

TABLE IV

THE MUTAROTATION OF MANNOSE *o*-, *m*-, AND *p*-NITROPHENYLHYDRAZONE IN 1:1 PYRIDINE-ALCOHOL MIXTURE

Ortho		Meta			
Time	$[\alpha]_D$	Time, hours	$[\alpha]_D$	Time, hours	$[\alpha]_D$
15 min.	+52.0	10 min.	+26.5	26.5	+6.0
30 hours	+52.0 ^a	1	+26.0	29	+4.0
		2	+24.5	30.75	+2.5
		3	+22.0	47.5	-8.5
Para		5.5	+20.0	120	-7.8
Time	$[\alpha]_D$	6.5	+19.0	144	-8.3
15 min.	+56°	23.5	+ 7.5		
4 hours	+56° ^{as}				

^a Values obtained at intervals during the thirty-hour period (*o*-nitrophenylhydrazone) and the four-hour period (*p*-nitrophenylhydrazone) did not change from the initial rotations.

The results reported above show clearly the futility of applying rules which have been found to hold for other classes of optically active position isomers, to position isomers in the sugar hydrazone group. This is not surprising in view of the complexity of the reaction between sugars and hydrazines.

Summary

The optical rotations of the three isomeric nitrophenylhydrazones of rhamnose and mannose herein recorded do not agree with those which might be expected on the basis of rules found to hold for other classes of optically active position isomers, but the variations appear less erratic than the variations in the rotations previously recorded.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

ELECTRON SHARING ABILITY OF ORGANIC RADICALS. NITROGEN HETEROCYCLICS

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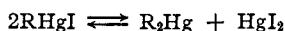
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In a preceding paper by Hixon and Johns¹ it was pointed out that if the electronic concepts of valence are at all correct, there must be a correlation between the affinities of different polar groups attached to identical organic radicals. In support of this generalization a mathematical relationship was demonstrated between the dissociation constants of the five series of compounds, R(NH₂), R(COOH), R(CH₂COOH), R(CH₂CH₂COOH) and R(OH), all data in Landolt-Börnstein being included which permitted at least one comparison of any radical. In a later paper by Johns and Hixon²

¹ Hixon and Johns, *THIS JOURNAL*, **49**, 1786 (1927).

² Johns and Hixon, *J. Phys. Chem.*, **34**, 2226 (1930).

this relationship was further tested for six radicals of the above series by conductivity measurements on the organomercuric nitrates and by measurements of equilibrium constants for the reaction



The following paper demonstrates that this relationship also holds for the nitrogen heterocyclics, data being reported for both the R-N $\left\langle \begin{array}{c} \square \\ \square \end{array} \right\rangle$ series and the R-N $\left\langle \begin{array}{c} \square \\ \square \\ \square \end{array} \right\rangle$ series. These studies form a portion of the systematic investigation of the relationship between structure and insecticidal action³ in the nitrogen heterocyclics, together with a study of the chemistry of nicotine.

From the dissociation constant of nicotine as compared with the α -substituted pyrrolidines which were prepared and measured, it was possible to predict that the pyridyl radical was extremely negative. This negativity was confirmed by preparing and measuring the dissociation constants of both α - and β -picolylamine.

Preparation of Compounds

It was necessary to study in detail the methods of preparation of each compound in order to prepare sufficient quantities for purification. These studies have been chiefly reported in previous papers.⁴ The preparations of α -picolylamine and β -picolylamine are reported here. Metanicotine was prepared according to the directions of Maass and Zabliński.⁵

α -Picolylamine.— α -Pyridyl aldehyde was synthesized by the method of Lénárt⁶ from α -stilbazole. To convert the aldehyde to the oxime it was treated with a small volume of water, an equivalent of hydroxylamine hydrochloride and an excess of potassium carbonate. Upon warming the oil soon solidified. It was recrystallized once from benzene and showed a melting point of 113° as reported by Lénárt.

