The Reduction of Nitrogen Heterocycles by Lithium in Liquid Ammonia. III. Indoles and Quinolines[1]

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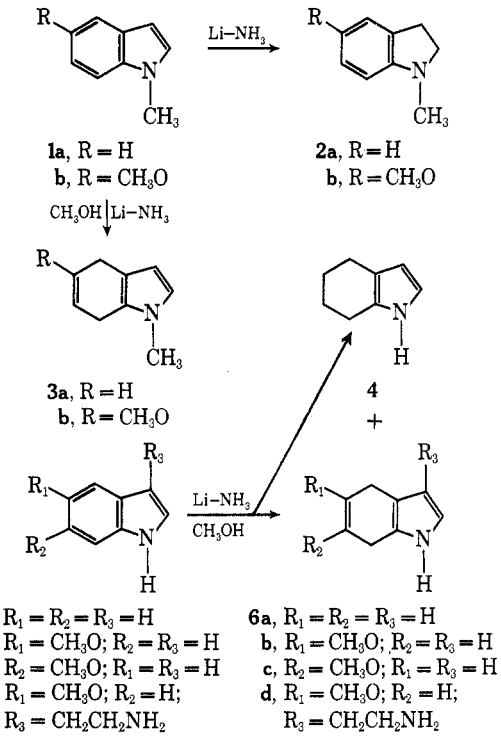
Either the benzene rings or heterocyclic rings of certain quinolines and *N*-alkylindoles may be preferentially reduced by lithium in ammonia, depending upon the proton source. When excess methanol is present the benzene rings are preferentially reduced, possibly by protonation of intermediate radical anions. If methanol is omitted or added later the heterocyclic rings are preferentially reduced, presumably by protonation of intermediate dianions. Indoles unsubstituted on nitrogen afford salts which are not reduced in the absence of a proton source such as methanol. In the presence of methanol they give only benzene ring reduction.

Although the metal-in-ammonia reduction of aromatic carbocycles has been extensively investigated, comparatively little is known about the corresponding reductions of aromatic heterocycles.[3] Since the nitrogen heterocycles are of great importance in chemistry and biology, we have undertaken an investigation of the reduction of certain of these compounds, attempting both to elucidate the reduction processes and to utilize this knowledge in controlling which products are formed. This paper is concerned with the reduction of indoles and quinolines by lithium and methanol in liquid ammonia.

The most significant result of our study was that ring selectivity could be controlled in the reductions of certain of these heterocycles. In the example with highest selectivity, 5-methoxy-1-methylindole (**1b**) was reduced by lithium in ammonia containing excess methanol to the corresponding 4,7-dihydroindole **3b** in 60% yield. Only 5% of 5-methoxy-1-methylindoline (**2b**) was obtained. Reduction of **1b** in the absence of methanol contrasted the previous reaction both in rate and in product distribution. Whereas reaction in the presence of methanol was almost instantaneous, reaction in its absence required excess lithium and much longer times (4 hr) for appreciable reduction. The latter reaction gave only indoline **2b** in 70% yield. (Scheme I).[4,5]

1-Methylindole (**1a**) was also reduced with a high degree of specificity to the corresponding indoline **2a** by excess lithium. However, reduction in the presence of methanol was less selective. It afforded a mixture which contained both **2a** (32%) and the 4,7-dihydro derivative (**3a**, 37%), plus four minor components (total 5%). Similar ratios of **2a** and **3a** were reported

SCHEME I



previously for the reduction of **1a** in the presence of methanol.[6]

When indoles are unsubstituted on nitrogen, the NH proton is sufficiently acidic ($pK_a \approx 17$) to give indolyl salt formation with metals in ammonia. These salts are not reduced in the absence of a proton source such as methanol. An earlier publication revealed that addition of methanol to a mixture of indole **5a** and a large excess of sodium in ammonia gave a mixture composed of equal parts of 4,7-dihydroindole (**6a**) and 4,5,-6,7-tetrahydroindole (**4**).[6] The authors suggested that methanol is the optimum proton source for this reduction because it is acidic enough ($pK_a = 16$) to maintain a portion of the indole in the NH form, but not so acidic that it competes with this form for reduction by the metal.

We have reinvestigated the reduction of indole and confirmed these findings. However, we have also found that the large excess of alkali metal is unnecessary. Reduction with only 2 equiv of lithium afforded (glc analysis of the crude product) 44% of dihydroindole **6a**, 15% of tetrahydroindole **4**, and 39% of starting mate-

(1) (a) Part of the investigation was described in a preliminary communication: W. A. Remers, G. J. Gibs, C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **89**, 5513 (1967). A brief account also appears in "Topics in Heterocyclic Chemistry," R. N. Castle, Ed., Wiley, New York, N. Y., 1969, p 178. (b) For the second paper in this series, see W. A. Remers and M. J. Weiss, *Tetrahedron Lett.*, 81 (1968).

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(3) H. Smith in "Chemistry in Nonaqueous Ionizing Solvents," Vol. I, part 2, G. Jander, H. Spandau, and C. C. Addison, Ed., Wiley-Interscience, New York, N. Y., 1963.

