THE REDUCTION OF INDOLES AND RELATED COMPOUNDS

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Received February 18, 1969

Contents

I. Introduction

The reductions referred to in this article are limited to reactions involving the saturation of multiple bonds by addition of hydrogen, the removal of oxygen, which is usually accompanied by addition of hydrogen, and hydrogenolysis of C–C and C–N bonds. The reduction of aminochromes by sodium dithionite, sodium borohydride, zinc–dilute acetic acid, ascorbic acid, and various thiols to afford 5,6-dihydroxyindoles, *via* formation of the corresponding 3-hydroxyindolines, and various further reaction products is not discussed since these reactions and their probable mechanisms, together with studies effected so far upon the reduction of adrenochrome alkyl ethers, are included in a recent review[1] (see also ref 2). Where it is thought necessary, studies carried out prior to 1952 are briefly mentioned and are covered in most cases by reference to the two well-known treatises on indole chemistry published in 1952[3] and 1954.[4] Literature references up to and through the 1967 issues of *Current Chemical Papers* and *Chemical Abstracts*, and several papers published in 1968 which became available, are covered.

II. Reduction of Indoles

Many methods have been employed in the reduction of indoles, the nature of the product(s) depending upon the method used.

The indole nucleus is not reduced by sodium–amyl alcohol[5] or by sodium–butyl alcohol,[6] but indolines are produced by electrolytic reduction of indoles in acid media[3d, 4a, 7] and by reduction with phosphonium iodide in hydrogen iodide–saturated hydriodic acid.[8]

A. METAL–ACID REDUCTION

The reduction of indole with zinc dust,[4a] tin,[3f, 4a] or zinc amalgam[9] in hydrochloric acid affords indolines, but the yield of indoline produced from indole by such reductions is lowered by simultaneous polymerization of indole in the acidic media. This side reaction has now[10] been eliminated by effecting this reduction with zinc dust in 85% phosphoric acid, under nitrogen to prevent aerial oxidation. Under these conditions the 3H-indolium cation which is formed by protonation of the indole nucleus at C_3, and which is presumably[10-12] the intermediate in reductions carried out under acid conditions, is stable to polymerization and indoline is produced in 64–69% yield.[10] However, reduction of 2,3-dimethylindole to the

(1) R. A. Heacock, *Advan. Heterocycl. Chem.*, 5, 205 (1965).

(2) G. L. Mattok and R. A. Heacock, *Can. J. Chem.*, 44, 565 (1966).

(3) P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y.; Chapman and Hall Ltd., London, 1952: (a) p 7; (b) p 8; (c) p 102; (d) p 115; (e) p 117; (f) p 118; (g) p 120; (h) p 129; (i) p 130; (j) p 174; (k) p 193; (l) p 196; (m) p 212; (n) p 213; (o) p 214; (p) p 231; (q) 234; (r) p 244; (s) p 245; (t) p 268; (u) p 269; (v) p 303; (w) p 307.

(4) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y.; Interscience Publishers Ltd., London, 1954: (a) p 36; (b) p 37; (c) p 38; (d) p 39; (e) p 94; (f) p 95; (g) p 117; (h) p 118; (i) p 132; (j) p 135; (k) p 139; (l) p 140; (m) p 148; (n) p 149; (o) p 166; (p) p 182; (q) p 183; (r) p 184; (s) p 206.

(5) H. Booth, F. E. King, and J. Parrick, *J. Chem. Soc.*, 2302 (1958).

(6) V. Boekelheide and C.-T. Liu, *J. Amer. Chem. Soc.*, 74, 4920 (1952).

(7) S. G. P. Plant and D. M. L. Rippon, *J. Chem. Soc.*, 1906 (1928).

(8) C. B. Hudson and A. V. Robertson, *Aust. J. Chem.*, 20, 1935 (1967).

(9) A. N. Kost, A. K. Sheinkman, and N. F. Kazarinova, *Khim. Geterotsikl. Soedin.*, 722 (1966); *Chem. Abstr.*, 66, 115538 (1967).

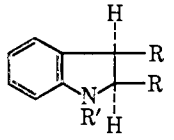
(10) L. J. Dolby and G. W. Gribble, *J. Heterocycl. Chem.*, 3, 124 (1966).

(11) A. Smith and J. H. P. Utley, *Chem. Commun.*, 427 (1965).

(12) A. Cohen and B. Heath-Brown, *J. Chem. Soc.*, 7179 (1965).

corresponding *cis*- and *trans*-2,3-dimethylindolines (see below) by this method occurs in only 28% total yield,[10] and 1,2,3,4-tetrahydrocarbazole is reduced to 1,2,3,4,4a,9a-hexahydrocarbazole in only 49% yield.[10] The reduction of these two indoles, which do not polymerize under acidic conditions, to the corresponding indolines is effected in higher yields by the earlier metal–acid methods.

Reduction of 2,3-dimethylindole by metal–acid affords a mixture of *cis*-2,3-dimethylindoline (**1**, R = Me; R′ = H) and *trans*-2,3-dimethylindoline (**2**, R = Me) in a yield ratio of approximately 2:1, respectively.[10,13] Although the earlier[13] assignment of the relative configuration of these two isomeric products is not very convincing, the later[10] assignment was made by comparison of the pmr spectral properties of the two isomers with the similar data published previously[14] and would appear to be satisfactory. Similar reduction of 1,2,3,4-tetrahydrocarbazole affords, as would be expected, mainly *cis*-1,2,3,4,4a,9a-hexahydrocarbazole [**1**, R + R = $(CH_2)_4$; R′ = H], in one instance[15] 1.3% of what was presumed to be the *trans* isomer [**2**, R + R = $(CH_2)_4$] being isolated. In another case[10] the formation of this isomer probably occurred, but the compound remained undetected. Similarly, the electrolytic reduction of **3** affords only the *cis*-indoline **1** [R + R = $(CH_2)_8$; R′ = H][7] as would be expected since now the formation of the corresponding *trans* isomer is sterically impossible.



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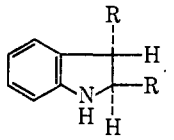

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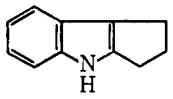

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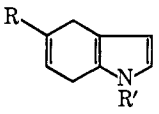
B. BIRCH REDUCTION

Early studies[16] led to the conclusion that sodium–ammonia reduction of indole affords indoline. However, the product from this reaction has now[17] been shown to be a mixture of indole and a product resulting from reduction in the benzenoid ring. It was found[17] that lithium–ammonia has very little reducing effect upon indole owing to the formation of the nonreducible indole lithium salt (see also ref 18). However, in the presence of methanol (an effective proton source which will liberate indole from its lithium salt) and excess lithium, indole is converted[17] into a mixture of 4,7-dihydroindole (**4**, R = R′ = H) and 4,5,6,7-tetrahydroindole (**5**) which are formed in about equal yields. 1-Methylindole, in which salt formation



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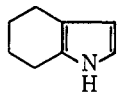

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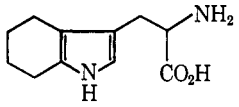
is impossible, is much easier to reduce and is converted[17] by treatment with sodium–ammonia–ethanol into 1-methylindoline (by reduction in the pyrrolic ring) and 4,7-dihydro-1-methylindole (**4**, R = H; R′ = Me) (by reduction in the benzenoid ring). It could be that nonbonding interaction between the 1-methyl group and the C_7 hydrogen atom in 1-methylindole is responsible for the reducibility of the 2,3 double bond in 1-methylindole.[17] Reduction of tryptophan by lithium–ammonia–methanol affords 7% of 4,5,6,7-tetrahydrotryptophan (**6**) and 55% of 4,7-dihydrotryptophan (**7**).[19] These products are analogous to those obtained from the similar reduction of indole[17] as described above.



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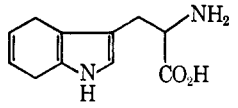

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These studies have now been extended[20] to 5-methoxyindoles, 5-methoxy-1-methylindole affording only 5-methoxy-1-methylindoline by reduction with lithium–ammonia, a mixture of 60% of 4,7-dihydro-5-methoxy-1-methylindole (**4**, R = OMe; R′ = Me), 4% of 5-methoxy-1-methylindoline, and 8% of starting material by reduction with lithium–ammonia–methanol (present prior to the addition of the lithium) and a mixture of **4** (R = OMe; R′ = Me) and 5-methoxy-1-methylindoline by reduction with lithium–ammonia–methanol (added during the reaction). The yield ratio of the two products in this latter reduction depends upon the time after reaction initiation at which the methanol was added. However, irrespective of whether the methanol was present before the addition of the lithium or was added during the reaction, the lithium–ammonia–methanol reduction of 5-methoxyindole affords only 4,7-dihydro-5-methoxyindole (**4**, R = OMe; R′ = H).[20]

C. REDUCTIONS WITH SODIUM BOROHYDRIDE, LITHIUM ALUMINUM HYDRIDE, AND BORANE

Indole is not reduced by either sodium borohydride[21] or lithium aluminum hydride,[21,22] nor are other 1-unsubstituted indoles[22–24] reduced with lithium aluminum hydride. This nonreducibility has been illustrated in numerous cases in studies connected with the indole alkaloids where sodium borohydride (see for examples ref 25) and lithium aluminum

