REDUCTION BY METAL-AMINE SOLUTIONS: APPLICATIONS IN SYNTHESIS AND DETERMINATION OF STRUCTURE

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WORK since the last reviews of the subject [1, 2] has been concerned chiefly with the exploitation of metal-amine solutions in synthesis and in the investigation of natural products. Theoretical developments have been mainly incidental and have added little to what was already known.[1] We are here concerned with the practical aspects but an appreciation of the theoretical background is essential for use of the reagents to the best purpose, since variations in technique are possible. So references to theoretical aspects are made below where necessary, but overlapping with earlier reviews has been avoided as far as possible.

1. Reduction by metal–ammonia and metal–amine solutions

Two main types of reduction are observed: (*a*) partial or complete saturation of a wide variety of unsaturated substances including polycyclic aromatic compounds, dienes, and trienes which are conjugated or are rendered so under the alkaline conditions of the reaction, and in some cases of simple olefins; and (*b*) reductive fission of alkyl aryl or diaryl ethers and sulphides and the hydrogenolysis of various groups attached to nitrogen, oxygen, and sulphur. Which particular reagent is used depends on the nature of the substrate and on how far it is desired that reduction shall proceed.

Metal and an " Acid " in Liquid Ammonia.—The reagents so far examined consist of an alkali metal and an " acid " such as methanol or ammonium chloride in liquid ammonia, sometimes with co-solvents such as ether or tetrahydrofuran. The reagents are powerful if the " acid " is an alcohol, and are then capable of reducing a terminal double bond or an isolated benzene ring. In this they differ from ammonia reagents lacking the alcohol, although solutions of lithium in ethylamine are also capable of reducing benzene rings and terminal double bonds (see below). The alcohol also has the effect of buffering the reaction mixture, preventing accumulation of strongly basic NH_2. This explains the comparative simplicity of the results since base-catalysed rearrangements of double bonds are usually avoided. Reduction of a benzene ring leads to the $\alpha\delta$-dihydro-derivative, unlike the lithium–ethylamine reagent where the $\alpha\delta$-dihydro-derivative which is probably formed initially is rearranged to the conjugated $\alpha\beta$-dihydro-derivative which is then rapidly reduced further. As will be seen, similar results to the latter are obtained with calcium hexammine and by reduction with sodium and ethanol in liquid ammonia followed by

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[1] Birch, *Quart. Rev.*, 1950, **4**, 69. [2] Watt, *Chem. Rev.*, 1950, **46**, 317.

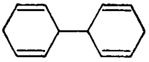
an excess of sodium in ammonia.[3] The $\alpha\delta$-hydrogen atoms added by the metal–alcohol–ammonia reagent avoid carbon atoms carrying dimethylamino-, alkoxy-, or alkyl groups in that order, and are attracted to positions carrying carboxyl groups. The latter effect outweighs the others ; carboxyl groups labilise *o*- and *p*-methoxyl groups [4] to hydrogenolysis.

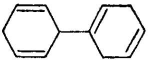
The requirement for an added source of protons is now interpreted [5] in terms of the following equilibria :

$$\mathrm{Ar} + \varepsilon \rightleftharpoons \mathrm{Ar}^{-*} + \mathrm{HOR} \rightleftharpoons \mathrm{Ar^*H} + \mathrm{OR}^- \xrightarrow{\varepsilon} \mathrm{ArH}^- \xrightarrow{\mathrm{ROH}} \mathrm{ArH_2} + \mathrm{OR}^-$$

The anion-radical Ar^{*-} formed initially must add a proton in order that reduction may be completed ; it appears not to be sufficiently basic to abstract this proton from ammonia and requires a more acidic proton source. If the acidity of this source is high, as with ammonium salts, the predominant reaction is evolution of gaseous hydrogen unless the substance is very rapidly and readily reduced ; alcohols seem to have about the optimum $\mathrm{p}K_a$ for the reduction of benzene rings.

The reduction with sodium and methanol or ethanol in liquid ammonia of *o*-xylene,[6] naphthalene,[7] tetralin,[8] and 1 : 4-dihydronaphthalene [7] has been subjected to a rigorous re-examination. The results confirm the originally defined reducing properties of the reagent. Diphenyl has been reduced in both rings, giving a product showing no selective ultraviolet absorption which is either compound (I) or, more probably, compound (II).[9]

(I) 

 (II)

An important modification in technique has been the use of lithium instead of sodium or potassium for the reduction of aromatic rings. The greater solubility of lithium in liquid ammonia enables larger proportions of co-solvents to be used without the formation of two-phase systems ; consequently, difficulties arising from the low solubility of substrates in ammonia systems can be overcome. Higher yields of reduction products may be associated with the high concentration of metal and also with the higher normal reduction potential of lithium in ammonia (—2·99 v) compared with that of potassium or sodium (—2·59 and —2·73 v respectively).[10] An earlier device for increasing the solubility of phenyl ethers in ammonia systems, *viz.*, the formation of glyceryl or 2-hydroxyethyl ethers,[11, 12] enables the cheaper sodium or potassium to be used. This technique has not yet been fully investigated, but in reduction of 3-2′-hydroxyethoxyœstra-

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[3] Birch, *J.*, 1946, 593. [4] Ref. 1, p. 88.

[5] Birch, *J. Roy. Inst. Chem.*, 1957, **80,** 100.

[6] Hückel and Wörffel, *Chem. Ber.*, 1955, **88,** 338.

[7] Hückel and Schlee, *ibid.*, p. 346.

[8] *Idem, ibid.*, p. 2098.

[9] Hückel and Schwen, *ibid.*, 1956, **89,** 150.

[10] Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75,** 5360.

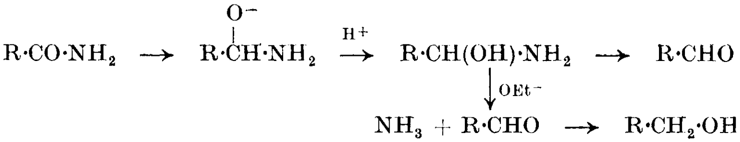
[11] Birch and Mukherji, *J.*, 1949, 2531.

[12] Birch *J.*, 1950, 367.

1 : 3 : 5-trien-17β-ol [13] the yield of 19-nortestosterone is of the same order as by the lithium method.[14] In cases where there are serious losses of alkoxyl groups by reductive fission the method may be superior in that it inhibits hydrogenolysis through alkoxide formation by the side-chain hydroxyl group. It is possible also that reduction is facilitated by cyclic donation of a proton to an anionic intermediate.

