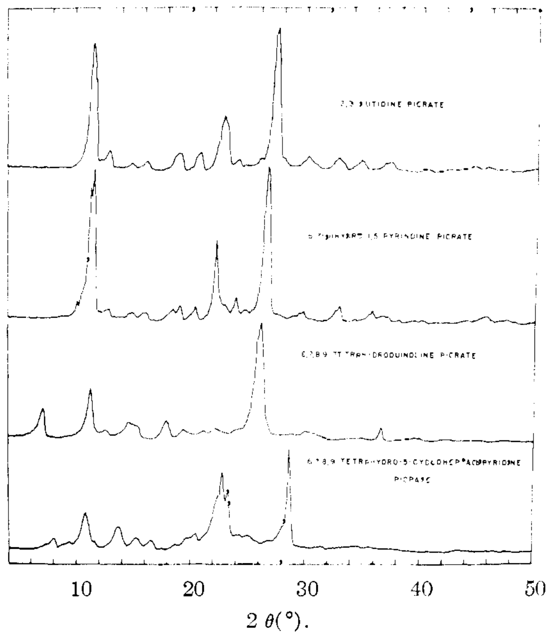


Fig. 6.—X-Ray powder diffraction patterns; copper $K\alpha_1$ radiation, λ 1.54050 A.

The differences in the spectra of these compounds can be explained on the basis of ring strain effects. Friedel and Orchin,[11] in their discussion of the theoretical aspects of ultraviolet spectra, state that some molecular distortions produce effects which are just opposite to those associated with steric hindrance. These effects are bathochromic shifts, increased intensities and loss of fine structure. When an aromatic ring is substituted by two methyl groups in vicinal positions, ring strain is incurred due to the spatial overlap of the two groups. The bathochromic shift is due to the decrease in energy difference of the ground and excited states.

Table I

Data from the Ultraviolet Spectra

	Solvent							
	Sulfuric acid		Water		Ethanol		Cyclohexane	
Compound	λ_{max}, mμ	log ε max	λ_{max}, mμ	log ε max	λ_{max}, mμ	log ε max	λ_{max}, mμ	log ε max
2,3-Lutidine	265	3.85	266	3.77	266	3.56	264	3.45
6,7-Dihydro-1,5-pyrindine	274	3.92	272	3.77	272	3.69	272	3.63
,7,8,9-Tetrahydroquinoline	272	3.93	268	3.78	268	3.66	268	3.54
6,7,8,9-Tetrahydro-5-cyclohepta(b)-pyridine	269	3.96	269	3.89	266	3.64	266	3.53

With this principle in mind, the ultraviolet spectra of the 2,3-disubstituted pyridines presented in Figs. 1 through 4 can be interpreted readily. In all cases the compound containing the cyclopentano ring absorbs at the longest wave length. This is the compound which would be expected to impose the largest amount of strain on the pyridine ring. It can be demonstrated from a study of the molecular models that there is still an appreciable amount of ring strain present on the aromatic carbons connecting the rings in III. The cyclohep-

---

[11] R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

tano ring introduces more strain than the two adjacent methyl groups.

log ϵ for pyridine in ethanol is 3.42 and is slightly lower for the methylpyridines; log ϵ values for the compounds studied here appear in Table I. From this table it is apparent that all these compounds have higher log ϵ values than do pyridine and the monosubstituted pyridines. These compounds also have higher log ϵ values in acid solution than does pyridine. The value for log ϵ of pyridine in ethanolic hydrochloric acid is 3.72.

These compounds all have λ_{max} at longer wave lengths than pyridine also. The peak of the main band in pyridine is at about 256 mμ.

Therefore, it seems most plausible to explain these results on the basis of ring strain effects in the pyridine nucleus due to the effects of the various substituent groups in the 2,3-position.

Discussion of the Infrared Spectra

Pyridines have two characteristic absorption bands in the 800–700 cm.$^{-1}$ region of the infrared spectrum. The higher frequency band of the two is characteristic of pyridines in general and occurs at 732–710 cm.$^{-1}$. The frequency of the other band is characteristic of the number of adjacent hydrogens on the aromatic nucleus and is analogous to the vibration frequencies of similarly substituted benzene rings. Pyridine absorbs at 749 cm.$^{-1}$, α-picoline at 790 cm.$^{-1}$, β-picoline at 755 cm.$^{-1}$ and γ-picoline at 800 cm.$^{-1}$, corresponding to mono-, *o*-, *m*- and *p*-substituted benzenes, respectively.

These assignments hold very well for all the compounds listed, with one notable exception. The two low frequency bands in IV are shifted to much higher frequencies than could be expected for a compound of this type. The lower frequency band of the two has shifted to 767 cm.$^{-1}$ from the expected range of 720–730 cm.$^{-1}$. The higher frequency band has not only shifted to higher frequencies but has also split into a doublet at 793–803 cm.$^{-1}$, from the characteristic frequency of 785 cm.$^{-1}$.

