STUDIORUM PROGRESSUS

Some Generalizations Relative to Lithium Aluminium Hydride Reactions

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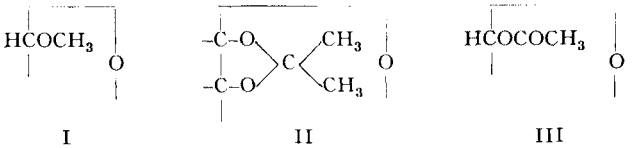
A thorough examination of the chemical literature for the purpose of reviewing the reactions of lithium aluminium hydride (LAH) indicates that sufficient data are now available to permit the statement of several generalizations relative to the course of such reactions. Such generalizations permit the possible prediction of reaction products on a sound factual basis and serve an even more important function in guiding the elucidation of the structures of complex molecules. The present exposition is concerned with the reactions of organic molecules containing a carbon atom singly bound with two atoms from the group nitrogen, oxygen or sulfur, and where the two remaining valances of carbon are not doubly bonded.

The $-\overset{|}{\underset{|}{O-C-O}}$ *grouping*

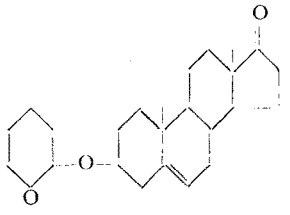
The use of acetals and ketals to protect carbonyl groups during LAH reductions has become widespread. These acetals have included open structures, as in acetal[2], as well as cyclic structures, as in the dioxolanes[3]. The latter type of compound has been used for the blocking of carbonyl groups or glycols in the LAH reduction of sugars[4], steroids[5] as well as other aliphatic and aromatic compounds[6]. Compounds containing the methylenedioxy group can be considered as cyclic acetals of formaldehyde and similarly are not attacked by LAH[7].

The reduction by LAH of pyranosides (I)[1], pyranose and furanose derivatives containing the partial structures II[2] or III[3], as well as disaccharides containing glycosidic linkages[4], results in the retention of these structural features.



I II III

The reaction of 2,3-dihydropyran with steroidal alcohols results in the formation of ethers such as IV. Reduction of IV with LAH results in conversion of the ketone group to a carbinol while the $-\overset{|}{\underset{|}{OCO}}-$ group remains intact[5].



IV

Among the steroidal sapogenins, a 22,26-oxido-22-ol compound (V) has been subjected to LAH reduction. The initial product of the reaction containing the intact $-\overset{|}{\underset{|}{OCO}}-$ group is apparently dehydrated readily to form an isospirostane (VI)[6].

[1] Contribution No. 8 from the Yerkes Research Laboratory, E. I. du Pont de Nemours & Co., Inc., Buffalo 7, New York.

[2] C. S. MARVEL and H. W. HILL, Jr., J. Amer. Chem. Soc. *73*, 481 (1951). – W. SWOBODA, Mh. Chem. *82*, 388 (1951). – L. SCHMID, W. SWOBODA, and M. WICHTEL, Mh. Chem. *83*, 185 (1952).

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[5] P. L. JULIAN, E. W. MEYER, and I. RYDEN, J. Amer. Chem. Soc. *71*, 756 (1949); *72*, 367 (1950). – L. H. SARETT, M. FEURER, and K. FOLKERS, J. Amer. Chem. Soc. *73*, 1777 (1951).

[6] R. GREWE and E. NOLTE, Ann. Chem. *575*, 1 (1951). – M. STOLL and M. HINDER, Helv. chim. Acta *34*, 334 (1951). – K. BRACK and H. SCHINZ, Helv. chim. Acta *34*, 1523 (1951). – G. STORK and H. CONROY, J. Amer. Chem. Soc. *73*, 4743 (1951). – J. C. SHEEHAN and B. M. BLOOM, J. Amer. Chem. Soc. *74*, 3825 (1952).

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[3] R. K. NESS, H. G. FLETCHER, Jr., and C. S. HUDSON, J. Amer. Chem. Soc. *73*, 3742 (1951).

