2. By chromatographic adsorption these products have been initially resolved into four characteristic fractions according to their aromatic content and the presence or absence of oxygen, nitrogen and sulfur.

3. By a study of the ultraviolet spectra and ultimate analyses, information has been obtained concerning the structure of the components of these various fractions.

PITTSBURGH, PA. RECEIVED FEBRUARY 10, 1947

---

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

# The Reduction of Certain Organic Compounds in Liquid Ammonia[1]

BY GEORGE W. WATT, CECIL M. KNOWLES[2] AND L. O. MORGAN[3]

Earlier publications[4-9] show that addition of sodium to liquid ammonia solutions containing an organic compound together with a substance containing active hydrogen (*e. g.*, ammonium salts, methanol or water) sometimes leads to reduction products that differ from those obtained upon addition of sodium to liquid ammonia solutions containing only the organic compound. Some additional examples are presented in the present paper.

## Experimental

**Materials.**—In addition to reactants prepared and/or purified as previously described,[8,9] the following purified reactants were employed: nitrobenzene, b. p., 210°; 1-nitronaphthalene, m. p., 61°; 1-naphthylamine, m. p., 50°; 2-nitrofluorene, m. p., 156°.

**Methods.**—The reduction reactions employing only the organic compound and sodium were conducted by Method II as described previously.[9] Reduction by means of ammonium bromide and sodium was effected as described by Knowles and Watt,[9] and a similar procedure was employed when methanol (10 g./200 ml. of liquid ammonia) and sodium were used. In conformity with observations recorded previously,[9] the interaction of the organic compounds and sodium alone was accompanied by series of intense colorations. For example, in the case of 1-nitronaphthalene, green, blue, purple and maroon colored liquid ammonia solutions were observed before the appearance of the characteristic blue color that denoted the presence of excess sodium. *No such color changes were observed when either ammonium bromide or methanol was employed.*

The essential numerical data are given in Table I.

**Nitrobenzene.**—From an ether extract of the product of reduction with ammonium bromide and sodium, aniline was isolated in 85% yield as the hydrochloride, m. p. 198°, and as acetanilide, m. p. 114°. Similarly, using methanol and sodium, aniline was isolated as the hydrochloride, m. p. 198°, and in 92% yield as 2,4,6-tribromoaniline, m. p. 119°.

*Anal.* Calcd. for $C_6H_4NBr_3$: N, 4.25. Found: N, 4.53.

The identity of the derivatives was established by determination of the melting points of mixtures with authentic samples.

TABLE I

DATA ON REDUCTION REACTIONS IN LIQUID AMMONIA

| Compound reduced Name | Compound reduced g.-mole | Gram-atoms Na/mole compound reduced Added | Gram-atoms Na/mole compound reduced Unreacted[a] excess | Gram-atoms Na/mole compound reduced Consumed[b] |
|---|---|---|---|---|
| Compound reduced + sodium[c,d] | | | | |
| 1-Naphthylamine | 0.0145 | 6.97 | 4.93 | 2.04 |
| 1-Nitronaphthalene | .0319 | 8.95 | 1.05 | 7.90 |
| 2-Nitrofluorene | .0168 | 14.05 | 4.37 | 9.68 |
| Compound reduced + ammonium bromide + sodium | | | | |
| Nitrobenzene | .0340 | 7.06 | 1.17 | 5.89 |
| 1-Naphthylamine | .0250 | 4.47 | 3.38 | 1.09 |
| 1-Nitronaphthalene | .0094 | 13.23 | 12.14 | 1.09[e] |
| 2-Nitrofluorene | .0095 | 7.08 | 7.08 | 0 |
| Compound reduced + methanol + sodium | | | | |
| Nitrobenzene | .0413 | 6.63 | 0.75 | 5.88 |
| 1-Nitronaphthalene | .0114 | 10.39 | 1.91 | 8.48 |
| 2-Nitrofluorene | .0052 | 17.48 | 6.50 | 10.98 |

[a] Measured in terms of molecular hydrogen liberated and collected (1) upon addition of ammonium bromide following addition of excess sodium, or (2) during the reactions that ensued upon addition of sodium to the liquid ammonia solutions containing the "Compound reduced" and excess ammonium bromide or methanol. In the latter cases, this mode of presentation of data is not intended to imply the necessity of direct interaction of sodium and the compound reduced. [b] This is equivalent to the "Reaction ratio" tabulated in earlier publications.[9] [c] See ref. 9, Table I, footnote *d*. [d] Reactions conducted by Method II as described in ref. 9 [e] Because of the slight solubility of 1-nitrophthalene in liquid ammonia, reduction was very slow. Use of 20 ml. of toluene as a diluent led to a value of 4.30 gram-atoms of sodium/mole of 1-nitronaphthalene.