(4) If methanol was added to an ongoing reduction of **1b**, the faster reduction to **3b** superseded that which gave **2b**. The relative proportions of **3b** and **2b** then reflected the time which had elapsed before the methanol was added (see Table I).

(5) Both indoline **2b** and 4,7-dihydroindole **3b** were stable in the presence of lithium amide. Excess lithium further reduced **2b** when methanol was present, but not in its absence. Neither set of conditions lead to further reduction of **3b**, which agrees with a previous report[6] on the resistance of the pyrrole ring to such reductions.

(6) S. O'Brien and D. C. C. Smith, *J. Chem. Soc.*, 4609 (1960).

rial. When a third equiv of lithium was used, the recovery of starting material fell to 11% and yields of the two products were increased correspondingly (Table I). If methanol was not present prior to the addition

TABLE I

PRODUCTS FROM THE REDUCTION OF INDOLE 5a WITH LITHIUM IN AMMONIA[a]

Experimental conditions	—Product, %— 4	6a	Recovered 5a, %
Excess CH_3OH, 2 Li added	14	43	38
Excess CH_3OH, 3 Li added	26	56	11
Excess CH_3OH, 4 Li added	31	57	6
4 Li, CH_3OH added	20	59	12

[a] A CH_2Cl_2 solution of the product mixture (totally distillable at reduced pressure) was passed through a 6-ft column of 20% SE-30 at 200°. Compounds are listed in the order in which they came off the glc column.

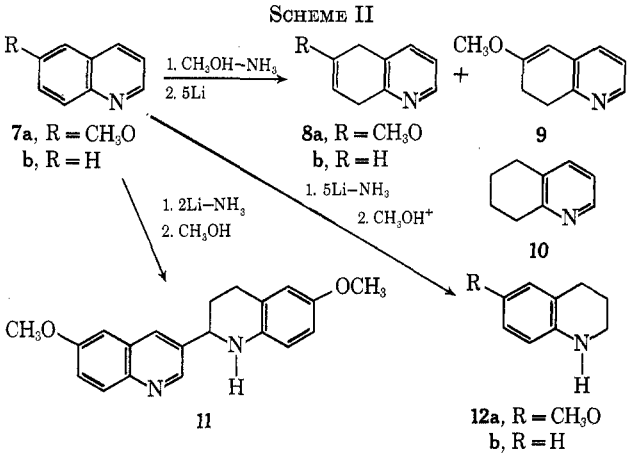
of lithium, 1 equiv of this metal was immediately consumed in forming the indolyl salt. However, a relatively small additional amount of lithium sufficed for reduction of this salt when methanol was added. Thus, 4 equiv of lithium followed by methanol (until discharge of the blue color) gave 63% of **6a**, 21% of **4**,[7] and only 6% of starting material. It should be noted that the ratio of **6a**:**4** is essentially the same whether the methanol was present in excess before addition of lithium or if it was added after the lithium.

The previously reported[6] mixture of **6a** and **4** had not been resolved into its pure components; hence some doubt remained about the proof of their structures. We resolved this mixture by preparative glc and confirmed the assigned structures. The identity of **4** with a known sample prepared by an independent route was established (Experimental Section), whereas the structure of **6a** was clearly delineated by its nmr spectrum (Table II) which showed two protons on a pyrrole ring, two protons on a double bond, and four aliphatic protons strongly deshielded. Reduction of 5-methoxyindole (**5b**) under similar conditions was highly specific. The 4,7-dihydro derivative **6b** was obtained in 83% yield (after recrystallization). As in the example of **1b** the methoxy group appears to enhance selectivity in the reduction of an indole. It also helps accelerate the reduction, which is in agreement with a rate-enhancing effect of the methoxy group in other Birch reductions.[8,9] Thus, in a competitive experiment **5b** was reduced more rapidly than indole.

6-Methoxyindole (**5c**) was also reduced to a crystalline 4,7-dihydro derivative (**6c**, 65% yield) but an appreciable amount of tetrahydrofuran was required as cosolvent. Attempted reduction of 7-methoxyindole was unsuccessful. More complex indoles, such as 5-methoxytryptamine (**5d**) were also reduced to their 4,7-dihydro derivatives (*e.g.*, **6d**). These reductions were less efficient than those of the simpler indoles and generally required a large excess of lithium. The conversion of tryptophan into its 4,7-dihydro derivative was reported previously.[10] Tryptamine quaternary salts afforded either cleavage at the quaternary center or reduction of the indole nucleus, depending upon whether or not methanol was present during the reduction (cleavage occurred in the absence of methanol).[11]

In contrast to the indoles, quinoline derivatives immediately decolorized 2 equiv of lithium even in the absence of methanol. This probably resulted in dianion formation as discussed below. Addition of methanol and work-ups gave mixtures of products which were separated by liquid–liquid partition chromatography. From 6-methoxyquinoline **7a** the main product isolated was an interesting unsymmetrical dimer, **11** (Scheme II). The structure of this dimer was revealed by its

SCHEME II



nmr spectrum (Table II), which showed two methoxy groups, six protons on benzene rings, two protons meta on a pyridine ring, and five protons on aliphatic carbons. The last five protons appeared as two two-proton multiplets and a one-proton doubled doublet. Addition of HCl to a dimethyl sulfoxide solution of **11** broadened the one-proton pattern, but did not broaden the other aliphatic protons. This result showed that the single proton was on a carbon next to nitrogen and uniquely determined the structure of the dimer. Other products isolated from this reduction of 6-methoxyquinoline were 5,8-dihydro derivative **8a** (15%) and starting material (14%). An appreciable quantity of amorphous solid (polymer ?) was also present, but it could not be further resolved.