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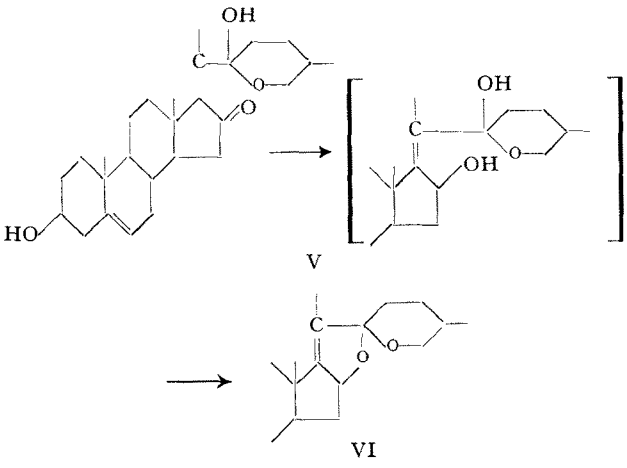
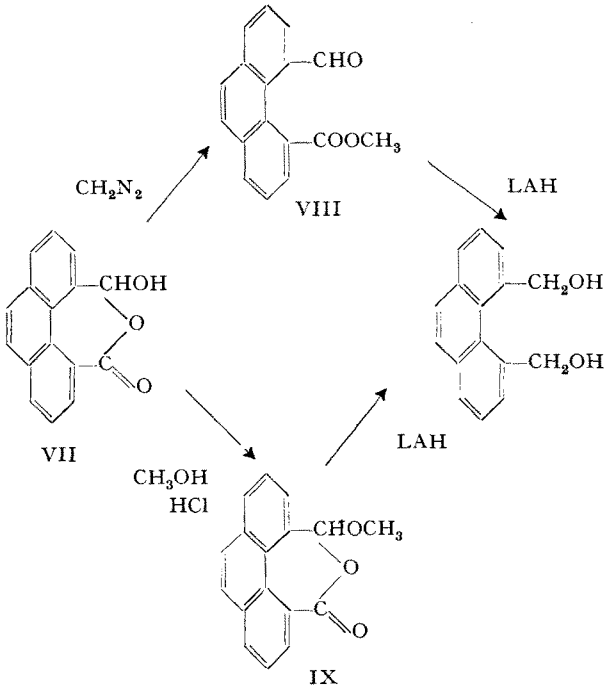
[6] A. SANDOVAL, J. ROMO, G. ROSENKRANZ, S. KAUFMAN, and C. DJERASSI, J. Amer. Chem. Soc. *73*, 3820 (1951). – A. L. NUSSBAUM, A. SANDOVAL, G. ROSENKRANZ, and C. DJERASSI, J. Org. Chem. *17*, 426 (1952).



V VI

Various isospirostanes such as VI have been subjected to LAH reduction and in all cases no reaction with the –OCO– linkage has occurred[1]. If the LAH reduction of the spirostane is carried out in the presence of anhydrous hydrogen chloride cleavage occurs at carbon *22* and opens the *22,26*-oxido ring[2].

The foregoing data permits the generalization to be made that under the usual conditions the –O–C–O– grouping is not attacked by LAH.



VII VIII IX

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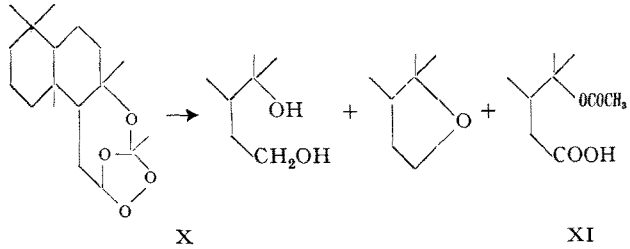
The reactions of LAH and the pseudo esters of 4-formyl-5-phenanthrenecarboxylic acid[1] would appear to be an exception to this generalization. The aldehyde-acid, which gives no carbonyl derivatives, has been assigned the lactol structure VII. Treatment with diazomethane yields the normal aldehydo-ester (VIII), which forms carbonyl derivatives while acid-catalyzed esterification yields the pseudo ester (IX) which does not form such derivatives. However, on treatment with LAH both ester forms yield the same diol in excellent yield.

