Base-Catalyzed Hydrogen–Tritium Exchange Rates of ω-Tritium-Substituted Picolines and Methylquinolines[1]

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The sodium methoxide catalyzed exchange rates between methanol and ω-tritium-substituted picolines and methylquinolines were determined. The relative reactivities were 2-methylquinoline > 4-picoline > 2-picoline > 3-methylquinoline > 3-picoline. These results have been interpreted by use of the qualitative resonance theory and correlated by means of LCAO–MO calculations.

The weak acidity of alkylated pyridines, quinolines, and other similar heterocyclic systems has long been recognized and has been utilized in condensation reactions of these substances to effect the synthesis of desired carbon skeletons.[3] However, there seems to be no definite information regarding the relative reactivities of various substituted alkylpyridines or alkylquinolines. Knowledge of this sort should be of interest not only from a practical standpoint but also for theoretical reasons. With regard to the latter, a quantitative evaluation and interpretation of the effect of a ring nitrogen on reactivity of side chains should lead to a better understanding of the fundamental nature of such systems.

Previous studies of the reactivity of alkylated pyridines have not yielded results capable of quantitative comparison. In some instances they are confusing or conflicting. Thus, although 2,4-lutidine is preferentially metallated on the 2-methyl group with phenyllithium,[4] it has been shown that alkylation of the same compound with methyl iodide in the presence of sodamide gives mainly the 4-methyl-alkylated product.[5] The studies of Pines and coworkers[6] also support a higher alkylation reactivity for the 4-alkylated pyridines. Since it is very difficult to alkylate 3-picoline[7] and because 2,3-dimethylpyridine is alkylated on the 2-methyl,[5] the available information with regard to the base-catalyzed alkylation reactions leads to the reactivity order 4-picoline > 2-picoline ≫ 3-picoline. However, the results (except for those of Pines and his coworkers[6]) do not lend themselves to quantitative comparisons and there is no established relationship between the pyridine series and the quinoline series. Furthermore, the alkylation reaction is a two-step process (anion formation and alkylation) and either or both stages may be responsible for the over-all rate. The rate of alkylation is therefore not necessarily a true reflection of the acidity of the substrate.

The condensation of alkylpyridines and quinolines with aldehydes and ketones may also involve ionization of an α hydrogen on the alkyl group. Again the results are often conflicting. Thus, 2,4-lutidine reacts with formaldehyde to give the 4-ethanol derivative[8] but 2,4,6-collidine with formalin at 200° yields the 2-ethanol.[9]

There are quite a few other contradictory examples of reactivities of alkylpyridines and quinolines. In view of this it is desirable to have some unambiguous, quantitative relative reactivity data for reactions of these systems. In particular, hydrogen exchange rates which can be related to acidities should be especially valuable.

Results

ω-Tritiated 2-, 3-, and 4-picolines and 2- and 3-methylquinolines were prepared by decarboxylation of the corresponding pyridyl- or quinolylacetic acids in tritium water (eq 1). 2-Pyridylacetic acid, 4-pyridyl-

$$ArCH_2CO_2H \xrightarrow{T_2O} ArCH_2T + CO_2 \qquad (1)$$

acetic acid, and 2-quinolylacetic acid decarboxylated readily at 100° in neutral solution. Decarboxylation of 3-pyridylacetic acid and 3-quinolylacetic did not occur under these conditions and was carried out at 215–220°.

To determine the extent of nuclear tritiation during decarboxylation, quinoline was subjected to the decarboxylation conditions. Quinoline rather than picoline or methylquinoline was used to eliminate the possibility of methyl-group tritiation. Methylquinolines should undergo nuclear tritiation faster than quinoline, but picoline should react more slowly if the reaction is an electrophilic substitution. In an experiment at 220°, the relative activities of the recovered quinoline and of the tritium water used indicated that tritium in the nucleus of 3-picoline-ω-*t* and 3-methylquinoline-ω-*t* could account for no more than 1% of the total activity. At 100° nuclear tritiation of quinoline did not occur; thus the other compounds probably contain no nuclear tritium.