When the previous experiment was repeated with 5 equiv of lithium, no dimer **11** was found in the product mixture. The only products isolated were 6-methoxy-1,2,3,4-tetrahydroquinoline (**12a**, 32%) and 5,8-dihydro derivative **8a** (5%). Some starting material (9%) was recovered.

Reduction of 6-methoxyquinoline (**7a**) in the presence of excess methanol (5 equiv of lithium) resulted in a significant change in the ring selectivity, at least in the isolated products. Products of benzene ring reduction, 5,8-dihydro derivative **8a** (32%) and the isomeric 7,8-dihydro derivative **9** (16%), were obtained,[12] but the only isolated product of pyridine ring reduction was **12a** (5%).

(7) Since 4,7-dihydroindole **6a** is stable in the presence of excess lithium and methanol in ammonia, it is apparent that tetrahydroindole **4** is not formed from **6a**. Probably **4** is formed by way of an isomer of **6a** in which the double bond is conjugated with the pyrrole ring.

(8) A. J. Birch and D. Nasipuri, *Tetrahedron*, **6**, 148 (1959).

(9) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959).

(10) O. Yonemitsu, P. Cerutti, and B. Witkop, *ibid.*, **88**, 3941 (1966).

(11) The important role of the proton source in determining preferential reduction was especially evident in these quaternary salts.[1b]

(12) The 7,8-dihydro derivative **9** could arise either from isomerization of 5,8-dihydro derivative **8a** or from protonation of the intermediate (radical anion) at a different site. Thermal isomerization of **8a** to **9** was evident when the crude reaction mixture was distilled. More **9** was present in the distillate than had been in the crude according to tlc.

TABLE II

SPECTROSCOPIC DATA FOR NEW COMPOUNDS[a]

Compd	Bp (mm) or mp, °C	Uv, mμ (ε), in CH_3OH	δ, ppm, in $CDCl_3$ (J in Hz)[b]
3b[c,d]	94 (4)		6.55 (d, J = 3, C_2), 5.91 (d, J = 3, C_3), 4.75 (m, C_6), 3.23 [4, s (broadened), C_4, C_7]
6a	37–39		6.85 (dd, J = 3, J = 3, C_2), 6.04 (dd, J = 3, J = 3, C_3), 5.95 [2, s, (broadened), C_5, C_6], 3.14 [4, s (broadened), C_4, C_7]
6b	65–68		6.67 (dd, J = 3, J = 3, C_2), 6.00 (dd, J = 3, J = 3, C_3), 4.79 (m, C_5), 3.27 [4, s (broadened), C_4, C_7]
6c	70–71		6.15 (dd, J = 3, J = 3, C_2), 6.02 (dd, J = 3, J = 3, C_3), 4.88 (m, C_5), 3.28 [4, s (broadened), C_4, C_7]
6d	151–153[e]		6.50 (broadened, C_2), 4.78 (m, C_3), 3.25 [4, s (broadened), C_4, C_7], 2.9–2.5 (4, m, side chain CH_2CH_2)
8a[f]	138–140 (8)	269 (4100)	8.41 (J = 5, J = 2), 7.45 (J = 5, J = 2), 7.08 [J = 5, J = 5, pyridine ring], 4.77 (m, vinyl), 3.60 (m, 4, aliphatic)
9[g]	164–168	275 (5900)	8.35 (J = 5, J = 2), 8.02 (J = 5, J = 2), 7.08 (J = 5, J = 5, pyridine ring), 5.90 (broad s, vinyl), 3.25 (m), 2.63 (m, aliphatic)[g]
11	159–160	225 (23,400), 329 and 322 (3680)	8.71 (J = 2), 8.00 (J = 2, meta on pyridine ring), 7.30, 6.95, 6.60 (3 protons, aromatic), 4.50 [m, NCH–aromatic (broadens when HCl is added)], 2.75 (2), 2.05 (2, aliphatic)
8b[h,i]	157–169	240 (13,500), 270 (6300) sh, 350 (15,300), 390 (9900) sh	8.75 (J = 5, J = 2), 8.40 (J = 5, J = 2), 7.90 (J = 5, J = 5, pyridine ring), 5.97 (2, vinyl), 3.67 (4, aliphatic)

[a] Satisfactory analytical values (±0.35%) in C, H, and N were reported for all compounds in the table: Ed. [b] Methyl group and NH absorptions omitted. [c] $n^{25}D$ 1.5465. [d] Calcd for N: 8.58. Found: 9.02. [e] Melting point of acetate salt. [f] Calcd for N: 8.69. Found: 9.08 [g] Melting point and nmr of picrate. [h] Melting point and analysis of picrate. [i] Calcd for C: 50.39. Found: 50.00.