In this case it is probable that under the influence of LAH the pseudo ester is converted to the normal ester before reduction occurs. In this connection it is of interest that under the influence of aluminium isopropoxide, which might be expected in this respect to behave in a manner similar to that of LAH, the pseudo ester is converted to the lactone of 4-(hydroxymethyl)-5-phenanthrenecarboxylic acid[2]. It has been shown that in the case of substituted 2-benzoylbenzoic acids, which also form pseudo as well as normal esters, a keto acid-hydroxylacetone equilibrium exists[3].

The reported LAH reductions of ozonides introduce structural features which enable these reactions to fit within the scope of the generalization. Thus, the reduction of the ozonide X is reported to yield a glycol, the oxyde arising from the dehydration of the glycol and a trace of the ester-acid XI[4].



X XI

The initial reaction might involve cleavage of the peroxide linkage[5]. The isolation of XI among the reaction products indicates that the resultant ortho ester structure would be cleaved at the oxygen bridge occupying the site of the original double bond. The cleavage of a carbon-oxygen bond in ortho esters to form acetals has been reported[6]. The order of occurrence of the above cleavages may be reversed without impairing the reasoning. The resultant derivatives of XI would react normally with LAH to yield the indicated products.

The LAH reduction of the ozonide XII followed by hydrolysis and chromic acid oxidation is reported to yield the diketone XIII[7].

[1] M. S. NEWMAN and H. S. WHITEHOUSE, J. Amer. Chem. Soc. *71*, 3664 (1949). – G. M. BADGER, J. E. CAMPBELL, J. W. COOK, R. A. RAPHAEL, and A. I. SCOTT, J. Chem. Soc. *1950*, 2326.

[2] M. S. NEWMAN and H. S. WHITEHOUSE. J. Amer. Chem. Soc. *71*, 3664 (1949).

[3] M. S. NEWMAN and C. W. MUTH, J. Amer. Chem. Soc. *73*, 4627 (1951).

[4] M. HINDER and M. STOLL, Helv. chim. Acta *33*, 1308 (1950).

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[6] C. J. CLAUS and J. L. MORGENTHAU, JR., J. Amer. Chem. Soc. *73*, 5005 (1951).

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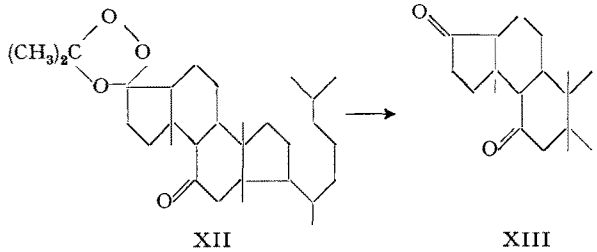
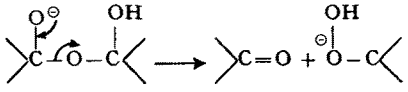


XII XIII

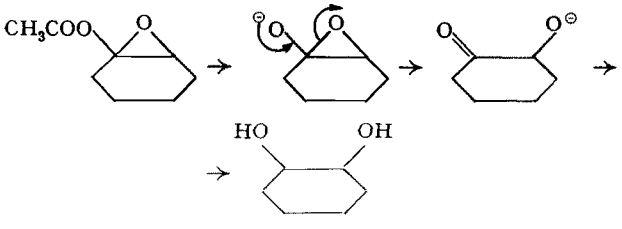
The cleavage of the peroxide linkage in XII would result in the formation of XIV which would be cleaved as shown.



XIV

The resultant carboxylic acid derivative would be reduced to the carbinol and chromic acid oxidation would yield the carbonyl function.

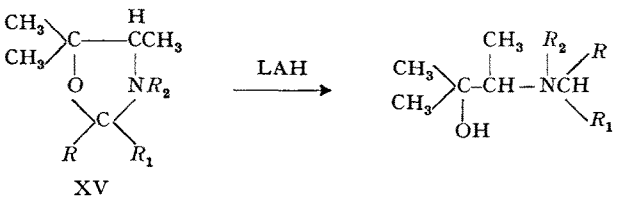
The reduction of 1-acetoxy-1, 2-epoxycyclohexane to yield a mixture of *cis*- and *trans*-cyclohexanediol-1, 2[1] can also be shown not to be contrary to the generalization. The presence of the acetoxy group results in the formation of an intermediate analogous to XIV which can undergo a similar reaction.