In order to account for the discrepancies which appear in the spectrum of IV, it is assumed that they are due to the steric inhibition of the vibration of the 4-hydrogen on the pyridine ring. One of the methylene groups of the cycloheptano ring is close enough to interfere with the deformation vibration of this hydrogen during some phase of its vibrations.

On a purely qualitative basis this would appear to be so since the high frequency band of the 793, 803 cm.$^{-1}$ doublet appearing in this spectrum appears in the region where absorption bands occur due to only two adjacent hydrogens vibrating perpendicular to the plane of the ring.[12] Even the lower frequency band of this doublet is very high for 2,3-substitution where three hydrogens are adjacent, although it is at the extreme edge of the region in which it is expected. The only other possibility for this phenomenon is bond fixation, which is known to cause splitting of the band and absorption at the extreme edge of the expected region. This explanation was rejected since, if any bond fixation were to be present in these compounds, it would be in 6,7-dihydro-1,5-pyrindine and 6,7,8,9-tetrahydroquinoline because of the Mills–Nixon effect. There is no indication of this in these compounds, and this absorption band is present in the region normally assigned to this vibration.[12] The only spectrum examined in the course of this work which shows any evidence of what might be bond fixation is the spectrum derived from 2-amino-3-methylpyridine, which shows splitting of this band, and absorption at 767, 777 cm.$^{-1}$. The amino group in the 2-position might be sufficiently electronegative to cause some degree of bond fixation to occur as a result of its tendency to change the electron distribution of the aromatic ring. The free electron pair could either cause hyperconjugation of the adjacent methyl group or shift to the position *para* to the amino group, either of which would result in bond fixation.

Also on a purely qualitative basis, an inspection of the low frequency bands of this series of compounds seems to show a correlation between frequency of absorption and expected steric effects of the side chain. 6,7-Dihydro-1,5-pyrindine absorbs at 722 cm.$^{-1}$, 6,7,8,9-tetrahydroquinoline at 728 cm.$^{-1}$, 2,3-lutidine at 738 cm.$^{-1}$ and 6,7,8,9-tetrahydro-5-cyclohepta(b)pyridine at 767 cm.$^{-1}$. This regular progression in the frequencies would indicate that steric hindrance is increasing in the series cyclopentano ring $<$ cyclohexano ring $<$ dimethyl $<$ cycloheptano ring. The shift due to the cycloheptano ring is much more pronounced than the shifts observed in the compounds containing the other substituents. This is the absorption band which Bellamy[13] says may prove to be the characteristic which will differentiate between pyridines and other aromatic compounds.

These effects may also be explained in more theoretical terms. The infrared spectrum of pyridine has been analyzed thoroughly by Kline and Turkevich,[14] Corrsin, Fax and Lord[12] and by Andersen, Bak, Brodersen and Rastup-Andersen.[15] These authors have based their arguments and calculations on the analysis of the infrared spectrum of benzene, which appears in Herzberg,[16] based on the work reported by Wilson,[17] Bailey, Hale, Ingold and Thompson,[18] Langseth and Lord[19] and others. The assignments have been substantiated by results obtained with the use of compounds deuterated to various degrees. Indications from Raman spectra prove the validity of the calculations. The observed frequencies correlate well with their calculated values.

The 10b vibration occurs at 749 cm.$^{-1}$ as a strong band in the spectrum of pyridine because it

---

(12) L. Corrsin, B. J. Fax and R. C. Lord, *J. Chem. Phys.*, **21**, 1170 (1953).

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

(14) C. H. Kline and J. Turkevich, *J. Chem. Phys.*, **12**, 300 (1944).

(15) F. A. Andersen, B. Bak, S. Brodersen and J. Rastup-Andersen, *ibid.*, **23**, 1047 (1955).

(16) G. Herzberg, "Molecular Spectra and Molecular Structure. II. Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Company, Inc., New York, N. Y., 1945.

(17) E. B. Wilson, Jr., *Phys. Rev.*, **45**, 706 (1934).

(18) C. R. Bailey, J. B. Hale, C. K. Ingold and J. W. Thompson, *Proc. Roy. Soc. (London)*, **161**, 107 (1937).

(19) A. Langseth and R. C. Lord, *J. Chem. Phys.*, **6**, 203 (1938).

is due to degeneracy. This band appears at 567 cm.$^{-1}$ in C_5D_5N, 743 cm.$^{-1}$ in 4D-pyridine, 717 cm.$^{-1}$ in 3D-pyridine and at 748 cm.$^{-1}$ in 2D-pyridine. This band has probably shifted to lower frequencies in the spectra of the substituted pyridines because of their higher moments of inertia and therefore this vibration is assigned to the band which appears near 730 cm.$^{-1}$ in the spectra of the compounds included herein. This is the band which shows a regular progression of frequency in the series: II, III, I, IV mentioned above. In the representation of the molecule during this vibration, the 4-hydrogen is in the plane of the ring and is not vibrating. It might be expected to be affected to some extent due to the spatial requirements of the substituent in the 3-position. The cyclopentano-ring should offer very little interference. It is planar so that the enforced 108° interior valence angles of the cyclopentano-ring pull the methylene groups away from the aromatic ring by simultaneously increasing the exterior valence angle. The *o*-methylene groups of the cyclohexano ring would thus be slightly closer to the 4-hydrogen. Two adjacent methyl groups in the 2,3-position of the aromatic ring probably lead to some distortion of the normal valence angle between them due to spatial requirements of the groups. The *o*-methylene groups of the cycloheptano ring should be close enough to the 4-hydrogen to cause some interaction with it.