Terminal double bonds may be reduced by the alcohol-containing reagent. This has been observed with various dialkylallylamines [15] and with hex-1-ene, which has been converted into hexane in 41% yield by two atomic proportions of sodium and methanol in liquid ammonia.[16] In the last case no reduction occurs in the absence of an alcohol or when ammonium bromide is used as proton donor. Of particular interest is the observation that 2-*cyclo*propylpent-1-ene gives 2-*cyclo*propylpentane [16] and no ring-open products with the sodium–ammonia–methanol reagent, whereas methyl *cyclo*propyl ketone affords a mixture of methyl propyl ketone and pentan-2-ol with sodium and ammonium sulphate in liquid ammonia.[17]

A further illustration of the control exerted by the acid strength of the proton donor over the reduction products is the ultimate formation of aldehydes rather than alcohols when ammonium acetate is substituted for ethanol as the proton source in the sodium–ammonia reduction of amides.[18] Alcohol production is ascribed to the ethoxide-catalysed decomposition and further reduction of the intermediate 1-amino-alcohol (aldehyde–ammonia). The buffering of the medium by use of the more acidic ammonium acetate as proton source avoids this decomposition and the amino-alcohol is converted into the aldehyde during the working up:



$$\begin{array}{ccccccc} R{\cdot}CO{\cdot}NH_2 & \rightarrow & R{\cdot}\overset{\overset{O^-}{|}}{C}H{\cdot}NH_2 & \xrightarrow{H^+} & R{\cdot}CH(OH){\cdot}NH_2 & \rightarrow & R{\cdot}CHO \\ & & & & \downarrow{\scriptstyle OEt^-} & & \\ & & & & NH_3 + R{\cdot}CHO & \rightarrow & R{\cdot}CH_2{\cdot}OH \end{array}$$

Aldehydes may also be ultimately obtained by the sodium–ammonia–*alcohol* reduction of amidines (even arylamidines), presumably *via* the 1 : 1-diamines.[18] This result is due to the lower acidity of NH than of OH and also to absence of hydrogenolysis of the C–N bonds. In contrast to the reductive fission of C–O bonds which in general occurs readily in benzyl ethers and in aryl acetals [19] and ketals,[20] C–N bonds conjugated with aromatic nuclei are not split, because nitrogen is less electrophilic than oxygen.

Pyridine compounds are reduced more readily than the hydrocarbons

[13] Birch and Bauer, unpublished work.

[14] Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5366.

[15] King, *J.*, 1951, 898.

[16] Greenfield, Friedel, and Orchin, *J. Amer. Chem. Soc.*, 1954, **76**, 1258.

[17] Volkenburgh, Greenlee, Derfer, and Boord, *ibid.*, 1949, **71**, 3595.

[18] Birch, Cymerman-Craig, and Slaytor, *Austral. J. Chem.*, 1955, **8**, 512.

[19] Birch, Hextall, and Sternhell, *ibid.*, 1954, **7**, 256.

[20] Pinder and Smith, *J.*, 1954, 113.

of the same ring size because the heteroatom is better able than carbon to stabilise a negative charge. Pyridine and quinoline compounds, for example, readily give 1 : 4-dihydro-derivatives ; [21] di-, tri-, and tetra-meric dihydro-compounds are also produced. Reduction can be effected even in the absence of added proton sources, but the products may then contain larger amounts of polymers.

Thiophen with sodium and ethanol in liquid ammonia gives a complex mixture of 2 : 3- and 2 : 5-dihydrothiophen, but-2-ene-1-thiol, but-1- and -2-ene, and hydrogen sulphide.[22] Presumably reduction occurs to 2 : 3- and 2 : 5-dihydrothiophen, which then undergo further reactions because of the known ready reductive fission of C–S bonds. Pyrrole and furan rings appear to be unaffected.

Sodium, Potassium, or Lithium in Liquid Ammonia.—In a number of instances little difference would be expected from the "buffered" and protonated reagents mentioned above. For example, (—)-α-phellandrene (mentha-1 : 5-diene) is reduced by sodium or by sodium and ethanol in liquid ammonia to the same mixture of (—)- (60%) and (+)-menth-1-ene (40%),[23] showing a large proportion of αβ-reduction. The reduction of other 1 : 3-dienes to the 1 : 4-dihydro-derivatives, *e.g.*, 2-methyl-, 2 : 3-dimethyl-, and 1 : 1 : 3-trimethyl-butadiene to the but-2-enes in yields of 98—99, 93—94, and 72% respectively,[24] should not be altered by the presence of alcohols. In other cases, if addition of protons to the intermediate anions is avoided, by ensuring the absence of proton sources other than ammonia, the occurrence of further reduction is inhibited by the negative charges present. Proton-addition occurs during the working-up. Sodium–ammonia reduction of diphenyl has been shown to be analogous to that of naphthalene,[25] two atoms of sodium being added, to give a deep red sodium salt decomposed by ammonium chloride to 1 : 4-dihydrodiphenyl.[9] The phenyl group here exerts an effect similar to that of carboxyl,[27] as is to be expected from its ability to stabilise an adjacent anionic charge. Similarly, fluorene yields an unstable dihydrofluorene of undetermined constitution which readily disproportionates to fluorene and 1 : 4 : 11 : 12-tetrahydrofluorene.[28] In related work it was shown that *cyclo*pentadiene and indene give *cyclo*pentene and indane respectively.[9]

The reduction of αβ-unsaturated ketones to the saturated ketones, of which examples are given below, also illustrates the protective effect of a negative charge in an intermediate in permitting eventual isolation of the saturated ketone. Similar reactions have been carried out with unsaturated esters and acids. The protection of allyl alcohols against hydrogenolysis

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[21] Ref. 2, p. 362 ; Birch, unpublished work.

[22] S. F. Birch and McAllan, *Nature*, 1950, **165**, 899.

[23] Birch, unpublished work.

[24] Levina, Svarchenko, Kostin, Treschova, and Okimevich, *Sborkin obshchei Khim., Akad. Nauk S.S.S.R.*, 1953, **1**, 355 ; *Chem. Abs.*, 1955, **49**, 829.

[25] Ref. 1, p. 81.

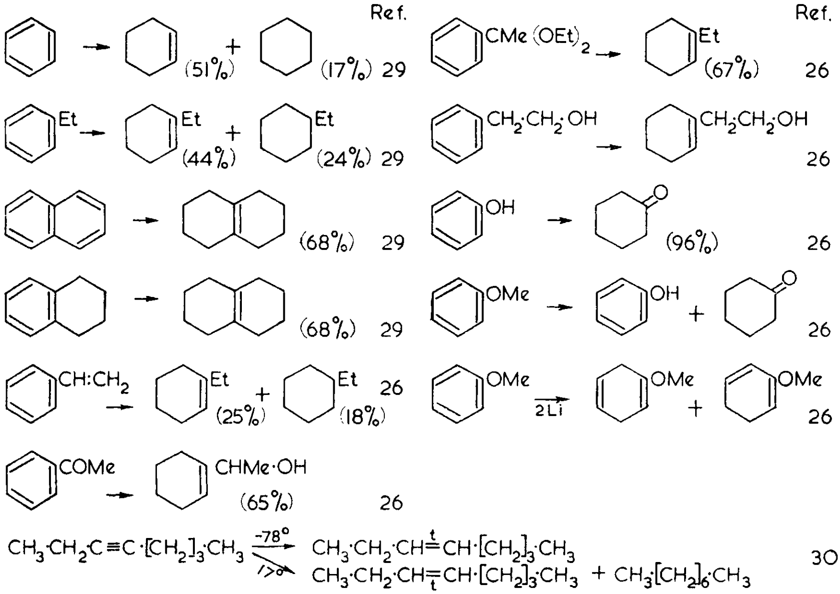
[26] Benkeser, Arnold, Lambert, and Thomas, *J. Amer. Chem. Soc.*, 1955, **77**, 6042.