The –N–C–O– *Grouping*

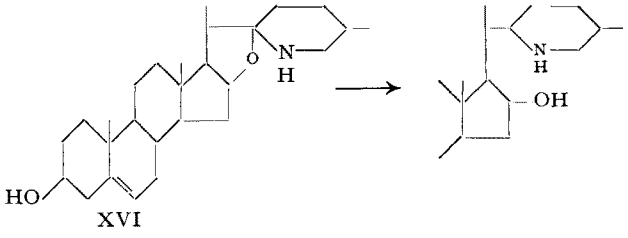
In the reductive cleavage of unsymmetrical epoxides, as in the steroids, by LAH, a secondary oxide linkage is cleaved in preference to a tertiary[2]. Similarly, LAH reductions of 1-cyano-1, 2-epoxycyclohexane and 1-methyl-1, 2-epoxycyclohexane yield the expected tertiary alcohols[3]. In contrast, LAH reduction of 1-dimethylamino-1, 2-epoxycyclohexane which contains an –NCO– linkage yields the secondary alcohol resulting from cleavage of the oxide ring at the tertiary carbon[3].

Treatment of oxazolidines (XV) with LAH results in cleavage at the C–O– linkage yielding α-aminoalcohols[4]. In this case the –NCO– grouping is part of a heterocyclic ring.



XV

In contrast to the stability of the –OCO– grouping in sapogenic spirostanes, the –NCO grouping in solasodine (XVI) is cleaved at the C–O– linkage with LAH[1].

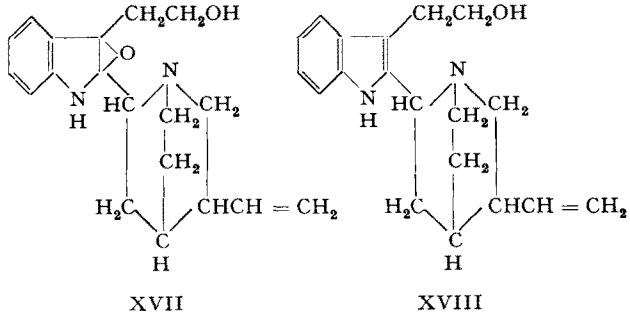


XVI

Solasodine hydrochloride behaves in a similar manner.

Tomatidine, the aglycone of tomatine extracted from tomato leaves, is reduced by LAH to dihydrotomatidine, the reaction being considered as the opening of an oxidic ring[2]. The identity of tomatidine and solasodanol, the saturated analog of XVI, has recently been reported[3].

The cinchona alkaloid quinamine was assumed to contain an epoxide group and on reduction with LAH gave cinchonamine. GOUTAREL *et al.*[4] therefore postulated the structure of quinamine as XVII and it was assumed that reduction of the epoxide group gave an alcohol which split out water to give cinchonamine (XVIII).



XVII XVIII

The intermediate dihydro derivative was isolated by CULVENOR *et al.*[5] and subsequently dehydrated to cinchonamine by heat. The intermediate was not further examined and consequently the direction of ring opening to give the tertiary alcohol was not determined. WITKOP[6]

[1] M. MOUSSERON, R. JACQUIER, M. MOUSSERON-CANET, and R. ZAGDOUN, C. r. Acad. Sci. *235*, 177 (1952). – M. MOUSSERON, M. CANET, and R. JACQUIER, Bull. Soc. chim. France [5] *19*, 698 (1952).

[2] P. A. PLATTNER, H. HEUSSER, and M. FEURER, Helv. chim. Acta *32*, 587 (1949).

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[4] H. HEUSSER, P. T. HERZIG, A. FÜRST, and P. A. PLATTNER, Helv. chim. Acta *33*, 1093 (1950). – E. D. BERGMANN, D. LAVIE, and S. PINCHAS, J. Amer. Chem. Soc. *73*, 5662 (1951).

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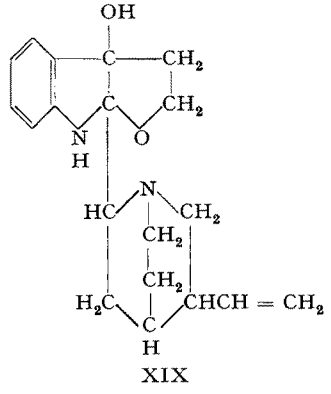
[4] R. GOUTAREL, M. M. JANOT, V. PRELOG, and W. I. TAYLOR, Helv. chim. Acta *33*, 150 1950).

