892. *The Reduction of Indole and Carbazole by Metal–Ammonia Solutions.*

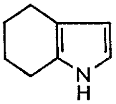
By S. O'Brien and D. C. C. Smith.

Indole and carbazole, but not pyrrole, can be reduced by solutions of metals in liquid ammonia, in the presence of alcohol or ammonium chloride. *N*-Substituted indoles and carbazoles are reduced more readily than the unsubstituted compounds.

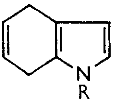
Pyrrole is not reducible by a solution of potassium in liquid ammonia,[1] nor by the combination sodium–ammonia–ammonium bromide.[2] Replacement of the last by ethanol is equally ineffective, although this combination efficiently reduces benzene [3] and thiophen.[4] Two factors may be responsible, the principal one being the anionoid character of the nucleus, relative to benzene, since the initial stage of reduction would involve electron-addition.[5] Pyrrole also possesses an acidic hydrogen, and salt formation would protect it from reduction; however, 1-methylpyrrole is also not reducible. Pyrrole can be reduced by zinc and hydrochloric acid,[6] presumably through the conjugate acid.

Fernelius and Field [7] are quoted as showing that the action of sodium in ammonia on indole gives 2,3-dihydroindole, and only 10% of the theoretical amount of hydrogen expected from salt formation. This product has been re-examined: its ultraviolet absorption spectrum is similar to that of a mixture of indole and pyrrole, and the characteristic absorption of 2,3-dihydroindole is absent, indicating reduction only in the benzene ring.

In the absence of an added source of protons a lithium–ammonia solution reduces indole to only a small extent, and this occurs immediately on addition of the indole. The residual indole, as lithium salt, is not further reduced by lithium–ammonia, but it is reduced, to a varying extent, on addition of a proton source, *e.g.*, an alcohol. The most effective alcohol is methanol, presumably because of its high acidity and therefore greater ability to release indole from the salt. Water is less effective, probably because of the increased rate of the competing reaction to give hydrogen. When a large excess of lithium and methanol in ammonia is used, reduction gives a product free from indole and consisting of 4,7-dihydroindole (II) and 4,5,6,7-tetrahydroindole (I) in about equal amounts, as judged from spectroscopic and analytical data.

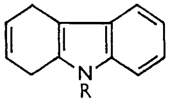


(I)



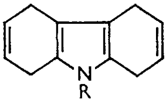
(II) R=H

(III) R=Me



(IV) R=H

(V) R=Me



(VI) R=Me

(VII) R=H

The effect of salt formation in inhibiting reduction is clearly shown by the comparative ease of reduction of 1-methylindole by sodium–ammonia–ethanol. Both rings are, moreover, reduced; the basic product is 2,3-dihydro-1-methylindole and this is itself further reduced. Reduction of 2,3-dihydro-1-methylindole gives a similar mixture. The neutral product of the reduction of 1-methylindole is 4,7-dihydro-1-methylindole (III).

While salt formation by indole probably explains its very slow reduction in sodium–ammonia proton-donor solutions, the greater effectiveness of more-acidic proton donors in

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[1] Franklin, *J. Phys. Chem.*, 1920, **24**, 81.

[2] Fernelius and Cappel, quoted in ref. 7.

[3] Wooster, U.S.P., 2182242 (*Chem. Abs.*, 1940, **34**, 1993).

[4] Birch and McAllan, *Nature*, 1950, **165**, 899.

[5] Birch, Nasipuri, and Smith, *Experientia*, 1959, **15**, 126.

[6] Andrews and McElvain, *J. Amer. Chem. Soc.*, 1929, **51**, 887.

[7] Watt, *Chem. Rev.*, 1950, **46**, 317.

promoting reduction suggests that, even here, reaction takes place only by initial electron addition to free indole. If so, the reducibility of the pyrrole ring in 1-methylindole, but not in indole itself, may be due to some factor other than salt formation by the latter. It is possible that non-bonding interaction between the 1-methyl and the 7-hydrogen increases the reducibility of the pyrrole nucleus in 1-methylindole by making the pyrrole ring non-planar and therefore less "aromatic." This factor is not present in 1-methylpyrrole and indole and, accordingly, neither is reducible in the pyrrole nucleus.

Carbazole might be expected to resist reduction under conditions of salt-formation; alternatively, it has a more extended aromatic system which is more favourable to reduction. 9-Methylcarbazole is stated not to be reduced by sodium in ammonia,[7] but it is difficult to assess this contention without full details; frequently solubility is a limiting factor in reduction. Franklin [1] observed only a small evolution of hydrogen from carbazole and potassium–ammonia, and Fernelius and Cappel [7] are quoted as noting the production of 1,4-dihydrocarbazole, and, in the presence of ammonium bromide, of the same product together with 1,2,3,4-tetrahydrocarbazole. Schmidt and Schall [8] claimed to have prepared 1,4-dihydrocarbazole by reducing carbazole with sodium and pentyl alcohol, but re-investigation by Barclay *et al.*[9] showed that the product contained more than 50% of carbazole, together with other, unidentified, components.