**1-Naphthylamine.**—Following reduction with sodium, the residue that remained after repeated extraction with cold water consisted of pure 5,8-dihydro-1-naphthylamine, m. p. 37–38°. The benzylidene derivative formed by reaction with benzaldehyde and recrystallized from petroleum ether melted at 69°.

*Anal.* Calcd. for $C_{17}H_{15}N$: N, 6.01. Found: N, 5.92.

The benzylidene derivative was hydrolyzed with dilute hydrochloric acid, the benzaldehyde removed by steam distillation and the residual oil crystallized from petroleum ether to afford the original base, m. p., 37–38°. The melting points of both the amine and its benzylidene derivative correspond to those reported by Rowe and Levin.[10]

Reduction with ammonium bromide and sodium was slow and incomplete. The reaction product appeared to

---

[1] This work was supported in part by grants from The University Research Institute, Project No. 25.

[2] Present address: General Aniline and Film Corporation, Grasselli, New Jersey.

[3] Present address: Radiation Laboratory, University of California, Berkeley, California.

[4] Wooster and Godfrey, THIS JOURNAL, **59**, 596 (1937).

[5] Fuller, Lieber, and Smith, *ibid.*, **59**, 1151 (1937).

[6] Wooster, U. S. Patent 2,182,242, December 5, 1939.

[7] Cappel and Fernelius, *J. Org. Chem.*, **5**, 40 (1940).

[8] Knowles and Watt, *ibid.*, **7**, 51 (1942); **8**, 540 (1943).

[9] Knowles and Watt, THIS JOURNAL, **65**, 410 (1943).

[10] Rowe and Levin, *J. Chem. Soc.*, **117**, 1574 (1920).

consist of a mixture of 5,8-dihydro-1-naphthylamine and unchanged 1-naphthylamine but the former could not be separated in a pure condition.

**1-Nitronaphthalene.**—Addition of dry gaseous hydrogen chloride to an ether extract of the product from reduction with sodium gave a 97% yield of the hydrochloride of a dihydro-1-naphthylamine. This compound decomposed over a wide temperature range that was markedly dependent upon rate of heating.

*Anal.* Calcd. for $C_{10}H_{12}ClN$: N, 7.72. Found: N, 7.85.

Evaporation of the solvent from an aliquot of the ether extract yielded an oil which had an evil odor and could not be crystallized from any common organic solvent. Attempts to prepare *crystalline* benzylidene or other derivatives and to diazotize and couple with dimethylaniline were unsuccessful.

From the reduction with ammonium bromide and sodium in the absence of a diluent, the ether extract of the crude product yielded 71% of unchanged 1-nitronaphthalene and the remainder was isolated as 1-naphthylamine hydrochloride.

*Anal.* Calcd. for $C_{10}H_{10}ClN$: N, 7.80. Found: N, 7.79.

From the hydrochloride, the benzoyl derivative, m. p. 161–162°,[11] was made by treatment with benzoyl chloride in 10% sodium hydroxide solution.

From the reaction that employed a toluene diluent (Table I, footnote *e*), 1-naphthylamine was isolated in 62% yield as the hydrochloride whereas the yield calculated from the reaction ratio is 72%.

The crude product from reduction with methanol and sodium was extracted with ether, the ether was evaporated, and the residue suspended in 10% sodium hydroxide solution and treated with benzoyl chloride. After recrystallization from 95% ethanol, the benzoyl derivative (74% yield) melted at 159.5°.

*Anal.* Calcd. for $C_{17}H_{15}NO$: N, 5.62; H, 6.02. Calcd. for $C_{17}H_{17}NO$: N, 5.58; H, 6.77. Found: N, 5.77; H, 6.30.

Calculations based on the ratio of 8.5 equivalents of reducing agent per mole of 1-nitronaphthalene (Table I) show that the probable composition of the reaction mixture was approximately 25% tetrahydro-1-naphthylamine and 75% dihydro-1-naphthylamine. Unchanged 1-nitronaphthalene was not present in the mixture.

**2-Nitrofluorene.**—Following reduction with sodium, the reaction product was extracted with ether and treated with dry hydrogen chloride to provide the white crystalline hydrochloride of a tetrahydro-2-aminofluorene which was recrystallized from water.

*Anal.* Calcd. for $C_{13}H_{16}ClN$: N, 6.33; HCl, 16.47. Found: N, 6.55; HCl, 16.70.