(13) A. R. Bader, R. J. Bridgwater, and P. R. Freeman, *J. Amer. Chem. Soc.*, 83, 3319 (1961).
(14) F. A. L. Anet and J. M. Muchowski, *Chem. Ind.* (London), 81 (1963).
(15) J. Gurney, W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 2676 (1927).
(16) C. Fernelius and A. Fields, quoted as ref 108 in G. W. Watt, *Chem. Rev.*, **46**, 317 (1950).
(17) S. O'Brien and D. C. C. Smith, *J. Chem. Soc.*, 4609 (1960).
(18) S. Wilkinson, *ibid.*, 2079 (1958).
(19) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Amer. Chem. Soc.*, **88**, 3941 (1966).
(20) W. A. Remers, G. T. Gibs, C. Pidacks, and M. J. Weiss, *ibid.*, 89, 5513 (1967).
(21) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.*, 6, 78 (1966).
(22) P. L. Julian and H. C. Printy, *J. Amer. Chem. Soc.*, 71, 3206 (1949).
(23) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).
(24) A. S. F. Ash and W. R. Wragg, *ibid.*, 3887 (1958).
(25) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 2, 1 (1958); M. M. Robison, W. G. Pierson, R. A. Lucas, I. Hsu, and R. L. Dziemian, *J. Org. Chem.*, 28, 768 (1963); E. E. Van Tamelen and C. Placeway, *J. Amer. Chem. Soc.*, 83, 2594 (1961); M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi, and E. Wenkert, *ibid.*, **84**, 622 (1962); F. E. Bader, D. F. Dickel, C. F. Huebner, R. A. Lucas, and E. Schlittler, *ibid.*, 77, 3547 (1955).

hydride (see for examples ref 26) reductions of functional group(s) present in these complex molecules have been effected without reduction of the indole nucleus. Indole is reduced to indoline in 48% yield, however, by borane in tetrahydrofuran.[27] Although 1-methyl- and 1,3-dimethylindole have been reported[22] to be reduced by lithium aluminum hydride to the corresponding indolines in 25–30% yields, later related studies[5] failed to support these observations. 1,2,3,4-Tetrahydro-9-methylcarbazole remains unreduced when treated with lithium aluminum hydride,[5] and 1,3-disubstituted oxindoles afford 1,3-disubstituted indoles upon reduction with this reagent (see section VII).

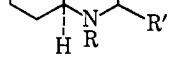
Photolysis of tryptophan in the presence of sodium borohydride effects, among other reactions, its photoreduction to afford a 9.4% yield of 4,7-dihydrotryptophan (7) and 4% of 2,3-dihydrotryptophan.[19]

D. CATALYTIC HYDROGENATION

Two early detailed studies on the catalytic hydrogenation of indoles were carried out.[28,29] Whereas metal–acid reductions of indoles (see section II.A) afford indolines as end-products, catalytic hydrogenation of indoles often proceeds further than the indoline stage or occurs at positions alternative to the indolic 2,3 double bond, and may even cause rupture of the pyrrolic ring.[4b] Hydrogenation of indole with a nickel catalyst in ethanolic solution affords 1-ethyloctahydroindole by saturation of the aromatic system and reductive ethylation of the nitrogen atom.[4d] Catalysts used for the hydrogenation of indoles to indolines are platinum, nickel, nickel salts, copper, copper salts,[4b] and palladium hydroxide–barium sulfate.[30] It is interesting that under vigorous conditions using a copper chromite catalyst, hydrogenation of 2,3-dimethylindole has been reported[13] to afford only *trans*-2,3-dimethylindoline (2, R = Me), the *cis* isomer being the expected sole product from this reaction. It is suggested[13] that under the vigorous conditions used the hydrogenation reaches an equilibrium involving appreciable dehydrogenation of the indoline and thus the indoline formed is the more stable *trans* isomer. Presumably such an equilibration–dehydrogenation, if it occurs, would have to involve the formation of some 2,3-dimethyl-3H-indole in order that it could ultimately effect the formation of the *trans*-indoline. However, the establishment of the *trans* configuration of the product in this work[13] leaves much to be desired and further investigation of this product would be of interest. Compound **3**,[5] 1,2,3,4-tetrahydrocarbazole,[5] and its 9-methyl derivative[5,29] afford, as expected, the *cis*-indolines **1** [R′ = H; R + R = $(CH_2)_3$ and $(CH_2)_4$] and **1** [R′ = Me; R + R = $(CH_2)_4$], respectively, upon catalytic hydrogenation.

2,3-Disubstituted indoles have recently[11] been hydrogenated to the corresponding 2,3-disubstituted indolines in very high yields, often quantitative, using a platinum catalyst in ethanolic 42% w/w aqueous fluoroboric acid at room temperature and atmospheric pressure. It is claimed[11] that this procedure is extremely valuable since chemical reduction of indoles to indolines is often inconvenient and other methods of catalytic hydrogenation of 2,3-dialkylindoles often afford relatively much lower yields. It is essential, however, that the indole being hydrogenated must either be acid stable or be very rapidly reduced relative to being polymerized.[11]

When the above-mentioned hydrogenation of 1,2,3,4-tetrahydro-9-methylcarbazole is continued, a second product is formed[31] which is probably dodecahydro-9-methylcarbazole.[31] Under the appropriate conditions indole, 2- and 3-methylindole, and 1,2-dimethylindole can be catalytically hydrogenated to the corresponding octahydroindoles.[4b] The A–B ring junction in such compounds is *cis*-fused as shown in **8**[32–36] (see also ref 12).



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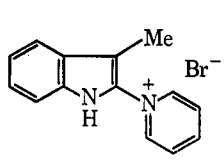
Several examples are known[6,12,37,38] in which catalytic hydrogenation of an indole ring affords the 4,5,6,7-tetrahydroindole derivatives. In one of these cases[37] an aliphatic nitro group in the molecule remains unreduced under conditions which would normally effect its conversion to an amino group (*cf.* ref 12).

E. REDUCTIVE CLEAVAGE OF SUBSTITUENTS FROM THE INDOLE NUCLEUS

2-Ethoxyindole affords 66% of indole and 9.8% of indoline upon reduction with borane in tetrahydrofuran.[27] Similar cleavage of a 2 substituent occurs when compound **9** is exhaustively hydrogenated in the presence of a platinum catalyst to afford skatole and piperidine hydrobromide.[39] If this hydrogenation is arrested after the uptake of 3 moles of hydrogen or if it is effected in the presence of palladium–carbon instead of platinum, it affords compound **10**.[39]



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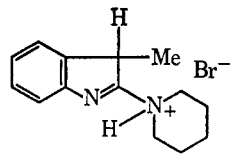

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III. Reduction of Indolines

Indolines are probably formed as intermediates in the catalytic

(26) N. Neuss, H. E. Boaz, and J. W. Forbes, *J. Amer. Chem. Soc.*, 75, 4870 (1953); 76, 2463, (1954); M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *ibid.*, 80, 126 (1958); P. L. Julian and A. Magnani, *ibid.*, 71, 3207 (1949); K. Biemann, *ibid.*, 83, 4801 (1961); R. C. Elderfield and A. P. Gray, *J. Org. Chem.*, 16, 506 (1951); R. C. Elderfield and S. L. Wythe, *ibid.*, 19, 683 (1954); P. Karrer, R. Schwyzer, and A. Flam, *Helv. Chim. Acta*, 35, 851 (1952); K. Freter, H. H. Hübner, H. Merz, H. D. Schroeder, and K. Zeile, *Ann. Chem.*, 684, 159 (1965); J. Harley-Mason and A.-u.-Rahman, *Chem. Commun.*, 1048 (1967).

(27) H. Plieninger, H. Bauer, W. Bühler, J. Kurze, and U. Lerch, *Ann. Chem.*, 680, 74 (1964).

(28) H. Adkins and H. L. Coonradt, *J. Amer. Chem. Soc.*, 63, 1563 (1941).

(29) H. Adkins and R. E. Burks, *ibid.*, 70, 4174 (1948).

(30) I. Butula and R. Kuhn, *Angew. Chem.*, 7, 208(1968).

(31) K. H. Bloss and C. E. Timberlake, *J. Org. Chem.*, 28, 267 (1963).

(32) F. E. King, D. Bovey, K. Mason, and R. L. Whitehead, *J. Chem. Soc.*, 250 (1953).

(33) F. E. King, J. A. Barltrop, and R. J. Wally, *ibid.*, 277 (1945).

(34) A. Betho and J. F. Schmidt, *Chem. Ber.*, 97, 3284 (1964).

(35) M. A. Voladina, G. V. Kiryushkina, and A. P. Terent'ev, *Dokl. Akad. Nauk SSSR*, 162, 90 (1965); *Chem. Abstr.*, 63, 5583 (1966).

(36) M. P. Mertes and S. A. Nerurkar, *J. Med. Chem.*, 11, 106 (1968).

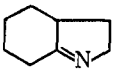
(37) D. V. Young and H. R. Snyder, *J. Amer. Chem. Soc.*, 83, 3160 (1961).

(38) H. M. Kissman and B. Witkop, *ibid.*, 75, 1967 (1953).

(39) T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, 23, 1441 (1967).

hydrogenation of indoles to octahydroindoles (see section II.D).