When quinoline **7b** was reduced under the same sets of conditions just described for 6-methoxyquinoline, the results were qualitatively similar, although the yields of isolated products were lower and more amorphous solid was obtained. Thus, when excess methanol was present, the isolated products resulted mainly from benzene ring reduction. They were 5,8-dihydroquinoline (**8b**, 24%), 5,6,7,8-tetrahydroquinoline (**10**, 7%), and 1,2,3,4-tetrahydroquinoline (**12b**, 5%), plus 9% of starting material. In contrast, addition of 5 equiv of lithium followed by methanol afforded 36% of **12b**, but only 8% of **8b** and 1% of **10**. Appreciable starting material (26%) also was recovered.[13] The low material balances obtained from some of these quinoline reductions make evaluations of the ring selectivity less certain than in the corresponding indole reductions. However, at least in the reduction of 6-methoxyquinoline with methanol initially present, the material balance allowed ring selectivity to be conclusively established.

At the present time the mechanisms for the metal-in-ammonia reductions of aromatic carbocycles are fairly well understood. They are based upon product distributions,[8] kinetic studies,[9] and molecular orbital calculations.[14] The following application of the salient features of these mechanisms to related nitrogen heterocycles gives a reasonably coherent explanation for the products and ring selectivity observed in their reduction. The most important assumption inherent in this application is that π-electron densities are more important than solvation and counterion effects in determining the site of protonation on intermediate radical anions and dianions. This assumption appears to be true for the carbocycles[15] but remains unproven for nitrogen heterocycles.

The ease of adding electrons to the π-electron system of a molecule is related directly to the energy of the lowest unoccupied molecular orbital (LUMO) of that system.[14] In liquid ammonia, which is especially effective in stabilizing dianions,[16] molecules such as naphthalene (LUMO at -0.60β)[14] readily form dianions when treated with an alkali metal. Both of these electrons go into the LUMO. Our observations on quinoline (-0.43β) and 6-methoxyquinoline (-0.45β)[17] are consistent with this view. Both of these compounds immediately decolorized 2 equiv of lithium in ammonia, forming colored (greenish) intermediates. Benzene does not readily give a dianion because its LUMO is too high (-1.00β). It does not decolorize a solution of lithium in ammonia, nor does it undergo reduction. However, if methanol is added the benzene is readily reduced. This reduction is thought to occur by rapid protonation of the radical anion formed to a small extent in an equilibrium with benzene and solvated electrons.[9] *N*-Alkylindoles (**1a** and **1b**) lie between naphthalene and benzene in LUMO energy (-0.87β).[19] They were reduced in the absence of methanol but only very slowly. In the presence of methanol their reduction was rapid. We suggest that in the presence of methanol (pK_a = 16) the radical anion is protonated as it forms in equilibrium with the *N*-alkylindole. In the absence of methanol, the only proton source is ammonia (pK_a = 34), which is not acidic enough to protonate this

(13) W. Huckel and L. Hagedorn reported [*Chem. Ber.*, **90**, 752 (1957)] the preparation in 85% yield of 1,2-dihydroquinoline by treatment of quinoline with 2 equiv of sodium followed by ammonium chloride (−65° under N_2).

(14) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1962.

(15) H. E. Zimmerman, *Tetrahedron*, **16**, 169 (1961).

(16) W. Huckel, *Fortschr. Chem. Forsch.*, **6**, 197 (1966).

(17) LCAO–MO calculations based upon parameters ($\alpha_N = \alpha_C + 0.5\beta$, $\beta_{CN} = \beta_{CC}$) which afforded a reasonable correlation between calculated and observed hyperfine splitting constants in the esr spectrum of quinoline radical anion.[18] For oxygen, $\alpha_O = \alpha_C + 2.0\beta$, $\beta_{CO} = 0.8\beta_{CC}$ were used.

(18) J. Chaudhuri, S. Kume, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, **90**, 6421 (1968).

(19) LCAO–MO calculations based upon the parameters suggested by Streitwieser (ref 14).

radical anion. However, ammonia will protonate the dianion which exists to a small extent in equilibrium with the radical anion. Benzene apparently does not give a sufficient concentration of dianion to allow significant reduction when ammonia is the only proton source.

The ring selectivity observed in the reduction on *N*-alkylindoles can be related to this difference in the intermediate protonated in the presence or absence of methanol. Thus, the radical anion might be preferentially protonated in the benzene ring, whereas protonation in the pyrrole ring might be favored with the dianion. Support for this view is afforded by the NH indoles (**5a**, **5b**, and **5c**) which are reduced exclusively in their benzene rings. These compounds could give only the radical anion since methanol must be present to reverse indolyl salt formation.