The base was liberated by treatment with dilute sodium hydroxide solution and recrystallized from water, m. p. 109°.

*Anal.* Calcd. for $C_{13}H_{15}N$: N, 7.57. Found: N, 7.70.

The same product was isolated in 89% yield by repeated leaching of the crude reaction product with cold water followed by recrystallization of the water-insoluble fraction from a mixture of ethanol and water.

2-Nitrofluorene is only slightly soluble in liquid ammonia and is not reduced by ammonium bromide and sodium. By substitution of anhydrous methanol for ammonium bromide, however, the solubility was enhanced noticeably although undissolved solid remained. After addition of sodium and evaporation of the solvent, the crude product was extracted with ether, the ether was evaporated, and the residue benzoylated. The benzoyl derivative was recrystallized from a mixture of ethanol and water and melted at 119°.

*Anal.* Calcd. for $C_{20}H_{19}NO$: N, 4.84; H, 6.57. Calcd. for $C_{20}H_{21}NO$: N, 4.82; H, 7.22. Found: N, 4.67; H, 6.97.

The ratio of 11 equivalents of reducing agent per mole of 2-nitrofluorene (Table I) indicates that the reduction product consisted of an equimolar mixture of tetrahydro-2-aminofluorene and hexahydro-2-aminofluorene and, within the limits of error of the analytical method, this conclusion is supported by the analytical data on the hydrogen content.

## Discussion

The reactions of 1-naphthylamine, 1-nitronaphthalene and 2-nitrofluorene in liquid ammonia with sodium alone resulted in higher reaction ratios than the reactions in the presence of ammonium bromide. Reduction of 1-nitronaphthalene was more extensive in the absence of ammonium bromide and reduction of 2-nitrofluorene was completely inhibited by the presence of ammonium bromide. In the latter case, it seems evident that the only reaction that occurred was the formation of sodium bromide and molecular hydrogen from the ammonium bromide and sodium The rate of this reaction was such that appreciable reaction between the 2-nitrofluorene and sodium was prevented. It is also clear that there was no reaction between the 2-nitrofluorene and the hydrogen liberated. It is possible that the decreased extent of reduction of 1-naphthylamine and 1-nitronaphthalene is also attributable to a similar competition between the ammonium salt and the organic compounds for sodium. On the other hand, previous investigations[7,8] have shown that certain other organic substances are more extensively reduced by the sodium–ammonium salt combination than by the metal alone.

Increased reaction ratios and products with more extensive nuclear hydrogenation resulted when 1-nitronaphthalene and 2-nitrofluorene were treated with sodium in the presence of methanol. These results are in agreement with earlier observations[4,6] regarding the relatively greater effectiveness of the sodium–methanol combination for nuclear reduction. Toward nitrobenzene, sodium–methanol and sodium–ammonium bromide are equally effective. In view of the results reported by Wooster,[6] it is surprising that reduction of nitrobenzene by the sodium–methanol combination yielded aniline and not a dihydroaniline which on the basis of Wooster's seemingly well-supported generalization would be anticipated. Under substantially the same experimental conditions as were employed in the present investigation, Wooster found that "whatever benzene ring or rings that are present will be reduced to the corresponding dihydrogenated ring." On the other hand, White and Knight[12] have reported aniline as the product of reduction of nitrobenzene with sodium.[13] Although enhanced solubility due to the presence of methanol may be a factor, neither these nor the results of Wooster can be explained satisfactorily on this basis alone since both studies

---

[11] Kuhn, *Ber.*, **18**, 1477 (1885).

[12] White and Knight, THIS JOURNAL, **45**, 1780 (1923).

[13] Unpublished results obtained by Watt and Morgan show that the reaction between nitrobenzene and sodium in liquid ammonia is extremely complex and that, under certain conditions, aniline is not formed.

involved some substances that are abundantly soluble in liquid ammonia alone.

The reduction of 1-naphthylamine with sodium does not proceed beyond the dihydro compound probably for the same reasons advanced to explain the limited extent of reduction of quinolines.[9] The reduction of naphthalene to tetrahydronaphthalene in liquid ammonia has been reported but the reactions were allowed to proceed over a much longer period of time[14] or were conducted at higher temperatures.[15] Under such conditions, sodium amide formed by the ammonolysis of the primary reduction product would cause the double bond in the 6,7-position to migrate to the 7,8-position.[16] Thus, conjugation with the unsaturation in the benzenoid ring would render the double bond susceptible to reduction by sodium.[17]

Although the reduction of 1-nitronaphthalene by sodium undoubtedly led to the formation of a dihydro-1-naphthylamine, the product bore no resemblance to the 5,8-dihydro-1-naphthylamine formed by the action of sodium upon 1-naphthylamine. It seems probable that hydrogenation of the ring to which the nitrogen was attached must have occurred and that the hydrogen probably entered the 1,4-positions.[9]

The reduction of 2-nitrofluorene to a tetrahydro-2-aminofluorene by means of sodium is a result analogous to that reported by Lebeau and Picon[18] for the reduction of dimethylfluorene.