[27] Ref. 1, p. 86 ; Birch, Hextall, and Sternhell, *Austral. J. Chem.*, 1954, **7**, 256.

[28] Hückel and Schwen, *Ber.*, 1956, **89**, 481.

and of acetylenes against reduction can be achieved by initial formation of the salts.

Lithium in Alkylamines.—Solutions of lithium in amines of low molecular weight, such as methylamine, ethylamine, and the propylamines, constitute reducing agents of very great power if little selectivity. The amines are, in general, more powerful solvents for organic substances than ammonia and have higher boiling points ($C_2H_5{\cdot}NH_2$, b.p. 16·5° ; NH_3, b.p. −33°). Accordingly their use may avoid a common and serious difficulty often encountered in liquid ammonia reductions, namely, the low solubility of the substrate in the solvent system. The higher working temperature also undoubtedly facilitates the initial steps in the reduction and favours the conjugation and therefore further reduction of the primary products. The annexed examples illustrate typical reductions by these reagents. Simple olefins may be saturated, tetrasubstituted double bonds being least readily reduced in accord with the view that the process involves initial electron addition.[1] A similar reduction of double bonds, which must however be terminally situated, occurs with sodium and methanol in liquid ammonia (see above). Inhibition of the reduction of di- and tri-substituted double bonds by working at low temperatures (*e.g.*, −78°) has been observed.[26, 30]



Isolated benzene rings are reduced to the tetrahydro-state or partly to the hexahydro-state depending on the conditions. Acetophenone gives the allylic alcohol 1-1′-hydroxyethyl*cyclo*hexene, whereas its diethyl ketal gives 1-ethyl*cyclo*hexene in agreement with the view that hydrogenolysis of the

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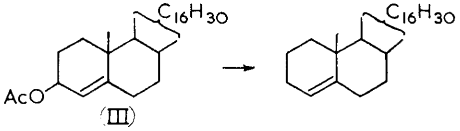
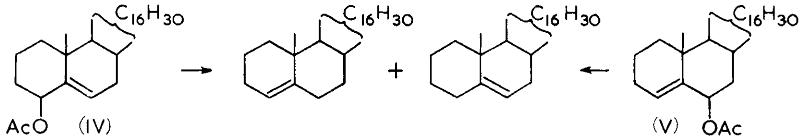
[29] Benkeser, Robinson, Sauve, and Thomas, *J. Amer. Chem. Soc.*, 1955, **77**, 323.
[30] Benkeser, Schroll, and Sauve, *ibid.*, p. 3378.

hydroxyl group in the intermediate benzyl alcohol is inhibited by salt formation. Similarly, reduction of phenol (more correctly lithium phenoxide) is very largely stopped at the *cyclo*hexanone stage, probably by protection of the carbonyl group as the enol anion. In contrast, formation of the phenoxide anion or the acetophenone enol anion [20] is sufficient to inhibit reduction by metal–ammonia–alcohol reagents. Use of excess of lithium favours dealkylation of anisole since the product then consists of phenol and *cyclo*hexanone; the theoretical amount of lithium leads to a mixture of 2 : 5-dihydroanisole (the initial product) and the conjugated 2 : 3-dihydro-isomer.

Although allyl (and benzyl) alcohols may resist hydrogenolysis owing to salt-formation, allyl ethers, for which salt-formation is impossible, are readily cleaved. The course of the reaction is similar to that with the alkali metal–ammonia reagent, but alkylamine systems offer the practical advantage of greater solvent power and reactivity. The cleavage of *cis*-(+)-carvotanacetyl methyl ether with lithium and ethylamine yields (±)-*p*-menth-1-ene,[31] in agreement with the view that the reaction proceeds through a symmetrical intermediate, probably the mesomeric anion produced together with alkoxide ion by the addition of two electrons.[32] It is known that compounds capable of producing very stable anions in a fission reaction are reduced readily,[33] so it would be expected that allyl acetates and benzoates should be cleaved more easily than the free alcohols provided the first stage is not reduction of the ester-carbonyl group. This has been demonstrated in the steroid series, where, for example, lithium in ethylamine converts 3β-acetoxycholest-4-ene (III) to cholest-4-ene, and 4-β-acetoxycholest-5-ene





(IV) and 6-β-acetoxycholest-4-ene (V) both give the same mixture of cholest-4- and -5-ene.[31] There is no evidence of formation of a thermodynamically unstable isomer since 3-β-acetoxycholest-1-ene gives cholest-2-ene and none of the less stable cholest-1-ene.[31]

Work on the fission of steroid epoxides has confirmed that the direction of reductive ring opening, as with propylene oxide,[34] is consistent with a potential-determining stage involving the addition of 2 electrons. The

[31] Hallsworth, Henbest, and Wrigley, *J.*, 1957, 1969.

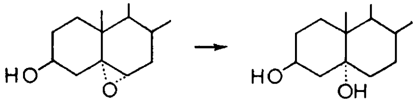
[32] Ref. 1, p. 71.

[33] Dean and Berchet, *J. Amer. Chem. Soc.*, 1930, **52,** 2823.

[34] Birch, *J. Proc. Roy. Soc. New South Wales*, 1949, **83,** 245.

planar geometrical requirements for the transition state [35] in such cases ensure that axial alcohols are produced stereospecifically. Thus 5α : 6α-epoxides (VI) are converted into 5α-alcohols, and 2α : 3α-, 7α : 8α-, and

(VI)



9α : 11α-epoxides similarly give 3α-, 8α-, and 9α-alcohols, respectively.[36] Lithium aluminium hydride may reduce steroid *vic*-epoxides similarly,[37] but it has no effect on the sterically hindered 7α : 8α- and 9α : 11α-epoxides, thereby illustrating the power and low steric hindrance associated with the metal–amine reagents.

Calcium Hexammine.—The reducing capabilities of calcium hexammine have been but little investigated during the period since the last review. Reductions are usually carried out with a suspension of the reagent in an inert solvent (*e.g.*, ether, dioxan, 1 : 2-dimethoxyethane, tetrahydrofuran) so that solubility may usually be achieved by choosing a suitable solvent. Under sufficiently vigorous conditions the reagent saturates the double bond in simple olefins (2 : 5-dimethylhex-2-ene, for example, gives 2 : 5-dimethylhexane [38]) and reduces isolated benzene rings to the dihydro- or tetrahydro-state.[39, 40] Methoxyl groups may be cleaved from the ring by fission of intermediates, *e.g.*, methyl *m*-tolyl ether gives 1-methyl*cyclo*hexene,[3] and 2-methoxynaphthalene gives a mixture of hexahydronaphthalenes having homoannular conjugated diene systems.[40] Conjugation is probably due to the presence of calcium amide.