[5] C. C. J. CULVENOR, L. J. GOLDSWORTHY, K. S. KIRBY, and R. ROBINSON, J. Chem. Soc. *1950*, 1485.

[6] B. WITKOP, J. Amer. Chem. Soc. *72*, 2311 (1950).

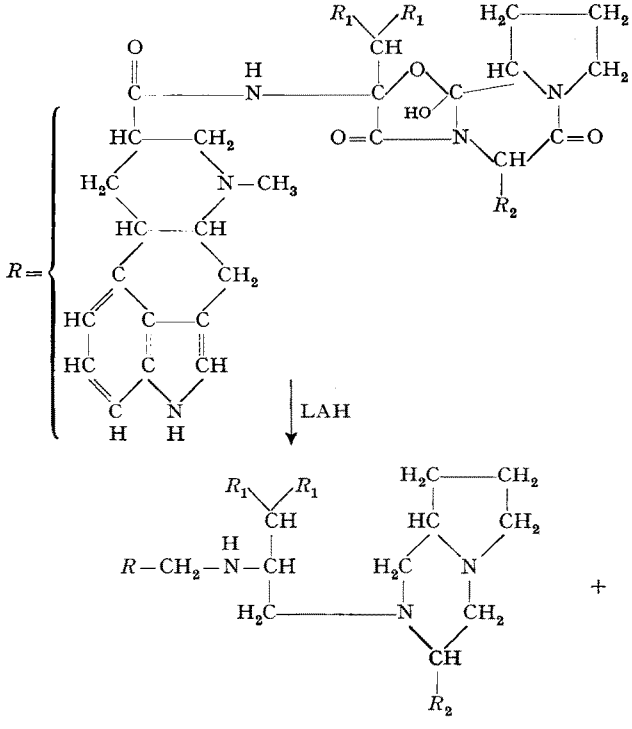
proposed a new structure for quinamine XIX. Although LAH reduction in this case does not distinguish between the two postulated structures, the intermediate cleavage product having the same structure in both cases, opening of the tetrahydrofuran ring does not seem improbable due to the presence of the –NCO– grouping.



XIX

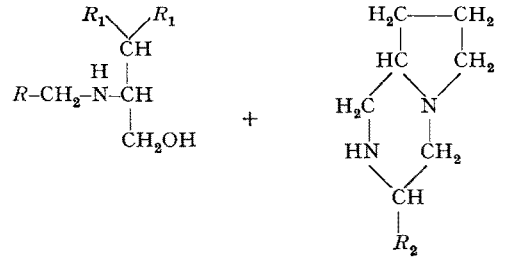
Epiquinamine which is considered as a diastereoisomer of quinamine due to epimerization at C_8 in the quinuclidene nucleus, is reduced by LAH to an isomeride of cinchonamine termed epicinchonamine[1]. The same structural considerations would apply in this case.

The dihydro derivatives of the ergot alkaloids, ergotamine, ergosine, ergocristine, ergocryptine, and ergocornine, have recently been subjected to LAH reduction and three reduction products have been isolated and their constitution and configuration identified by synthesis[2]. The reaction can be represented by the following equation:

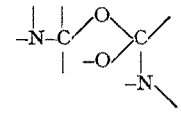


[1] C. C. J. CULVENOR, L. J. GOLDSWORTHY, K. S. KIRBY, and R. ROBINSON, J. Chem. Soc. *1950*, 1485.

[2] A. STOLL, A. HOFMANN, and T. PETRZILKA, Helv. chim. Acta. *34*, 1544 (1951).



Examination of the postulated ergot structure reveals the presence of the following elements:

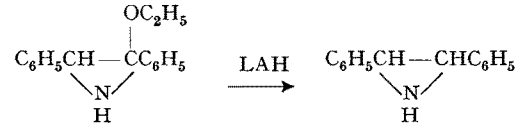


The reduction products, in all cases, reveal the cleavage of the C–O linkage. The generalization postulated here is further evidence for the structure advanced for the ergot alkaloids.

