[CONTRIBUTION FROM THE RESEARCH LABORATORY, E. BILHUBER, INC.]

The Cleavage of 1,5-Disubstituted Tetrazoles by Lithium Aluminum Hydride

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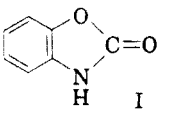
Under the influence of lithium aluminum hydride, 1,5-disubstituted tetrazoles undergo reductive ring cleavage with the loss of three of the ring nitrogen atoms and the production of a secondary amine. The reaction appears to be quite general and has been successfully applied to pentamethylenetetrazoles, 1,5-dialkyltetrazoles, 1,5-disubstituted tetrazoles containing ether and tertiary amino groups, and 1,5-disubstituted tetrazoles containing reducible functional groups such as ketones, carboxylic acids, esters, and amides. Detailed studies with 1-phenyl-5-methyltetrazole suggest that three equivalents of lithium aluminum hydride are required and that the cleavage of the tetrazole ring and production of a secondary amine occur more or less simultaneously without the formation of a stable, isolable intermediate.

Comparatively little information is recorded in the literature regarding the influence of lithium aluminum hydride on heterocyclic ring systems. Saturated derivatives possessing a cyclic lactam structure such as naphthostyril,[1] oxindoles,[2] and *alpha*-pyrrolidones[3] have been reduced to the saturated heterocycles in a normal manner with good to excellent yields by an excess of this reagent. Somewhat similarly, certain hydantoin derivatives[4] have been reduced to the corresponding imidazolone, imidazole, and imidazolidine derivatives. With regard to the unsaturated heterocyclic ring systems, Schmid and Karrer[5] have reported the reduction of N-alkylquinolinium salts and related compounds to the corresponding N-alkyl-1,2-dihydroquinolines under the influence of lithium aluminum hydride while Wooten and McKee[6] and, more recently, Bohlmann[7] have described the similar reduction of nitrogen heterocycles containing a double bond between the carbon and nitrogen atoms wherein that double bond is reduced to the dihydro derivative and other carbon-carbon double bonds are not attacked. The limits of applicability of this latter reaction are not well established since in the imidazole,[8] pyrazole,[9] thiazole,[10] and triazole[11] series, all of which contain the carbon-nitrogen double bond, functional groups have been successfully reduced in good yield using an excess of this reagent with no reported evidence that reduction of the ring has occurred.

The reductive cleavage of heterocyclic ring systems under the influence of lithium aluminum hydride has also been reported. Galinovsky and Weiser[12] have demonstrated that by using only the calculated quantities of this reagent the reduction of cyclic lactams can be controlled so as to produce the corresponding amino aldehydes, *viz.*, 3-keto-octahydropyrrocoline yields 3-(2-piperidyl)propionaldehyde. Likewise Bergmann, *et al.*[13] have shown that oxazolidines are cleaved by lithium aluminum hydride to yield N-substituted 2-aminoalkanols and Gaylord, *et al.*[14] have found that benzoxazolone (I), benzoxazole (II) and benzoxazolethiol (III) are all reduced to *o*-methylaminophenyl with this reagent.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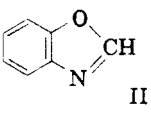
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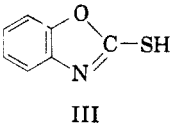
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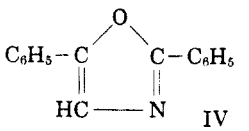
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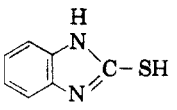
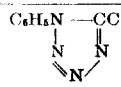
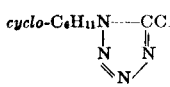
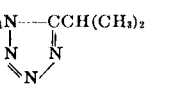
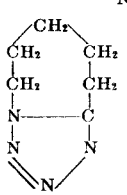
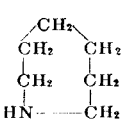
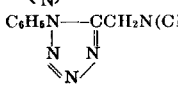
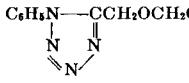
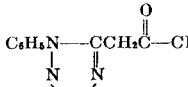
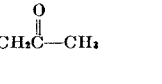
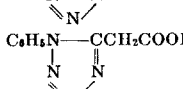
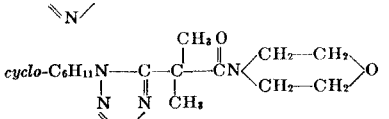
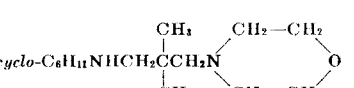
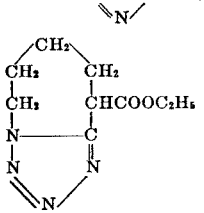
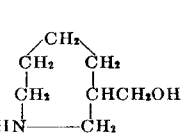