It is also conceivable that the ring selectivity observed in the quinoline examples reflects preferential protonation of a dianion when methanol is not initially present and protonation of a radical anion when methanol is initially present in excess. This concept would require that the radical anion, formed by reversible addition of one electron to the π system of the quinoline, be protonated by methanol before the second proton adds. The selective benzene ring reduction observed by treatment of 6-methoxyquinoline with lithium in the presence of methanol fits this picture. Unfortunately, the low material balances obtained in most of the other examples do not afford further concrete evidence for this point.

In an important paper by Zimmerman,[15] the site of protonation of radical anions derived from various methoxybenzene derivatives was successfully correlated with the total π-electron density at the several carbon atoms in the aromatic rings of those anions. Although in certain cases the difference in π-electron density between two atoms was very small, it was always considered to be the determining factor. It was further noted that in certain compounds the pattern of π-electron density in the radical anion differed from that in the starting material. Thus, for anisole, the increase in total π-electron density afforded by addition of one electron to the π system was much higher at the ortho and meta positions than at the para position.

An extension of these ideas to the nitrogen heterocycles might help explain the observed ring selectivity in their reductions. For example, in 5-methoxy-1-methylindole (**1b**) the highest total π-electron density on carbon is at C-3, whereas it is at C-4 in the radical anion and at C-2 in the dianion. It should be noted that protonation at these positions in the radical anion and in the dianion would lead to the observed selective products of benzene ring reduction and pyrrole ring reduction, respectively. Similarly, there is correspondence between the sites of protonation and highest total π-electron densities on carbon[20] for the radical anion and dianion derived from 6-methoxyquinoline. However, the calculated total π-electron densities for quinoline do not predict the correct products from protonation of the radical anion (although the material balance was very poor in this case).

(20) The total π-electron densities on pyridyl nitrogens are actually much higher than those on carbon atoms. Product determining protonation on carbon would, therefore, require that protonation on nitrogen be reversible under the experimental conditions.

At the present time the experimental evidence is not strong enough to compel acceptance of the above interpretation of ring selectivity in the reduction of nitrogen heterocycles. For one thing, the assumption that solvent and counterion effects do not determine the site of protonation might not be as valid for nitrogen heterocycles as it appears to be for carbocycles. Furthermore, the position of highest total π-electron density can vary with the choice of parameters used in the LCAO–MO calculations (we used parameters recommended in the literature).[17,19] However, it still seems valid to call attention to this interpretation, since it should serve as the most reasonable starting point for more rigorous calculations and mechanistic studies in this important area of heterocyclic chemistry.

Finally, some further comment will be made on the formation of unsymmetrical dimer **11**. It seemed at first that such a dimer might be produced by the coupling of two molecules of 6-methoxyquinoline radical anion or by the addition of one molecule of radical anion to one molecule of starting material. However, treatment of 6-methoxyquinoline with either 1 or 0.5 equiv of lithium, hypothetical conditions for these modes of formation, gave no dimer. Only starting material was recovered. These results suggest that the dimer is produced instead by intermediates which occur after formation of a dihydroquinoline reduction product.[21]

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are corrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide disks or neat with a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform (unless otherwise specified) with a Varian A-60 spectrometer. Solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure on a rotary evaporator.

5-Methoxy-1-methylindole (1b).—This compound was previously prepared by a less direct method.[23] In the present method, a solution of 0.1 mol of methylsulfinyl carbanion in 50 ml of dimethyl sulfoxide[24] was treated with a solution of 14.7 g (0.1 mol) of 5-methoxyindole in 50 ml of dimethyl sulfoxide. After 1 hr 28.4 g (0.2 mol) of methyl iodide was added. The resulting solution was stirred overnight under N_2 and then carefully diluted with water, whereupon the product crystallized. Recrystallization from ethanol gave 11.8 g (74%) of colorless prisms, mp 97–103°. Another recrystallization gave mp 102–104° (lit.[24] mp 103–104°).

5-Methoxy-1-methylindoline (2b).—This compound was previously obtained as a picrate.[23] In the present investigation, an authentic sample was prepared as a standard for glc determinations. A mixture of 500 mg of 5-methoxy-1-methylindole (**1b**), 6 ml of ethanol, 6 ml of concentrated HCl and 2.0 g of granular tin was heated at reflux temperature for 18 hr, cooled, and filtered. The filtrate was brought to pH 10 with NaOH solution and re-

(21) When quinoline is heated with sodium in toluene, a related dimer, 2,3′-diquinoline, is obtained in 30–40% yield [Weidel, *Monatsh. Chem.*, **2**, 491 (1881)]. The mechanism of this dimerization is not known, although it seems likely that a dimeric dianion of the type observed in tetrahydrofuran solvent is initially formed,[22] and then aromatization occurs with loss of hydride ion. Dimer formation in liquid ammonia probably does not occur by this process because a monomeric dianion is the predominant species in equilibrium, even when less than 2 equiv of lithium is involved.[16]

(22) With typical aromatic compounds in tetrahydrofuran, a dimeric dianion is the predominant species, whereas in hexamethylphosphoramide the corresponding radical anion is favored in equilibrium with this dimeric dianion.[18] The special role of amine solvents in stabilizing monomeric dianions has been pointed out by Huckel.[16]

(23) J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 1203 (1951).

