[Contribution from the Department of Chemistry, Iowa State College]

Electron Sharing Ability of Organic Radicals. X. Alpha-Substituted Tetrahydroquinolines

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A few measurements are recorded in the literature on the basicity of quinoline[1-5] and quinaldine.[1,3,6] With the exception of the constants found by Goldschmidt for these two heterocyclics, the results are in good agreement. However, the basic strength of the α-substituted tetrahydroquinolines has not been investigated. This manuscript reports the comparison of the ionization constants in absolute methanol of some members of the tetrahydroquinoline series with the constants of the α-substituted pyrrolidine series previously measured in this Laboratory.[7,8]

A most convenient and general method for the preparation of a series of α-substituted quinolines involves the reaction of an organometallic compound, such as RMgX[9] or RM,[10] with quinoline. The action of sodamide on quinaldine[11] was employed in the preparation of α-n-butylquinoline, this reaction being followed by treatment with n-propyl bromide.

Reduction to the tetrahydroquinolines was accomplished by means of metallic sodium in boiling ethyl alcohol,[12,13] since this method besides giving excellent yields is very easily carried out.

Synthesis of Compounds

Tetrahydroquinoline.—Eastman Kodak Co. synthetic practical quinoline, purified by fractionation, was reduced with a seven times excess of metallic sodium in boiling absolute ethyl alcohol. The resulting solution was diluted with water, made acidic with hydrochloric acid and the alcohol removed by heating under a water pump vacuum. The base was freed with solid sodium hydroxide and extracted with ether. Tetrahydroquinoline was recovered in a yield of 85%, b. p. 126° (18 mm.). The hydrochloride melted at 180–181°.

α-**Methyltetrahydroquinoline.**—Redistilled Eastman quinaldine was reduced exactly as was quinoline. A 70% yield of α-methyltetrahydroquinoline, b. p. 125° (17 mm.), was obtained. The hydrochloride melted at 195–196°.

α-**Ethyltetrahydroquinoline.**—α-Ethylquinoline was prepared in 20% yield by heating 0.25 mole of ethylmagnesium bromide for three hours in a sealed bomb at 155° with 0.22 mole of quinoline.[9] The recovered product boiled at 110–112° at 6 mm. The picrate melted at 145–146°.

Reduction with sodium and alcohol gave a 62% yield of α-ethyltetrahydroquinoline, b. p. 110–113° (5 mm.).

Anal. Calcd. for $C_{11}H_{15}N$: N, 8.70; C, 81.90; H, 9.32. Found: N, 8.79, 8.90; C, 81.6, 82.0; H, 9.47, 9.47.

The picrate, prepared in absolute ether, melted at 119–120°. Reher[14] states that the salts of this base are amorphous but the picrate prepared here was not and gave melting point depressions when mixed with the picrate of α-ethylquinoline and with picric acid.

α - n - **Butyltetrahydroquinoline.**—α - n - Butylquinoline was prepared by the action of 10 g. of sodamide on 0.105 mole of quinaldine[11] followed by treatment with 0.105 mole of n-propyl bromide. The base was isolated in a yield of 42%, b. p. 145–146° (11 mm.). The picrate melted at 163–164°. Reduction with sodium and alcohol gave α-n-butyltetrahydroquinoline in 55% yield, b. p. 138° (6 mm.).

Anal. Calcd. for $C_{13}H_{19}N$: N, 7.41; C, 82.54; H, 10.05. Found: N, 7.32, 7.39; C, 82.6, 82.8; H, 9.97, 9.87.

The picrate would not precipitate. The p-bromobenzenesulfonamide, recrystallized from petroleum ether, melted at 160–160.5°.

α-**Phenyltetrahydroquinoline.**—Phenyllithium was prepared in ether according to procedure "C" of Gilman.[15] After filtering off the excess lithium by means of a glass wool plug, an equivalent amount (0.07 mole) of quinoline was added. Hydrolysis with aqueous ammonium chloride, extraction with ether and distillation yielded the 1,2-dihydro compound,[10] which was dehydrogenated to α-phenylquinoline by distillation from zinc dust. The yield was 85%, the base melting at 82.5° after recrystallization from alcohol. The picrate melted at 188.5–189° and the p-bromobenzenesulfonamide at 190–191°.