The benzenoid nuclei of the indoline moieties in several alkaloids have been fully saturated by catalytic hydrogenation in acidic solution over platinum.[40] Catalytic hydrogenation of indolines in the presence of a ruthenium catalyst affords only the *cis*-octahydroindoles (**8**),[36] and hydrogenation of indoline in 1 *N* hydrochloric acid in the presence of a palladium hydroxide–barium sulfate catalyst affords as the main product compound **11** along with a little octahydroindole.[30]



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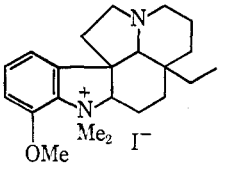
Hydrogenolysis of the indoline nucleus in deacetyl-1,1-dimethylaspidospermium iodide (**12**) by sodium in dry ammonia (Emde degradation) affords, along with other unidentified products, compound **13**, resulting from scission of the 1,7a bond in the indoline nucleus.[41] When this reaction was extended[42–44] to simple model 1-methylindoline methiodides, it was found that the position of ring scission depended upon



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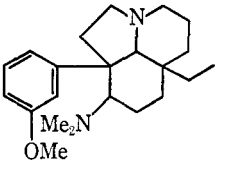

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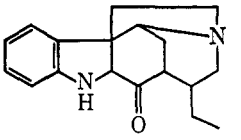
the conditions used to effect the cleavage. With sodium–dry ammonia,[42] sodium–ammonia + 0.5% water,[43] electrolytic reduction in dry ammonia,[44] and electrolytic reduction in ammonia + 0.5% water,[44] ring cleavage of the indoline nucleus occurs between the 1,7a and 1,2,1,7a, 1,7a, and 1,2 $^{+}$N–C atoms, respectively. The above result with sodium–dry ammonia[42] is similar to that previously[45] obtained when 1,3-dimethylindoline methiodide is reduced with sodium amalgam. Although the main product from this reduction was 1,3-dimethylindoline (76%), dimethyl(2-phenylpropyl)amine (24%), resulting from 1,7a cleavage, and a trace of N,N-dimethyl-2-isopropylaniline, resulting from 1,2 cleavage, were also formed.[45] However, another attempt[46] to cleave the indoline nucleus in a 1-methylindoline methiodide using modified Emde reduction conditions (*i.e.*, hydrogenation over Raney nickel) failed.[46]

The 1,2 bond in the indoline nucleus of **14** has also been cleaved by zinc amalgam in concentrated hydrochloric acid to afford **15**.[47] This reaction is effectively a cleavage of an α-amino ketone.[47]



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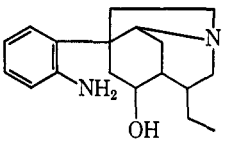
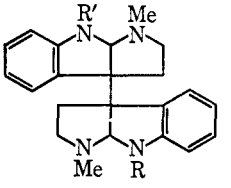


15

Reductive cleavage of the 3,3′ bond of the 3,3′-diindoline systems present in the alkaloids folicanthine, calycanthidine, and chimonanthine (**16**, R = R′ = Me; R = H, R′ = Me; R = R′ = H, respectively) can be effected[48] with zinc–hydrochloric acid to afford 1-methyl-3-(2′-methylaminoethyl)-indoline, a mixture of 3-(2′-methylaminoethyl) indoline and 1-methyl-3-(2′-methylaminoethyl) indoline, and 3-(2′-methylaminoethyl)indoline, respectively.



16

IV. Reduction of 3H-Indoles and 1-Alkyl-3H-indolium Salts

A. CHEMICAL AND CATALYTIC REDUCTIONS

There are numerous examples in the literature of reductions of this type, and only representative examples will be given to indicate the scope of the reaction, which results in the formation of the corresponding indolines.

3H-Indoles are converted into the corresponding indolines by reduction with zinc and acetic acid,[3e] zinc amalgam and hydrochloric acid,[3e] tin and hydrochloric acid,[5,49] sodium in alcohol,[3c,5] sodium borohydride,[50] and lithium aluminum hydride[51,52] and by high-pressure catalytic hydrogenation using platinum[3c,g,58] and copper–chromium oxide[29] as catalysts. The report[54] that simple 3,3-dialkyl-3H-indoles are not catalytically reduced in neutral or alkaline media whereas hydrogenation to indolines is very rapid in acetic media probably refers to hydrogenations carried out at room temperature and atmospheric pressure. Catalytic hydrogenation of 3H-indoles **17** in which R is a bulkier group than the methyl group affords predominantly the indolines **18**, as would be expected by the addition of hydrogen at the 2 position of **17** from the least sterically hindred side.[55] Reduction of 1,2,3,4-tetrahydro-4a-methyl-4aH-carbazole to 1,2,3,4,4a,9a-hexahydro-4a-methylcarbazole has also been effected by photolysis in isopropyl alcohol solution.[51]

(40) H. Leuchs and H. S. Overberg, *Chem. Ber.*, 66, 951 (1933); H. Leuchs, H. Beyer, and H. S. Overberg, *ibid.*, 66, 1378 (1933); M. Hesse, H. Hiltebrand, C. Weissman, W. von Philipsborn, K. Bernauer, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 44, 2211 (1961); F. A. L. Anet, D. Chakravarti, R. Robinson, and E. Schlittler, *J. Chem. Soc.*, 1242 (1954).

(41) G. F. Smith and J. T. Wrobél, *ibid.*, 1463 (1960).

(42) J. T. Wrobél and A. M. Konowa, *Rocz. Chem.*, 39, 1437 (1965); *Chem. Abstr.*, 64, 17522 (1966).

(43) J. T. Wrobél, A. S. Bién, and K. M. Pazdo, *Chem. Ind.* (London), 1759 (1966).

(44) J. T. Wrobél, K. M. Pazdo, and A. S. Bién, *ibid.*, 1760 (1966).

(45) J. von Braun, K. Heider, and L. Neumann, *Chem. Ber.*, 49, 2613 (1916).

(46) W. E. Noland and F. J. Baude, *J. Org. Chem.*, 31, 3321 (1966).

(47) C. Weissmann, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 42, 2201 (1960).

(48) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 1877 (1957); H. F. Hodson, B. Robinson, and G. F. Smith, *Proc. Chem. Soc.*, 465 (1961); J. E. Saxton, W. G. Bardsley, and G. F. Smith, *ibid.*, 148 (1962).

(49) G. Plancher, B. Cecchetti, and E. Ghigi, *Gazz. Chim. Ital.*, 59, 334 (1929).

(50) F. J. Evans, G. G. Lyle, J. Watkins, and R. E. Lyle, *J. Org. Chem.*, 27, 1553 (1962).

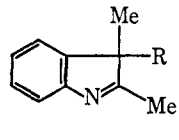
(51) P. Cerutti and H. Schmid, *Helv. Chim. Acta*, 45, 1992 (1962).

(52) G. Stork and J. E. Dolfini, *J. Amer. Chem. Soc.*, 85, 2872 (1963).

(53) M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi, and E. Wenkert, *ibid.*, 84, 622 (1962).

(54) A. H. Jackson and A. E. Smith, quoted as unpublished results in ref 64.

(55) A. H. Jackson and P. Smith, *J. Chem. Soc., C*, 1667 (1968).



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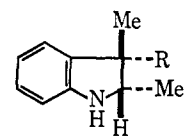

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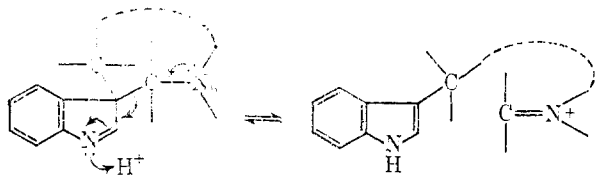
The 3-aminomethyl-3H-indole system **19**, present in several alkaloids, is reduced by lithium aluminum hydride in ether to the corresponding indoline system **21**.[56,57] However, reduction of **19** by sodium borohydride in methanol affords the indolic system **22** *via* the formation of **20**, in equilibrium with **19**, by retro-Mannich condensation as shown.[56-61] In ether and other aprotic solvents, the equilibrium **19** ⇌ **20** cannot exist; hence **21** is produced from the reduction with lithium



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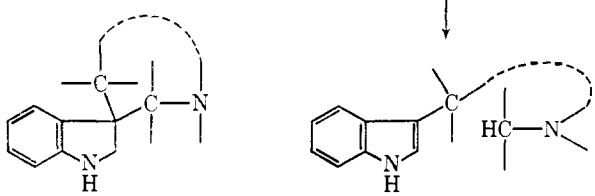
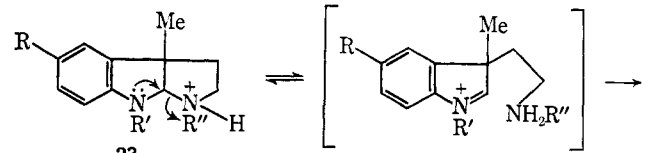


21 22

aluminum hydride in ether solution. The C=N$^+$ group in the ring-opened species **20** is much more readily reduced than the 3H-indole moiety. Therefore only low concentrations of it are necessary to afford high yields of **22** by reduction in protic media,[56] although small amounts of the indolines **21** have also been isolated from such reductions.[57] Sodium borohydride reduction of **19** in acidic solution, in which N_b is protonated,[56] or of the N_b quaternary salts of **19**,[59] affords only **21**; in both these cases the retro-Mannich reaction is precluded by removal of the N_b p-electron pair.[56,59]

3H-Indolium cations, formed by protonation of the indole moiety at C_3, have been postulated[10-12] as the reducible species in the reduction of indoles to indolines in acid media (see section II.A). 1-Alkyl-3H-indolium salts are reduced to the corresponding 1-alkylindolines with sodium borohydride[51] or potassium borohydride[62] and by catalytic hydrogenation,[63] and 1,2,3,4-tetrahydro-4a,9-dimethyl-4aH-carbazolium iodide affords[51] 1,2,3,4,4a,9-hexahydro-4a,9-dimethylcarbazole upon reduction by photolysis in isopropyl alcohol.

