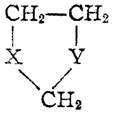
[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

The Cleavage of Oxazolidines by Lithium Aluminum Hydride

BY ERNST D. BERGMANN, DAVID LAVIE AND S. PINCHAS

Lithium aluminum hydride cleaves the oxazolidine ring between the 1- and 2-positions, leading to N-substituted 2-aminoalkanols, when the nitrogen atom is unsubstituted, and to N,N-disubstituted 2-aminoalkanols, when it is substituted. In this respect, lithium aluminum hydride resembles catalytically activated hydrogen and Grignard compounds.

In a series of investigations,[1] the physical properties of five-membered heterocyclic ring systems of the general type A have been studied. The present



A

paper supplements these results, by a study of the behavior of such systems, especially of the oxazolidines (A, X = O, Y = NH or NR), toward lithium aluminum hydride.

Heusser, Herzig, Fuerst and Plattner[2] have recently shown that the acetylated condensation product of $\Delta^{5,6}$ - 3β,17β - dihydroxy - 17α - aminomethylandrostene and acetone is reduced by lithium aluminum hydride, but the authors have not offered evidence as to the oxazolidine structure of their condensation product. The experiments reported here have shown that oxazolidines are cleaved by the mixed hydride to give N-substituted 2-aminoalkanols. Indeed, substances of type A do not always behave as saturated compounds. 1,3-Dioxolanes (A, X = Y = O) are hydrogenolyzed under pressure to glycol monoalkyl ethers[3,4]; oxazolidines, analogously, yield N-alkylated 2-aminoalkanols[5,6]; in the same way, Grignard reagents cleave the heterocyclic ring.[6]

Little appears to be known regarding the response of heterocyclic ring systems to lithium aluminum hydride. Whilst the tetrahydrofuran ring[7] and cyclic lactams are cleaved,[8] this does not apply to the hydantoin,[9] the thiazole[10] and the tetrahydroquinoline[11] systems.

The oxazolidines studied are summarized in Table I; their structure was either known from previous investigations[1] or was determined by means of infrared spectrum. As shown before,[1] the oxazolidines exhibit a characteristic triplet of bands in the 1080–1190 cm^{-1} region.

In all cases, the oxazolidine ring was cleaved and a 2-aminoalkanol was formed, having a secondary or tertiary amino-group, respectively, depending on whether the oxazolidine contained a NH– or NR– group. The structure of the aminoalkanols (Table II) was again proven by the infrared spectrum, which showed the presence of a free hydroxyl group and of a secondary or tertiary amino group, respectively.

TABLE I

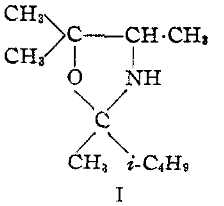
OXAZOLIDINES

(The wave lengths in *italics* indicate the strongest bands)

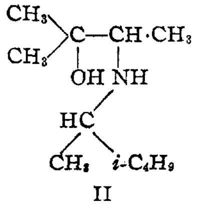
No.	Substituents at positions: 2	3	4	5	B.p., °C.	Mm.	Infrared spectrum (cm.$^{-1}$) in the 1080–1190 cm.$^{-1}$ region (cell thickness 0.1 mm.)
1(X)[a]	Pentamethyleno	H	CH_3	CH_3, CH_3	115	27	(1043, *1061*), 1109, *1126*, 1153, 1186[f]
2(XI)[a]	n-C_3H_7, n-C_3H_7	H	CH_3	CH_3, CH_3	112–113	22	1101, *1128*, *1174*[d]
3(I)[a,b]	CH_3, i-C_4H_9	H	CH_3	CH_3, CH_3	92–94	27	1109 (shoulder), *1133*, 1185[d]
4(III)[c]	n-C_3H_7, H	C_6H_{13}[e]	CH_3	CH_3, CH_3	120–122	20	1065, 1110, 1131, *1165*, *1181*[d]
5(XII)[a]	C_2H_5, H	C_6H_5	H	H, H	115–116	4	. . .
6(XIII)[d]	p-$CH_3O\cdot C_6H_4$, H	CH_3	H	H, H	133–136	3	*1036*, *1057*, 1108, 1142, *1165*, 1172[d]