Sodium and alcohol reduction[16] gave α-phenyltetrahydroquinoline in 73% yield, b. p. 196° (8 mm.). The picrate, prepared by evaporating to dryness an ethereal solution of equivalent amounts of the base and picric acid and recrystallizing from alcohol, melted at 129°. The p-bromobenzenesulfonamide melted at 201–202°.

(1) Bredig, *Z. physik. Chem.*, **13**, 191 (1894).

(2) Hahn and Klockmann, *ibid.*, **A146**, 373 (1930).

(3) Goldschmidt and Mathiesen, *ibid.*, **119**, 439 (1926).

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

(5) Walker and Aston, *J. Chem. Soc.*, **67**, 576 (1895).

(6) Felsing and Biggs, This Journal, **55**, 3624 (1933).

(7) Goodhue and Hixon, *ibid.*, **56**, 1329 (1934).

(8) Kirchner, "Insecticidal Action of Some Substituted Pyrrolidines," Ph.D. Thesis, Iowa State College, 1939.

(9) Bergstrom and McAllister, This Journal, **52**, 2845 (1930).

(10) Ziegler and Zeiser, *Ann.*, **485**, 174 (1931).

(11) Tchitchibabine, *Bull. soc. chim.*, [5] **3**, 1607 (1936); *Rec. trav. chim.*, [6] **57**, 582 (1938).

(12) Kaku, *J. Pharm. Soc. Japan*, **48**, 693 (1928); *C. A.*, **23**, 392 (1929).

(13) Koenigs, *Ber.*, **14**, 100 (1881).

(14) Reher, *Ber.*, **19**, 2996 (1886).

(15) Gilman, Zoellner and Selby, This Journal, **55**, 1252 (1933).

(16) Since the completion of this manuscript we have found that platinum on zirconium oxide catalyst, prepared by The American Platinum Works, will reduce α-phenylquinoline to α-phenyltetrahydroquinoline, while the platinum oxide of Adams and Shriner will reduce α-phenylquinoline to α-cyclohexyldecahydroquinoline.

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α-p-Tolyltetrahydroquinoline.—In exactly the same manner as with α-phenylquinoline, α-p-tolylquinoline was prepared from p-tolyllithium and 0.13 mole of quinoline. Distillation from zinc dust and fractionation at 190° and 3 mm. pressure gave the base in the theoretical yield. After recrystallization from alcohol, crystals melting at 83° were obtained. The picrate melted at 198.7°.

α-p-Tolyltetrahydroquinoline was prepared for the first time by reduction of the corresponding quinoline in 73% yield. It was an almost colorless, viscous liquid, b. p. 210° (14 mm.).

Anal. Calcd. for $C_{16}H_{17}N$: N, 6.28; C, 86.10; H, 7.62. Found: N, 6.41, 6.39; C, 86.20, 86.25; H, 7.81, 7.58.

The picrate after several recrystallizations from alcohol melted at 134–134.5°.

α-o-Tolyltetrahydroquinoline.—α-o-Tolyllithium, prepared from 0.15 mole of o-iodotoluene and an excess of lithium, was treated with 19 g. of quinoline and gave α-o-tolylquinoline in 90% yield. Nitrobenzene was used for the dehydrogenation.[10] This base was a heavy oil that solidified on cooling, b. p. 197° (4 mm.). Purification was effected through the picrate. Regeneration with dilute sodium hydroxide yielded crystals that melted at 76–76.2° after being deposited from an ethereal solution.

Anal. Calcd. for $C_{16}H_{13}N$: N, 6.39. Found: N, 6.32, 6.30.

The picrate melted at 176°.

The corresponding tetrahydro compound solidified on cooling, b. p. 200–202° (6 mm.). Recrystallization from 70% alcohol gave α-o-tolyltetrahydroquinoline, in 85% yield, melting at 69.5°. A mixed melting point determination with α-o-tolylquinoline showed a depression to 45–48°.

Anal. Calcd. for $C_{16}H_{17}N$: N, 6.28; C, 86.10; H, 7.62. Found: N, 6.36, 6.27; C, 85.90, 85.90; H, 7.64, 7.75.