The Protection of Functional Groups.—The protection of reducible groups in some cases can be accomplished by salt formation to give anions. This has already been illustrated for allyl alcohols and carbonyl compounds. Ethynyl groups may be similarly protected ; thus, the sodium salt of undeca-1 : 7-diyne is converted into undec-7-en-1-yne by sodium in liquid ammonia.[41] This method which is simple in operation is only useful when the alcohol, enol, or acetylene is considerably the strongest acid present. The presence of an acid of comparable strength (*e.g.*, ethanol) permits reduction to occur.[20] Conversion of a carbonyl into a non-reducible group can be achieved through formation of an acetal, ketal, or enol ether provided the alkoxyl groups are not in an allylic or a benzyl position and the enol-ether double bond is unconjugated. Accordingly there are difficulties when the carbonyl group is in the α- or β-position to an aromatic ring.[19, 20] The problem has been solved for benzaldehyde derivatives by converting them

[35] See, *e.g.*, Barton and Cookson, *Quart. Rev.*, 1956, **10**, 67.

[36] Hallsworth and Jenbest, *J.*, 1957, 4604.

[37] *E.g.*, Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1949, **32**, 265 ; Plattner, Fürst, Koller, and Kuhn, *ibid.*, 1954, **37**, 258.

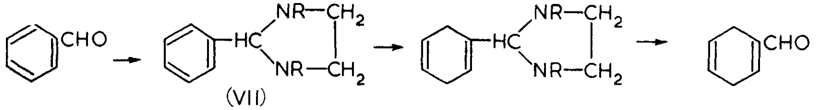
[38] Kazanskii and Gostunskaya, *J. Gen. Chem.* (*U.S.S.R.*), 1955, **25**, 1659.

[39] Kazanskii and Glushev, *ibid.*, 1938, **8**, 642 ; *Bull. Acad. Sci. U.R.S.S.*, 1938, 1061, 1065, and earlier papers.

[40] Birch and Dunstan, unpublished work.

[41] Dobson and Raphael, *J.*, 1955, 3558.

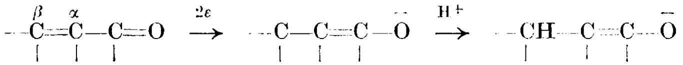
into tetrahydroglyoxalines, *e.g.*, (VII), which resist hydrogenolysis whilst the aromatic nucleus is reduced.[18] The aldehyde group can then be regenerated by acid treatment. The presence of other reducible groups is



(VII)

undesirable, *e.g.*, tetrahydro-1 : 2 : 3-triphenylglyoxaline (VII ; R = Ph) undergoes fission [18] because the *N*-phenyl groups stabilise the negative charge on the intermediate nitrogen anion. Hence dialkyltetrahydroglyoxalines are generally used. Unfortunately the method is inapplicable to ketones, which fail to react with *NN'*-dialkyethylenediamines.

Stereochemical Aspects of Reduction.—A review [42] of the products formed by the reduction of various multiple bond systems by dissolving metal reagents which act through the formation of intermediate carbanions has indicated that where stereoisomeric products are possible the thermodynamically stable ones are usually formed. The rule holds in many cases, *inter alia*, the reduction of acetylenes to *trans*-ethylenes,[41, 43] ketones to secondary alcohols, oximes to amines, conjugated dienes and trienes to olefins, and $\alpha\beta$-unsaturated ketones, esters, and acids to the corresponding saturated derivatives, although recent work has shown that it is not universally applicable. The case of $\alpha\beta$-unsaturated ketones is of particular importance. The reduction has been interpreted [42] as following the reaction



$$-\overset{\beta}{\text{C}}{=}\overset{\alpha}{\text{C}}-\text{C}{=}\text{O} \xrightarrow{2\epsilon} -\text{C}-\text{C}{=}\text{C}-\overset{-}{\text{O}} \xrightarrow{\text{H}^+} -\text{CH}-\text{C}{=}\text{C}-\overset{-}{\text{O}}$$

(VIII) (IX)

path delineated. The stability of the enol anion (IX) in the absence of an excess of " acid " of comparable strength permits the eventual isolation of the saturated ketone. In a further discussion [44] of this type of reaction it has been pointed out that (VIII) should add a proton at the very basic β-position by a process involving little activation energy, in which case the nature of the product is determined by the most stable conformation of the anion rather than the least hindered approach of the proton donor. This accounts for the fact that when the β-position is capable of yielding stereoisomers, the most stable one is invariably formed. For the α-position other considerations apply and the nature of the final product may depend on whether ketonisation of the enol anion is thermodynamically or kinetically controlled. Kinetic control at this stage has been observed to give the thermodynamically unstable isomer in reduction of the ketone (X), which gives the *cis*-isomer [44] (XI), readily convertible into the *trans*-isomer. A closely related example is formation of the *cis*-product (XIII) by lithium–ammonia reduction of the styrene (XII).[45] The mechanism of reduction of

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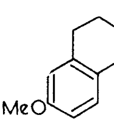
[42] Barton and Robinson, *J.*, 1954, 3045. [43] Campbell, *Chem. Rev.*, 1942, **31,** 77.

[44] Birch, Smith, and Thornton, *J.*, 1957, 1339.

[45] Johnson, Ackerman, Eastham, and Dewalt, *J. Amer. Chem. Soc.*, 1956, **78,** 6303.

such styrene compounds is not clear, but if it involves an 8 : 9-dianion (steroid numbering) the first proton should be added at the more reactive 9-position. The formation of the less stable isomer in this case has been ascribed to the influence of the 5α-hydroxyl group which by alkoxide formation induces the negative charge at $C_{(9)}$ to adopt the β-position. When the less stable isomer is formed there is apparently a requirement that an aromatic ring shall be attached to the ring system, since reduction of Δ^9-octal-1-one gives only the *trans*-decalone.[46] A possible explanation for this is that the aromatic ring reduces the energy difference between the *cis*- and the *trans*-form of an anion such as (XIV) and thereby ensures an appreciable concentration of the former at equilibrium. In a more complex case in the steroid series the aromatic ring may not be necessary, provided that approach of the proton-donor required for the formation of the more stable product is sufficiently hindered : this may be so in the reduction of 3β-acetoxyergosta-8 : 22-dien-7-one [46] (XV).