[a] For preparation and analyses, see ref. 1. [b] $C_{11}H_{23}NO$. Calcd.: active H, 0.5. Found: active H, 0.3. [c] $C_{15}H_{31}NO$. Calcd.: C, 74.6; H, 12.8; *MR*, 75.01. Found: C, 74.3; H, 12.9; n^{21}D 1.4406; d_{21} 0.8500; *MR*, 74.53. [d] E. Bergmann and E. Zimkin, results to be published elsewhere. [e] C_6H_{13} = α,γ-dimethylbutyl. [f] 0.078 g. of substance + 1 cc. of carbon tetrachloride.

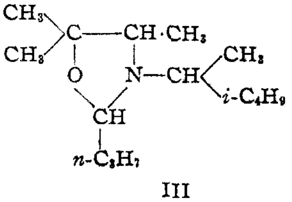
Additional proof was supplied in the following manner. The product (II) obtained from lithium aluminum hydride and 2,4,5,5-tetramethyl-2-isobutyloxazolidine (I) could again be condensed with



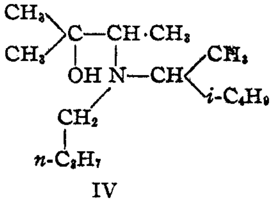
I



II



III



IV

---

(1) E. D. Bergmann and co-workers, *Rec. trav. chim.*, **70**, in press (1951).

(2) H. Heusser, P. Th. Herzig, A. Fuerst and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

(3) L. W. Covert, R. Connor and H. Adkins, THIS JOURNAL, **54**, 1651 (1932).

(4) Hydrogenation of 13-dioxanes: W. S. Emerson, *et al.*, *ibid.*, **72**, 5314 (1950).

(5) A. C. Cope and E. M. Hancock, *ibid.*, **64**, 1503 (1942).

(6) M. Senkus, *ibid.*, **67**, 1515 (1945).

(7) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3020 (1950).

(8) F. Galinovsky and R. Weiser, *Experientia*, **6**, 377 (1950).

(9) I. J. Wilk and W. J. Close, *J. Org. Chem.*, **15**, 1020 (1950).

(10) L. H. Conover and D. S. Tarbell, THIS JOURNAL, **72**, 5221 (1950).

(11) A. Stoll, Th. Petrzilka and J. Rutschmann, *Helv. Chim. Acta*, **33**, 2254 (1950).

TABLE II

REDUCTION PRODUCTS OF THE OXAZOLIDINES

(The wave lengths in *italics* represent the strongest bands)

	Name of substance[a]	Formula	Yield, %	B.p., °C.	B.p., Mm.	n^{21}_D	d^{21}_4	Mol. refr. Calcd.	Mol. refr. Found	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found	Concentration, g. (1 cc. of solvent)	Infrared spectrum (cm.$^{-1}$, cell thickness 0.1 mm.)
1	2-Cyclohexylamino-3-methyl-3-butanol (XIV)	$C_{12}H_{25}NO$	..	135	20	1.4619	0.894	60.69	61.21	72.4	72.8	12.5	12.1	0.083	*1122*,[b] 1178,[b] 3430[c]
2	2-γ-Heptylamino-3-methyl-3-butanol (XV)	$C_{12}H_{27}NO$	62.5	108–110	20	1.4394	0.843	62.89	62.76	72.0	71.4	13.5	13.7	.060	*1120*,[b] *1180*,[b] 3430[c]
3	2-(α,γ-Dimethylbutyl)-amino-3-methyl-3-butanol (II)	$C_{11}H_{25}NO$	58.0	109–110	20	1.4350	0.854	58.27	57.10	70.6	71.0	13.3	13.3	.079	*1116*,[d] 1160 (weak),[d] 1180,[d] 3450[c]
4	N-(α,γ-Dimethylbutyl)-N-*n*-butyl-2-amino-3-methyl-3-butanol (IV)	$C_{15}H_{33}NO$	57.0	148	20	1.4472	0.860	77.10	75.72	74.1	73.6	13.6	13.3	.085	1071,[e] 1106,[b] 1180,[b] 3320 (broad, strong)[c]
5	2-(N-Propylanilino)-ethanol (XVI)	$C_{11}H_{17}NO$	55.5	131	3	1.5470	1.028	55.21	55.16	73.7	74.1	9.5	9.5	.109	*1035*, 1133, 1186, 3380 (broad),[c] 3600 (shoulder)[f]
6	N-(*p*-Methoxybenzyl)-N-methyl-2-aminoethanol (XVII)	$C_{11}H_{17}NO_2$	50.0	180–181	20	1.5301	1.054	57.35	57.30	67.7	68.1	8.7	9.1	.116	*1070*,[g] 1105, 1123,[h] 1151,[i] *1175*,[k] 3450 (strong, broad)[c]