Five grams of the oxime dissolved in 75 cc. of 95% alcohol was treated alternately over a period of several hours with small portions of zinc dust and glacial acetic acid until 40 g. of each had been added. The flask was allowed to stand for twenty-four hours, the zinc and zinc acetate were filtered off and washed with fresh alcohol. The alcoholic solution was concentrated to a thick sirup under reduced pressure on a water-bath, water was then added and the evaporation repeated three successive times to remove as much of the acetic acid as possible. The residue was saturated with potassium hydroxide and the oil coming to the surface drawn off. The caustic solution was subjected to steam distillation to remove the base retained by the viscous solution, the base being recovered from the distillate by adding hydrochloric acid, evaporating off the water and decomposing the residue with potassium hydroxide. The combined fractions were dried over solid potassium hydroxide and distilled, 3 g. of base being collected at a con-

³ The estimation of insecticidal action is being carried out in coöperation with Dr. C. H. Richardson of the Department of Entomology and will be reported elsewhere.

⁴ Craig and Hixon, *THIS JOURNAL*, 52, 804 (1930); 53, 187 (1931); 53, 1831 (1931).

⁵ Maass and Zabliński, *Ber.*, 47, 1164 (1914).

⁶ Lénárt, *Ann.*, 409, 95 (1915).

stant temperature of 91° under 15 mm. pressure. The oil was colorless, had only a faint odor and was soluble in water in all proportions.

The picrate of the base was found to be unsuitable as a derivative; the color changed on repeated crystallizations and the melting point was indefinite. An oxalate, prepared from ether solution, could readily be recrystallized from alcohol and melted at 167° on repeated crystallization. The base formed a chloroaurate that crystallized from water acidified with hydrochloric acid and melted with decomposition at 204°. A sample for analysis was dried in a vacuum desiccator at room temperature.

Anal. Calcd. for $C_8H_8N_2AuCl_4 \cdot HCl$: Au, 40.7. Found: Au, 40.3, 40.1, 41.2.

As the separate analyses did not agree very well, a chloroplatinate was prepared. It behaved in solubility like the chloroaurate and was prepared in the same way.

Anal. Calcd. for $C_8H_8N_2PtCl_6$: Pt, 37.7. Found: Pt, 37.7, 37.7.

A report of the compound could not be found in the literature.

β -Picolylamine.— β -Pyridyl aldehyde was prepared according to the directions of Lénárt. From it the oxime was prepared as in the preceding synthesis. The β -pyridyl-methanaldoxime melted at 148° when recrystallized from benzene. It was less soluble in benzene than was the alpha isomer. The oxime was reduced to the amine as was the alpha oxime. The yields throughout the synthesis were somewhat lower than in the case of α -picolylamine.

A chloroplatinate when recrystallized from water acidified with hydrochloric acid did not melt at as high a temperature as 320°, although it darkened slightly.

Anal. Calcd. for $C_8H_8N_2H_2PtCl_6$: Pt, 37.7. Found: Pt, 37.7, 37.7.

A picrate of the base was not very soluble in alcohol but crystallized nicely in leaves. It melted sharply at 211° on repeated crystallization.

β -Picolylamine was a colorless oil that boiled at 112° under 18 mm. pressure. It had very little odor, was soluble in water in all proportions and gave a solid carbonate when a drop was allowed to stand in the atmosphere.

Measurement of Dissociation Constants

The steps taken to specially purify pyrrolidine, α -ethylpyrrolidine, α -phenylpyrrolidine, α -picolylamine, β -picolylamine (α -pyrrole)-methylamine and α -ethylpyrroline are already reported in their syntheses. The tertiary amines were all run through a Hinsburg primary-secondary-tertiary amine separation. Nicotine was purified by recrystallization of the hydrochloride⁷ and regeneration of the pure base by caustic. All compounds measured distilled with a constant boiling point. Small ampules were filled by distillation as described by Carothers, Bickford and Hurwitz⁸ using a modified Brühl vacuum receiver.

The first compound measured was pyrrolidine. In order to remove all traces of water from the base, it was found necessary to add metallic sodium to it in the distillation flask and, after allowing it to stand in contact with the sodium for several hours, to distil directly into the receiver. Solid potassium hydroxide failed to remove as much as 2% of water from the base. This method of drying was used with all the other derivatives measured except in the case of (α -pyrrole)-methylamine. This material could be dried in the cold over solid potassium hydroxide but if the temperature was raised it

⁷ Harlan and Hixon, *THIS JOURNAL*, **52**, 3385 (1930).