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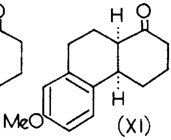

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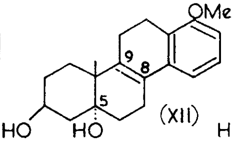

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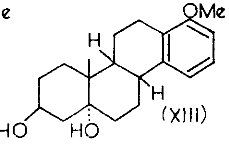

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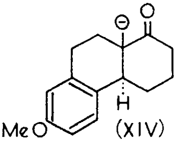

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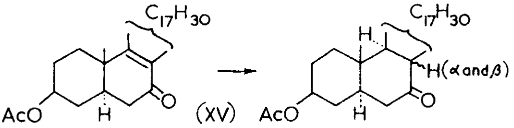

It has recently been shown that the sodium–ammonia reduction of dideuteroacetylene gives *trans*-dideuteroethylene,[47] in line with the fact that this method of producing *trans*-olefins from acetylenes is completely stereospecific.[43, 41] It is noteworthy that equilibrium mixtures contain appreciable amounts of *cis*-ethylenes.[48]

2. Use of metal–amine reagents in synthesis

(a) **Metal–Ammonia Solutions.**—(i) *Removal of protecting groups.* Solutions of potassium or sodium in liquid ammonia have found widespread application in synthesis for the reductive removal of unsaturated groups used as protecting agents for amino-, imino-, hydroxyl, and thiol groups. They are of particular importance in peptide synthesis, having the obvious general advantage over hydrolytic or catalytic methods for compounds which are labile in acid or contain sulphur. Benzyl, toluene-*p*-sulphonyl, and benzyloxycarbonyl groups are all efficiently replaced by hydrogen, and

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[46] Birch, Smith, and Wilson, unpublished work.

[47] Rabinowitz and Looney, *J. Amer. Chem. Soc.*, 1953, **75**, 2652.

[48] Kilpatrick, Prosen, Pitzer, and Rossini, *J. Res. Nat. Bur. Stand.*, 1946, **36**, 559.

cystinyl-peptides are cleaved to cysteinyl derivatives. These applications are summarised as follows :

(i) $RS{\cdot}CH_2Ph \longrightarrow R{\cdot}SH + PhMe$
(ii) $R{\cdot}NH{\cdot}SO_2{\cdot}C_6H_4Me\text{-}p \longrightarrow R{\cdot}NH_2 + p\text{-}C_6H_4Me{\cdot}SH$
(iii) $R{\cdot}NH{\cdot}CO_2CH_2Ph \longrightarrow R{\cdot}NH_2 + CO_2 + PhMe$
(iv) $RS{\cdot}SR \longrightarrow 2R{\cdot}SH$
(v) $RO{\cdot}CH_2Ph \longrightarrow ROH + PhMe$

The use of reactions (i)—(iv) in the synthesis of sulphur-containing peptides ranging from glutathione [49] to oxytocin [50] has been reviewed.[51] Cleavage by sodium–ammonia has also been used to remove benzyl groups protecting the hydroxyl groups in serine- and tyrosine-containing peptides [52] and the cyclic amino-groups in histidinyl-peptides.[53] Peptide groups are apparently unaffected, probably because of salt formation. After the observation that dibenzyl and diphenyl hydrogen phosphate are converted into inorganic phosphate by sodium in liquid ammonia,[54] the reagent has proved of crucial importance for the removal of protecting groups including benzyl, tosyl, and benzyloxycarbonyl in the synthesis of various phosphates and pyrophosphates of biological interest.[54, 55] Thus the last stage in the synthesis of the "*Acetobacter* stimulatory factor" (ASF) involved the sodium–ammonia fission of four benzyl groups : [54]

$$(PhCH_2O)_2P(O){\cdot}O{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OCH_2Ph){\cdot}[CO{\cdot}NH{\cdot}CH_2CH_2]_2{\cdot}S{\cdot}CH_2Ph \longrightarrow (HO)_2P(O){\cdot}O{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OH){\cdot}[CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2]_2{\cdot}SH$$

An interesting fission of an alkyl aryl ether is the selective demethylation of the readily available homoveratrylamine [2-(3 : 4-dimethoxyphenyl)ethylamine] to 2-(3-hydroxy-4-methoxyphenyl)ethylamine [56] which can serve as a starting material for the synthesis of naturally occurring *iso*vanillyl derivatives. The fission is based on the earlier conversion [57] of 3 : 4-dimethoxytoluene into 3-hydroxy-4-methoxytoluene. The resistance of the 4-methoxyl group to hydrogenolysis follows from the proposed mechanism for the fission, since the negative charge which must develop on oxygen for demethylation to ensue is destabilised by the electron-releasing *para*-group. Selectivity is therefore different from that observed in acid-catalysed demethylation.

A cleavage that has found use in partial synthesis of steroids is the

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[49] Loring and du Vigneaud, *J. Biol. Chem.*, 1935, **111,** 385.

[50] du Vigneaud, Ressler, Swan, Roberts, and Katsoyannis, *J. Amer. Chem. Soc.*, 1954. **76,** 3113.

[51] du Vigneaud, "Symposium on Peptide Chemistry", Chem. Soc. Spec. Publ. No. 2, 1955, p. 49.

[52] Grassman, Wünsch, and Deufel, and Grassman, Wunsch, and Fries, quoted by Grassman, *Fortschr. Chem. org. Naturstoffe*, 1956, **13,** 547.

[53] du Vigneaud and Behrens, *J. Biol. Chem.*, 1936. **117,** 27 ; Katchalski and Patchornik, XIVth Int. Congr. Pure Appl. Chem., 1955.

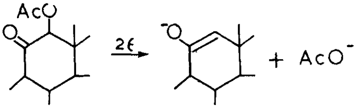
[54] Baddiley and Thain, *J.*, 1953, 1611.

[55] Baddiley and Mathias, *J.*, 1954, 2801 ; Arris, Baddiley, Buchanan, and Thain, *J.*, 1956, 4968.

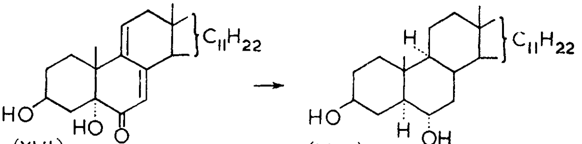
[56] Hamlin and Fischer, *J. Amer. Chem. Soc.*, 1953, **75,** 5119.

[57] Birch, *J.*, 1947, 102.

reductive removal of the 12-acetoxy-group in hecogenin, to give 11-oxotigogenin.[58] The reagent of choice was calcium in ammonia ; the reaction



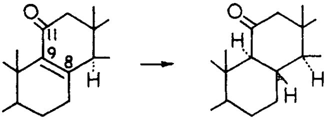
most probably proceeds as annexed. The free ketol gave the diequatorial diol whereas the α-ketol (XVI) and the vinylogous ketol 6β-hydroxytestosterone both suffer loss of hydroxyl, to give (XVII) [59] and testosterone [60] respectively.