It is now found that when carbazole is reduced, either by sodium–ammonia–ethanol or by sodium–ammonia–ammonium chloride, 1,4-dihydrocarbazole (IV) is formed. This is entirely different from Schmidt and Schall's " dihydrocarbazole." The melting point of their product is 229°, whereas 1,4-dihydrocarbazole, even when pure, does not melt sharply, presumably because of some decomposition. The most convincing evidence that Schmidt and Schall's " dihydrocarbazole " is a mixture is obtained from its absorption spectra; its infrared spectrum contains bands characteristic only of carbazole *and* 1,4-dihydrocarbazole, and its ultraviolet spectrum indicates that there is 55% of carbazole and 45% of 1,4-dihydrocarbazole.

When 9-methylcarbazole, in a sodium–ammonia solution is reduced by the addition of ammonium chloride, the process proceeds only to 1,4-dihydro-9-methylcarbazole (V); if 9-methylcarbazole is reduced by sodium–ammonia–ethanol 1,4,5,8-tetrahydro-9-methylcarbazole (VI) is produced. 1,4-Dihydro-9-methylcarbazole is presumably an intermediate and this, unlike 1-methylindole, is further reduced only in the six-membered ring; this is understandable since the electron-releasing methylene groups will further stabilise the five-membered ring toward reduction.

Since carbazole in sodium–ammonia–ethanol did not give a tetrahydro-derivative, 9-methoxymethylcarbazole was prepared * in the hope that it would be similarly reduced to 9-methylcarbazole and afford 1,4,5,8-tetrahydrocarbazole (VII) on hydrolysis. When 9-methoxymethylcarbazole was reduced, with sodium–ammonia–ammonium chloride, and hydrolysed, 1,4-dihydrocarbazole resulted. Reduction of 9-methoxymethylcarbazole with sodium–ammonia–ethanol yielded a mixture; hydrolysis and separation of this into neutral and basic fractions gave (yields in parentheses), in the former: 1,4-dihydrocarbazole (8%) and 1,4,5,8-tetrahydrocarbazole (VII) (42%), which together formed mixed crystals and so could not be separated; and, in the latter: a low-melting solid whose ultraviolet absorption spectrum indicated the presence of arylamine chromophore (chief constituent) and small amounts of the conjugated dienamine chromophore.[10] Presumably this mixture of bases is produced by the further reduction of 1,4-dihydro-9-methoxymethylcarbazole in both the five- and the six-membered ring.

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* We are indebted to Dr. G. F. Smith and Mr. H. A. Potts for details of the preparation and hydrolysis of 1-methoxymethylindole (unpublished) which we followed for the analogous carbazole compound.

[8] Schmidt and Schall, *Ber.*, 1907, **40**, 3225.
[9] Barclay, Campbell, and Gow, *J.*, 1946, 997.
[10] Millward, *J.*, 1960, 26.

EXPERIMENTAL

Reductions, unless otherwise stated, were carried out in conical flasks with industrial liquid ammonia. If the ammonia is said to be " anhydrous " this indicates that it was distilled from sodium, and that the reaction was carried out under a potassium hydroxide guard-tube. Auto-oxidisable products were kept either under nitrogen or under high vacuum according to their volatilities. Ultraviolet spectra were measured in ethanol, and infrared spectra in carbon disulphide.

Reduction of Indole.—Indole (2 g.) in ether was added to liquid ammonia (1·5 l.) and lithium (12 g.) was introduced gradually in small pieces. After 30 min. methanol was run in slowly until the colour disappeared. Ammonia was evaporated, water was added, and the product was isolated (with ether); it had b. p. 57—58°/0·05 mm., n_D^{23} 1·5596, $\lambda_{max.}$ 217 mμ (ε 5300). In the infrared spectrum the characteristic bands of indole (especially the strong ones at 718, 738, and 762 cm.$^{-1}$) were completely absent. The spectrum possesses bands characteristic of a *cis*-olefinic bond at 3024 and 1658 cm.$^{-1}$ and two bands at 706 and 666 cm.$^{-1}$ (Found: C, 79·9; H, 8·1; N, 11·6. Calc. for equal amounts of C_8H_9N and $C_8H_{11}N$: C, 80·0; H, 8·3; N, 11·7%).

Attempted Reduction of Pyrrole and 1-*Methylpyrrole.*—This was carried out by the use of the same method and proportions as in the reduction of indole; each product was made up to standard volume in ethanol and analysed spectrophotometrically. Recoveries of unchanged material were: pyrrole, 94; 1-methylpyrrole, 92%.