In all cases, the activity of the tritiated compound was approximately equal to that of the tritium water used (10^6 to 10^8 cpm/mmol).

The exchange rates were determined by heating samples of the tritiated compounds with methanolic sodium methoxide (ionic strength was maintained constant with sodium chloride) for varying lengths of time. The reaction mixture was acidified, the meth-

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anol was distilled off, and its tritium content was determined.

The exchange reaction was found to be first order in the tritiated compound and first order in the base concentration. For each of the compounds, the rates of exchange were determined at two temperatures and extrapolated to 135°. The results are summarized in Tables I and II.

TABLE I

TRITIUM EXCHANGE RATES IN METHANOLIC SODIUM METHOXIDE AT 135° (EXTRAPOLATED)

Compound	k_2[a] × 10[6]
2-Methylquinoline-ω-t	2200
4-Picoline-ω-t	760
2-Picoline-ω-t	54
3-Methylquinoline-ω-t	2.9
3-Picoline-ω-t	0.42

[a] l. mol^{-1} sec^{-1}.

TABLE II

TRITIUM EXCHANGE RATES IN METHANOLIC SODIUM METHOXIDE

Compound	Temp, °C	M NaOMe	M NaCl	k_1[a] × 10[6]	k_2[b] × 10[6]
2-Picoline-ω-t	129.8	0.102	0.000	3.53 ± 0.01	3.50 ± 0.01
	149.5	0.100	0.000	17.4 ± 0.2	17.4 ± 0.2
	149.5	0.054	0.048	9.54	17.6
3-Picoline-ω-t	169.8	0.100	0.000	1.36 ± 0.04	1.36 ± 0.04
	184.2	0.098	0.000	4.93 ± 0.02	5.00 ± 0.02
	184.2	0.051	0.048	2.53 ± 0.05	4.97 ± 0.10
4-Picoline-ω-t	101.0	0.102	0.000	3.56 ± 0.02	3.49 ± 0.02
	119.7	0.098	0.000	20.1 ± 0.4	20.6 ± 0.5
	119.7	0.051	0.048	10.3 ± 0.1	20.2 ± 0.2
2-Methylquinoline-ω-t	85.8	0.102	0.000	3.33 ± 0.07	3.26 ± 0.06
	105.1	0.100	0.000	19.3 ± 0.8	19.3 ± 0.8
	105.1	0.061	0.040	10.9 ± 0.7	17.9 ± 1.2
3-Methylquinoline-ω-t	149.5	0.100	0.000	1.08 ± 0.01	1.08 ± 0.01
	169.8	0.099	0.000	5.98 ± 0.04	6.08 ± 0.06
	169.8	0.052	0.048	2.94 ± 0.08	5.70 ± 0.14

[a] sec^{-1}. [b] l. mol^{-1} sec^{-1}.

Discussion

Hydrogen exchange rates of very weak acids often parallel the acidities of this type of compound.[10] This parallelism would be expected from the Brønsted catalysis law[11] if k is the rate constant for the protonation of the strong base by the weak acid and k_a is the dissociation constant of the weak acid. This procedure for evaluating relative acidities of weak acids is not without some ambiguities. The mechanism of the exchange process must be the same for each of the weak acids and must be a true acid–base reaction. The results are least equivocal if the reaction is uncomplicated by ion-pair formation or recombination of the anion of the weak acid with its original proton before exchange with the bulk solvent can occur. Andreades has shown that these phenomena do not occur in sodium methoxide–methanol solutions.[12] In this medium, the transition state for the hydrogen-exchange reaction has considerable carbanionic character and the relative exchange rates can be interpreted by comparison of the factors stabilizing the anion and its conjugate acid.