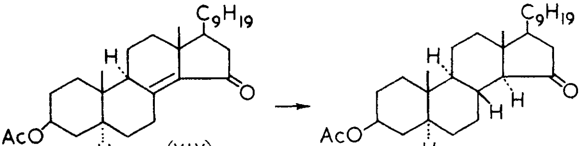


(XVI) (XVII)

(ii) *Reduction of αβ-unsaturated ketones.* The reaction which, quantitatively at least, is the most important application of the metal–ammonia reagent is the stereospecific reduction of various steroid αβ-unsaturated ketones capable of giving rise to one or two new centres of asymmetry.

(XVIII)





(XIX)

The conversion of a number of 8-en-11-ones (XVIII) into the corresponding 8β : 9α-dihydro-derivatives in high yield has proved invaluable in routes for the partial synthesis of cortisone.[61] In these cases, as in the reduction of 3β-acetoxycholest-8(14)-en-15-one [62] (XIX), proton addition to give the 9β- and the 14α-compound may be kinetically as well as thermodynamically favoured because of the influence of the bulky β-methyl groups.

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[58] Chapman, Elks, and Wyman, *Chem. and Ind.*, 1955, 603 ; Chapman, Elks, Philips, and Wyman, *J.*, 1956, 4344.

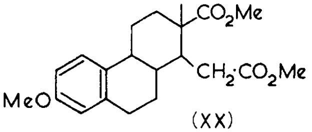
[59] Zurcher, Heusser, Jeger, and Geistlich, *Helv. Chim. Acta*, 1954, **37**, 1562.

[60] Amendolla, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1954, **76**, 1226.

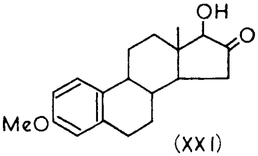
[61] *E.g.*, Sondheimer, Yashin, Rosenkranz, and Djerassi, *ibid.*, 1952, **74**, 2696 ; Sondheimer, Mancera, Rosenkranz, and Djerassi, *ibid.*, 1953, **75**, 1282 ; Schoenewaldt, Turnbull, Chamberlin, Rheinhold, Erikson, Ruyle, Chemerda, and Tishler, *ibid.*, 1952, **74**, 2696 ; Bladon, Henbest, Jones, Lovell, and Woods, *J.*, 1954, 125.

[62] Barton and Laws, *J.*, 1954, 52.

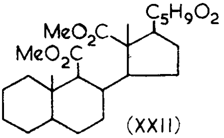
(iii) *Acyloin condensations.* Solutions of sodium in liquid ammonia enable the acyloin condensation to be carried out in a homogeneous solution. The method offers obvious practical advantages over the conventional method using sodium dispersed in boiling toluene, and conditions have been found which lead to high yields of acyloin, particularly in intramolecular condensations. Thus dimethyl marrianolate methyl ether (XX) gives the ketol (XXI),[63, 64] which is readily converted into œstrone, and the method becomes the one of choice for the completion of ring D in a steroid synthesis. None of the ketol (XXI) was obtained by the older technique. Similarly, dimethyl 11 : 12-*seco*cholanate (XXII) gave a high yield of the tetracyclic 11 : 12-acyloin.[63] The reaction has also been employed to provide 16-oxotestosterone.[65]



(XX)

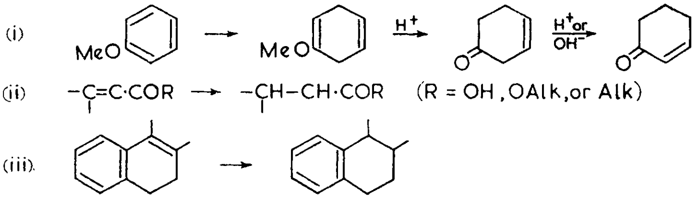


(XXI)



(XXII)

(b) **Metal-Ammonia and Alcohols.**—These reagents were originally developed for use in steroid synthesis with the object of preparing *cyclo*hexenones from anisole derivatives by the reaction path (i). Chiefly as a result of their tendency to give the thermodynamically most stable products where stereoisomerism is possible, they were later used for reductions of types (ii) and (iii). Although reactions (ii) and (iii) do not require alcohols, better yields have been obtained in many cases in their presence (because there are then fewer side reactions). However, fairly slow reactions of type (ii) in presence of large excesses of alcohol normally give the alcohol rather than the ketone. A process of type (i) was applied in 1949 to 3-2′-hydroxyethoxyœstra-1 : 3 : 5-trien-17β-ol which gave 19-nortesto-



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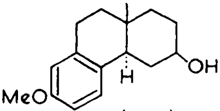
[63] Sheehan, Coderre, Cohen, and O'Neill, *J. Amer. Chem. Soc.*, 1952, **74**, 6155.

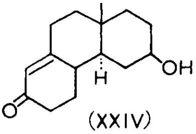
[64] Sheehan, Coderre, and Cruikshank, *ibid.*, 1953, **75**, 6231.

[65] Adams, Patel, Petrow, and Stuart-Webb, *J.*, 1956, 297.

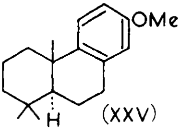
sterone,[12] a hormone which had 30% of the androgenic activity of testosterone and was the first active androgen to be made by total synthesis. Subsequently a wide range of 19-nor-hormones [66] was prepared by this process, some more active than the analogues of the natural series. 19-Nortestosterone β-phenylpropionate (" Durabolin ") [67] and 17α-ethyl-19-nortestosterone (" Nilevar ") [68] are recommended for use as anabolic agents. Similar applications of the process to 3 : 4-disubstituted anisoles have provided essential steps in the total synthesis of steroids, terpenes, and alkaloids. Thus the anisole derivative (XXIII) gave the ketone (XXIV) [69] which formed the basis of rings B, C, and D in a total synthesis of 11-oxygenated steroids ; the anisole (XXV) gave the ketone (XXVI),[70] used to complete a total synthesis of (±)-totarol, and the anisole (XXVII) gave the ketone (XXVIII) [71] which was converted into yohimbone.



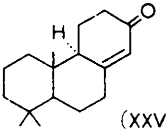
(XXIII)



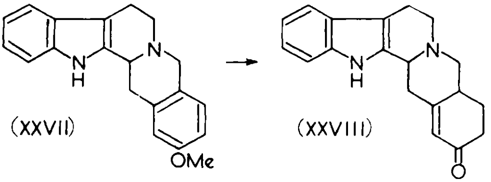
(XXIV)



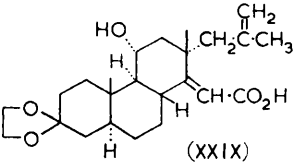
(XXV)



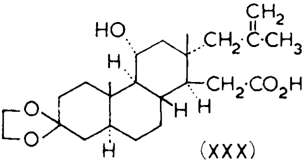
(XXVI)



(XXVII) (XXVIII)



(XXIX)



(XXX)

A process of type (ii) proved of primary importance in the Merck total synthesis of cortisone, in ensuring the correct *trans*-configuration at the C–D ring junction : reduction of the acid (XXIX) with potassium and propan-2-ol in liquid ammonia gave the dihydro-derivative (XXX) stereospecifically.[72] It is of theoretical interest that with an 11β-hydroxyl group (axial) a predominant amount of the unwanted product with a 14β-hydrogen atom was obtained. Two possible explanations for this result are that (*a*)

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[66] *E.g.*, Djerassi, Miramontes, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 4440 ; Sandoval, Miramontes, Rosenkranz, Djerassi, and Sondheimer, *ibid.*, p. 4117 ; Djerassi, Lippman, and Grossman, *ibid.*, 1956, **78**, 2479 ; Ringold, Rosenkranz, and Sondheimer, *ibid.*, p. 2477.