V

The latter workers have also shown that in the reduction of 2,5-diphenyloxazole (IV) reduction of the carbon-carbon double bond accompanies reduction of the carbon-nitrogen double bond and cleavage of the ring to give 2-benzylamino-1-phenylethanol. In the abnormal ring cleavages (I, II, III, IV) the grouping —N=C(|)—O— has been present within the ring system *per se* or *via* tautomerization. Attempts to cleave 2-benzimidazolethiol[14] (V), which contains the —N=C(|)—N(|)— moiety

(1) Stoll, Petrzilka, and Rutschmann, *Helv. Chim. Acta*, **33**, 2254 (1950).
(2) Julian and Printy, *J. Am. Chem. Soc.*, **71**, 3206 (1949).
(3) Karrer and Portmann, *Helv. Chim. Acta*, **31**, 2088 (1948).
(4) Wilk and Close, *J. Org. Chem.*, **15**, 1020 (1950).
(5) Schmid and Karrer, *Helv. Chim. Acta*, **32**, 960 (1949).
(6) Wooten and McKee, *J. Am. Chem. Soc.*, **71**, 2946 (1949).
(7) Bohlmann, *Chem. Ber.*, **85**, 390 (1952).
(8) Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949).
(9) Jones, *J. Am. Chem. Soc.*, **71**, 3994 (1949).
(10) Conover and Tarbell, *J. Am. Chem. Soc.*, **72**, 5221 (1950).
(11) Ainsworth and Jones, *J. Am. Chem. Soc.*, **76**, 5651 (1954).
(12) Galinovsky and Weiser, *Experientia*, **6**, 377 (1950).
(13) Bergmann, Lavie, and Pinchas, *J. Am. Chem. Soc.*, **73**, 5662 (1951).
(14) Gaylord and Kay, *American Chemical Society, Abstracts of Minneapolis Meeting*, 1955, p. 71-O.

TABLE I

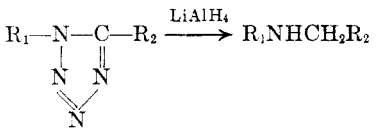
PRODUCTS FROM THE LITHIUM ALUMINUM HYDRIDE REDUCTION OF TETRAZOLES

No.	Starting Material	Product	Mole Ratio LAH	React. Time, Hrs.	Yield, %	B.P., (M.P.) °C.	HCl M.P., °C.	Analyses Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
VI		$C_6H_5NHCH_2CH_3$	2:1 1:1 1:1 0.75:1 0.5:1	48 24 6 24 24	96 95 96 81 49	96–96.5/ 19 mm.	177–179	60.95[a]	61.10 61.00	7.67	7.83 7.74	8.89	8.87 8.84
VII			2:1	8	80.5		277–279	62.63[a]	62.70 62.50	11.58	11.42 11.42	7.31	7.44 7.38
VIII			2:1	32	66	136	235–236 (dec.)	53.13[a]	53.10 53.25	10.40	10.45 10.35	10.33	10.36 10.45
IX		$C_6H_5NHCH_2CH_2N(CH_3)_2$	2:1	24	92	98–99/ 1.5 mm.	174–176 (dec.)	50.64[b]	50.60 50.50	7.65	7.80 7.75	11.81	11.95 11.80
X		$C_6H_5NHCH_2CH_2OCH_2CH_2N(CH_3)_2$	2:1	6	91	120–122/ 0.4 mm.	156–158	51.25[b]	51.40 51.55	7.88	7.90 7.92	9.96	10.05 9.98
XI			2.5:1	24	67	136–140/ 2.5 mm. (60–61)		72.69[c]	72.85 72.75	9.15	9.22 9.25	8.48	8.43 8.50
XII		$C_6H_5NHCH_2CH_2CH_2OH$	3:1	24	30	140–144/ 1.5 mm.		71.49[c]	71.40 71.35	8.67	8.71 8.60	9.26	9.31 9.35
XIII			2:1	8	37		214.5–216	55.03[b]	54.95 55.15	9.86	9.94 10.03	8.56	8.34 8.27
XIV			2:1	2	34	97–98/ 1 mm.	122–124	50.75[a]	50.85 50.95	9.74	9.73 9.67	8.46	8.33 8.42

[a] Hydrochloride salt. [b] Dihydrochloride salt. [c] Free base.

within the ring, by reduction with lithium aluminum hydride were unsuccessful and failure was attributed to the fact that in solution the compound existed as the tautomeric thiourea structure (—N—C(=S)—N—). However, reduction of benzimidazole[7] which contains the —N=C—N— moiety without question, yields the expected reduction product, dihydrobenzimidazole, with no evidence of ring cleavage.