The picrate could not be obtained. The p-bromobenzenesulfonamide melted at 193–193.5°.

α-2-Mesityltetrahydroquinoline.—2-Mesityllithium, prepared from 0.166 mole of 2-bromomesitylene and lithium, was treated with 21 g. of quinoline in the way described. After dehydrogenation by means of nitrobenzene, α-2-mesitylquinoline was isolated in a yield of 25%, b. p. 200° (4 mm.). Considerable quantities of bromomesitylene were recovered. The base was recrystallized from petroleum ether and then melted at 69–69.5°.

Anal. Calcd. for $C_{18}H_{17}N$: N, 5.66. Found: N, 5.45, 5.65, 5.64.

The picrate prepared in absolute ether melted at 216.5°.

Reduction gave α-2-mesityltetrahydroquinoline in 83% yield as a heavy, very viscous liquid, b. p. 218° (6 mm.).

Anal. Calcd. for $C_{18}H_{21}N$: N, 5.57; C, 86.06; H, 8.37. Found: N, 8.50, 8.50; C, 86.10, 86.10; H, 8.20, 8.34.

The picrate melted at 164.5–165°.

Measurements of Ionization Constants.—The method used here is the same as that previously used by Goodhue[7] in this Laboratory. The hydrogen-ion concentrations of half-neutralized solutions of the bases in absolute methyl alcohol were determined by means of the normal hydrogen electrode in conjunction with a vacuum tube potentiometer.

The calomel half-cells employed were of the sealed Schollenberger type[17] and were prepared in duplicate using 0.1 f sodium chloride in absolute methanol. They were standardized by means of silver–silver chloride electrodes prepared in triplicate both by the method of Harned (type 2)[18] and by that of Rule and La Mer.[19] This latter method, involving the decomposition of a paste mixture of silver oxide and silver chlorate, was found to be more convenient although reproducible results were obtained by both procedures.

Platinum black was deposited on small platinum flags and used as the hydrogen electrodes. These were prepared and used in duplicate.

The purified bases were sealed in glass ampoules for weighing except the α-o-tolyltetrahydroquinoline which, being a solid, was weighed in a stoppered weighing bottle. All solutions were made by weight and the concentrations are expressed in molalities.

TABLE I

E. M. F. OF CELLS FOR A SERIES OF ALPHA-SUBSTITUTED TETRAHYDROQUINOLINES IN METHANOL

Pt/H_2 (1 atm.) Amine//NaCl (0.1 f), Hg_2Cl_2/Hg salt

α-Substituted radical	Total concn., molal	E. m. f. corr. to 760 mm.	$-\log a_H$	$pK_{B_{CH_3OH}}$
2-Mesityl	0.2710	0.3366	3.78	12.93
	.0385	.3389	3.82	12.89
o-Tolyl	.0378	.3806	4.53	12.18
	.0303	.3802	4.53	12.18
Phenyl	.0407	.3838[a]	4.52	12.19
	.0275	.3859[b]	4.55	12.16
p-Tolyl	.0283	.3981[a]	4.76	11.95
	.0390	.3987[b]	4.77	11.94
H	.0507	.4559	5.81	10.90
	.0370	.4562	5.81	10.90
Methyl	.0240	.4544	5.79	10.92
	.0538	.4607[a]	5.82	10.89
Ethyl	.0410	.4569[a]	5.86	10.85
	.0475	.4565	5.82	10.89
n-Butyl	.0514	.4457	5.63	11.08
	.0450	.4460	5.63	11.08

[a,b] The e. m. f. values were measured using a calomel half-cell of 0.1134 v. except those marked "a" in which the value was 0.1174 and those marked "b" in which the value was 0.1171 when referred to the normal hydrogen electrode.

The results of the e. m. f. determinations are shown in Table I. The method of calculation is the same as for primary amines in water solutions. The hydrogen-ion activities were calculated from the equation

$$-\log a_H = (E - E_{calomel})/0.059$$

As noted in Table I, the potentials of the calomel cells were 0.1134, 0.1171, and 0.1174 volt.