Partial Reduction of Indole.—This was performed to compare the effectiveness of various proton donors in promoting reduction. Indole (1 g.) in ether was added to anhydrous ammonia (700 c.c.) containing lithium (0·6 g.). This mixture was stirred continuously and samples were run into a second vessel fitted with a CO_2-cooled condenser and a side arm, through which potassium nitrate (to oxidise the lithium), or a proton donor, was subsequently introduced. The products were isolated with ether, and their indole contents measured spectrophotometrically.

		Ultraviolet absorption of product		Calculated % of indole in product	
Substance added to discharge colour	Interval between addition of indole and discharge of colour	$\frac{\varepsilon\ 276\ m\mu}{\varepsilon\ 230\ m\mu}$ before isolation	ε 271 mμ of isolated product	from $\frac{\varepsilon\ 276\ m\mu}{\varepsilon\ 230\ m\mu}$	from ε 271 mμ
KNO_3	10 min.	2·08	—	84	—
	1 hr.	1·84	—	78	—
	2 hr.	2·01	—	82	—
Bu^tOH	½ hr.	0·74	2,000	40	35
Pr^iOH		0·13	770	10	13
EtOH		0·33	1,000	20	17
MeOH		0·05	160	3	3
H_2O		0·69	—	40	—
$(NH_4)_2SO_4$		0·44	—	28	—
KNO_3 *	15 min.	2·33	5,100	90	88
	3 hr.	2·60	—	95	—

* Lithium indole used in place of indole, prepared from equivalent amounts of lithium butyl and indole.

Reduction of 2,3-*Dihydro*-1-*methylindole.*—This compound (1·0 g.), in ether, was added to liquid ammonia (150 c.c.) and ethanol (10 c.c.). Sodium (2·0 g.) was introduced in small pieces, with stirring, and when the blue colour was discharged and the ammonia had evaporated, the product was isolated in light petroleum (b. p. 30—40°) as a liquid (0·94 g.). Its ultraviolet absorption spectrum, when compared with that of the starting material, showed a decrease in extinction at shorter wavelengths and an increase at longer wavelengths, indicating the presence of starting material (40%) and a conjugated dieneamine ($\lambda_{max.}$ calculated by subtraction of the starting material spectrum: 310 mμ) [cf. Millward [10] who quotes $\lambda_{max.}$ 303 mμ (ε 10,500), for 2,3-dihydro-*NN*-dimethyl-*p*-toluidine].

Reduction of 1-*Methylindole.*—This compound (1·0 g.) was reduced as in the previous experiment. The product (0·96 g.) was dissolved in light petroleum (b. p. 30—40°; 25 c.c.) and extracted with 2½% hydrochloric acid (3 × 15 c.c.). The aqueous layer was immediately basified with sodium hydrogen carbonate and an ether extract obtained; this was dried ($MgSO_4$) and yielded, on evaporation, an oil (0·15 g.). The oil yielded a picrate in benzene which was recrystallised twice from benzene and had m. p. 158—164°, undepressed after admixture with the picrate of 2,3-dihydro-1-methylindole, m. p. 160—165°. The light petroleum layer was washed with sodium hydrogen carbonate solution, dried, and evaporated to leave 4,7-*dihydro*-1-*methylindole* (0·20 g.), b. p. 102—106°/15 mm., n_D^{18} 1·5490, $\lambda_{\text{max.}}$ 211 mμ (ε 6000) (Found: C, 80·9; H, 8·2. $C_9H_{11}N$ requires C, 81·2; H, 8·3%).

1,4-*Dihydro*-9-*methylcarbazole*.—9-Methylcarbazole (1 g.) in tetrahydrofuran was added to liquid ammonia (150 c.c.). Sodium (1·3 g.) was added and, after it had dissolved, the solution was kept for 30 min. Ammonium chloride was added until the blue colour was discharged, the ammonia was evaporated, and water (200 c.c.) was added. The product was collected, washed, and dried (1·30 g.). Crystallised three times from ethanol, 1,4-*dihydro*-9-*methylcarbazole* had m. p. 93—95°, $\lambda_{\text{max.}}$ 228, 285 mμ (ε 31,000; 6300) (Found: C, 85·2; H, 7·1; N, 7·65. $C_{13}H_{13}N$ requires C, 85·3; H, 7·1; N, 7·6%).