It is the purpose of this paper to report the novel destructive cleavage of the tetrazole ring in 1,5-disubstituted tetrazoles. To our knowledge this is the first instance in which the lithium aluminum hydride cleavage of a heterocyclic ring system containing the —N=C—N— moiety has been reported. While the mechanism of this reaction is not known at the present time, the over-all results may be summarized as follows:



The reaction appears to be general and has been successfully applied to pentamethylenetetrazoles, 1,5-dialkyltetrazoles, 1,5-disubstituted tetrazoles containing non-reducible ether and tertiary amino groups, and 1,5-disubstituted tetrazoles possessing reducible functional groups such as ketones, carboxylic acids, esters and amides. The results are summarized in Table I.

With those tetrazoles containing no functional groups which are readily attacked by lithium aluminum hydride the yields are good to excellent (66–96%). When reducible functional groups are present, the functional group is also reduced although the yields are lower. In only one instance has the reaction failed. Two attempts to reduce 1-phenyl-5-cyanomethyltetrazole to 1-phenyl-5-*beta*-aminoethyltetrazole or 3-anilinopropylamine using an excess (3:1) of lithium aluminum hydride in refluxing tetrahydrofuran for reaction periods of 24 and 72 hours gave no recovered starting material and none of the desired product. Only traces of aniline could be isolated and identified from the tarry reaction product.

In five out of the nine successful reductions the products have been reported in the literature by other methods of synthesis. The reduction products obtained from two others, *viz.*, 1-cyclohexyl-5-isopropyltetrazole (VII) and 1-phenyl-5-dimethylaminoethoxymethyltetrazole (X), have been synthesized in this laboratory by unequivocal means. Since the products obtained here are in all respects identical to those obtained by other means and are obtained in a high state of purity, their structure seems well established and there is no evidence that any rearrangement of the 1,5-substituents has occurred during the course of the reaction.

The results of more detailed studies on the reduction of 1-phenyl-5-methyltetrazole (VI) using different reaction times and varying the lithium aluminum hydride/tetrazole ratios are summarized in Table I. The data indicate that reaction is essentially complete within six hours, and perhaps within a much shorter period. The results of varying the ratio of reducing agent to tetrazole suggest that the stoichiometry of the reaction requires 0.75 mole (3 equivalents) of lithium aluminum hydride to cleave the tetrazole ring and produce a secondary amine. This is based on the fact that substantially quantitative yields are obtained with a 1:1 mole ratio of lithium aluminum hydride to 1-phenyl-5-methyltetrazole. With a 0.75:1 mole ratio only an 81% yield of N-ethylaniline is obtained. However, if the stoichiometry of the reaction required a 1:1 mole ratio of hydride to tetrazole, the maximum theoretical yield obtainable from a 0.75:1 mole ratio would be only 75%. It is also of interest to note that from those reactions which do not go to completion (0.75 or 0.5:1 mole ratios) the unreacted 1-phenyl-5-methyltetrazole is recovered essentially quantitatively, which suggests that the cleavage of the tetrazole ring with formation of a secondary amine occurs more or less spontaneously under the influence of three equivalents of lithium aluminum hydride and does not proceed *via* a stable, isolable intermediate.

While this reaction has no general preparative value it may be a very useful tool in certain special cases. For example, in an earlier paper[15] the preparation of *beta*-dimethylamino-*beta'*-anilinodiethyl ether was reported *via* a four step synthesis starting from chloroacetyl chloride and benzyl aniline with an over-all yield of 18.9%. In this work 1-phenyl-5-dimethylaminoethoxymethyltetrazole (X), which can be prepared in three steps from aniline and chloroacetyl chloride by published procedures[15,16] in an over-all yield of 44.8%, was reduced to *beta*-dimethylamino-*beta'*-anilinodiethyl ether in 91% yield, giving an over-all yield of 40.8% for the four-step process.

Similarly, Arbuzov[17] hydrated the double bond in the N-acetyl and N-benzoyl derivatives of N-(2-butenyl)aniline by refluxing with concentrated hydrochloric acid but was unable to assign a precise structure to the resulting $C_{10}H_{15}NO$ hydroxy amine. The apparent identity of the 1-anilino-2-butanol obtained here by the reductive cleavage of 1-phenyl-5-acetonyltetrazole with that described by Arbuzov strongly suggests that his hydration of N-(2-bu-

(15) Cosgrove and LaForge, *J. Org. Chem.*, **21**, 197 (1956).