Since in half-neutralized solutions of amines

(17) Schollenberger, *Ind. Eng. Chem.*, **17**, 649 (1925).
(18) Harned, THIS JOURNAL, **51**, 416 (1929).
(19) Rule and La Mer, *ibid.*, **58**, 2339 (1936).

the degree of hydrolysis becomes equal to the hydrogen-ion activity, then

$$K_{B_{CH_3OH}} = K_{CH_3OH/H} \text{ ion activity}$$

and

$$K_{B_{CH_3OH}} = -\log K_{CH_3OH} - (-\log a_H) = 16.71 - (-\log a_H)$$

The dissociation constant of methyl alcohol was taken as 1.95×10^{-17}.[20]

The ionization constants of the α-substituted quinolines could not be measured by this method because of reduction of the unsaturated bases. Goodhue encountered the same difficulty in attempting to use the hydrogen electrode in measuring the ionization constants of α-substituted pyrrolines in alcohol.[7] Reduction does not occur so readily in aqueous solutions. Felsing and Biggs[6] used the hydrogen electrode to measure the constants for some methylquinolines in water and Starr[21] used this method for some pyrrolines, also in aqueous solution.

Discussion

In Fig. 1 the ionization constants of the α-substituted tetrahydroquinolines have been plotted as functions of the electron sharing ability of the radicals. For purposes of comparison the curves are included for the primary amines measured by Goodhue[7] and for the α-substituted pyrrolidines measured by Goodhue[7] and by Kirchner.[8] The radicals have been placed along the x axis in the way that they were initially arranged by Hixon and Johns[22] from the ionization constants in water of a series of primary amines.

An inspection of these curves shows that the substitution of various groups in the tetrahydroquinoline nucleus affects the ionization constants in exactly the same manner as did substituting the same groups in the primary amines and in the pyrrolidine nucleus. This is to be expected if the substituent radicals affect the polar properties of these amines by means of their valence electrons.

Curve (1) for the pyrrolidines and curve (111) for the tetrahydroquinolines are of the same shape

(20) Buckley and Hartley, *Phil. Mag.*, [7] **8**, 320 (1929).

(21) Starr, Bulbrook and Hixon, THIS JOURNAL, **54**, 3971 (1932).

(22) Hixon and Johns, *ibid.*, **49**, 1786 (1927).

and their difference in slope from the primary amine curve represents the effect of having the substituent radical one carbon removed from the polar group.
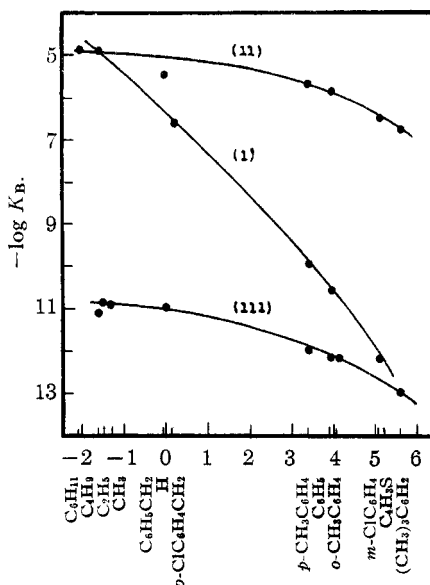
Electron sharing ability of organic radicals.

Fig. 1.—The ionization constants of various types of amines in absolute methanol plotted as functions of the electron sharing ability of the organic radicals. Curve (1) is for primary amines, (11) for α-substituted pyrrolidines, and (111) for α-substituted tetrahydroquinolines.

Summary

1. The ionization constants of a series of α-substituted tetrahydroquinolines have been determined in absolute methanol. The substituent radicals were: H, methyl, ethyl, *n*-butyl, phenyl, *o*-tolyl, *p*-tolyl and 2-mesityl.

2. These constants plotted against electron sharing ability functions give a curve similar to that for a series of α-substituted pyrrolidines previously reported.

3. α-Substituted quinolines prepared for the first time were the *o*-tolyl and the 2-mesityl. New α-substituted tetrahydroquinolines include *n*-butyl, *p*-tolyl, *o*-tolyl, and 2-mesityl.