$$\log k = \alpha \log k_a + \log G$$

Qualitative resonance theory[13] can be used to estimate the relative acidities of the heterocyclic "acids" if several features of the resonance structures of the acids and their anions are taken into account. The location of the negative charge in the anion and the relative number of important resonance structures of the acid and anion appear to be important. The possibility of positioning a portion of the anion's negative charge on the electronegative nitrogen atom appears to be the principal factor in determining the exchange rates of these compounds. Thus, 2- and 4-picolines are more reactive than 3-picoline, and 2-methylquinoline reacts faster than 3-methylquinoline. Superimposed upon this consideration is that of the number of resonance structures of the anion compared with the acid. There is a larger difference between the numbers of resonance contributors to the anion and the acid for the methylquinolines than for the picolines. For this reason, 2-methylquinoline undergoes exchange more rapidly than 2-picoline and 3-methylquinoline is more reactive than 3-picoline. The difference in reactivity between 2-picoline and 4-picoline may be the result of additional stabilization of the 4-picoline anion occasioned by the fact that there are two pairs of equivalent contributors to the 4-picoline anion and no equivalent resonance structures for the 2-picoline anion. Thus, the exchange rates of the picolines and methylquinolines can be interpreted qualitatively by application of the resonance theory.

A quantitative correlation of the exchange rates of the picolines and methylquinolines by means of molecular orbital calculations was also attempted. The exchange rate should be related to the π-electron energy change of the reaction, which is simply the difference between the π-electron energies of the heterocyclic anion and its conjugate acid.[14] These π-electron energies are readily calculated by the LCAO–MO method. In treating compounds that contain atoms other than carbon, it is necessary to take account of the perturbing influence of the electronegative heteroatom on the rest of the system[14] by assigning different parameters to the carbons bonded to the heteroatom since they will be inductively affected. The best correlation resulted when the coulomb and resonance integrals were defined as shown in Chart I. h was varied from 0.50 to 2.50, while $h_{\alpha C}$ was allowed to assume values from 0.100 to 0.417. The best fit of the experimental data resulted when $h = 1.00$ and $h_{\alpha C} = 0.125$ (see Figure 1) with $\beta_{eff} = 49.6$ kcal/mol.

CHART I

$$\alpha_C = \alpha_0$$
$$\alpha_N = \alpha_0 + h\beta_0$$
$$\alpha_{\alpha C} = \alpha_0 + h_{\alpha C}\beta_0$$
$$\beta_{CN} = \beta_{CC} = \beta_0$$

In conclusion, it appears that the rates of anion formation for picolines and methylquinolines is that

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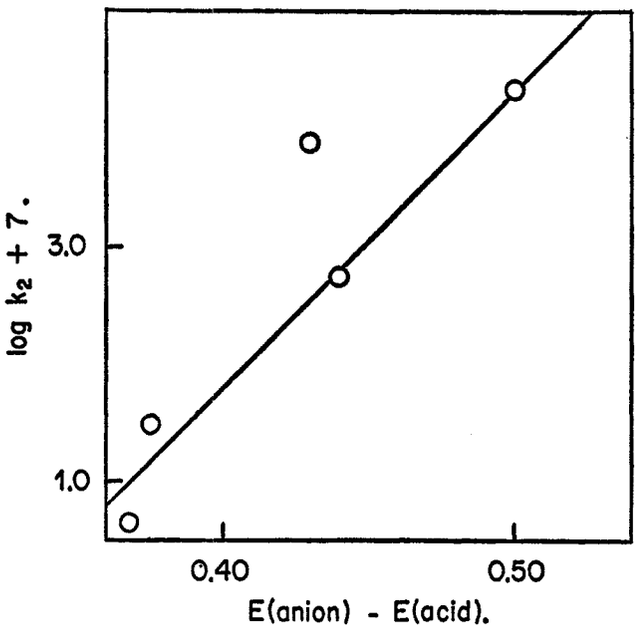

Figure 1.—Logarithms of the exchange rates of picolines and methylquinolines *vs.* the calculated π-electron energy changes (h = 1.0, $h_{\alpha C}$ = 0.125) for anion formation from these compounds.

suggested by the results of alkylation and condensation reactions of these compounds. The semiquantitative correlation of these rates by the molecular orbital approach is obviously not completely satisfactory. This may be due to deficiencies in the computational methods used or to complicating features in the exchange reaction. However, the fundamental validity of these procedures is indicated by the fact that they lead to the approximately correct ordering of reactivities. The exchange rates can be satisfactorily interpreted qualitatively by the resonance theory.

