[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

The Reduction of Quinoline and Certain Substituted Quinolines in Liquid Ammonia

BY CECIL M. KNOWLES AND GEORGE W. WATT

Numerous studies on the reduction of organic substances by liquid ammonia solutions of alkali or alkaline earth metals, or by hydrogen generated by the addition of alkali metals to liquid ammonia solutions of ammonium salts have been described.[1-4] Since efforts to evaluate the relative effectiveness of the two reducing agents have been made in only three instances,[2-4] it seemed worth while to make additional comparative studies.

Experimental

Materials.—Eastman Kodak Co. synthetic quinoline, b. p. 238° (cor.), was used. 5-Aminoquinoline (m. p. 64–65°, cor.) and 8-aminoquinoline (m. p. 109–110°, cor.) were prepared as described by Dufton[5] and by Claus and Setzer,[6] respectively. 5-Nitroquinoline (m. p. 72–73°, cor.) and 8-nitroquinoline (m. p. 88–89°, cor.) were prepared as described by Fieser and Hershberg.[7] Other materials were prepared as described by Knowles and Watt.[4]

Reduction by Hydrogen.—Using equipment and methods described previously,[4] a known weight of the substance to be reduced and an excess of ammonium bromide were dissolved in approximately 200 ml. of anhydrous liquid ammonia maintained at −33.5°. To the resulting solution, sodium was added slowly in small pieces. *In no case was any notable color change observed.* Of the hydrogen generated in the primary reaction between sodium and ammonium ion, that part which was not subsequently consumed in secondary reactions (*i. e.*, between hydrogen and the organic material) was collected as molecular hydrogen. Upon completion of a reaction, the solvent and any volatile reactants were evaporated and residual ammonia was removed by evacuation. Data relative to these reactions are shown in Table I.

Reduction by Sodium.—Addition of small pieces of sodium to a known weight of the organic compound dissolved in approximately 200 ml. of anhydrous liquid ammonia at −33.5° until the first appearance of the characteristic blue color of ammonia solutions of sodium (Method I) or addition of an excess of sodium followed by elimination of unreacted sodium by the addition of ammonium bromide and collection of the hydrogen thereby liberated (Method II) was carried out in the manner described in detail in an earlier publication.[4] In either case, *intensely green, orange, or red colored liquid ammonia solutions preceded the appearance of the blue color characteristic of solutions containing dissolved sodium.* Data on reactions involving both procedures are listed in Table I.

Quinoline.—The organic product of reduction by hydrogen was extracted in benzene and treated with dilute sodium hydroxide solution and an excess of benzoyl chloride. After stirring for several hours, the benzene was evaporated and the resulting viscous yellow oil was crystallized several times from ethanol. The yellow crystals of monobenzoyldihydroquinoline thus obtained melted above 100° (dec.).

Anal. Calcd. for $C_{16}H_{13}NO$: N, 5.96. Found: N, 6.13.

TABLE I

REDUCTION OF QUINOLINES IN LIQUID AMMONIA

Compound reduced Name	g.-mole	Na (g.-atom)	H (g.-atom)	Reaction ratio[a]
	Reduction by Hydrogen			
Quinoline	0.0350	0.0878	0.0293	1.67
5-Aminoquinoline	.0104	.0883	.0727	1.51
5-Nitroquinoline	.0205	.2190	.0812	6.72[b]
8-Aminoquinoline	.0138	.1296	.1080	1.57
8-Nitroquinoline	.0204	.1413	.0988	2.08[c]
	Reduction by Sodium[d]			
Quinoline	0.0316	0.1146	0.0358	2.49[e]
5-Aminoquinoline	.0144	.0360	.0058	2.10[f]
5-Nitroquinoline	.0193	.1880	.0438	7.49
8-Aminoquinoline	.0216	.0492	.0044	2.07
8-Nitroquinoline	.0190	.2355	.0895	7.70