[a] The arabic numbers correspond to those in Table I. [b] Absorption of the isopropyl alcohol grouping. [c] Hydroxyl, weakly hydrogen-bonded. [d] Absorption of the N-isobutyl or isopropyl alcohol grouping. [e] Tertiary amine. [f] Absorption of non-hydrogen-bonded hydroxyl. [g] C–OH Frequency (?). [h] *p*-Disubstituted phenyl. [i] C–N–C Frequency (?). [k] C–O–C_6H_5-Frequency (?).

butyraldehyde to 2-*n*-propyl-3-(α,γ-dimethylbutyl)-4,5,5-trimethyloxazolidine (III); its structure followed from the infrared spectrum. When treated with lithium aluminum hydride, (III) was again cleaved, and the alcohol (IV) formed.

For the purpose of comparison, the response of two Schiff bases, N-α-naphthylideneaminoethanol (V) and N-*p*-bromobenzylideneaminoethanol (VI) was investigated. Both were reduced by lithium aluminum hydride in the expected manner[12] to the corresponding N-α-naphthylmethyl- and N-*p*-bromobenzylaminoethanol (VII, VIII). These experiments were of interest in connection with the question whether the condensation products of 2-aminoalkanols with carbonyl compounds are oxazolidines or Schiff bases.[1,13] It is evidently not possible to differentiate between these two possibilities by means of lithium aluminum hydride. This reagent, however, offers a possibility of alkylating the nitrogen atoms of 2-aminoalkanols in a well-defined manner.

Marvel and Hill[14] have shown recently that 1,3-dioxolanes (A, X = Y = O) are not cleaved by lithium aluminum hydride. It was found that also 1,3-thioxolanes (A, X = O; Y = S) appear to behave in the same manner. 2-Pentamethyleno-1,3-thioxolane (IX) was not cleaved by the mixed hydride in boiling dioxane.

Experimental Part

General Procedure.—To one molar equivalent of $LiAlH_4$ in boiling dry dioxane, the dioxane solution of one mole of the oxazolidine was slowly added, and the mixture refluxed for 3 to 4 hours. After cooling, ice and an excess of 10% sodium hydroxide solution was added, and the resulting product extracted with benzene or an ether–benzene mixture. Alternatively, the alkaline product was filtered, the solid washed with benzene and the filtrate extracted. The extract was washed with water till neutral, dried and concentrated, and the residue purified by distillation *in vacuo*.

2-*n*-Propyl-3-(α,γ-dimethylbutyl)-4,5,5-trimethyloxazolidine (III).—The mixture of equivalent amounts of 2-(α,γ-dimethylbutyl)-amino-3-methyl-3-butanol (II) (6.8 g.) and butyraldehyde (3.2 g.) with benzene (50 cc.) was azeotropically distilled in presence of a trace of iodine, until the theoretical quantity of water had collected. The solution was washed with dilute sodium carbonate solution, dried and distilled; yield, 7 g. (80%).