The other strong band in this region appears at 703 cm.$^{-1}$ in the spectrum of pyridine. This is also a hydrogen deformation mode designated as vibration 11 in the spectra of pyridine and benzene. This deformation mode is species B_2, antisymmetric with the plane of the ring. The displacement vectors of the carbon atoms of the ring is forward, those of the hydrogen atoms, backward. In this vibration the 4-hydrogen would not be expected to interact or suffer interference to its normal vibration by a planar substituent.

The cycloheptano ring is the only one which is definitely puckered and undergoing ring deformations during which the C atoms away from the pyridine ring are alternately free to move out of the plane of the cycloheptano ring. The hydrogens of the cycloheptano-ring are undoubtedly also undergoing deformation vibrations, although they would be of a different frequency than those of the pyridine hydrogen deformations. Therefore, interference could arise due to a bending or twisting vibration of the cycloheptano ring which brings it close enough to the 4-hydrogen of the pyridine ring to interfere with its vibration and thus raise the frequency of vibration of the remaining two hydrogens. These out-of-plane hydrogen deformation vibrations bring the groups into closer contact than the in-plane vibrations do. One result of this would be hindered rotation of the ring methylene group. During this rotation the 4-hydrogen could be prevented from following its normal vibration mode. The effect of interference with the 4-hydrogen would be to increase the frequency of the vibration. Therefore it seems that the splitting of the 800 cm.$^{-1}$ band in the spectrum of 6,7,8,9-tetrahydro-5-cyclohepta(b)pyridine is due to the steric strain and resultant hindered deformation vibration produced by the proximity of one of the methylene groups of the cycloheptano ring to the 4-hydrogen atom on the pyridine nucleus.

The absorption bands for these substituted pyridines appear at 787 cm.$^{-1}$ in 2,3-lutidine, 786 cm.$^{-1}$ in 6,7-dihydro-1,5-pyrindine, 782 cm.$^{-1}$ in 6,7,8,9-tetrahydroquinoline and at 793, 803 cm.$^{-1}$ in 6,7,8,9-tetrahydro-5-cyclohepta[b]pyridine. The effect of placing substituents other than hydrogen on the ring is to raise the frequency of the deformation vibration. This is a well established characteristic of aromatic molecules, and the number of adjacent hydrogens may be determined from the frequency of this absorption band in the infrared spectrum of the compound.[13]

CHICAGO 26, ILLINOIS

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE GEORGIA INSTITUTE OF TECHNOLOGY]

The Relative Rates of Formation of Carbanions by Haloforms[1]

BY JACK HINE, NORBERT W. BURSKE, MILDRED HINE AND PAUL B. LANGFORD

RECEIVED OCTOBER 15, 1956

The effect of structure on reactivity in carbanion formation of haloforms was studied by measurements of the rates of hydroxide ion catalyzed transformation of deuterated bromoform, iodoform, dibromochloromethane, dichloroiodomethane and bromochlorofluoromethane to the corresponding protium compounds in homogeneous aqueous solution. Comparison of the resultant data with those known for other haloforms gives the reactivity series $CDI_3 \sim CDBr_3 > CDBr_2Cl > CDBrCl_2 \sim CDCl_2I > CDBr_2F > CDCl_3 > CDBrClF > CDCl_2F$ showing that α-halogen substituents facilitate carbanion formation in the order $I \sim Br > Cl > F$. The observed order is thought to be due to some combination of the inductive effect, polarizability and *d*-orbital resonance. The relative rates of carbanion formation from haloform are fairly well correlated with the rates of formation of the same carbanions by the decarboxylation of the corresponding trihaloacetic acids in the cases where quantitative data on the latter are available. The effect on reactivity of the replacement of one halogen by another decreases as the reactivity of the haloform in which the replacement is made increases. For bromochlorofluoromethane the rate constant for hydrolysis and the deuterium kinetic isotope effect were also obtained.

Introduction

In order to learn more about the effect of structure on reactivity in carbanion formation as well as to investigate more thoroughly a mechanism for the basic hydrolysis of haloforms involving intermediate trihalomethyl anions[2] we have been studying

---

[1] Part VI in the series, "Carbon Dihalides as Intermediates in the Basic Hydrolysis of Haloforms." For Part V see ref. 4. Abstracted in part from the Ph.D. thesis of Norbert W. Burske, Georgia Institute of Technology, 1957.

[2] J. Hine, THIS JOURNAL, **72**, 2438 (1950); J. Hine and A. M. Dowell, Jr., *ibid.*, **76**, 2688 (1954).