The LAH reduction of N-(α-alkoxybenzyl)-amides (XX) results in the cleavage of the C–O linkage as well as reduction of the amide grouping[1].

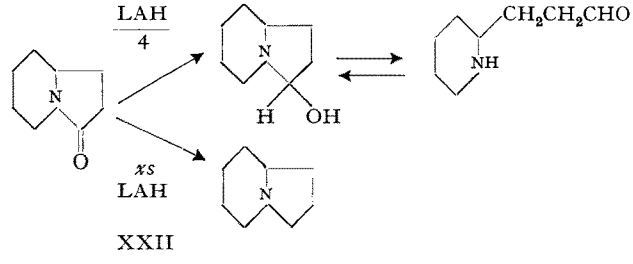
XX

The reduction of 2,3-diphenyl-2-ethoxyethylenimine (XXI) with LAH yields *cis*-diphenylethylenimine[2].



XXI

The reduction of N-methyl-α-pyrrolidone or 3-keto-octahydropyrrocoline (XXII) with one-quarter mole of LAH permits the isolation of the carbinol-amine in the form of the tautomeric aldehyde[3].



XXII

The use of excess LAH prevents the stopping of the reduction of the lactam at the intermediate stage. Here the first stage of the reduction proceeds to the carbinol-

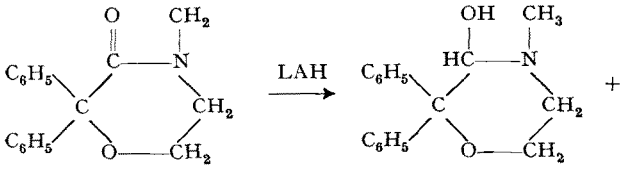
[1] A. W. BURGSTAHLER, J. Amer. Chem. Soc. *73*, 3021 (1951).

[2] M. J. HATCH and D. J. CRAM, J. Amer. Chem. Soc. *75*, 38 (1953).

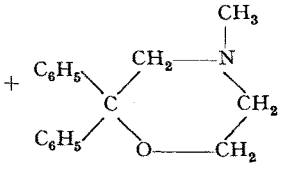
[3] F. GALINOVSKY and R. WEISER, Exper. *6*, 377 (1950). – J. A. KING, V. HOFMANN, and F. H. MC MILLAN, J. Org. Chem. *16*, 1100 (1951). – F. GALINOVSKY, A. WAGNER, and R. WEISER, Mh. Chem. *82*, 551 (1951). – F. GALINOVSKY, O. VOGL, and R. WEISER, Mh. Chem. *83*, 114 (1952).

amine containing the –NCO– grouping. Employment of excess LAH results in the cleavage of the C–O grouping.

Reduction of 3-keto-4-methyl-2, 2-diphenylmorpholine (XXIII) with 2 moles of LAH yields a mixture of 4-methyl-2, 2-diphenylmorpholine, the expected product, and 3-hydroxy-4-methyl-2, 2-diphenylmorpholine (XXIV)[1].

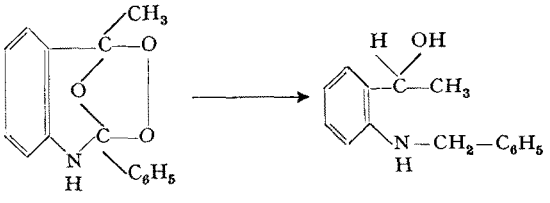


XXIII XXIV



The carbinol-amine (XXIV) is converted to the cyclic amine by the further action of LAH[1].

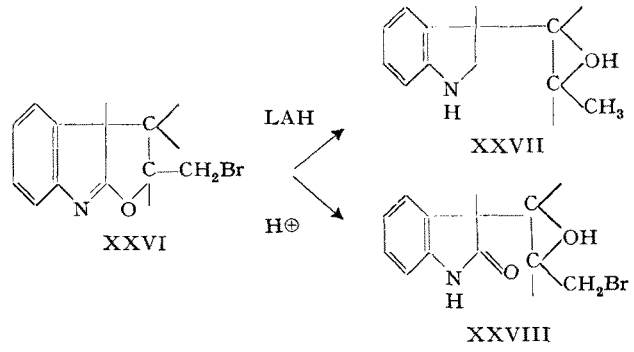
The recently reported[2] reductive cleavage of the stable ozonide of 2-phenylskatole (XXV) serves to illustrate two of the structural features discussed here.