The observations that the Ph-N-C-N system in physostigmine and related compounds **23** is stable to reduction in neutral or alkaline media whereas reduction in acidic media affords the ring-opened indolines **25** has led to the suggestion[64] that these reductions occur *via* the 3H-indolium cations **24** which are formed from **23** as shown. By analogy with this,



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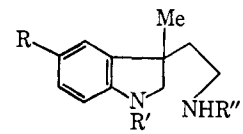
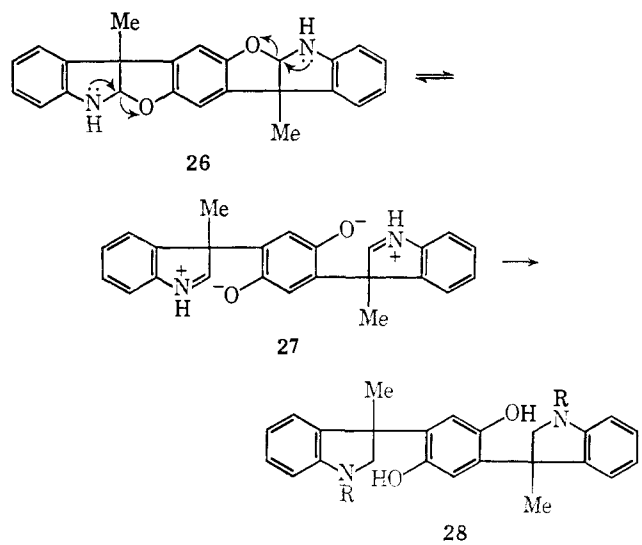


25

the reduction of compound **26** with hydrogen in the presence of Raney nickel in ethanol solution to **28** (R = Et)[46] and in N,N-dimethylformamide or dioxane solution to **28** (R = H)[46] may proceed *via* the 3H-indolium cation **27**.



26 27

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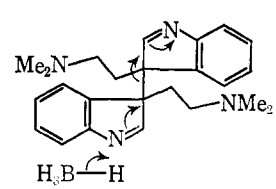
Treatment of compound **29**, a degradation product of chimonanthine, with methanolic sodium borohydride affords 2 moles of 3-(2′-dimethylaminoethyl)indole per mole of **29**,[65]



29

a possible mechanism for this cleavage being shown in **29**. A similar cleavage played an important role in the elucidation of the structure of hodgkinsine by chemical methods[66] (this

(56) G. F. Smith and J. T. Wrobel, *J. Chem. Soc.*, 792 (1960).
(57) G. F. Smith and M. A. Wahid, *ibid.*, 4002 (1963).
(58) K. Biemann and G. Spiteller, *J. Amer. Chem. Soc.*, 84, 4578 (1962).
(59) J. A. Joule and G. F. Smith, *J. Chem. Soc.*, 312 (1962).
(60) A. Z. Britten, G. F. Smith, and G. Spiteller, *Chem. Ind.* (London), 1492 (1963).
(61) J. A. Joule and G. F. Smith, *Proc. Chem. Soc.*, 322 (1959).
(62) B. Robinson and G. F. Smith, *J. Chem. Soc.*, 4574 (1960).
(63) R. B. Longmore and B. Robinson, University of Manchester, Manchester, England, unpublished observation, 1967.
(64) A. H. Jackson and A. E. Smith, *J. Chem. Soc.*, 5510 (1964).
(65) G. F. Smith, University of Manchester, Manchester, England, personal communication, 1968.
(66) G. F. Smith, presented in a lecture delivered at the 4th International Symposium on the Chemistry of Natural Products, Stockholm, Sweden, Sept 1966.

structure was subsequently confirmed by X-ray crystallographic methods[67]).

B. MECHANISM OF ENZYMIC DEHYDROGENATION REACTIONS

Using the enzyme yeast alcohol dehydrogenase with CH_3CHTOH as substrate, it has been observed[68] that the tritium label is stereospecifically transferred during the reaction to the methylene group of the tryptophan in the enzymic protein. This led to[68] the following postulation, as shown in Figure 1, for the mechanism of action of the dehydrogenase, involving the reversible dehydrogenation of the indole moiety in the tryptophan to a 3H-indolium cation containing an sp^2-hybridized C_3 atom. Evidence was subsequently[69] obtained suggesting that this mechanism also operates with L-malate and L-lactate dehydrogenases and could therefore be of a general character.

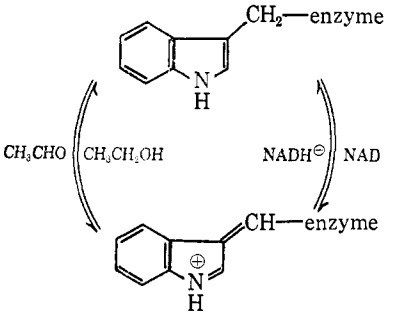
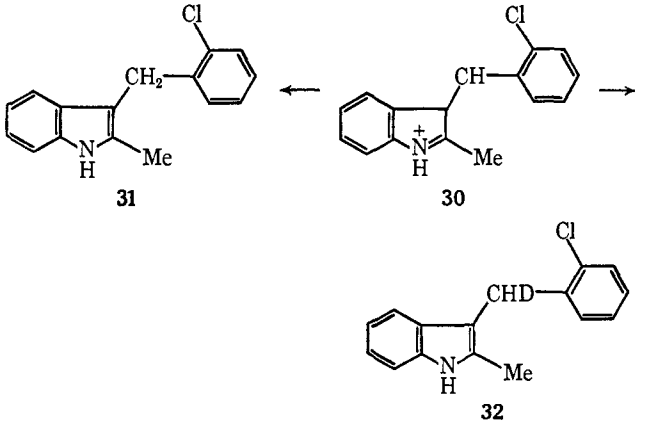
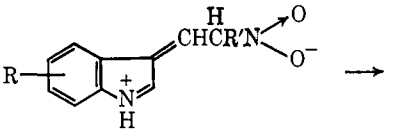


Figure 1. The postulated mechanism of action of yeast alcohol dehydrogenase.

Model chemical experiments have now been effected[70-72] to investigate the feasibility of this postulation. The 3H-indolium salt **30** has been[70] reduced to **31** by either sodium borohydride or 1-benzyl-1,4-dihydronicotinamide and to **32**, in which the deuterium is in a position analogous to that occupied by the tritium on the tryptophan after the earlier enzymic studies,[68,69] by 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide. An analogous reduction to these has appeared[73] in which the tryptamines **34** have been synthesized by the reduction of **33** with lithium aluminum hydride. Compound **30** is not, however,





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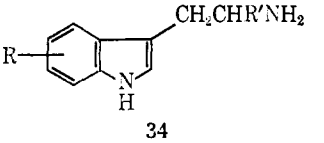
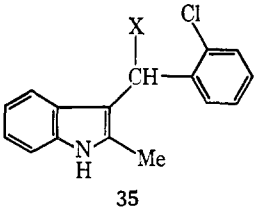


34

reduced by ethanol. This suggests that the above model reactions only mimic part of the enzymic reaction and that other, as yet unidentified, groups in the enzyme (or enzyme system) serve to activate the substrate and the indolic moiety.[70,71]

Comparative kinetic studies on the reduction of **30**, and **30** in which the *o*-chloro substituent is replaced by *p*-methoxy and *p*-nitro substituents, showed that the rate of reduction was increased by electron-withdrawing substituents in this ring, suggesting that the reduction is effected by a hydride transfer mechanism.[70,71] Other evidence[70-72] also suggested that free radicals are not involved. Further kinetic studies effected[72] on the reduction of compounds related to **30** by diethyl 2,6-dimethyl-1,4-dihydropyridyl-3,5-dicarboxylate supported the above conclusions.

Compound **30** reacts with mercaptans to afford **35** (X = SR), from which it can be reductively regenerated by treat-



35

ment with sodium dithionite.[70,71] It could be that the 3H-indolium moiety in the proposed enzymic reaction (Figure 1) is stabilized *in vivo* by similar reaction with the thiol group of a cysteine unit in the enzymic protein chain, from which it could be reductively regenerated when required.[70,71] Compounds related to **30**, however, also react with secondary amines to afford products related to **35** (X = NRR′) and so alternatively it could be that the 3H-indolium moiety in the proposed enzymic reaction is stabilized *in vivo* by an analogous reaction and regenerated when required by acid catalysis.[72]

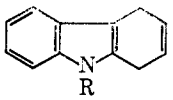
V. Reduction of Carbazoles

A. SODIUM–ALCOHOL REDUCTIONS

The reduction of carbazole with sodium in boiling amyl alcohol has led to many conflicting results. Initially[74] the reduction was found to afford only 1,2,3,4-tetrahydrocarbazole, whereas later[75] 1,4-dihydrocarbazole (**36**, R = H) was claimed to be produced. This latter product was subsequently shown[76]

(67) J. Fridrichsons, M. F. Mackay, and A. M. Mathieson, *Tetrahedron Lett.*, 3521 (1967).
(68) K. A. Schellenberg, *J. Biol. Chem.*, 240, 1165 (1965); 241, 2446 (1966).
(69) K. A. Schellenberg, *ibid.*, 242, 1815 (1967); T.-L. Chan and K. A. Schellenberg, *Fed. Proc.*, 26, 1709 (1967).
(70) K. A. Schellenberg and G. W. McLean, *J. Amer. Chem. Soc.*, 88, 1077 (1966).
(71) K. A. Schellenberg, G. W. McLean, H. L. Lipton, and P. S. Lietman, *ibid.*, 89, 1948 (1967).
(72) R. W. Huffman and T. C. Bruice, *ibid.*, 89, 6243 (1967).
(73) B. Heath-Brown and P. G. Philpott, *J. Chem. Soc.*, 7165 (1965).
(74) C. U. Zanetti, *Chem. Ber.*, 26, 2006 (1893).
(75) J. Schmidt and R. Schall, *ibid.*, 40, 3226 (1907).
(76) B. M. Barclay, N. Campbell, and R. S. Gow, *J. Chem. Soc.*, 997 (1946).

to consist of a mixture of 50% of carbazole together with un-



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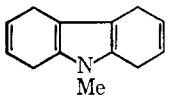
identified hydrocarbazoles. In a still later paper[77] it is claimed that this reduction affords a mixture of 1,4-dihydro- and 1,2,3,-4-tetrahydrocarbazoles and, if prolonged, affords 1,2,3,4,-4a,9a-hexahydrocarbazole although an attempt[5] to repeat this work afforded only 1,2,3,4-tetrahydrocarbazole. Further investigation of this reaction would be of interest.