Experimental Section

Methyl 2-Pyridylacetate.—The ester was purified by conversion into the picrate which was crystallized from absolute methanol to give yellow crystals, mp 141.6–142.8° (lit.[15] mp 142–144°).

Methyl 4-Pyridylacetate.—Treatment of the ester with picric acid yielded a picrate which melted at 146.4–147.7° (lit.[16] mp 146.5–147.5°) after crystallization from methanol.

Methyl 2-Quinolylacetate.—A solution of 21.4 g (0.15 mol) of quinaldine in 50 cc of anhydrous ether was added during 15 min to 160 cc of 0.95 *M* phenyllithium in ether. The mixture was stirred for 3 hr at room temperature and then rapidly poured on Dry Ice. After completion of the reaction, the ether was allowed to evaporate at room temperature, and the residue was suspended in 250 cc of absolute methanol. The suspension was saturated with dry hydrogen chloride and the resulting solution was allowed to stand for 24 hr at 25°. At the end of this period the methanol was distilled off under reduced pressure, and to the residue was added 100 cc of water and sufficient sodium carbonate to make the solution basic. The basic solution was extracted three times with 100-cc portions of ether, and the combined ether extracts were dried over magnesium sulfate and evaporated. The residue was dissolved in a small volume of benzene and chromatographed on a 2.5 × 40 cm column of activity grade II Woelm alumina, using Skellysolve F as the eluent. The first fraction of the eluate, which corresponded to a light yellow band on the column, yielded 14 g (65%) of quinaldine. The residue obtained upon evaporation of the second fraction (corresponding to a dark yellow band) was chromatographed a second time. The ester so obtained was converted into the picrate, which was crystallized from absolute methanol. The yield of the ester picrate, mp 161.0–162.6° (lit.[17] mp 162°) was 10.5 g (15%).

3-Cyanoquinoline.—Heating of 3-bromoquinoline with cuprous cyanide[18] until the mixture liquefied followed by immediate distillation of the product and recrystallization from methanol yielded 62% of 3-cyanoquinoline, mp 106.8–107.4° (lit.[18] mp 106–108°).

Methyl 3-Quinolinecarboxylate.—Reaction of 3-cyanoquinoline with hydrogen chloride in methanol[19] followed by crystallization of the product from Skellysolve B at 0° yielded 58% methyl 3-quinolinecarboxylate as white crystals, mp 70–72° (lit.[19] mp 73–74°).

3-Acetylquinoline.—Methyl 3-quinolinecarboxylate was condensed with ethyl acetate in the presence of sodium methoxide,[20] and the crude keto ester was hydrolyzed and decarboxylated in 25% sulfuric acid at 100°. The crude product was crystallized from Skellysolve F to give 3-acetylquinoline in 37% yield as tan flakes, mp 98.4–99.2° (lit.[20] mp 97.5–98.5°).

3-Quinolylacetic Acid Hydrochloride.—3-Acetylquinoline was subjected to the Willgerodt reaction under the conditions described by Jones, Soper, Behrens, and Corse.[20] The procedure was modified as described below so that the acid hydrochloride rather than the methyl ester was isolated. The solution remaining after hydrolysis of the 3-quinolylthioacetamide was evaporated to 50 cc, made basic with solid potassium carbonate, and filtered. The filtrate was extracted five times with 150-cc portions of ether to remove nonacidic substances. The aqueous solution was then evaporated to dryness under reduced pressure, and the residue was extracted three times with 50-cc portions of absolute ethanol. The volume of the ethanol solution was reduced to 50 cc under vacuum, and the solid which precipitated was collected by filtration. To the filtrate was added 200 cc of ether, and the precipitate formed was filtered off. Both precipitates appeared to be mixtures of potassium chloride and the organic product; so they were combined. The 3-quinolylacetic acid hydrochloride was isolated by boiling the combined residues with 25 cc of absolute ethanol for a few minutes, filtering the hot suspension, and allowing the product to crystallize from the filtrate. This extraction was repeated three times with 10-cc portions of absolute ethanol. In this way there was obtained 2.35 g (15%) of 3-quinolylacetic acid hydrochloride, mp 194.8–197.4°.