(16) Harvill, Herbst, and Schreiner, *J. Org. Chem.*, **17**, 1597 (1952).

(17) Arbuzov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 547 (1952) [*Chem. Abstr.*, **47**, 4874 (1953)].

tenyl)aniline yielded 4-anilino-2-butanol rather than the isomeric 1-anilino-2-butanol.

EXPERIMENTAL

All reductions were carried out using an excess of lithium aluminum hydride. Wherever possible the reactions were carried out in ether solution, although in several cases the low solubility of the tetrazole compound in ether necessitated the use of tetrahydrofuran, mixtures of tetrahydrofuran and ether, or the ether extraction of the tetrazole into the lithium aluminum hydride suspension *via* the Soxhlet technique. Since all of the products were bases the isolation procedures were similar. The following typical examples serve to illustrate the procedures used:

Reduction of 1-phenyl-5-dimethylaminoethoxymethyltetrazole (X). A solution of 37.0 g. (0.15 mole) of 1-phenyl-5-dimethylaminoethoxymethyltetrazole[15] in 200 ml. of anhydrous ether was added dropwise to a refluxing suspension of 11.4 g. (0.30 mole) of lithium aluminum hydride in 600 ml. of anhydrous ether and refluxing was continued after addition was completed. After a total reaction time of six hours the reaction mixture was chilled and 60 ml. of water was cautiously added dropwise to destroy excess lithium aluminum hydride. The precipitated hydroxides were removed by filtration and the filtrate was dried over sodium sulfate and distilled to yield *beta*-dimethylamino-*beta'*-anilinodiethyl ether, n_D^{25} 1.5280. The melting point of the dihydrochloride salt was not depressed when mixed with an authentic sample of *beta*-dimethylamino-*beta'*-anilinodiethyl ether dihydrochloride previously prepared in this laboratory[15] by another method.

The following tetrazoles were reduced in a similar manner in ether solution:

Pentamethylenetetrazole (VIII). Hexamethylenimine, n_D^{25} 1.4646 was obtained in 53% yield (66% based on unrecovered pentamethylenetetrazole). Müller and Sauerwald[18] report n_D^{23} 1.4654 and m. p. 236° for the hydrochloride.

Ethyl pentamethylenetetrazole-6-carboxylate[19] (XIV). The product, n_D^{25} 1.5014, was presumably 3-hydroxymethylhexamethylenimine on the basis of the established course of the reaction and the elemental analysis recorded in Table I. In addition, the following analysis was obtained for the *hydrochloride salt:*

Anal. Calc'd for $C_7H_{16}ClNO$: Cl, 21.40. Found: Cl, 21.20, 21.15.

1-Phenyl-5-dimethylaminomethyltetrazole (IX). A mixture of 41.0 g. (0.21 mole) of 1-phenyl-5-chloromethyltetrazole,[16] 300 ml. of 25% aqueous dimethylamine, and 250 ml. of methanol was refluxed for seven hours with additional 200-ml. portions of 25% aqueous dimethylamine added after periods of 1½ and three hours of the elapsed time. The methanol and part of the water were removed by distillation under reduced pressure and the residue was made strongly acid with concentrated hydrochloric acid and extracted with ether to remove non-basic materials. The aqueous phase was made strongly alkaline and the product was extracted into ether and dried over sodium sulfate. Distillation of the residue from the ether extract yielded 38.5 g. (90%) of 1-phenyl-5-dimethylaminomethyltetrazole (IX), b.p. 148–151°/0.4 mm., n_D^{25} 1.5430. The distillate solidified on chilling, m.p. 42–43° and readily formed a *hydrochloride salt*, m.p. 94–95°.

Anal. Calc'd for $C_{10}H_{13}N_5$: C, 59.09; H, 6.45; N, 34.46. Found: C, 59.20, 59.30; H, 6.64, 6.55; N, 34.10, 34.05.