(24) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

filtered. The solids were washed with ether and the combined filtrate and washes were diluted with ether, washed with water, dried, and concentrated. Treatment of a portion of the residual oil (435 mg, $n^{25}D$ 1.5865) with picric acid in ethanol afforded a yellow picrate, mp 171–172° dec after recrystallization from methanol (lit.[23] mp 171–173° dec).

1-Methylindoline (2a).—This compound was prepared by the procedure described for **2b**. From 500 mg of 1-methylindole (**1a**) was obtained 428 mg of pale yellow oil which showed only one peak on glc. It gave a picrate with mp 161–164° after two recrystallizations from benzene (lit.[6] mp 160–165°).

Typical Lithium-in-Ammonia Reduction Procedures for Indoles. A. Excess Methanol Present.—A solution of 10 mmol of the indole derivative in 6 ml of methanol was added to 50 ml of distilled liquid ammonia. The resulting solution was treated portionwise with 280 mg (40 mg-atoms) of Li wire, which reacted very rapidly. After evaporation of the ammonia and removal of the methanol under reduced pressure, the residue was treated with ether and water. The ether layer was dried and concentrated and the residue was weighed and assayed by chromatography as described in Tables I and III. Pure products were obtained by crystallization or distillation as described in Table II. Nmr spectra of these products are recorded in Table II.

Several compounds were insoluble in ammonia or methanol–ammonia mixtures and required modified reduction procedures. Thus, on the same scale, 1-methylindole, 6-methoxyindole, and 7-methoxyindole were dissolved in a mixture of 35 ml of ammonia, 25 ml of tetrahydrofuran, and 8 ml of methanol.

B. Methanol Added Later.—A solution of 10 mmol of the indole derivative in 60 ml of distilled ammonia was treated portionwise with 280 mg (40 mg-atoms) of Li wire. After specified times the blue mixture was then treated dropwise with methanol until this color was discharged. After evaporation of the ammonia the residue was worked up as described above.

C. Methanol Not Used.—A solution of 7.5 mmol of the indole derivative in 10 ml of tetrahydrofuran and 125 ml of distilled ammonia was treated portionwise with 420 mg (60 mg-atoms) of lithium. After 4 hr the excess lithium was discharged by the addition of a small amount of ferric chloride hexahydrate. Methanol was added to neutralize the amide ion and the ammonia was evaporated. The residue was worked up as described above.

Typical Lithium-in-Ammonia Reduction Procedures for Quinolines. A. Excess Methanol Present.—A solution of 10 mmol of the quinoline derivative in 6 ml of methanol was added to 50 ml of distilled liquid ammonia. The resulting solution was treated portionwise with 280 mg (40 mg-atoms) of Li wire, which reacted immediately. After evaporation of the ammonia and removal of the methanol under reduced pressure, the residue was treated with ether and water. The ether layer was dried and concentrated, and the residue was resolved by liquid–liquid partition chromatography as described in Tables IV and V. Monomeric products were examined by glc on a 6-ft column of Carbowax 20M at 200° as a check on the liquid–liquid separation. The results were in agreement.

The isolated products were purified by crystallization, distillation, or picrate formation as described in Table II. Their structures were confirmed by spectral data as recorded in Table II.

TABLE III

PRODUCTS FROM THE REDUCTION OF 5-METHOXY-1-METHYLINDOLE (1b) WITH LITHIUM IN AMMONIA[a]

Experimental conditions	Product, % others	2b	3b	Recovered 1b, %
8 Li, $FeCl_3$ after 4 hr	0	70	0	5
2 Li, $FeCl_3$ after 4 hr	0	18	0	72
Excess CH_3OH, 4 Li added	3	5	60	8
4 Li, CH_3OH added immediately	6	9	38	7
4 Li, CH_3OH added after 45 min	4	11	25	2
4 Li, CH_3OH added after 4 hr	5	25	8	4

[a] The neat product mixture (totally volatile) was passed through a 6-ft Carbowax 20M column at 250°. Compounds are listed in the order in which they came off the glc column.

TABLE IV

PRODUCTS FROM THE REDUCTION OF 6-METHOXYQUINOLINE (7a) WITH LITHIUM IN AMMONIA[a]

Experimental conditions	Product, % 10	8a	9	11	12a	Recovered 7a, %
2 Li, CH_3OH added	0	15	0	35	0	14
5 Li, CH_3OH added	0	0	0	0	32	9
Excess CH_3OH, 5 Li added	3	32	16	0	5	8

[a] The crude product mixtures were resolved by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methyl cellosolve system. In a typical experiment 1.94 g of crude product was dissolved in 45 ml of the lower phase, mixed with 60 g of diatomaceous earth, and packed atop a column prepared from 450 ml of the lower phase and 600 g of diatomaceous earth. The resulting column was eluted with the upper phase, and the effluent was passed through a recording uv spectrophotometer set at 260 mμ. Eluate corresponding to the recorded peaks was then concentrated and the residue was weighed and further purified by crystallization or picrate formation. Compounds are listed in the order in which they came off the chromatography column.