⁸ Carothers, Bickford and Hurwitz, *ibid.*, **49**, 2908 (1927).

reacted to give the potassium pyrrole derivative. It was accordingly dried in the cold over potassium hydroxide, placed in the flask and immediately distilled. The pyridine derivatives and α -phenylpyrrolidine reacted to a certain extent when distilled directly from metallic sodium. However, the material distilling showed as high a degree of purity as the other derivatives which did not decompose.

After distillation, the ampules were sealed as quickly as possible. To prepare for sealing, the bulb of each ampule was immersed in warm water and then in cold. The expansion and contraction removed the base from the mouth of the ampule and allowed it to be sealed easily. After sealing each bulb was washed first in alcohol and then in ether. Samples of such unstable compounds as nicotine keep indefinitely without developing any trace of color when prepared in this way.

Each fraction was tested for purity by titration using sodium alizarin sulfonate as indicator. The sample was rejected if the neutralization equivalent varied more than 0.3% from the theoretical. Very weakly basic compounds such as *N*-phenylpyrrolidine which are also very insoluble in water will not give a satisfactory end-point in titration. The purity of these compounds was checked by constant boiling point and by determining the dissociation constant for at least three separate fractions. In the case of α -pyridylamine, β -pyridylamine, nicotine and (α -pyrrole)-methylamine it was necessary to resort to electrometric titration to obtain a sharp end-point although these compounds are quite soluble in water.

Before the hydrogen-ion concentration of a solution was determined, the hydrogen electrode was always checked by measurement of a 0.05 normal standard potassium acid phthalate buffer solution. The values of the solutions were always checked by duplicate electrodes against a saturated potassium chloride calomel half cell. The temperature was maintained constant by use of an air-bath with a variation of not more than $\pm 0.2^\circ$ or a water-bath with the same variation.

In measuring the P_H of some of the solutions the e. m. f. soon reached a maximum and then showed a gradual drop indicating electrode poisoning. The measurements could be duplicated on another solution of the same base and the electrode showed the correct value when placed in the standard buffer solution immediately after use. The solutions, in general, did not accurately follow Ostwald's dilution law, for those that were

TABLE I
DISSOCIATION CONSTANTS FOR NITROGEN BASES

Compound	E. m. f. against satd. calomel	Purity by neutralization		Acid added, equiv.	Dissociation constants
		Calcd.	Found		
Pyrrolidine	0.9009	71.1	71.3	0.5	1.3×10^{-8}
<i>N</i> -cyclohexyl-	.8787	153.19	153	.5	5.0×10^{-4}
<i>N-n</i> -butyl-	.8581	127.1	127.1	.5	2.3×10^{-4}
<i>N</i> -methyl-	.8474	85.1	85.4	.5	1.5×10^{-4}
<i>N</i> -benzyl-	.8070	161.12	161.7	.5	3.2×10^{-5}
<i>N-p</i> -tolyl-	.4772	1	5×10^{-10}
<i>N</i> -phenyl-	.4490	1	2×10^{-10}
α -Ethyl-	.8630	99.1	99.0	0.5	2.7×10^{-4}
α -Phenyl-	.8143	147.1	147.3	.5	4×10^{-5}
β -Pyridyl- α - <i>N</i> -methyl-	.7157	162.2	160	.5	9×10^{-7}
Metan nicotine	.8310	162.2	163.0	.5	9×10^{-5}
α -Ethylpyrroline	.6850	97.1	96.8	.5	2.7×10^{-7}
(α -Pyrrole)-methylamine	.7760	96	96	.5	9×10^{-6}
β -Picolyamine	.7220	108.1	108	.5	1.1×10^{-6}
α -Picolyamine	.7165	108.1	108	.5	1×10^{-6}

one-half neutralized showed a slight change in K_B when measured at other dilutions. This method for measuring dissociation constants is the most accurate method available.

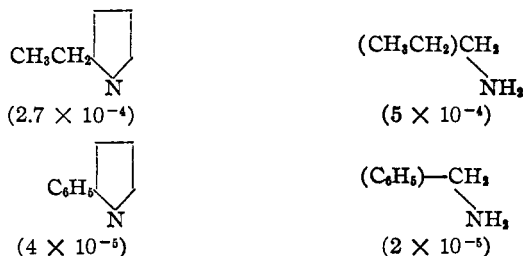
The dissociation constants for a number of nitrogen bases are reported in Table I.