XXV

The cleavage of the peroxide linkage and the cleavage of both –NCO– linkages result in the formation of a carboxylic acid derivative whose normal LAH reduction yields the indicated product.

Reaction of gelsemine with bromine in a chloroform solution yields bromoallogelsemine hydrobromide (XXVI). Treatment of XXVI with LAH in dioxane gives a compound $C_{20}H_{26}O_2N_2$ for which the constitution of desoxohydroxytetrahydrogelsemine (XXVII) has been advanced. On warming XXVI with acid one mole of water is taken up and a compound is formed which is formulated as bromohydroxydihydrogelsemine hydrobromide (XXVIII). The reduction of XXVI to XXVII with LAH is postulated as proceeding through XXVIII[3].



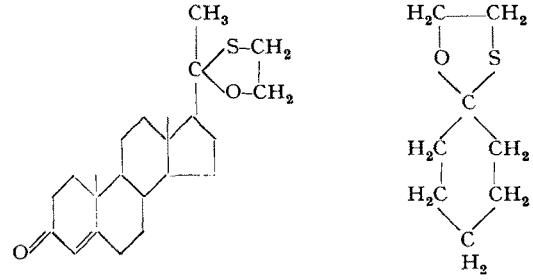
XXVI XXVII XXVIII

The anhydrous medium utilized in LAH reductions should preclude XXVIII as an intermediate in the reduction. A more likely explanation involves the reduction of the –N=C–O– grouping to –NH–CH–O–, followed by cleavage of the latter under the influence of LAH to yield XXVII.

From this multitude of reported reductions, the generalization can be made that under the usual conditions the –N–C–O– grouping is attacked by LAH to yield products resulting from cleavage of the C–O linkage.

The –S–C–O– *grouping*

Analogous to the use of acetals for the protection of carbonyl groups during LAH reductions, is the use of hemithioketals (XXIX) for the same purpose[1]. Similarly, 1, 3-thioxolanes (XXX) are not cleaved by LAH[2].



XXIX XXX

Thus, the –S–C–O– grouping as well as the –O–C–O– grouping is not attacked by LAH.

The –N–C–S– *Grouping*

Reduction of 1-nitroethyl p-tolylsulfide (XXXI) with LAH yields thiocresol among the reaction products[3].

[1] A. L. Morrison, R. F. Long, and M. Königstein, J. Chem. Soc. *1951*, 952.

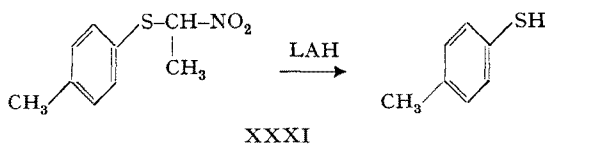
[2] B. Witkop and J. B. Patrick, J. Amer. Chem. Soc. *74*, 3855 (1952).

[3] R. Goutarel, M. M. Janot, V. Prelog, R. P. A. Sneeden, nd W. I. Taylor, Helv. chim. Acta *34*, 1139 (1951).

[1] J. Romo, G. Rosenkranz, and C. Djerassi, J. Amer. Chem Soc. *73*, 4961 (1951); Abstracts of Papers, XIIth International Congress of Pure and Applied Chemistry, New York, September 1951, p. 406.

[2] E. D. Bergmann, D. Lavie, and S. Pinchas, J. Amer. Chem. Soc. *73*, 5662 (1951).

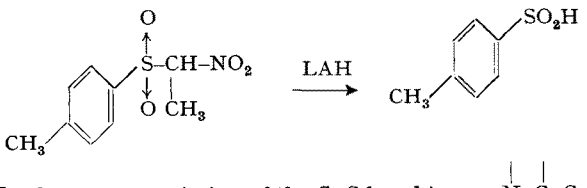
[3] N. Kharasch and J. L. Cameron, J. Amer. Chem. Soc. *75*, 1077 (1953).



XXXI

+ other products

LAH reduction of the corresponding sulfone yields p-toluenesulfinic acid in good yield.



In these cases, scission of the C–S bond in an –N–C–S– grouping has occurred under the influence of LAH.