TABLE V

PRODUCTS FROM THE REDUCTION OF QUINOLINE 7b WITH LITHIUM IN AMMONIA[a]

Experimental conditions	Product, % 10	8b	12b	Recovered 7b, %
5 Li, CH_3OH added	1	8	36	26
Excess CH_3OH_3, 5 Li added	7	24	5	9

[a] The chromatography system and procedure were the same as those described in the footnote of Table I. Compounds are listed in the order in which they came off the chromatography column.

The reduction of 6-methoxyquinoline (**7a**) was carried out on a larger scale. Treatment of 50 g of **7a** and 400 ml of methanol in 21 ml of ammonia afforded 33 g of an oil which upon distillation afforded 17 g of a mixture of isomeric dihydro derivatives **8a** and **9**.

B. Methanol Added Later.—A solution of 10 mmol of the quinoline derivative in 60 ml of distilled ammonia was treated portionwise with Li wire (20 or 50 mg-atoms, depending upon the particular experiment). The mixture was stirred for 1 hr and treated dropwise with methanol until the color was discharged. After evaporation of the ammonia, the residue was worked up as described above.

Identification of Certain Reduction Products with Compounds Previously Reported in the Literature. A. 4,7-Dihydro-1-methylindole (3a) was isolated from a mixture with 1-methylindoline according to the published procedure.[6] It had an $n^{20}D$ 1.5482 that was equivalent to the literature value of $n^{18}D$ 1.5490.

B. 4,5,6,7-Tetrahydroindole (4) was isolated from a mixture with 4,7-dihydroindole by preparative glc on a 10% SE-30 column (8 ft × 0.5 in.) at 158° and He flow rate 75 ml/min. It had, after recrystallization from *n*-hexane, mp 54–55° (lit.[25] mp 55°).

C. 6-Methoxy-1,2,3,4-tetrahydroquinoline (12a), isolated as described in Table IV, had an ir spectrum superimposable with that of a commercial sample. The two samples had identical retention times on glc.

D. 5,6,7,8-Tetrahydroquinoline (10), isolated as described in Table IV, had an ir spectrum identical with the published one.[26] It gave a picrate with mp 158° (lit.[27] mp 158.5°).

Structure Proofs for New Compounds.—The structures of new compounds were verified by their spectral data (Table II) in addition to microanalyses (Table II). In the ir spectra, the vinyl ether groups showed characteristic sharp peaks at 6.0 μ (KBr disks except **8a** which was neat between salt plates). Dimer **11** showed an NH band at 3.1 μ. The uv spectra of the new compounds are recorded in Table II. Also in this table are listed

(25) J. M. Patterson and S. Soedigdo, *J. Org. Chem.* **32**, 2969 (1967).
(26) E. Godar and R. P. Mariella, *J. Amer. Chem. Soc.*, **79**, 1402 (1957).
(27) M. M. Janot, J. Keufer, and J. LeMen, *Bull. Soc. Chim. Fr.*, 230 (1952).

those nmr peaks most essential to the structure proof. Dimer **11** had a molecular ion at *m/e* 320 in its mass spectrum.

Registry No.—Lithium, 7439-93-2; **1b**, 2521-13-3; **3b**, 17052-38-9; **5a**, 120-72-9; **6a**, 26686-10-2; **6b**, 17052-39-0; **6c**, 26686-12-4; **6d**, 26573-83-1; **6d** acetate, 26686-14-6; **7a**, 5263-87-6; **7b**, 91-22-5; **8a**, 17052-40-3; **8b**, 26686-17-9; **8b** picrate, 17052-42-5; **9** picrate, 17052-41-4; **11**, 18995-96-5.

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Alkylation of Benzohydroxamic Acid[1]