N-α-Naphthylmethylaminoethanol (VII).—A solution of 2.0 g. of N-α-naphthylideneaminoethanol (V) (m.p. 49°)[1] in 10 cc. of dioxane was treated with 0.5 g. of lithium aluminum hydride in 20 cc. of the same solvent. The product, a viscous oil, boiled at 155–160° (1 mm.); $n^{21}D$ 1.6071.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.6; H, 7.5. Found: C, 77.5; H, 8.1.

The infrared spectrum did not show any longer the absorption of the C=N double bond of the starting material (in the 1620–1670 cm.$^{-1}$ region).

N-*p*-Bromobenzylaminoethanol (VIII).—The oily product from 2.3 g. of N-*p*-bromobenzylideneaminoethanol (VI)[1] in 10 cc. of dioxane and 0.5 g. of $LiAlH_4$ in 20 cc. of dioxane, boiled at 130° (0.5 mm.).

Anal. Calcd. for $C_9H_{12}NOBr$: N, 6.1. Found: N, 6.5.

The infrared spectrum did not show the absorption characteristic of the C=N double bond.

2-Pentamethyleno-1,3-thioxolane (IX).—A mixture of 22 g. of 2-mercaptoethanol and 33 g. of cyclohexanone was

---

(12) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **70**, 3738 (1948).

(13) As shown elsewhere,[1] the determination of the physical properties of the condensation products permits an unequivocal decision between the two structures. Schiff bases, *e.g.*, are characterized by the C=N absorption at about 1656 cm.$^{-1}$.

(14) C. S. Marvel and H. W. Hill, THIS JOURNAL, **73**, 481 (1951).

distilled azeotropically with 50 cc. of benzene in presence of 0.5 g. of *p*-toluenesulfonic acid. When the expected quantity of water had been liberated, the solution was neutralized with calcium carbonate, filtered and distilled; b.p. 111° (22 mm.); yield 31 g. (70%); n^{21}D 1.5108; d^{21}_4 1.085; *MR* calcd. 44.35, *MR* found 43.31.

Anal. Calcd. for $C_8H_{14}OS$: C, 60.8; H, 8.8. Found: C, 60.6; H, 8.6.

No reaction took place when the product was refluxed with lithium aluminum hydride in dioxane for 4 hours.

DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, ISRAEL

RECEIVED MARCH 15, 1951

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY AND THE NATIONAL HEART INSTITUTE]

Twofold Wagner–Meerwein Rearrangements. II

BY BERNHARD WITKOP[1] AND ARVID EK[2]

The reaction of N-methylisatin with phenylmagnesium bromide leads to N-methyl-2,2-diphenyl-ψ-indoxyl (VI), previously considered to be 2,3-diphenyl-2,3-epoxy-1-methylindoline (III) and to N-methyl-3,3-diphenyl-ψ-oxindole (XIV). The mechanism of the formation of the two products is discussed and amplified by the direct conversion of the indoxyl (VI) to the oxindole (XIV) by the action of phenyl Grignard reagent as well as of boron trifluoride in ether. N-Unsubstituted ψ-indoxyls, such as 2,2-dibenzyl-ψ-indoxyl (XV), undergo this twofold 1,2-shift not only under acid conditions, but also with sodium hydroxide in isoamyl alcohol. The significance of these transformations is discussed in terms of the possible intermediate indole epoxide structures, a number of cases in the literature is taken up and revised, and the potential usefulness of these twofold rearrangements with regard to synthetic studies in the strychnine and gelsemine series is pointed out.

Although the double bond in the pyrrole part of indoles possesses some individual character and independence,[3] no indole epoxide has ever been prepared.[4] Where such structures have been proposed, as for the alkaloid quinamine,[5] subsequent revision[6] led to a different formulation. However, the literature still lists a number of indole epoxides. Although such epoxides have never been isolated as such, they may have some significance as the hypothetical transitory intermediates in a number of interesting, hitherto-unrecognized twofold Wagner–Meerwein rearrangements.