Discussion of Results

The dissociation constants of the N-substituted pyrrolidines are practically identical with the dissociation constants of the corresponding primary amines, as the following tabulation of the available data shows.

	N-subst. pyrrolidine	Primary amine
Methyl-	1.5×10^{-4}	5×10^{-4}
Butyl-	2.3×10^{-4}	5×10^{-4}
Benzyl-	3.2×10^{-5}	2×10^{-5}
Tolyl-	5×10^{-10}	2×10^{-9}
Phenyl-	2×10^{-10}	3×10^{-10}

The same relationship holds when the α -substituted pyrrolidines are compared with the corresponding amines with one intervening CH_2 unit.



These relationships are shown graphically in Fig. 1, using the same method of plotting as in the preceding papers.

When the dissociation constants of α -phenylpyrrolidine and N-methylpyrrolidine were considered, it seemed that the dissociation constant of nicotine, 7×10^{-7} , measured by Kolthoff⁹ colorimetrically, was unusually high. A value of 9×10^{-7} was obtained potentiometrically in this Laboratory. This value for nicotine could be explained only by concluding that the pyridyl radical was extremely negative.

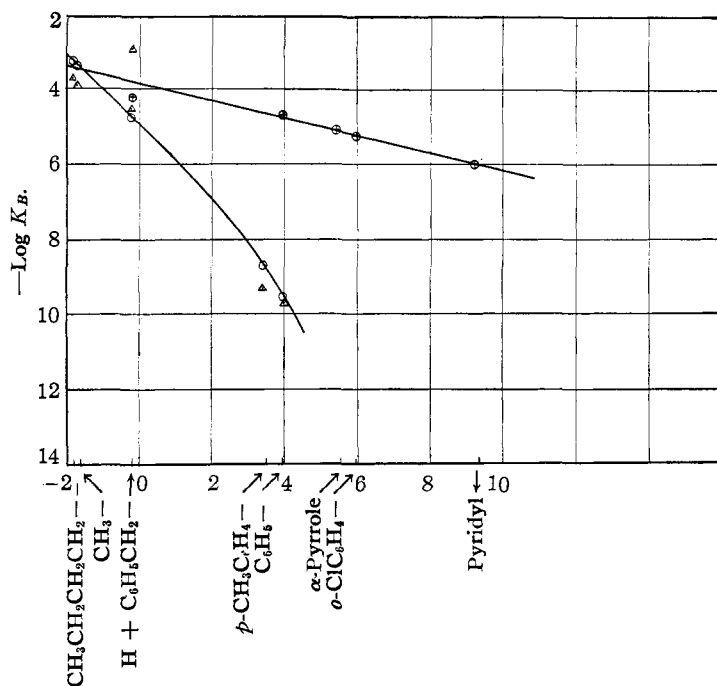
This indication of high negativity of the pyridyl radical was confirmed by preparing and measuring the α - and β -picolylamines. If the curve for the RCH_2NH_2 series in Fig. 1 is extrapolated the dissociation constants of the picolylamines indicate the pyridyl radical to be almost as much more negative than the phenyl radical as the phenyl is more negative than the saturated aliphatic radicals. Various predictions have been made in the literature regarding the negativity of the pyridyl radical.¹⁰

A similar determination of the negativity of the pyrrole radical was made using (α -pyrrole)-methylamine prepared according to the directions of

⁹ Kolthoff, *Biochem. Z.*, **162**, 289 (1925).

¹⁰ Rath, *Ber.*, **57**, 840 (1924); Marckwald, *ibid.*, **26**, 2187 (1893).

Putochin.¹¹ The dissociation constant indicated that while the α -pyrrole radical is more negative than the phenyl radical, it is less negative than the pyridyl radical.



Electron sharing ability.

Fig. 1.—○, RNH_2 series; △, N-substituted pyrrolidine series;
⊕, RCH_2NH_2 series.

Summary

The dissociation constants have been measured for a number of cyclic nitrogen bases.

The relationship previously demonstrated between the electron sharing ability of the organic radicals and the affinities of the polar groups in the series RNH_2 , RCOOH , $\text{R}(\text{CH}_2)_x\text{COOH}$, and RHgX has been shown to hold for both the alpha substituted and nitrogen substituted pyrrolidines.

The preparations of α - and β -picolyamine are reported.

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¹¹ Putochin, *Ber.*, 59, 1987 (1926).