[67] Anon., *Angew. Chem.*, 1957, **69**, 69.

[68] Anon., *Chem. Eng. News*, 1956, **34**, 2134.

[69] Stork, Loewenthal, and Mukharji, *J. Amer. Chem. Soc.*, 1956, **78**, 501.

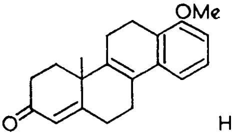
[70] Barltrop and Rogers, *Chem. and Ind.*, 1957, 20.

[71] Swan, *J.*, 1950, 1534.

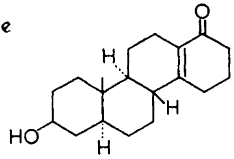
[72] Arth, Poos, Lukes, Robinson, Johns, Feurer, and Sarett, *J. Amer. Chem. Soc.*, 1954, **76**, 1715.

repulsion between negative charges on oxygen causes the methoxycarbonyl group to assume the *trans*-α-(axial)-configuration or (*b*) proton transfer through the solvent from the 11β-hydroxyl group results in proton addition to the β-side of the 14-carbanion.[73]

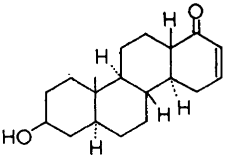
Unquestionably the most impressive application of metal–ammonia reagents in synthesis was afforded by the Wisconsin total synthesis of steroids.[74] Processes (i)—(iii) were carried out simultaneously on compound (XXXI), to give the ketones (XXXII) and (XXXIII) having respectively five and six new centres of asymmetry. Thirty-two racemates of ketone (XXXII) and sixty-four of ketone (XXXIII) were therefore possible, but in fact the mixture of the two compounds was obtained in 25% yield.



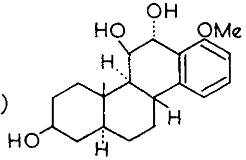
(XXXI)

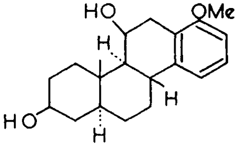


(XXXII)

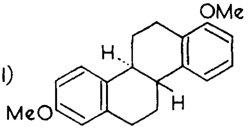


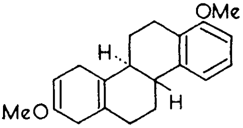
(XXXIII)

(XXXIV)




(XXXV)

(XXXVI)




(XXXVII)

Extension of the synthesis to 11-oxygenated steroids[75] exploited the benzyl alcohol fission, in the conversion of the triol (XXXIV) into the diol (XXXV). The latter can be reduced in much higher yield than its deoxy-analogue. This difference has been attributed to inhibition of hydrogenolysis of the methoxyl group by formation of the 11-alkoxide.[75] It is however significant that the 11-hydroxy-group is in the axial conformation where it can facilitate proton transfer to the 13-position by a cyclic (probably six-membered ring) mechanism. The reduction of 5-methoxytetralin systems which was a feature of these syntheses had previously presented difficulties[76] due to the fact that 1 : 4-addition of hydrogen must involve at least one position occupied by a charge-destabilising group. Workable yields were only obtained by use of a technique, originally developed for sodium

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[73] Kenner, *Ann. Reports*, 1954, **51,** 177.

[74] Johnson, Rogier, Szmuszkovicz, Hadler, Ackerman, Bhattacharya, Bloom, Stalmann, Clement, Bannister, and Wynberg, *J. Amer. Chem. Soc.*, 1956, **78,** 6289 ; Johnson, Bannister, Bloom, Kamp, Pappo, Roger, and Szmuszkovicz, *ibid.*, 1953, **75,** 2275.

[75] Johnson, Pappo, and Johns, *ibid.*, p. 6339.

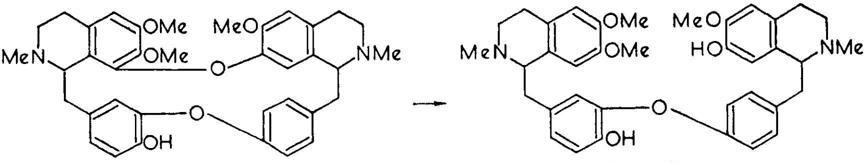
[76] Birch, Murray, and Smith, *J.*, 1951, 1945.

reductions in the Boots laboratories,[77] employing a two-phase system made by the addition of 40% or more of ethanol to the liquid ammonia. The resistance of vicinal dialkyl derivatives of anisole to reduction has been exploited, to afford a selective reduction of the 3 : 4-disubstituted anisole ring in the ether (XXXVI). The product (XXXVII) was used to synthesise (±)-18 : 19-bisnor-D-homotestosterone.[78]

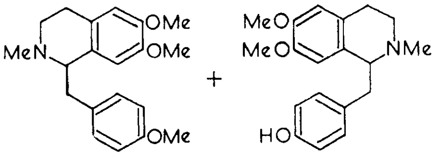
3. Uses in determinations of structure

These uses are based chiefly on fission reactions, largely of ethers.

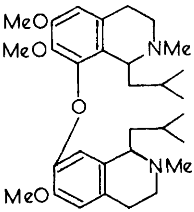
The metal–ammonia reagent has proved to be a tool of exceptional power in elucidating the structure and stereochemistry of alkaloids containing diaryl ether linkages. These ethers are very resistant to hydrolysis but can be reductively split in high yields with solutions of potassium or sodium in liquid ammonia. The simplest example is that of cularin which gives a 5-hydroxybenzyl-3 : 4-dimethoxy*iso*quinoline.[79] The method has been widely employed to determine the structure of biscoclaurin bases [80] which in general are cleaved into two benzyl*iso*quinoline fragments of known, or easily determined, structure. The optical rotations of such products give also the relative orientations of the asymmetric centres. Alkaloids containing free phenolic groups are more difficult to cleave because of phenoxide formation. In berbamine (XXXVIII) the free phenolic group protects the adjacent diphenyl ether linkage and the product [81] is a base of the dauricin type (XXXIX). This, on methylation, can be cleaved into two benzyl*iso*quinoline fragments (XXXIXa). Further examples of the use of the reagent are in the cleavage of phaeanthine, *OO'*-dimethylcurine, and *OO'*-dimethyl*iso*chondrodendrine.[82] The usual co-solvents for these reactions



(XXXVIII) (XXXIX)



(XXXIXa)



(XL)

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[77] Short, unpublished work.