Anal. Calcd for $C_{11}H_{10}O_2NCl$: C, 59.1; H, 4.5; N, 6.3; Cl, 15.9. Found: C, 59.4; H, 4.7; N, 6.6; Cl, 15.3.

2-Picoline-ω-t.—A suspension of 2.5 g of methyl 2-pyridylacetate picrate in 5 cc of concentrated hydrochloric acid was extracted with seven 20-cc portions of ether to remove the picric acid. The aqueous solution was then refluxed for 4 hr and evaporated to dryness under vacuum. The residual 2-pyridylacetic acid hydrochloride was dried by adding 5 cc of acetone and again evaporating to dryness. This was repeated three times. A methanol solution of a portion of the residue gave no precipitate with picric acid, indicating the absence of both the ester and 2-picoline. A solution of 0.9 g of the 2-pyridylacetic acid hydrochloride in 1 cc of tritium water was sealed in a tube and heated for 3 hr at 100°. The tube was then opened, the contents were made basic with solid potassium carbonate, and to the basic solution were added 5 cc of ether and 2 g of magnesium sulfate. The mixture was allowed to stand for several hours, and the ether was decanted. The residue was washed with 2-cc portions of ether until portions of the washings no longer gave a precipitate with picric acid. The combined ether solutions were distilled through a short column at atmospheric pressure until all of the ether appeared to have been removed. The residue was then distilled under vacuum to give 0.44 g (91%) of 2-picoline-ω-t with an approximate activity of 2.03 × 10^7 cpm/mmol. Gas phase chromatography indicated that this product was at least 98.5% pure 2-picoline. The picrate melted at 164.8–166.6° (lit.[21] mp 164°).

4-Picoline-ω-t.—This compound was prepared from methyl 4-pyridylacetate picrate in the way described above for 2-picoline-ω-t. One gram of 4-pyridylacetic acid hydrochloride yielded 0.48 g (89%) of 4-picoline-ω-t of approximate activity 2.03 × 10^7 cpm/

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mmol. This material was shown to be pure by gas phase chromatography. Its picrate melted at 166.8–168.2° (lit.[22] mp 167°).

2-Methylquinoline-ω-t.—A suspension of 2 g of methyl 2-quinolylacetate picrate (mp 161.0–162.6°) in 5 cc of concentrated hydrochloric acid was extracted seven times with 100-cc portions of ether. The hydrochloric acid solution was then evaporated to dryness under vacuum at 25°. The residue was dissolved in 2 cc of tritiated 4 N hydrochloric acid solution, sealed in a tube, and heated for 7 hr at 100°. The resulting solution was treated in the same way as was the reaction mixture obtained in the preparation of 2-picoline-ω-t. Upon distillation there was obtained 0.44 g (65%) of 2-methylquinoline-ω-t having an activity of about 3.79 $\times$ 10^5 cpm/mmol. The product was shown to consist entirely of this compound by gas phase chromatography. The picrate melted at 194.8–196.4° (lit.[23] mp 195°).

3-Picoline-ω-t.—A suspension of 1.0 g of 3-pyridylacetic acid in 1 cc of tritium water was sealed in a tube and heated for 7 hr at 220°. At the end of this period, the tube was cooled and opened and 2.0 g of magnesium sulfate was added. The 3-picoline-ω-t was isolated according to the procedure given for the isolation of 2-picoline-ω-t. The yield of 3-picoline-ω-t with an activity of 1.83 $\times$ 10^6 cpm/mmol was 0.59 g (87%). Gas phase chromatography indicated that the product was at least 98.5% pure. The picrate had mp 150.4–150.8° (lit.[21] mp 149.5°).