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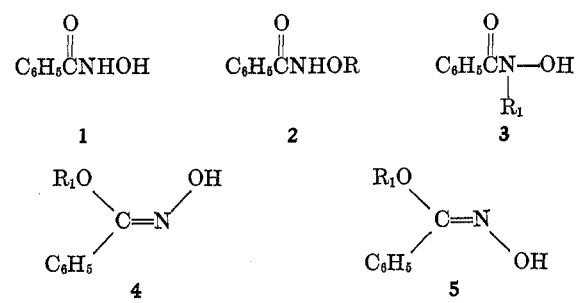
The alkylation behavior of the potassium and silver salts of alkyl benzohydroxamates **2** has been investigated. The structures of the alkylation products were determined by comparison of their nmr spectra and vpc retention times with independently synthesized compounds: ethyl *N*-ethylbenzohydroxamate (**6a**), the *Z* and *E* isomers of ethyl *O*-ethylbenzohydroximate (**7a** and **8a**), *n*-propyl *N*-*n*-propylbenzohydroxamate (**6b**), the *Z* and *E* isomers of ethyl *O*-*n*-propylbenzohydroximate (**7e** and **8e**), the *Z* and *E* isomers of *n*-propyl *O*-isopropylbenzohydroximate (**7f** and **8f**), *n*-propyl *N*-benzylbenzohydroxamate (**6h**), and the *Z* and *E* isomers of benzyl *O*-*n*-propylbenzohydroximate (**7h** and **8h**). Alkylation of the potassium salts of **2** with primary alkyl halides in methanol–water solutions gives mixtures of **6** (major product) and **7** (minor product). Isopropyl halides lead to mixtures of **6** and **7** in which **7** predominates. Oxygen alkylation of the potassium salts is increased considerably in dimethyl sulfoxide or dimethylformamide. Alkylation of potassium benzohydroxamate with 1,2-dibromoethane, 1,3-dibromopropane, and 1,4-dibromobutane gives cyclized products **16**, **17**, and **18**, respectively. Heterogeneous reactions of the silver salts of **2** with alkyl halides in anhydrous ether give mixtures of **7** and **8**. Alkyl iodides give mainly (*Z*)-hydroximates (**7**), whereas alkyl bromides favor hydroximates with the *E* configuration (**8**). The amount of the *Z* isomer increases when dimethylformamide is used as the solvent. The configuration of the products from the reactions of alkylbenzohydroximoyl chlorides (**19**) with sodium alkoxides were determined. In all of the reactions investigated only the *Z* isomers (**7**) of the hydroximates are formed. The alkylbenzohydroximoyl chlorides are prepared by the reaction of **2** with phosphorus pentachloride. Mechanisms for the alkylation reactions are discussed.

In connection with another study currently being carried out in our laboratory we have found it necessary to investigate methods of synthesizing and identifying the geometrical isomers of alkyl *O*-alkylbenzohydroximates[3] (**7** and **8**). The most direct route to these compounds appeared to be alkylation of alkyl benzohydroxamates **2**. Recent reports[4-6] on the alkylation of benzohydroxamates prompts us to describe our observations concerning alkylations of the ambident anions derived from this class of compounds.

Benzohydroxamic acid **1** offers three sites for alkylation: the hydroxylamine oxygen, the nitrogen, and the carbonyl oxygen. The four possible monoalkylation products are an alkyl benzohydroxamate **2**, an *N*-alkylbenzohydroxamic acid **3**, and the *Z* and *E* isomers of an alkyl benzohydroximate (**4** and **5**, respectively).[7]

Extensive study has shown that the monoalkylation of the potassium salt of benzohydroxamic acid results in the exclusive or preferential formation of a hydroxamate **2**.[8,9]



a, R or R_1 = C_2H_5
b, R = *n*-C_3H_7
c, R_1 = *i*-C_3H_7
d, R = *n*-C_4H_9
e, R_1 = $CH_2C_6H_5$

The dialkylation of **1** or the monoalkylation of **2** could give rise to an alkyl *N*-alkylbenzohydroxamate (**6**), an alkyl (*Z*)-*O*-alkylbenzohydroximate (**7**), or an alkyl (*E*)-*O*-alkylbenzohydroximate (**8**). In all of the earlier investigations the alkylation of either **1** or **2** has been reported to give exclusively an alkyl *O*-alkylbenzohy-

(1) A preliminary communication of this work, was presented at the Southwest Regional Meeting of the American Chemical Society, Little Rock, Ark., Dec 7, 1967, Abstracts p 61A.

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(3) We have named the compounds described in this paper as derivatives of benzohydroxamic acid, $C_6H_5C(=O)NHOH$, and its tautomer benzohydroximic acid, $C_6H_5C(OH)=N—OH$. Compounds substituted with alkyl or acyl groups on the hydroxylamine oxygen of benzohydroxamic acid are named alkyl or acyl benzohydroxamates. Substitution on the nitrogen is denoted with the prefix *N*-alkyl. A compound with alkyl substitution on the C–OH of benzohydroximic acid is named an alkyl benzohydroximate and substitution on the oxime oxygen is designated with the prefix *O*-alkyl.

(4) M. Chehata, F. Bocabeille, G. Thuillier, and P. Rumpf, *C. R. Acad. Sci., Ser. C*, **268**, 445 (1969).

(5) R. Blaser, P. Imfeld, and O. Schindler, *Helv. Chim. Acta*, **52**, 569 (1969).

(6) O. Exner and O. Schindler, *ibid.*, **52**, 577 (1969).

(7) In the past the configurational descriptors syn and anti have been used to designate the two geometrical isomers of alkyl benzohydroximates and their derivatives. However, in the older reports[10,21,22] a different convention was used than that proposed more recently by Exner.[19] To avoid confusion we will designate these isomers using the configurational descriptors *Z* and *E*. The rules which permit unambiguous description of double bond stereoisomerism in terms of the descriptors *Z* and *E* have been reported by J. E. Blackwood, G. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

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(9) J. H. Cooley, W. D. Bills, and J. R. Throckmorton, *J. Org. Chem.*, **25**, 1734 (1960).