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The Mechanism of Lithium Aluminum Hydride Reduction of 13α-Steroidal 16,17-Bromohydrins[1]

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The reaction mechanism of lithium aluminum hydride reduction was investigated with the 13α-steroidal 16,17-bromohydrins by means of tracer technique. The epimeric *cis*-bromohydrins were primarily led to the ketone resulting from hydride shift and then further reduced to the 17-hydroxylic compounds, where "mixed hydride" produced from the released bromide and lithium aluminum hydride would play a role of reducing agent. On the other hand the *trans*-bromohydrin was reduced to the corresponding alcohol by direct displacement of the halogen with hydride. Based upon these experimental results feasibility of the pathway involving reduction of the halohydrin in the five-membered ring has been discussed.

In the preceding papers the authors reported that lithium aluminum hydride (LAH) reduction of the C/D-*cis* steroidal 16-halo-17-ketone under usual conditions yields the 17-hydroxylic compounds with loss of halogen.[3] It is evident that reduction of the α-haloketone primarily provides the halohydrin, which in turn is further reduced to the alcohol with the excess reagent.[3b,c] The notable ease, with which dehalogenation takes place, may be ascribable to the characteristic situation around *cis*-fused C/D-rings. The similar instances involving the simultaneous loss of bromine have also been reported with the steroidal six-membered ring.[4] In those cases the reaction proceeds due to the extremely favorable geometrical alignment of the reaction centers. In earlier publications Eliel and his co-workers proposed the following three possible pathways of LAH reduction of the linear halohydrin leading to the corresponding alcohol: (A) assisted bimolecular displacement for primary and secondary halohydrins, (B) hydride shift for halohydrins in which the halogen is tertiary, and (C) formation of the epoxide and then of the ketone resulting from hydride

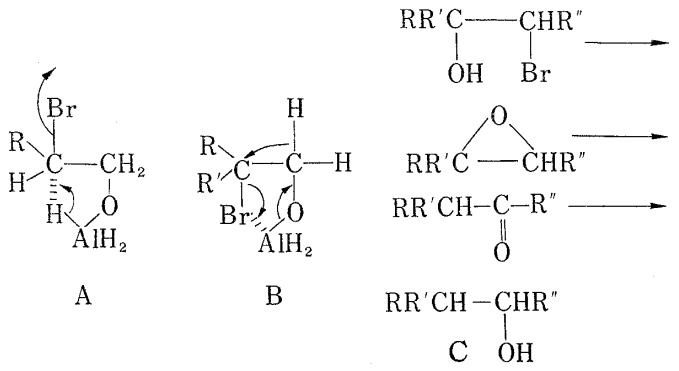

Fig. 1. Mechanisms ofor Reduction of Bromohydrins with Lithium Aluminum Hydride

1) This paper constitutes Part XXXII of the series entitled "Analytical Chemical Studies on Steroids"; Part XXXI: T. Nambara, T. Kudo, H. Hosoda, K. Motojima, and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **17**, 2366 (1969).

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3) *a*) T. Nambara and J. Fishman, *J. Org. Chem.*, **26**, 4569 (1961); *b*) T. Nambara, H. Hosoda, and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1266 (1968); *c*) T. Nambara, T. Kudo, H. Hosoda, K. Motojima, and S. Goya, *ibid.*, **17**, 2366 (1969).

4) *a*) H.B. Henbest, E.R.H. Jones, A.A. Wagland, and T.I. Wrigley, *J. Chem. Soc.*, **1955**, 2477; *b*) H.B. Henbest and T.I. Wrigley, *ibid.*, **1957**, 4596; *c*) E.R.H. Jones and D.J. Wluka, *ibid.*, **1959**, 907, 911; *d*) C. Djerassi, J. Fajkos, and A.R. VanHorn, *Steroids*, **6**, 239 (1965).

shift as the intermediates (see Fig. 1).[5] However, the experimental evidences for the reaction mechanisms have been associated with the linear system but not with the cyclic. A particular interest in stereochemistry of ring D prompted us to clarify this point by means of tracer technique.