The N-dimethylaminoethylaniline, n_D^{25} 1.5372, obtained from the lithium aluminum hydride reduction of IX formed a dihydrochloride salt whose melting point was not depressed when mixed with an authentic sample of N-dimethylaminoethylaniline dihydrochloride prepared as described by Huttrer, *et al.*[20]

1-Cyclohexyl-5-isopropyltetrazole[21] (VII). The product was shown to be N-isobutylcyclohexylamine hydrochloride by elemental analysis and by the lack of melting point depression on mixing with an authentic sample of N-isobutylcyclohexylamine hydrochloride prepared by the reductive alkylation of isobutylamine with cyclohexanone in the presence of activated aluminum in a procedure similar to that described by LaForge, *et al.*[22] The sample prepared by the latter method had b.p. 90–92°/27 mm., n_D^{25} 1.4495.

Reduction of 1-phenyl-5-methyltetrazole (VI). A solution of 20.0 g. (0.125 mole) of 1-phenyl-5-methyltetrazole[21] in a solvent mixture comprised of 750 ml. of anhydrous ether and 100 ml. of tetrahydrofuran was added dropwise to a suspension of 9.5 g. (0.25 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether. When addition was completed, refluxing was continued for a total reaction time of 48 hours and the product was isolated and purified as described above. The N-ethylaniline, n_D^{25} 1.5511, so obtained formed a hydrochloride salt which was identical with that of an authentic sample of N-ethylaniline as determined by the lack of depression of a mixture melting point. Comparable results were obtained using a 1:1 mole ratio of lithium aluminum hydride to 1-phenyl-5-methyltetrazole after reaction times of 24 and 6 hours respectively.

An identical experiment using 3.6 g. (0.094 mole) of lithium aluminum hydride and a reaction time of 24 hours gave 12.2 g. or an 81% yield of N-ethylaniline. The still pot residue solidified to yield 2.3 g. of unreacted 1-phenyl-5-methyltetrazole whose melting point was not depressed on admixture with an authentic sample. The yield of N-ethylaniline, based on unrecovered tetrazole, was 92%.

The same experiment using only 2.4 g. (0.063 mole) of lithium aluminum hydride gave 7.4 g. (49%) of N-ethylaniline and 9.9 g. of unreacted 1-phenyl-5-methyltetrazole. The yield, based on unrecovered tetrazole, was 97%.

1-Phenyl-5-tetrazoleacetic acid[19] (XII). A solution of 20.4 g. (0.10 mole) of 1-phenyl-5-tetrazoleacetic acid in 500 ml. of a 1:1 mixture of ether and tetrahydrofuran was reduced with 11.4 g. (0.30 mole) of lithium aluminum hydride in the usual manner. The 3-anilino-1-propanol (n_D^{25} 1.5682) thus obtained could not be induced to form crystalline salts. It has been prepared previously by Pierce and Adams[23] who report n_D^{18} 1.568.

1-Phenyl-5-acetonyltetrazole[24] (XI). A solution of 21.8 g. (0.10 mole) of 1-phenyl-5-acetonyltetrazole in 200 ml. of dry tetrahydrofuran was added dropwise to a suspension of 9.5 g. (0.25 mole) of lithium aluminum hydride in 250 ml. of dry tetrahydrofuran. After a reaction time of 24 hours the product was isolated and purified in the usual manner. The N-(3-hydroxybutyl)aniline thus obtained appears to be identical in physical constants with the product obtained by Arbuzov[17] from the hydration of N-(2-butenyl)aniline.

Reduction of alpha-(1-cyclohexyl-5-tetrazolyl)-isobutyryl-

(18) Müller and Sauerwald, *Monatsh.*, **48**, 727 (1927).

(19) Jacobson and Amstutz, *J. Org. Chem.*, **18**, 1183 (1953).

(20) Huttrer, Djerrasi, Beears, Mayer, and Scholz, *J. Am. Chem. Soc.*, **68**, 1999 (1946).

(21) Harvill, Herbst, Schreiner, and Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(22) LaForge, Whitehead, Keller, and Hummel, *J. Org. Chem.*, **17**, 457 (1952).

(23) Pierce and Adams, *J. Am. Chem. Soc.*, **45**, 790 (1923).

(24) D'Adamo and LaForge, *J. Org. Chem.*, **21**, 340 (1956).

morpholide[25] (XIII). *alpha*-(1-Cyclohexyl-5-tetrazolyl)-isobutyrylmorpholide (10 g., 0.0326 mole) was placed in the thimble of a Soxhlet extractor and was gradually extracted into a refluxing suspension of 2.5 g. (0.065 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether. After a reaction time of eight hours the product was isolated in the normal manner and the crude base was converted directly to the dihydrochloride salt. On the basis of the elemental analysis and the established course of the reaction this product is presumed to be N-cyclohexyl-2,2-dimethyl-3-(4'-morpholino)propylamine dihydrochloride.

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