[a] Expressed as g.-atom of H or Na/mole of compound reduced. [b] Due to the slight solubility of 5-nitroquinoline, reduction was extremely slow. The indicated extent of reduction was realized by the addition of 10 ml. of absolute ethyl ether which resulted in increased solubility and rate of reduction. [c] Using 5 ml. of absolute ethyl ether as a diluent, ratios ranging from 5.10 to 6.61 were obtained. [d] Since hydrogen which is evolved when excess Na is destroyed by addition of NH_4Br may also enter into a reduction reaction, the extent of reduction realized may not necessarily be attributed to sodium alone. However, close agreement between ratios obtained by Methods I and II indicates that reduction by Na is not complicated appreciably by the subsequent generation of small quantities of hydrogen. [e] Reaction was allowed to proceed for two hours before addition of NH_4Br. Using Method I, a ratio of 2.15 was obtained. [f] By Method I, the reaction ratio = 2.17.

Following reduction by sodium, the organic product was extracted in benzene, treated with an excess of acetic anhydride and refluxed for one hour. Evaporation of the benzene and hydrolysis of excess acetic anhydride by water, followed by neutralization with aqueous ammonia yielded an insoluble dark gum. Several crystallizations from low-boiling petroleum ether gave yellow crystals of the dimer of diacetyldihydroquinoline, m. p. >80° dec.

Anal. Calcd. for $(C_{13}H_{13}NO_2)_2$: mol. wt., 430; N, 6.51. Found: mol. wt., 485; N, 6.57.

From the product from another reaction involving reduction by sodium, the pale yellow dimer of the monobenzoyl

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(1) Fernelius and Watt, *Chem. Rev.*, **20**, 216–248 (1937).
(2) Fuller, Lieber and Smith, THIS JOURNAL, **59**, 1150 (1937).
(3) Cappel and Fernelius, *J. Org. Chem.*, **5**, 40 (1940).
(4) Knowles and Watt, *ibid.*, **7**, 56 (1942).
(5) Dufton, *J. Chem. Soc.*, **61**, 785 (1892).
(6) Claus and Setzer, *J. prakt. Chem.*, [2] **53**, 399 (1896).
(7) Fieser and Hershberg, THIS JOURNAL, **62**, 1643 (1940).

derivative, m. p. >100°, dec., was prepared in the manner described above.

Anal. Calcd. for $(C_{16}H_{13}NO)_2$: mol. wt., 470; N, 5.96. Found: mol. wt., 512; N, 5.84.

5-Aminoquinoline.—The product from the unusually slow reduction (by hydrogen) of the very soluble 5-aminoquinoline was extracted several times with hot water. There remained undissolved a straw-colored residue (1.10 g.) of the pure trimer of dihydro-5-aminoquinoline, m. p. >157° dec. The yield calculated from the reaction ratio amounts to 1.14 g.

Anal. Calcd. for $(C_9H_{10}N_2)_3$: mol. wt., 438; N, 19.18. Found: mol. wt., 427; N, 19.17.

During the course of reduction by sodium, the successive formation of a red solution, a white precipitate, and a colorless solution was observed. Extraction with ether and benzene followed by benzoylation resulted in 2.0 g. of the pale yellow tribenzoyl derivative of dihydro-5-aminoquinoline which, after recrystallization from ethanol, melted above 95° (dec.).

Anal. Calcd. for $C_{30}H_{22}N_2O_3$: N, 6.11. Found: N, 6.20.

The residue from the ether–benzene extractions was extracted with water, leaving 1.20 g. of pure dihydro-5-aminoquinoline, m. p. >157° dec., identical with that obtained from the reduction of 5-aminoquinoline by hydrogen. The weights of the products isolated correspond to 88% of the starting material.

5-Nitroquinoline.—The product from reduction by hydrogen, using ether as a diluent, was extracted with hot water and hot ethanol. There remained 2.40 g. (95% yield) of pure dihydro-5-aminoquinoline, m. p. >157° dec., identical with that obtained by reducing 5-aminoquinoline with either hydrogen or sodium.