The 16,17-bromohydrins of 5α,13α-androstanes appeared to be suitable substrates for this purpose, since the gas chromatographic method for determination of the epimeric 17-ols was readily available. It was anticipated that *cis*- and *trans*-bromohydrins would take a different course due to the stereochemical requirements, respectively. Accordingly an initial project was focused to reduction of the 16β, 17β-*cis*-bromohydrin (II) with LAH. The quantitation result tells us that the reaction products consist of 45% 17β- and 55% 17α-hydroxylic compounds. The formation of the 17α-ol starting from 17β-hydroxyl derivative is obviously indicative of participation of the 17-ketone as an intermediate. Nevertheless the result is not consistent with the previous finding that metal hydride reduction of the 17-ketone (IV) itself provides the epimeric 17β- and 17α-ols in a ratio of 22 to 78.[3b] The apparent discrepancy would tentatively be explained in such a way that the mixed type mechanism involving both direct displacement and hydride shift is operative for reduction of the *cis*-bromohydrin. In order to rationalize this assumption tracer studies using lithium aluminum deuteride (LAD) were carried out. If path A would be operative to a certain extent, the 16-deuterated species, which can be easily distinguished from the non-labelled 17-ols by infrared and nuclear magnetic resonance spectroscopy, should be produced. Contrary to the expectation, however, the reduction products did not exhibit any 17-proton signal and in consequence their structures were assignable to the 17-deuterio-17-ols. In addition the infrared spectra of these products proved to be identical with those of the authentic samples, respectively.

For the purpose of clarifying the fate of C-17 proton during the reaction process, utilization of the 17α-deuterated 16β, 17β-bromohydrin (IId) as a substrate was attempted. Reduction of the 16β-bromo-17-ketone with LAD at −15° gave the desired 16β-bromo-17α-deuterio-17β-ol accompanied with its 17-epimer, whose separation was effected by means of column chromatography. The labelled compound thus prepared being treated with LAH, deuterium shift did take place to furnish two epimeric 16α-deuterio-17-ols. Hereupon it was strongly

Table I. Reduction of 5α,13α-Androstanes with Lithium Aluminum Hydride and Lithium Aluminum Hydride-Aluminum Halide Mixture

Starting materials	Hydride employed	Reactive species	Product composition (%) 17β-OH	17α-OH
16β-Br-17β-OH (II)	$LiAlH_4$		45	55
16α-Br-17α-OH (I)	$LiAlH_4$		43	57
16β-Br-17α-OH (III)	$LiAlH_4$		0	100
17-Ketone (IV)	$LiAlH_4$		22	78
	$LiAlH_4$–$AlBr_3$ (1:3)	$HAlBr_2$	39	61
	$LiAlH_4$–$AlCl_3$ (1:3)	$HAlCl_2$	39	61
	$LiAlH_4$–$AlBr_3$ (1:1)	H_2AlBr	43	57
	$LiAlH_4$–$AlCl_3$ (1:1)	H_2AlCl	46	54
	$LiAlH_4$–$AlBr_3$ (3:1)	AlH_3	43	57
	$LiAlH_4$–$AlCl_3$ (3:1)	AlH_3	45	55

5) *a*) E.L. Eliel and T.J. Prosser, *J. Am. Chem. Soc.*, **78**, 4045 (1956); *b*) E.L. Eliel and J.T. Traxler, *ibid.*, **78**, 4049 (1956); *c*) E.L. Eliel and D.W. Delmonte, *ibid.*, **80**, 1744 (1958); *d*) E.L. Eliel and M.N. Rerick, *ibid.*, **82**, 1362, 1367 (1960); *e*) M.N. Rerick and E.L. Eliel, *ibid.*, **84**, 2356 (1962).

6) R.F. Nystrom, *J. Am. Chem. Soc.*, **77**, 2544 (1955); R.F. Nystrom and C.R.A. Berger, *ibid.*, **80**, 2896 (1958); E. L. Eliel and M.N. Rerick, *J. Org. Chem.*, **23**, 1088 (1958); E.L. Eliel and V.G. Badding, *J. Am. Chem. Soc.*, **81**, 6087 (1959); O.H. Wheeler and J.L. Mateos, *Chem. Ind.* (London), **1957**, 395; *idem*, *Can. J. Chem.*, **36**, 1431 (1958).

suggested that path B would be a predominant course for the *cis*-bromohydrin and the mode of reduction of the resulting ketone would be influenced by an unknown factor.

There have been several articles reporting that the reducing action of LAH-aluminum halide combination differs from that of metal hydride alone.[5c,d,6] Hence it seemed very likely that presence of the released bromide would modify the reduction as to increase the yield percentage of the 17β-ol relative to its epimer. This assumption was verified by the experimental results on the reduction of the 17-ketone with so-called "mixed hydride". Aluminum halide being employed together with LAH in the various proportions, the composition percentage of the 17β-ol was increased up to *ca.* 40%, which was substantially in accord with the percentage 17β-ol produced from the bromohydrin with LAH alone. The experimental results are collected in Table I. It is of interest that product development control, *i.e.*, formation of the more stable product (in the present case the 17α-ol)[7] is more marked with LAH alone than with the LAH-aluminum halide reagent.