[78] Birch and Smith, *J.*, 1956, 4909.

[79] Manske, *J. Amer. Chem. Soc.* 1950, **72**, 55.

[80] Tomita, Fujita, and Murai, *J. Pharm. Soc. Japan*, 1951, 226.

[81] *Idem*, *ibid.*, p. 301.

[82] Kidd and Walker, *J.*, 1954, 669 ; *Chem. and Ind.*, 1953, 243.

(largely determined by the solubilities of the alkaloids) are toluene and benzene ; in the presence of dioxan, phaeanthine yields in addition to the "normal" benzyl*iso*quinoline cleavage products a third benzyl*iso*quinoline formed by an alternative mode of scission. This result is possibly due to the participation of the more polar solvent in the solvent-induced stabilisation of intermediate anions. Cleavage of pilocereine methyl ether into four *iso*quinolines enables the skeletal structure to be unambiguously defined as in (XL).[83] The directions of fission are all predictable on the basis of the rules already set out.[1]

Alkali metal–ammonia solutions can effect Emde-type fission of quaternary ammonium salts [84] and may be the reagents of choice because they minimise the accompanying Hofmann reaction, but this property has not so far been appreciably used in alkaloid investigations.

It has recently been shown that axial methoxycarbonyl groups in steroid or terpenoid structures are converted into carboxylic acid groups by alkali metals in ammonia, whereas the corresponding equatorial group undergoes Bouveault–Blanc-type reduction to the hydroxymethyl group.[85] The same result is obtained in the presence of alcohols, and the reaction, which appears to be so specific as to be diagnostic, is clearly a hydrogenolysis similar to the fission of aryl methyl ethers.

Reductive fission of naturally occurring allyl alcohols and allyl and benzyl ethers may often be of great assistance. Thus the structure of lanceol (XLI) was confirmed by its reduction,[86] with sodium and alcohol in liquid ammonia, to the known bisabolene (XLII). As a further illustration, the terpenoid side chain of the mould metabolite mycelianamide was recognised [87] as being an allyl ether of the geranyl type by cleavage to methylgeraniolene and a derivative of *p*-hydroxybenzoic acid. Information as to the relative configurations of catechins and *epi*catechins can be procured by cleavage of the benzyl ether linkages in these compounds. (+)-Catechin itself and (—)-*epi*catechin give enantiomorphous alcohols, showing that the 3-hydroxyl groups are in opposed configurations as in (XLIII) and (XLIV),[88] *i.e.*, that (+)- or (—)-catechin and (+)- or (—)-*epi*catechin have the *same* configuration of the 3-hydroxyl group. Sodium–ammonia solutions have been used to cleave what are probably phenyl and benzyl ether links in various lignins and give notable yields of compounds of low molecular weight.[89] Evidence regarding the stereochemistry of the carbon skeleton of various tetrahydrofuranoid lignans with structures such as (XLV) has been obtained by sodium–ammonia cleavage of the benzyl ether links and

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[83] Djerassi, Figdor, Bobbitt, and Markley, *J. Amer. Chem. Soc.*, 1956, **78,** 3861.

[84] Clayson, *J.*, 1949, 2016 ; Haworth, Lunts, and McKenna, *J.*, 1956, 3749 ; see also ref. 34.

[85] Wenkert and Jackson, *J. Amer. Chem. Soc.*, 1958, **80,** 217.

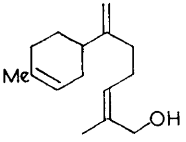
[86] Birch and Murray, *J.*, 1951, 1888.

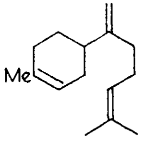
[87] Birch, Massy-Westropp, and Rickards, *J.*, 1956, 3717.

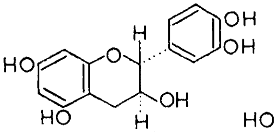
[88] Birch, Clark-Lewis, and Robertson, *J.*, 1957, 358.

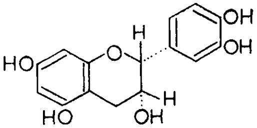
[89] Freudenberg, Engler, Flickinger, Sobek, and Klunk, *Ber.*, 1938, **71,** 1810 ; Shorygina, Kefeli, and Semechkina, *Doklady Akad. Nauk S.S.S.R.*, 1949, **64,** 689 ; *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19,** 1558 ; Shorygina and Kefeli, *ibid.*, 1950, **20,** 1199, 1243 ; Shorygina and Semechkina, *ibid.*, 1953, **23,** 617.

examination of the reactions of the resulting stereoisomeric alcohols (XLVI), including their cyclisations to the aryltetrahydronaphthalene derivatives (XLVII) some of which are natural lignans. Probable configurations for galbulin, galcatin, and galbelgin from *Himantandra* barks can be worked out.[90] The structure of the lignan, gmelinol (XLVIII), was finally determined [91] as the result of the ring-fission to the triol (XLIX) which on oxidation with lead tetra-acetate gave formaldehyde.


(XLI)


(XLII)


(XLIII)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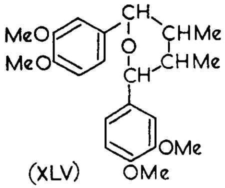
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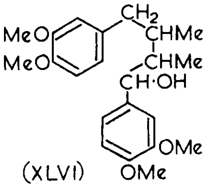
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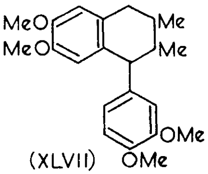
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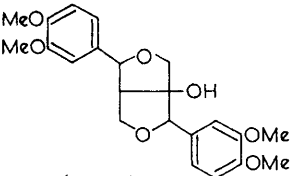
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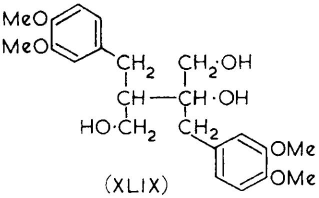
(XLIX)

It has recently been discovered that preliminary reduction with sodium and ethanol in liquid ammonia facilitates the hydrolysis of the sugar residue from pyrimidine nucleosides.[92] It is probable that the reagent, by destroying aromaticity, converts the nucleoside into an acid-labile enamine glycoside.

It will be obvious from the above brief survey that despite the large volume of work made possible by the introduction of the metal–amine reagents much remains to be done, especially in investigating the reactivities of various metal-amine–proton-source combinations and in explaining the observed reactions. It should also be clear that the variety of reagents available, and their great power, coupled with the specificity obtainable by an appropriate formulation, are amongst the factors which will ensure their continued use in structural and synthetic problems.

We thank Dr. H. B. Henbest for informing us of results before their publication.

[90] Birch, Milligan, (Mrs.) E. Smith, and Speake, unpublished work.
[91] Birch, Hughes, and Smith, *Austral. J. Chem.*, 1954, **7**, 83.
[92] Burke, *J. Org. Chem.*, 1955 **20**, 643.