Reduction by sodium yielded colored, high-melting, intractable solids which were soluble only in pyridine. Consequently, the *primary* reduction product was ethylated by addition of a large excess (20.0 g.) of ethyl bromide following completion of addition of sodium. The dark brown gummy product was dissolved in dilute hydrochloric acid, and reprecipitated by neutralization with aqueous ammonia to provide 4.0 g. of the brown solid tetraethyl derivative of dihydro-5-aminoquinoline which, after recrystallization from aqueous ethanol, melted above 160° (dec.).

Anal. Calcd. for $C_{17}H_{26}N_2$: N, 10.85. Found: N, 10.67.

8-Aminoquinoline.—By extraction with hot water, inorganic salts and unchanged 8-aminoquinoline were removed from the product of reduction by hydrogen. There remained 1.52 g. (96.5% yield) of the dimer of dihydro-8-aminoquinoline which, after recrystallization from ethanol, melted above 125° (dec.).

Anal. Calcd. for $(C_9H_{10}N_2)_2$: mol. wt., 292; N, 19.18. Found: mol. wt., 278; N, 19.20.

The product of reduction by sodium was extracted in benzene and benzoylated to provide a viscous yellow oil which, after three crystallizations from alcohol, afforded the tribenzoyl derivative of dihydro-8-aminoquinoline, m. p. >148° dec. Molecular weight determinations were inconsistent but indicated that the product consisted of a mixture of monomer and dimer.

Anal. Calcd. for $C_{30}H_{22}N_2O_3$: N, 6.11. Found: N, 5.93.

8-Nitroquinoline.—Reduction by hydrogen in the absence of a diluent resulted in incomplete reduction and heterogeneous intractable products. Products obtained using ether as a diluent (see Table I, footnote 3) were extracted with water to remove inorganic salts, leaving brown gummy residues from which unchanged 8-nitroquinoline was extracted by petroleum ether. By crystallization of the remaining residue from benzene, ethanol and methanol, dihydro-8-aminoquinoline, m. p. >125° dec., was isolated. In each case, the yields calculated from the reaction ratios and those actually obtained were substantially the same.

Anal. Calcd. for $C_9H_{10}N_2$: N, 19.18. Found: N, 19.15.

Reduction by sodium produced successively, green, red and blue solutions. The products were similar in character to those obtained in the case of 5-nitroquinoline. Accordingly, ethylation of the primary reduction product (as described for 5-nitroquinoline) was resorted to and yielded the brown tetraethyl derivative of dihydro-8-aminoquinoline, m. p. >155° dec.

Anal. Calcd. for $C_{17}H_{26}N_2$: N, 10.85. Found: N, 11.03.

Discussion

Earlier investigations[2–4] have led to the conclusion that "reduction by sodium" and "reduction by hydrogen" are essentially different in that the latter does not involve direct interaction of sodium and the organic component of the liquid ammonia solution. The results of the present study are entirely in agreement with this conclusion. In reactions with 1,2,3-benzotriazoles[3] and certain benzoxazoles and benzothiazoles,[4] reduction by hydrogen was found to be more extensive than reduction by sodium while toward nitroguanidine and nitrosoguanidine[2] exactly the opposite relationship was observed. Toward the quinolines included in the present work, the two reducing agents show less difference in the *extent* of reduction than has been found in any case previously investigated. However, the *rate* of reduction by sodium is greater and essentially independent of the solubility of the quinoline compound, while the rate of the relatively slow reduction by hydrogen is roughly proportional to the solubility of the compound reduced. In the case of less soluble compounds, increased rate of reduction by hydrogen may be realized by the use of an inert diluent such as ether.

In connection with earlier work on the reduction of quinolines, it has been assumed[8] that 1,2-dihydroquinolines were formed. The present in-

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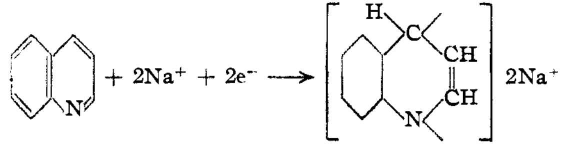
[8] Anschütz, "Chemie der Kohlenstoffverbindungen," Akademische Verlagsgesellschaft, Leipzig, 1931, Vol. 3, p. 245.

vestigation, however, suggests that 1,4-addition is more probable. It is assumed that reduction by sodium involves salt formation at the 1,4-positions, accompanied by a shift of the double bond to the 2,3-position.