B. BIRCH REDUCTION

Early studies[16] claimed that the reduction of carbazole with sodium–ammonia–ammonium bromide affords 1,4-dihydrocarbazole (**36**, R = H). Although experimental details of this work were not given, the results have been[17] verified by reduction of carbazole with either sodium–ammonia–ethanol or sodium–ammonia–ammonium chloride to **36** (R = H). Using a 4 molar excess of lithium in *n*-propylamine, carbazole is reduced[78] to 1,2,3,4-tetrahydrocarbazole. 9-Methylcarbazole is reduced by sodium–ammonia–ammonium chloride,[17] sodium–ammonia–ethanol,[17] and lithium (12 molar excess)–*n*-propylamine[78] to 1,4-dihydro-9-methylcarbazole (**36**, R = Me),[17] 1,4,5,8-tetrahydro-9-methylcarbazole (**37**),[17] and 1,2,3,4,-



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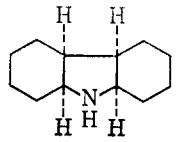
4a,9a-hexahydro-9-methylcarbazole,[78] respectively. Analogous results were obtained by reduction of 9-methoxymethylcarbazole, which with sodium–ammonia–ammonium chloride afforded[17] 1,4-dihydrocarbazole after hydrolysis of the reaction product, and with sodium–ammonia–ethanol afforded[17] a mixture, after hydrolysis of the reaction product, consisting of 8% of 1,4-dihydrocarbazole, 42% of 1,4,5,8-tetrahydrocarbazole, and an unidentified basic component(s).

Only a brief investigation[78] has been carried out upon similar reductions of benzenoid ring substituted carbazoles. Lithium–ethylenediamine reduction of 3-aminocarbazole affords[78] 27% of starting material as the only identified product, but a similar reduction of carbazole-3-carboxylic acid affords a product which was tentatively formulated[78] as 1,4-dihydrocarbazole-3-carboxylic acid.

C. CATALYTIC HYDROGENATION

Early investigations led to the claim that catalytic hydrogenation of carbazole in the presence of a nickel catalyst at 200–220° affords 2,3-diethylindole, but later studies failed to substantiate this claim. It is likely that the product from this reaction was a mixture of hydrogenated carbazoles.[3v,4f] Compared with other nitrogen heterocyclic compounds such as acridine, pyrrole, and phenylpyrrole, carbazole is much more resistant to hydrogenation.[78] However, depending upon the reaction conditions and the particular catalyst and carbazole used, the carbazole nucleus can be reduced to its 1,2,3,4-tetrahydro, 1,2,3,4,4a,9a-hexahydro, 1,2,3,4,5,6,7,8-octahydro, or dodecahydro derivatives.[3w,4e,28] The dodecahydrocarbazole produced by catalytic hydrogenation of carbazole is presumed[79] to be the *cis–cis* isomer **38**. Recently,[78] carbazole has been hydrogenated in the presence of 5% rhodium on carbon, 5% ruthe-



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nium on carbon, or nickel catalysts to afford excellent yields of either 1,2,3,4-tetrahydro- or dodecahydrocarbazole depending upon the catalyst and reaction conditions employed. Using a 5% palladium-on-carbon catalyst, 9-alkylcarbazoles are very readily hydrogenated to afford good yields of 9-alkyldodecahydrocarbazoles,[78] and 3-amino-9-methylcarbazole is also fully saturated by hydrogenation using a 5% rhodium-on-carbon catalyst.[78] Hydrogenation of 3-aminocarbazole under carefully controlled conditions using a 5% ruthenium-on-carbon catalyst affords, along with unchanged starting material, an 11% yield of 3-amino-1,2,3,4-tetrahydrocarbazole, formed by selective hydrogenation of the carbazole in the benzenoid moiety bearing the amino substituent.[78]

VI. Reduction of β-Carbolines

Depending upon the reagent used, the β-carboline moiety can be selectively reduced in either the pyridoid or benzenoid ring. Catalytic hydrogenation with a platinum catalyst in either acetic acid[80] or acetic–sulfuric acid[81] solution affords 5,6,7,8-tetrahydro-β-carbolines. These are produced by selective reduction in the benzenoid ring, whereas reduction with sodium in amyl alcohol effects selective reduction in the pyridoid ring and affords[81,82] 1,2,3,4-tetrahydro-β-carbolines.

Similarly, the selectivity of reduction of the quaternized β-carboline moiety is also controlled by the reducing agent employed. Reduction with sodium dithionite[83] and sodium borohydride[84–86] and catalytic hydrogenation with a platinum catalyst in ethanol or methanol,[83,85,87] with a platinum catalyst in methanol under pressure[87] and with a platinum catalyst in acetic acid,[80] afford the corresponding 1,2-dihydro-, 1,2,3,4-tetrahydro-, 1,2,3,4-tetrahydro-, 5,6,7,8-tetrahydro-, and 5,6,-7,8-tetrahydro-β-carbolines, respectively, the N-2 atom remaining quaternized in the latter two cases.

Further reduction of the 1,2,3,4-tetrahydro-β-carboline

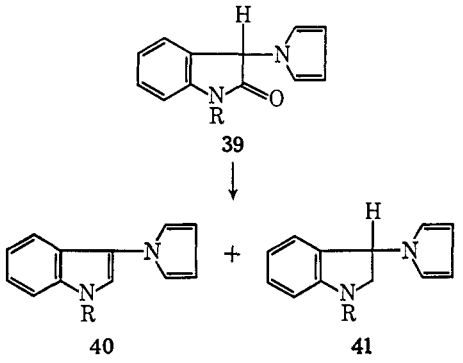
(77) G. Sanna, *Gazz. Chim. Ital.*, 80, 572 (1950).
(78) H. Dressler and M. E. Baum, *J. Org. Chem.*, 26, 102 (1961).
(79) B. Witkop, *J. Amer. Chem. Soc.*, 72, 614 (1950).
(80) H. Schwarz and E. Schlittler, *Helv. Chim. Acta*, 34, 629 (1951).
(81) M. M. Janot, J. Keufer, and J. LeMen, *Bull. Soc. Chim. Fr.*, 230 (1952).
(82) O. Fischer, *Chem. Ber.*, 22, 637 (1889).
(83) P. Karrer and P. Waser, *Helv. Chim. Acta*, 32, 409 (1949).
(84) K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, 28, 3066 (1963).
(85) A. P. Gray, E. E. Spinner, and C. J. Cavallito, *J. Amer. Chem. Soc.*, 76, 2792 (1954).
(86) B. Witkop, *ibid.*, 75, 3361 (1953); T. Wieland and E. Neeb, *Ann. Chem.*, 600, 161 (1956).
(87) A. LeHir, R. Goutarel, and M. M. Janot, *Compt. Rend.*, 235, 63 (1952); *Bull. Soc. Chim. Fr.*, 1091 (1952).

system by Emde degradation,[88,89] and by metal–acid[89,90] and lithium aluminum hydride[91] effects the rupture of the C_1–N_2 bond exclusively. This is as expected owing to the activation of this bond, by the indole nucleus, toward such fission.

VII. Reduction of Oxindoles

A. REDUCTIONS WITH LITHIUM ALUMINUM HYDRIDE

Early studies[22] upon the lithium aluminum hydride reduction of oxindoles led to the conclusion that 1-alkylated oxindoles having at least one hydrogen atom on the 3 position are reduced by this reagent mainly to the corresponding 1-alkylated indoles which are obtained along with smaller quantities of the corresponding 1-alkylated indolines, whereas 1-unsubstituted oxindoles are not reduced by this reagent. The validity of a later claim[92] that oxindole is reduced by lithium aluminum hydride to afford a 61% yield of indoline has been[93] questioned in view of the above-mentioned observations[22] with 1-unsubstituted oxindoles and since no experimental details of this latter reduction[92] were given. However, experimental details have been given[94] for the reduction of oxindole by lithium aluminum hydride to indole, although this product was only obtained in a 20% yield. Other 1-unsubstituted oxindole nuclei have also been reduced by this reagent in the structural elucidation studies which have been carried out upon the oxindole alkaloids rhyncophylline,[95] mitraphylline,[96] and gelsemine,[97–99] and the conclusion was drawn[99] that oxindoles having only a single 3 substituent undergo lithium aluminum hydride reduction to afford the corresponding indoles whereas 3,3-disubstituted oxindoles are reduced by this reagent to the corresponding indolines. However, to effect such reductions of 1-unsubstituted oxindoles, the reactions are carried out in boiling dioxane, no reduction taking place when they were attempted at 0° [97] and at room temperature.[96] The lithium aluminum hydride reduction of **39** (R = Me and Et) affords[98] in each case a mixture of the indole **40** (R = Me and Et, respectively) and the indoline **41** (R = Me and Et, respectively). An interesting elimination of the pyrrole unit occurs during the similar reduction of **39** (R = H) which affords[98] only indole. It is possible that this reaction proceeds by reduction of the oxindole to the indolin-2-ol which then looses the elements of water to afford the 3H-indole **42**. The pyrrole unit could then be eliminated by hydride attack as shown, this



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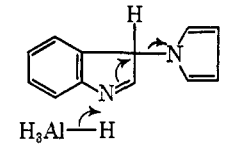
40 **41**

mechanism being similar to that already suggested for the reductive cleavage of compound **29**. 3,3-Dialkyloxindoles have



42

been reduced[100,101] using a calculated quantity of lithium aluminum hydride to the corresponding indolin-2-ols which under acidic conditions are rearranged, *via* formation of the 3H-indolium cation, to the corresponding 2,3-dialkylindoles.[100,102] Since such conditions often pertain during the "work-up" of lithium aluminum hydride reductions and cause such rearrangements, care should be taken to effect such "work-ups" entirely under alkaline conditions in order that the indolin-2-ols can be isolated.[100]

B. REDUCTION BY OTHER METHODS

Oxindole is reduced to indole by passage over hot zinc,[4k] to indoline electrolytically,[3e] and indirectly by reaction with phosphorus pentasulfide to afford thiooxindole which is then electrolytically reductively desulfurized.[3e,4c] This latter reductive sequence has been[103] extended to the reduction of benz-substituted oxindoles. Borane in tetrahydrofuran reduces oxindole to indoline (15% yield) and 1-methyloxindole to 1-methylindole (41% yield) and 1-methylindoline (27% yield).[27]

1,3,3-Trialkylated oxindoles are reduced by sodium in ethanol to the corresponding indolin-2-ols [*e.g.*, 1,3,3-trimethyloxindole (**43**) is reduced to 1,3,3-trimethylindolin-2-ol (**44**)],[41] reductions of the appropriately substituted oxindoles by this method having provided key stages in the syntheses of physostigmine,[3j,4s] physovenine,[104] and eseramine.[105] However, 3-monoalkylated oxindoles are reduced by sodium in alcohol to the corresponding 3-alkylindoles,[106] presumably formed by dehydration of the initially produced indolin-2-ols.