1,4,5,8-*Tetrahydro*-9-*methylcarbazole*.—9-Methylcarbazole (1 g.) in tetrahydrofuran, was added to a mixture of liquid ammonia (150 c.c) and ethanol (20 c.c.). Sodium (1·3 g.) was added, and when the blue colour was finally discharged, ammonia was evaporated and water (200 c.c.) added. The product was extracted with benzene, dried, and evaporated, yielding 1,4,5,8-*tetrahydro*-9-*methylcarbazole* (1·05 g.); this was recrystallised three times from ethanol and had m. p. 142—144°, $\lambda_{\text{max.}}$ 224 mμ (ε 5100) (Found: C, 83·9; H, 7·8; N, 7·4. $C_{13}H_{15}N$ requires C, 84·3; H, 8·2; N, 7·6%).

1,4-*Dihydrocarbazole*.—Carbazole (1·0 g.) was reduced in two ways: first, as in the preparation of 1,4-dihydro-9-methylcarbazole, and, secondly, as in the preparation of 1,4,5,8-tetrahydro-9-methylcarbazole. Each product was collected by filtration and dried (1·0 g.). Recrystallised twice from light petroleum (b. p. 80—100°) and once from ethanol, each sample of 1,4-dihydrocarbazole had m. p. 180—210°, $\lambda_{\text{max.}}$ 226, 281 mμ (ε 18,200, 5800) (Found: C, 85·0; H, 6·55; N, 8·5. Calc. for $C_{12}H_{11}N$: C, 85·2; H, 6·5; N, 8·3%).

9-*Methoxymethylcarbazole*.—Carbazole (4·5 g.), slurried in ether, was added to anhydrous, liquid ammonia containing sodamide (prepared from 0·9 g. of sodium), and stirred for 10 min. before chloromethyl ether (9 g.—an excess, as it is ammonolysed) was quickly added. After evaporation of the ammonia, the product was diluted with sodium hydroxide solution and isolated with ether as a solid (5·2 g.), containing carbazole (N–H stretching band at 3463 cm.$^{-1}$). The solid was taken up in benzene, a less soluble portion (1·0 g.) being discarded, evaporated, taken up in 4 : 1 light petroleum (b. p. 80—100°)–benzene, and washed through alumina with the same solvent mixture. The first 300 c.c. contained carbazole, after which pure 9-*methoxymethylcarbazole* (3·1 g.) was eluted, and recrystallised from ethanol; it had m. p. 58—59°, $\lambda_{\text{max.}}$ 232, 247, 257, 320, 332 mμ (ε 42,700; 19,000; 11,200; 3500; 3400) (Found: C, 79·5; H, 5·9; N, 6·7. $C_{14}H_{13}NO$ requires C, 79·6; H, 6·2; N, 6·6%).

Reduction and Hydrolysis of 9-*Methoxymethylcarbazole*.—(*A*) 9-Methoxymethylcarbazole (0·5 g.) was reduced as in the preparation of 1,4,5,8-tetrahydro-9-methylcarbazole. The product (0·45 g.), in ethanol containing phloroglucinol (1·35 g.; to remove formaldehyde) and concentrated hydrochloric acid (30 drops), was warmed under nitrogen for 7 min., cooled, basified with sodium hydroxide solution, and extracted with ether. The extract was washed with 2½% hydrochloric acid (3 × 20 c.c.) and sodium hydrogen carbonate solution, dried, and evaporated (0·16 g.). The product was crystallised from ethanol; it had m. p. 180—210°, $\lambda_{\text{max.}}$ 283 mμ ($E^{1\%}_{1\,\text{cm.}}$ 52·6, corresponding to 16% of 1,4,-dihydrocarbazole) (Found: C, 84·3; H, 7·3; N, 8·8. Calculated for 84% of $C_{12}H_{13}N$ + 16% of $C_{12}H_{11}N$: C, 84·4; H, 7·4; N, 8·2%).

The acid extracts were immediately basified with sodium hydrogen carbonate and extracted with ether to yield an oil (0·17 g.). This was distilled (bath temp. 100°/0·05 mm.) to a solid, m. p. 40—50°, $\lambda_{\text{max.}}$ 243 mμ ($E^{1\%}_{1\,\text{cm.}}$ 360), 293 mμ ($E^{1\%}_{1\,\text{cm.}}$ 134) (Found: C, 83·95; H, 8·0; N, 8·2. Calc. for 70% of $C_{12}H_{13}N$ + 30% of $C_{12}H_{15}N$: C, 83·9; H, 7·9; N, 8·2%).

(*B*) 9-Methoxymethylcarbazole (0·5 g.) was reduced as in the preparation of 1,4-dihydro-9-methylcarbazole. Hydrolysis of the reduced product, as above, yielded 1,4-dihydrocarbazole (0·35 g.).

The authors are indebted to Professor A. J. Birch for encouragement and valuable discussions and they thank the Department of Scientific and Industrial Research for a maintenance grant (to S. O'B.).

DEPARTMENT OF CHEMISTRY,
UNIVERSITY, MANCHESTER, 13.

[*Received, February* 26*th*, 1960.]