The intensely red colored ammonia solutions indicate the formation of sodium salts,[9] the stability of which is shown by their reactions with ethyl bromide and the fact that they are not readily ammonolyzed.[10] Addition of ammonium bromide would, of course, produce 1,4-dihydroquinoline, sodium bromide and ammonia. The above view is also supported by the fact that, even in the presence of a considerable excess of sodium, reduction does not proceed beyond the extent indicated above. If reduction should occur initially at the 1,2-position, the double bond in the heterocyclic ring would remain conjugated with the unsaturation in the aromatic ring and reduction should be expected to continue.[1] It is generally accepted[11] that an isolated double bond such as that proposed above would not be susceptible to reduction under the conditions employed in the present work. By analogy, it may be assumed that reduction by hydrogen must involve a similar mechanism since the extent of reduction is the same in both cases.

Summary

1. The reduction of quinoline to dihydroquinoline, 5-amino- and 5-nitroquinolines to dihydro-5-aminoquinoline, and 8-amino- and 8-nitroquinolines to dihydro-8-aminoquinoline by sodium in liquid ammonia at $-33.5°$ or by hydrogen generated by addition of sodium to liquid ammonia solutions of ammonium bromide at the same temperature, has been described.

2. Evidence has been presented in support of the view that reduction of the heterocyclic ring occurs at the 1,4-positions.

3. Although the extent of reduction is substantially the same in both cases, reduction by sodium is generally more rapid and more complete than reduction by hydrogen.

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(9) Hückel and Bretschneider, *Ann.*, **540**, 157 (1939).

(10) *Cf.* Wooster and Smith, THIS JOURNAL, **53**, 179 (1931).

(11) Campbell and Campbell, *Chem. Rev.*, **31**, 82 (1942).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF HOWARD UNIVERSITY]

2,4,6-Trimethylbenzylphenylglyoxal

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By substituting one of the alpha hydrogens in phenylbenzylglyoxal[2] by the phenyl group, the resulting benzhydryl phenyl diketone[3] shows a chemical behavior which is quite different from the parent substance.

We have already reported the chemical behavior of mesitylbenzylglyoxal.[4] The purpose of this paper is to show the preparation and properties of the isomeric alpha diketone 2,4,6-trimethylbenzylphenylglyoxal (II).

2,4,6-Trimethylbenzalacetophenone was oxidized to α-benzoyl-β-mesityl ethylene oxide (I), which in turn was isomerized to 2,4,6-trimethylbenzylglyoxal (II). This diketone is a low-melting yellow solid, producing no color with alcoholic ferric chloride, and giving negative results when titrated by the Kurt Meyer method. There is no doubt as to the structure of this diketone, for it is cleaved smoothly by alkaline hydrogen peroxide to mesitylacetic and benzoic acids. Thus the effect of the mesityl nucleus in this position is to make this diketone completely ketonic, thus causing it to resemble benzhydrylphenyldiketone much more closely than it does its isomeric alpha diketone. The mesityl nucleus does not affect the carbonyl groups, for 2,4,6-trimethylbenzyl phenyl diketone reacts with *o*-phenylenediamine, yielding a quinoxaline (III).

2,4,6-Trimethylbenzyl phenyl diketone further resembles benzhydryl phenyl diketone and differs from mesitylbenzylglyoxal in that it resists attempts to substitute alpha hydrogens by bromine.

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(1) In partial fulfillment of the requirements for the Master's Degree.

(2) Kohler and Barnes, THIS JOURNAL, **56**, 211 (1934).

(3) Kohler and Weiner, *ibid.*, **56**, 434 (1934).

(4) R. P. Barnes, *ibid.*, **57**, 937 (1935).