## Summary

1. Nitrobenzene has been reduced to aniline in liquid ammonia solution by sodium and ammonium bromide and by sodium and methanol.

2. 1-Naphthylamine has been reduced to 5,8-dihydro-1-naphthylamine by sodium but reduced to apparently the same product only to a very limited extent by sodium and ammonium bromide.

3. 1-Nitronaphthalene has been reduced by sodium to a dihydro-1-naphthylamine that is different from the 5,8-dihydro compound and is probably the 1,4-dihydro derivative. Sodium and ammonium bromide gave incomplete reduction to 1-naphthylamine, while sodium and methanol yielded a mixture of the di and tetrahydro-1-naphthylamines.

4. 2-Nitrofluorene has been reduced to a tetrahydro-2-aminofluorene by sodium, and has been shown to be unaffected by sodium and ammonium bromide, but reduced to a mixture of tetra- and hexahydro-2-aminofluorenes by sodium and methanol.

AUSTIN, TEXAS RECEIVED AUGUST 26, 1946

---

[14] Wooster and Smith, THIS JOURNAL, **53**, 179 (1931).

[15] Lebeau and Picon, *Compt. rend.*, **158**, 1514 (1914).

[16] Hückel and Bretschneider, *Ann.*, **540**, 157 (1939).

[17] Campbell and Campbell, *Chem. Rev.*, **31**, 82 (1942).

[18] Lebeau and Picon, *Compt. rend.*, **173**, 84 (1921).

---

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

# Studies in the Quinoline Series. VIII. Some 6-β-Hydroxyethoxy-4-aminoquinolines

BY VIRGINIA G. RAMSEY AND LEONARD H. CRETCHER

Previous work in this Laboratory[1] had shown that in some 6-methoxy-8-alkylaminoalkylaminoquinolines and 6-methoxy-8-dialkylaminoalkylaminoquinolines the replacement of the methoxy group at position 6 by a β-hydroxyethoxy group lessened the toxicity to mice, but also lessened the activity of the compounds against avian malarial infection. It was considered desirable to determine if, by introduction of a β-hydroxyethoxy group in the 6-position of 4-aminoquinolines, detoxification without serious diminution of antimalarial activity could be obtained. For this purpose some derivatives of 6-β-hydroxyethoxy-4-aminoquinoline were prepared.

The method chosen for the syntheses of the compounds involved, as a first step, the preparation of 6-methoxy-4-hydroxyquinoline (I) from ethoxymethylenemalonic ester and *p*-anisidine by the method of Price and Roberts.[2] With a mixture of phosphorus penta- and oxy- chlorides, in an application of the procedure recommended for the preparation of 4-chloroquinaldine,[3] I was converted to 6-methoxy-4-chloroquinoline (II) in better yield than with phosphorus oxychloride alone. By hydrolysis with strong sulfuric acid 6-hydroxy-4-chloroquinoline (III) was obtained from II. This compound (III) had been prepared by other workers[4] by diazotization of 6-hydroxy-4-aminoquinoline. Alkylation of III with ethylene carbonate proceeded smoothly to give 6-β-hydroxyethoxy-4-chloroquinoline (IV) which was then converted to 6-β-hydroxyethoxy-4-aminoquinoline (V) by refluxing in phenol in the presence of ammonia, a general method for the preparation of 4-aminoquinolines.[5]

6-β-Hydroxyethoxy-4-(1′-methyl-4′-diethylaminobutylamino)-quinoline (VI) was prepared by heating IV and Noval diamine in phenol. 6-β-Hydroxyethoxy-4-(3′-*i*-propylaminopropylam-

---

[1] (a) Morgan and Cretcher, THIS JOURNAL, **68**, 781 (1946); (b) Morgan and Tipson, *ibid.*, **68**, 1569 (1946).

[2] Price and Roberts, *ibid.*, **68**, 1204 (1946).

[3] Fisher, Diepolder and Wölfel, *J. prakt. Chem.*, **109**, 59 (1925).

[4] John and Andraschko, *ibid.*, **128**, 211 (1930).

[5] Eisleb, German Patent, 540,699 (1931); *Chem. Zentr.*, **103**, I, 1804 (1932).