Although it might not be pertinent in this consideration of singly bonded groupings, it is of interest to note that thiocyanates, containing the grouping –S–C≡N, are reduced by LAH to thiols indicating, as above, cleavage of the C–S bond[1].

Due to the lack of additional types of compounds containing the –NCS– grouping and the possible effect of the nitro group, a generalization cannot with justification be made in this case although the reported results appear to fall within the scope of this discussion.

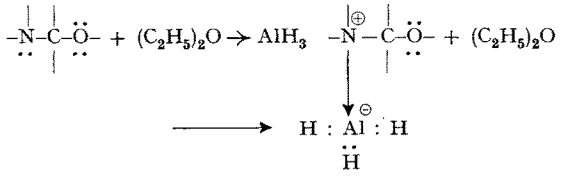
Mechanism

Paddock has shown that ether plays an essential part in LAH reductions[2]. The analogy with the GRIGNARD reagent has been extended to show the necessity for a donor solvent and evidence for monoetherate formation has been obtained. On this basis, PADDOCK has suggested that there is an equilibrium in solution

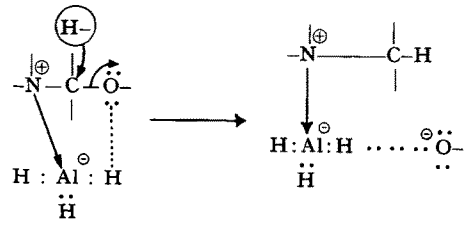
$$AlH_4^- \rightleftarrows H^- + AlH_3$$

and that the ether coordinates with the AlH_3 and the active entity in LAH reactions is the hydride ion.

If we utilize this suggestion we see that the cleavages and non-cleavages discussed above can be explained by analogy with GRIGNARD reactions. Thus, in the case of the –N–C–O– grouping coordination of the available electron pair on nitrogen can occur with AlH_3



The tendency for the electron pair on oxygen to take part in hydrogen bonding results in the formation of a quasi ring such as has been postulated in many GRIGNARD reactions. The electron deficient nitrogen would tend to withdraw electrons from the adjacent carbon giving the latter a positive character. The hydride ion present in the solution, according to PADDOCK's postulation, could displace the ethereal oxygen resulting in cleavage of the C–O bond:



In the case of the –O–C–O– grouping there is no reason to believe that the electron pair on oxygen should displace the electron pair on oxygen in the weakly acidic aluminium hydride monoetherate. The fact that cleavage of the spirostanes can be induced by carrying out the LAH reduction in the presence of hydrogen chloride[1] supports this view. In the case of the –S–C–O– grouping the same considerations hold.

Zusammenfassung

Unter den gewöhnlichen Reaktionsbedingungen bleiben –O–C–O– und –S–C–O–Gruppen durch $LiAlH_4$ unverändert, während –N–C–O– und möglicherweise auch –N–C–S–Gruppen an der C–O– bzw. C–S-Bindung gespalten werden. Diese Verallgemeinerungen, die sich auf aliphatische und aromatische Verbindungen, Zucker und Steroide, anwenden lassen, werden zur Bestätigung kürzlich aufgestellter Steroid- und Alkaloidformeln herangezogen. Es wird ein Reaktionsmechanismus vorgeschlagen.

[1] M. MOUSSERON and M. CANET, Bull. Soc. chim. France [5] 18, 792 (1951). – J. STRATING and H. J. BACKER, Rec. Trav. chim. *69*, 638 (1950); *69*, 909 (1950). – J. STRATING, U. S. Patent 2,549,991 (April 24, 1951); German Patent 820,435 (November 12, 1951).

[2] N. L. PADDOCK, Nature *167*, 1070 (1951).

[1] H. M. DOUKAS and T. D. FONTAINE, J. Amer. Chem. Soc. *73*, 5917 (1951).

Corrigendum

P. LOUIS, *Recherches sur la fraction Y des protéines de muscles de Lapin*, Exper. *10*, 258 (1954).

Dans la figure 1, fraction Y après 20640 s d'électrophorèse à 4,12 V/cm, μ 0,10, pH 7,6, la partie supérieure du cliché représente la frontière descendante et la partie inférieure la frontière ascendante.