When N-substituted isatins (I) react with phenylmagnesium bromide[7–10] two products are formed which have been presented as 2,3-diphenyl-2,3-epoxy-1-methylindoline (III), resulting by dehydration from the parent glycol (II), and 3,3-diphenyl-1-methyloxindole (XIV). When we repeated this reaction under carefully controlled conditions, we obtained the two products as yellow rods, m.p. 174–175° (the literature[9] records 137.5–138.5°), and colorless needles, m.p. 177.5 (previous m.p. 171–171.5°).

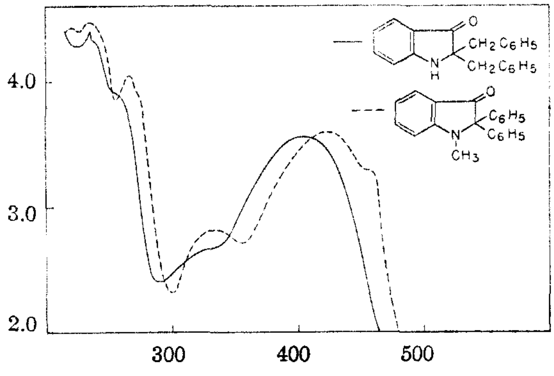
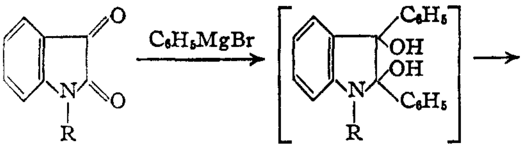
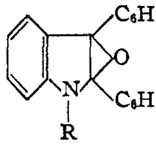


Fig. 1.—Ultraviolet spectra in ethyl alcohol.

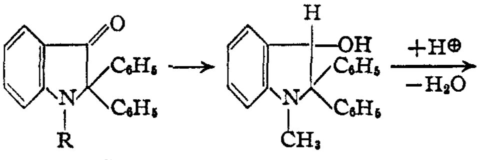


I II

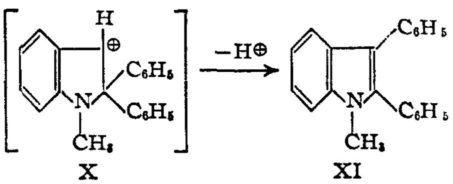


III, R = CH_3
IV, R = C_2H_5
V, R = C_6H_5

The ultraviolet (Fig. 1) and infrared (Fig. 2A) spectra of the yellow compound showed it to be the indoxyl derivative VI. Using the method previously employed in the structural elucidation of indoxyl compounds of unknown constitution[11,12] we reduced VI to the alkamine IX which, on treatment with hydrogen chloride in ether, underwent a Wagner–Meerwein rearrangement to yield, *via* the intermediate X, 1-methyl-2,3-diphenylindole



VI, R = CH_3 IX
VII, R = C_2H_5
VIII, R = C_6H_5



X XI

---

[1] National Heart Institute, Washington 14, D. C.

[2] Research Corporation Fellow 1949–1950.

[3] B. Witkop, *Ann.*, **556**, 105 (1944).

[4] B. Witkop and H. Fiedler, *ibid.*, **558**, 91 (1947).

[5] R. Goutarel, M. M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).

[6] B. Witkop, THIS JOURNAL, **72**, 2311 (1950).

[7] M. Kohn and A. Ostersetzer, *Monatsh.*, **34**, 787 (1913).

[8] R. Stollé, *J. prakt. Chem.*, **135**, 345 (1932).

[9] F. J. Myers and H. G. Lindwall, THIS JOURNAL, **60**, 2153 (1938).

[10] W. C. Sumpter, *ibid.*, **64**, 1736 (1942).

[11] B. Witkop, *ibid.*, **72**, 614 (1950).

[12] B. Witkop and J. B. Patrick, *ibid.*, **73**, 713 (1951).