(88) J. P. Kutney, N. Abdurahman, P. LeQuesne, E. Piers, and I. Vlattas, *J. Amer. Chem. Soc.*, 88, 3656 (1966); D. Herbst, R. Rees, G. A. Hughes, and H. Smith, *J. Med. Chem.*, 9, 864 (1966); J. Harley-Mason, A.-u.-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966); E. Wenkert, S. Garrett, and K. G. Dove, *Can. J. Chem.*, 42, 482 (1964); E. Leete, *Chem. Ind.* (London), 692 (1960); L. J. Dolby and G. W. Gribble, *J. Org. Chem.*, 32, 1391 (1967); M. Hesse, W. von Philipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedmann, W. I. Taylor, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 47, 878 (1964).

(89) A. J. Gaskell and J. A. Joule, *Tetrahedron*, 24, 5115 (1968).

(90) A. A. Gorman and H. Schmid, *Monatsh. Chem.*, 98, 1554 (1967).

(91) L. J. Dolby and D. L. Booth, *J. Org. Chem.*, 30, 1550 (1965).

(92) P. A. S. Smith, and T. Yu, *J. Amer. Chem. Soc.*, 74, 1096 (1952).

(93) C. B. Hudson and A. V. Robertson, *Aust. J. Chem.*, 20, 1699 (1967).

(94) C. S. Franklin and A. C. White, *J. Chem. Soc.*, 1335 (1963).

(95) J. C. Seaton and L. Marion, *Can. J. Chem.*, 35, 1102 (1957).

(96) J. C. Seaton, R. Tondeur, and L. Marion, *ibid.*, 36, 1031 (1958).

(97) M. Kates and L. Marion, *ibid.*, 29, 37 (1951).

(98) R. Goutarel, M. M. Janot, V. Prelog, R. Sneeden, and W. I. Taylor, *Helv. Chim. Acta*, 34, 1139 (1951).

(99) T. S. Stevens in "Recent Work on Naturally-Occurring Nitrogen Heterocyclic Compounds," Special Publication No. 3, The Chemical Society, London, 1955, p 23.

(100) A. H. Jackson and A. E. Smith, *Tetrahedron*, 24, 403 (1968).

(101) B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 75, 2572 (1953).

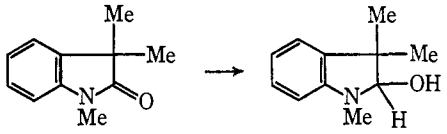
(102) E. Giovannini and F. Karrer, *Chimia*, 21, 517 (1967).

(103) T. Wieland and O. Unger, *Chem. Ber.*, 96, 253 (1963).

(104) R. B. Longmore and B. Robinson, *Chem. Ind.* (London), 1297 (1965); *Collect. Czech. Chem. Commun.*, 32, 2184 (1967).

(105) B. Robinson, *J. Chem. Soc.*, 3336 (1965).

(106) S. Pietra and G. Tacconi, *Gazz. Chim. Ital.*, 89, 2304 (1959); *Farmaco* (Pavia); 13, 893 (1958); 15, 451 (1960); 16, 492 (1961); *Chem. Abstr.*, 53, 21875 (1959); 55, 1574 (1961); 58, 5613 (1963), respectively.



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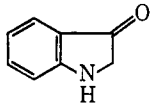
C. REDUCING REAGENTS WHICH DO NOT REDUCE OXINDOLES

In examples so far studied, 1-unsubstituted 3,3-disubstituted oxindoles are not affected[95b] by Wolff–Kishner reduction conditions, as expected, are not reduced by sodium borohydride[95,107] and sodium dithionite,[107] and are not catalytically reduced[98,108] to indolines, the oxindolyl carbonyl group remaining intact even under hydrogenation conditions which saturate the benzenoid ring.[95,98,109]

VIII. Reduction of Indoxyls

Catalytic hydrogenation of indoxyl (**45**) at high pressure over



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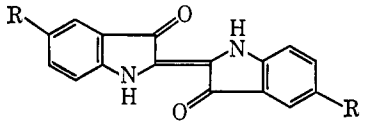
nickel, nickel–copper, or copper chromite catalysts[31] or over a nickel catalyst in aqueous borax solution[110] affords indolin-3-ol, whereas indoline has been isolated by its hydrogenation over a nickel–copper catalyst.[4b] A variety of reductions[3a,40] effected in alkaline media have converted indoxyl into indole, and reduction of 2-phenylindoxyl with zinc–acetic acid similarly affords[31] 2-phenylindole. Treatment with lithium aluminum hydride converts[111] indoxyl into a mixture containing 5% of indolin-3-ol, 25% of indole (presumably formed by dehydration of the indolin-3-ol), and 10% of indigo (**46**, R = H), which is formed during "work-up" by aerial oxidation of the true reduction product, leucoindigo (see ref 110 and section XI). Similar reduction of 2,2-dialkylindoxyls with lithium aluminum hydride[3k,111,112] or sodium borohydride[112]



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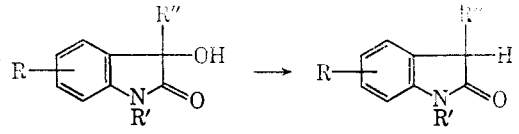
affords the corresponding 2,2-dialkyl-indolin-3-ols. In these compounds dehydration to indoles is blocked. 1-Formylindoxyl and 1-formyl-2,2-dimethylindoxyl are also reduced by lithium aluminum hydride to afford 1-methylindole and 1,2,2-trimethylindolin-3-ol, respectively.[113]

Under acidic conditions 2,2-dialkylindolin-3-ols loose hydroxyl ion and undergo subsequent 2 → 3 alkyl group migration followed by loss of a proton to afford 2,3-dialkylindoles.[102,112] Examples are known[106] in which a similar rearrangement occurs during the lithium aluminum hydride reduction of some 2,2-disubstituted indoxyls, although in these cases the migrating 2 substituents had high migratory aptitudes.[114]

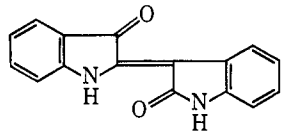
IX. Reduction of Dioxindoles

The primary reduction products of dioxindoles **47** are the cor-



47 48

responding oxindoles **48**.[3r] These reductions are effected by sodium amalgam, lithium aluminum hydride and tin–hydrochloric acid, and electrolytically[3hs] and by stannous chloride in acetic–hydrochloric acid.[115] Although it was initially[22] found that the reduction of dioxindole and 1-methyldioxindole with lithium aluminum hydride afforded 62% of oxindole and 14% of indole and 18% of 1-methyloxindole and 35% of 1-methylindole, respectively, later attempts[111,113] at the same reductions afforded mixtures of indolin-3-ol, indole, indigo (**46**, R = H), and indirubin (**49**) (formed during "work-up" by aerial oxidation of leucoindigo and leucoindirubin, respectively[110]) and of 1-methylindole and 1,1′-dimethylindigo (formed during "work-up" by aerial oxidation of the leuco compound), respectively. However, the formation of these complex mixtures of products from such reductions of dioxin-



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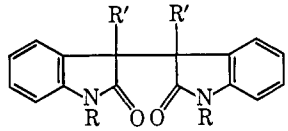
doles is not general, since 5-methoxy-1-methyldioxindole[116] and 3-alkyldioxindoles[94,117] are reduced by lithium aluminum hydride to 5-methoxy-1-methylindole[116] and 3-alkylindoles,[94,117] respectively. 3-Alkyldioxindoles have also been reduced to the corresponding 3-alkylindoles using[94] a sodium borohydride–aluminum chloride complex.

The reduction of 1-hydroxydioxindole with zinc–acetic acid affords isatide (**50**, R = H; R′ = OH), this reduction probably



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proceeding *via* formatin of dioxindole.[3s]

Dioxindole-4-carboxylic acid undergoes disproportionation in boiling alcohol to afford isatin-4-carboxylic acid and oxindole-4-carboxylic acid,[3s] an interesting reaction which is worthy of further study.