3-Methylquinoline-ω-t.—A solution of 0.7 g of 3-quinolylacetic acid hydrochloride in 0.7 cc of tritium water was neutralized with 0.15 g of solid potassium carbonate and sealed in a tube. The tube was heated for 7 hr at 215–220°. To the resulting suspension were added 2.0 g magnesium sulfate and 5 cc of ether. The ether solution was decanted and the residual magnesium sulfate was then washed with ether until portions of the washings no longer gave precipitates with picric acid. The combined ether solutions were evaporated to 10 cc. and chromatographed on a 1 $\times$ 12 cm column of activity grade I Woelm alumina, using ether as the eluent. Evaporation of the ether from the eluate gave 0.17 g (38%) of 3-methylquinoline-ω-t. Its picrate melted at 190.4–191.6° (lit.[24] mp 187.5°). To the 3-methylquinoline-ω-t was then added 0.15 g of pure inactive 3-methylquinoline and the mixture was further purified by evaporative distillation. The approximate activity of the product was 1.07 $\times$ 10^8 cpm/mmol. The presence of only one component was demonstrated by gas phase chromatography.

Tritiation of Quinoline.—A solution of 0.52 g of quinoline and *ca.* 0.3 g of Dry Ice in 0.5 cc of tritium water (activity 4.4 $\times$ 10^5 cpm/mmol) was sealed in a tube and heated for 7 hr at 215–220°. The tube was opened and the contents were extracted five times with 2-cc portions of ether. The combined ether solutions were dried over sodium oxide and evaporated. The residue was distilled under vacuum. The activity of the product was 4.34 $\times$ 10^3 cpm/mmol.

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In another experiment a solution of 0.30 g of quinoline in 0.5 cc of 6 N tritiated hydrochloric acid solution (activity 5.28 $\times$ 10^6 cpm/mmol) was sealed in a tube and heated for 7 hr at 100°. The tube was opened and the contents were made basic with solid potassium carbonate and then extracted five times with 2-cc portions of ether. The combined ether solutions were dried over sodium oxide and evaporated, and the residue was distilled under vacuum. The quinoline treated in this manner exhibited no activity.

Kinetic Procedure.—The rates of tritium exchange were determined in 0.1 N and 0.05 N sodium methoxide solutions. The ionic strength was maintained at 0.1 by the addition of sodium chloride. The solutions were prepared immediately before using by dissolving sodium in degassed absolute methanol (Mallinckrodt, reagent grade) and were titrated with standard 0.0999 N hydrochloric acid, using phenolphthalein as the indicator.

Aliquots (2.5 cc) of a solution of 10–20 mg of the tritiated compound in 25 cc of sodium methoxide solution were sealed in tubes under nitrogen and heated in a constant-temperature bath for varying timed intervals. After removal from the constant-temperature bath, a tube was cooled and opened and a 2.00-cc aliquot of the contents was added to 1.00 cc of 0.5 N sulfuric acid in 95% methanol. The resulting mixture was distilled almost to dryness under vacuum at 25°. A 2.00-cc aliquot of the distillate was then added to 15 cc of the scintillator solution {0.4 g of diphenyloxazole and 5 mg of 1,4-bis[2-(5-phenyloxazolyl)]benzene in 1 l. of reagent grade toluene} and the activity was determined in a Tracerlab CE-1B liquid scintillation counter.

In the runs using solutions containing sodium chloride the distillate contained traces of hydrochloric acid. It was therefore made basic with a small quantity of sodium oxide and redistilled.

Infinity values were calculated from the count rate obtained with 1.00 cc of the original solution in a mixture of 1.00 cc of absolute methanol and 15 cc of the scintillator solution. The quenching effect of the tritiated compound was ascertained by noting whether the count rate for a mixture of the original amine solution and 1.00 cc of a standard methanol-t solution was equal to the sum of the count rates of the two solutions determined individually. Significant quenching was found only in the runs with 3-picoline-ω-t and with 2-methylquinoline-ω-t at 105°. In these runs larger quantities of the tritiated compound were used than in the others. Infinity values were corrected for any quenching effect.

The counting results were treated by means of a first-order rate expression. When log $(a_\infty - a_t)$ was plotted against t, the points defined a straight line. The rate constant was determined from the slope of this line in the usual way.

Registry No.—2-Picoline-ω-t, 19656-78-1; 3-picoline-ω-t, 19656-79-2; 4-picoline-ω-t, 19656-80-5; 2-methylquinoline-ω-t, 19656-81-6; 3-methylquinoline-ω-t, 19656-82-7; 3-quinolylacetic acid hydrochloride, 19656-83-8.