(107) I. W. Elliott and P. Rivers, *J. Org. Chem.*, 29, 2438 (1964).
(108) J. B. Hendrickson, quoted as ref 7 in K. Freter, H. Weissbach, B. Redfield, S. Udenfriend, and B. Witkop, *J. Amer. Chem. Soc.*, 80, 983 (1958).
(109) H. Schwarz and L. Marion, *Can. J. Chem.*, 31, 958 (1953).
(110) E. Giovannini and T. Lorenz, *Helv. Chim. Acta*, 40, 1553 (1957).
(111) E. Giovannini and T. Lorenz, *ibid.*, 40, 2287 (1957).
(112) H. Bickel, E. Giesbrecht, J. Kebrle, H. Schmid, and P. Karrer, *ibid.*, 37, 553 (1954); H. Bickel, H. Schmid, and P. Karrer, *ibid.*, 38, 649 (1955).
113) E. Giovannini and T. Lorenz, *ibid.*, 41, 113 (1958).
(114) B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 73, 713 (1951).
(115) C. Marschalk, *Bull. Soc. Chim. Fr.*, 949 (1952).
(116) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, 23, 19 (1958).
(117) M. C. Bellembourg and S. David, *Bull. Soc. Chim. Fr.*, 772 (1962); S. David and M. C. Doucet, *ibid.*, 2152 (1967); C. S. Franklin and A. C. White, *J. Chem. Soc.*, 1335 (1963).

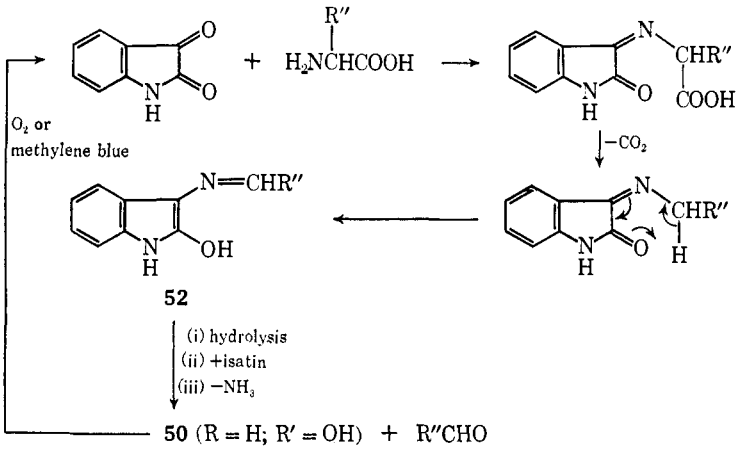
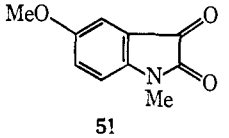


Figure 2. Postulated sequence of the isatin–α-amino acid reaction.

X. Reduction of Isatins

A. CHEMICAL REDUCTIONS OF ISATINS

Isatins are reduced to dioxindoles by sodium amalgam in alkaline solution, sodium bisulfite, sodium dithionite [a general and the most convenient reagent; for example, 5-methoxy-1-methylisatin (**51**) is reduced by it[116] in almost quantitative yield to 5-methoxy-1-methyldioxindole],



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zinc in acetic or hydrochloric acid, and hypophosphorus acid.[3h,o,q,4g,h,j,m,n] This reduction can also be effected catalytically over nickel (see also ref 118) and electrolytically,[3h] although, depending upon conditions, 1-methylisatin is electrolytically reduced[119] to either 1-methyldioxindole or 1-methyloxindole (which can be further reduced electrolytically to 1-methylindoline). Isatin has recently been reduced,[120] or more specifically its sp^2-hydridized C_3 has been converted into a sp^3-hybridized state, by the conversion of its *p*-toluenesulfonylhydrazone into 3-diazooxindole which upon reaction with methanol, ethanol, or *n*-propyl alcohol affords 3-methoxy-, ethoxy-, and *n*-propoxyoxindoles, respectively. This reaction sequence is claimed[120] to be easier to effect and affords better yields than the reaction of the corresponding alkylmagnesium halides on isatin. Isatin 3-oximes are reduced to 3-aminooxindoles by tin or stannous chloride in hydrochloric acid or by hydrogenation over palladium.[3i]

The above-formed dioxindoles can be further reduced to oxindoles (see section IX) which can also be obtained directly from isatins by reduction with sodium amalgam or by electrolytic or Wolff–Kishner reduction.[3h,4h,i] Isatin can also be indirectly reduced to oxindole by reaction with phosphorus pentachloride to afford 3,3-dichlorooxindole which upon reaction with zinc dust affords oxindole,[3h] or *via* formation of isatin ethylene thioketal which with Raney nickel affords[121] oxindole. When this latter reaction is effected in alcoholic solution, the corresponding 3-alkyloxindoles are the products.[121]

Several selective metal hydride reductions of isatin afforded no dioxindole,[120] although lithium aluminum hydride reduction of isatin affords[110] a mixture of indole, indigo (**46**, R = H), indirubin (**49**), and indolin-3-ol if acidic conditions are avoided. If acidic conditions are used during reaction "work up," only the former three products are isolated,[110] in both cases the indigo and indirubin being produced by aerial oxidation of their leuco derivatives, the true reduction products. 1-Methylisatin is similarly reduced[118] to a mixture of 1-methylindole and 1,1'-dimethylindigo, the yield of 1-methylindole from this reaction being very dependent upon reaction conditions and being obtained in a maximum of 56%. Subsequently[93] conditions were found which yielded 64% of 1-methylindole from this reduction and 76% of 1-ethylindole from the similar reduction of 1-ethylisatin.

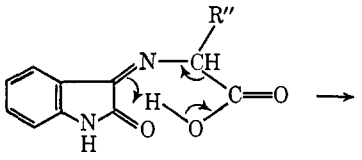
Isatin is reduced by zinc in acid solution or by ammonium sulfide to isatide (**50**, R = H; R' = OH),[3m,q,4g] by hydrogen sulfide to isatin thiopinacol (**50**, R = H; R' = SH),[4g] by zinc dust in boiling acetic anhydride to tetraacetylisatide (**50**, R = $COCH_3$; R' = $OCOCH_3$),[3n] and by stannous chloride in hydrochloric acid–acetic acid to isatide (**50**, R = H, R' = OH).[115]

B. ISATINS AS ENZYME MODELS

Isatin exerts an enzyme-like dehydrase activity in effecting the decarboxylation–deamination of α-amino acids.[3p,41] This reaction also results in the isatin being reduced to 3-aminooxindole which reacts with unchanged isatin to afford isatide. This is then oxidized by either atmospheric oxygen or methylene blue back to isatin. This reaction is postulated[3p,41,122] to occur by the sequence shown in Figure 2. Evidence suggested[122] that the initial condensation between the ketonic carbonyl group of isatin and the amino group of the α-amino acid is the rate-determining step. Alternatively, the decarboxylation of the initial condensation product could occur as shown in **53**, by a mechanism analogous to that operating in

(118) I. Telcs, S. Szabo, and F. Nagy, *Nagy. Kem. Folyoirat*, 71, 468 (1965); *Chem. Abstr.*, 64, 10447 (1966).
(119) B. Sakurai, *J. Shinshu Univ.*, 1, 1 (1951); *Chem. Abstr.*, 48, 12580 (1954).
(120) P. L. Creger, *J. Org. Chem.*, 30, 3610 (1965).
(121) E. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.*, 80, 5575 (1958).
(122) D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 2202 (1956).

the decarboxylation of β-keto acids. This would lead directly



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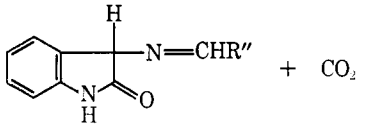

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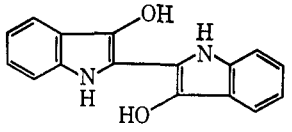
to **54**, the keto tautomer of **52**. This reaction has also been effected[123] with the isatin moiety suspended on a polymer, and the influence of substituents on the benzenoid ring of the isatin molecule on this reaction has been studied.[124] The reaction is general for 1,2-dicarbonyl compounds or their vinylogs[3p] in which at least one of the carbonyl groups has ketonic properties.[125] The dehydrase activity of isatin compared with that of several 1,2-quinones of similar special structure[126] and the comparative redox potentials–dehydrase activities of isatin and a further group of 1,2-quinones[125] have been investigated.[126–128]

XI. Reduction of Indigo

Indigo (**46**, R = H) is reduced by zinc dust, ferrous hydroxide, iron powder in alkaline, neutral, or weakly acidic media, silicon, sodium dithionite, and glucose[3t,4p,q] and by catalytic [an analytical method for the detection of palladium based upon it catalyzing the hydrogenation of indigo carmine (**46**, R = SO_3H) has been[129] published] and electrolytic techniques to afford leucoindigo (indigo white) (**55**). This reduction and its facile reversal by atmospheric oxygen is the basis of the



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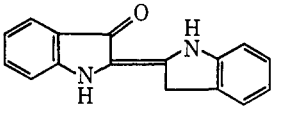
long-established use of indigo as a vat dyestuff. In this the indigo is reduced to the colorless **55** (sodium dithionite has been widely used as the reducing agent in this dyeing process[4q]) which is applied to the fabric as its water-soluble colorless disodium salt. The dyestuff is then regenerated on the fabric by oxidation with atmospheric oxygen.[3t,4q]

Indigo has also been reduced to leucoindigo microbiologically. An intensive study of this subject, including a study of the microorganisms involved and their application to dyeing, has been reported in two series[130] of papers. Indigo carmine (**46**, R = SO_3H) is also bio-reduced by the chloroplasts of the leaves of sugar beet,[131] spinach,[132] *Phytolacca americana*, and *Brassica campestris*,[133] in the presence of dichloroindophenol and ascorbate anion.

The facile interconversion of the indigo and leucoindigo moieties is further manifested in the catalytic oxidation of hydrogen sulfide by indigo carmine (**46**, R = SO_3H)[134] and also in the use[135] of this latter compound as a catalyst in reductions effected by model compounds related to dihydronicotinamide adenine dinucleotide.

Halogenoindigos are reduced to halogenoleucoindigos and leudoindigo,[4q] reduction of indigo by zinc dust in acetic anhydride in the presence of sodium acetate affords O,O-diacetylleucoindigo,[4r] and prolonged heating of indigo with benzoyl chloride in pyridine affords N,N,O,O-tetrabenzoylleucoindigo.[4r]

Desoxyindigo (**56**) is formed by the reduction of indigo with an alcoholic solution of hydrazine hydrate,[3u,4r] reduction with



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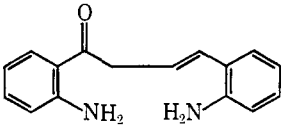
iron powder or ferrous chloride in alcoholic hydrogen chloride effects ring cleavage to afford **57**,[3u] and reduction in alkaline medium or distillation from zinc dust affords indole.[3b]



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XII. Reduction of 3-Acylindoles and Related Compounds

Although reduction of the carbonyl group in 3-acylindoles does not involve reduction of the indole nucleus, the nature of the product resulting from such reduction depends in some cases upon whether the indole nitrogen atom is secondary or alkylated, and therefore this section is included in the present article.

(123) G. Manecke and G. Kossmehl, *Makromol. Chem.*, 70, 112 (1964).
(124) E. Giovannini, P. Portmann, A. Jöhl, K. Schnyder, B. Knecht, and H. P. Zen-Ruffinen, *Helv. Chim. Acta*, **40**, 249 (1957); D. G. O'Sullivan and P. W. Sadler, *Arch. Biochem. Biophys.*, 66, 243 (1957).
(125) A. Schonberg, R. Moubasher, and A. Mostafa, *J. Chem. Soc.*, 176 (1948).
(126) B. Lukowczyk and W. Junghans, *J. Prakt. Chem.*, **24**, 148 (1964).
(127) H. Cassebaun, *Z. Elecktrochem.*, **62**, 426 (1958).
(128) H. Cassebaun, *Chem. Ber.*, 90, 287 (1957).
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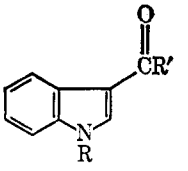
3-Acylindoles **58** (R = H or Me) are normally[136-142] reduced by alkali metal borohydrides to the corresponding 3-(1-hydroxyalkyl)indoles **59** (R = H or Me), exceptions being the failure[138] to reduce 3-dimethylaminoacetylindole (**58**, R = H; R′ = CH_2NMe_2) with lithium borohydride and the reduction[138] of 3-acetylindole to 3-ethylindole with the same reagent under vigorous conditions. Under milder conditions this latter reaction affords[138] the expected 3-(1-hydroxyethyl)-indole **59** (R = H; R′ = Me). The carbonyl group of the 2-acylindole moiety present in the 2-acylindole alkaloids is also reduced by sodium borohydride to a secondary alcohol group[143] although reduction of 2-acetyl-3-methylindole with diborane affords predominantly 2-ethyl-3-methylindole.[144] The imines derived from the reaction of indole-3-carboxaldehyde and various primary amines are reduced[145] by sodium borohydride to the corresponding 3-alkylaminomethylindoles.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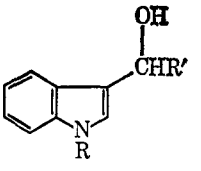
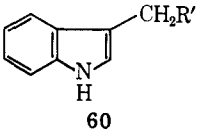

59

Whereas 1-unsubstituted 3-acylindoles **58** (R = H)[13,84,142,146] and 3-(1-hydroxyalkyl)indoles **59** (R = H)[136,139,146] are reduced by lithium aluminum hydride to the corresponding 3-alkylindoles **60**, 3-acyl-1-methylindoles **58** (R = Me) are reduced[139,147] by this reagent to the corresponding 3-(1-hydroxyalkyl)indoles **59** (R = Me) which are not further reduced under these conditions.[139,147] It is likely that the intermediate in the reduction of **58** (R = H) to **60** is **59** (R = H). It is suggested[139] that the initial step in the hydrogenolysis of **59** (R = H) is the elimination of water, not possible in **59** (R = Me), as shown below (B = AlH_4 or H) to afford the conjugate base **61**. Subsequent addition of hydride ion followed by protonation then affords **60** (see also ref 141 and 147). 2-Hydroxymethylindole is, like **59** (R = H), also a vinylog of a carbinolamine with a secondary nitrogen atom. However, it is not reduced by lithium aluminum hydride since such a reduction would involve the intermediate **62**, corresponding to **61**, in which the aromaticity of the benzenoid ring is destroyed, and the formation of which is therefore not favored[139] (see also ref 148).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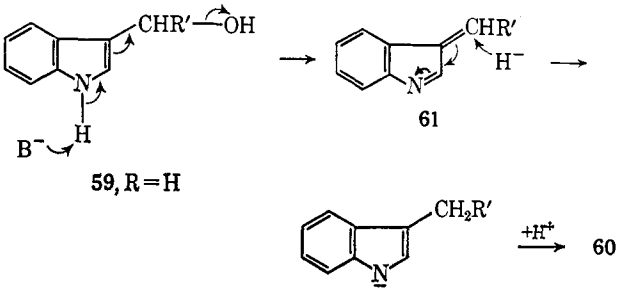
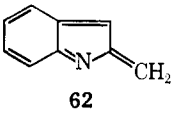
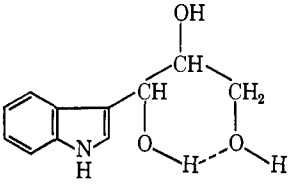

59, R=H 61 60


62

Exceptions to the above generalizations are known. Compounds **63** and **64** are not reduced by lithium aluminum hydride,[149,150] probably owing to stabilization of the 1′-hydroxyl group by intramolecular hydrogen bonding as shown,[139] and when **65** is reduced by lithium aluminum hydride, hydrogenolysis of the C=O group occurs, as suggested by ir spectral studies of the product, along with other reactions.[141]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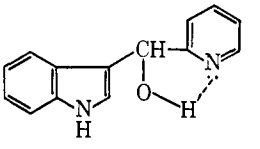
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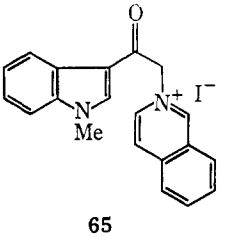
65

Also, reaction conditions appear to play a critical role in the lithium aluminum hydride reduction of 1-unsubstituted 3-acylindole, for whereas the reduction of **66** with this reagent in tetrahydrofuran affords **67**, similar reduction in ether affords the carbinol **68**.[151]

3-Acetyl-1-methylindole is reduced[147] to 3-ethyl-1-methylindole by a lithium aluminum hydride–aluminum chloride mixture, although a further attempted use of this mixture in a similar reduction failed to yield any pure product. It was therefore concluded[147] that rather than attempting to reduce 3-acyl-1-methylindoles to 3-alkyl-1-methylindoles it is more desirable to reduce the 1-unsubstituted analogs with lithium aluminum hydride and 1-methylate the product. However, both 3-acetyl- and 3-benzoylindoles and their 1-methyl deriva-

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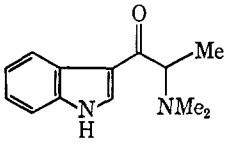

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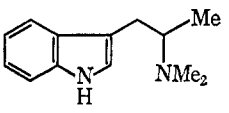

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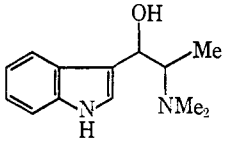
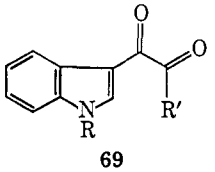


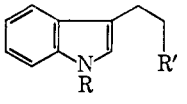
68

tives are reduced to the corresponding 3-ethyl- and 3-benzylindoles in excellent yields by diborane,[144] although with this reagent, and with the lithium aluminum hydride–aluminum chloride mixture, 3-formylindoles are converted into dimeric, trimeric, and polymeric products along with the expected 3-methylindoles.[144]

By analogy with the above generalizations concerning the lithium aluminum hydride reduction of 3-acylindoles, 1-unsubstituted 3-[2′-substituted (usually amino) 1′,2′-dioxoethyl]-indoles **69** (R = H) are usually[152] reduced to the corresponding 3-(2-substituted ethyl)indoles **70** (R = H) by lithium aluminum hydride, although in one case[153] no recognizable product could be obtained from such a reaction, and in another[154] the reduction of the 1′-carbonyl group afforded the corresponding secondary alcohol.

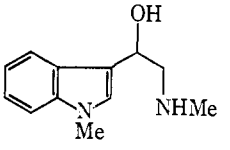


69



70

Apparently conflicting results have been obtained from the lithium aluminum hydride reduction of the 1-methyl derivatives of **69** (R = H), for whereas **69** (R = Me; R′ = NHMe) affords[155] **71**, expected by analogy with the similar reduction of the simple 3-acyl-1-methylindoles (see above, but see also ref 141), reduction of **69** (R = Me; R′ = NBz_2) affords[156] **70** (R = Me; R′ = NBz_2).



71

Diborane reduction of the indole-3-glyoxylamides **69** (R = H or Me) affords[144] the corresponding tryptamines **70** (R = H or Me), as might be expected by analogy with the similar reduction of both 1-unsubstituted and 1-alkylated 3-acylindoles to the corresponding 3-alkylindoles.

Acknowledgment. I thank Dr. G. F. Smith of the Department of Chemistry, University of Manchester, for permission to refer to the results of work not yet published, for reading the manuscript of the above article before submission, and for useful discussion connected with it.

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