The studies were then extended to the remaining α-*cis*-bromohydrin (I) to obtain further evidence for the above explanation. As was readily predicted treatment with LAD gave two epimeric 17-deuterio-17-ols, whose ratio was found almost identical with that of the β-*cis*-bromohydrin. Examinations were then made on reduction of the 17β-deuterio-16α,17α-bromohydrin (Id). The desired compound was prepared from the 16α-bromo-17-ketone in the same manner as its epimeric *cis*-bromohydrin. In actuality LAH reduction resulted in formation of the 16β-deuterio-17-ols with the deuterium shift to C-16. Based upon these evidences it follows that the *cis*-bromohydrins must be reduced by the hydride shift mechanism *via* the ketone.

Then the authors attempted to elucidate the reaction mechanism of the *trans*-bromohydrin with metal hydride. Reduction of the 16β-bromo-17α-ol (III) with LAH gave the 17α-hydroxylic compound as a single product. Furthermore treatment of III with LAD gave solely the 16α-deuterio-17α-ol, which proved to be identical with the authentic sample in every respect. As a result of these experiments it becomes clear that reduction of the *trans*-bromohydrin to the corresponding alcohol proceeds entirely without a hydride shift, *i.e.*, by direct displacement of the halogen with hydride.

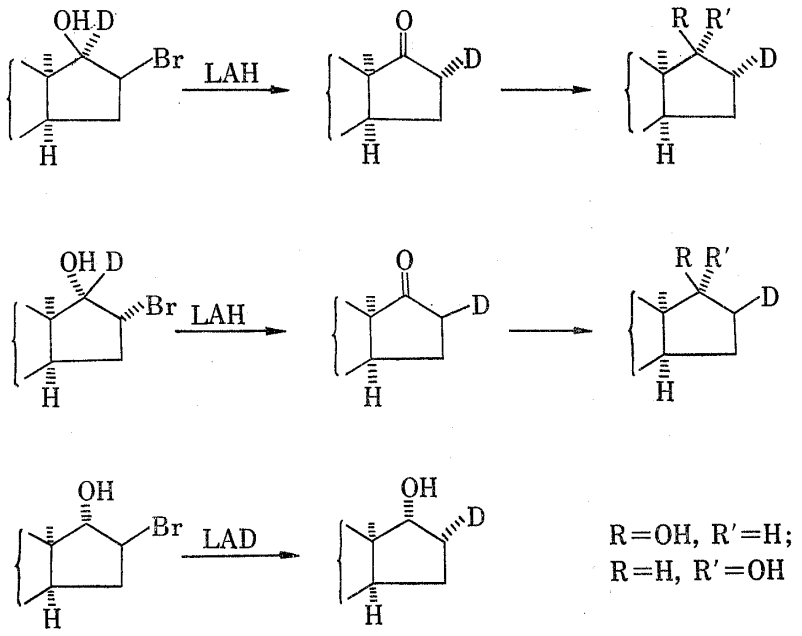

Fig. 2. Mechanisms for Reduction of 13α-Steroidal 16,17-Bromohydrins

7) L.J. Chinn, *J. Org. Chem.*, 30, 4165 (1965).

It seems very likely that the reaction pathway may be dependent upon the feasibility of preliminary coordination of aluminum and halogen to form a complex as a transition state. As to the *cis*-bromohydrin relationship between C-16 bromine and C-17 hydrogen is in *anti* and therefore the concerted hydride shift does readily occur yielding the 17-ketone. Indeed the formation of the 17-ketone was detectable in the experiment where a limited amount of reducing reagent was used. The relative ease, with which the reduction proceeds through path B, may be ascribable to the smaller dihedral angle (0—40°) between bromine and hydroxyl groups and abundant flexibility of the five-membered ring.

Also it is to be noted that in reduction of the *trans*-bromohydrin SN2 mechanism is principally operative and the reaction proceeds somewhat more slowly as compared with the *cis*-isomer. Henbest, *et al.* have already reported that under certain circumstances the α-bromoketone in the steroidal six-membered ring is led to the corresponding epoxide by metal hydride reduction.[4a,b] The marked difference in feasibility of the reaction pathway between these two ring systems appears to be dependent upon the magnitude of the dihedral angle of the bromohydrins.

Experimental[8]

16α-Bromo-5α,13α-androstane-3β,17α-diol 3-Acetate (I)——To a solution of 3β-acetoxy-16α-bromo-5α,13α-androstan-17-one (100 mg) in anhydrous ether (30 ml) was added $LiAlH_4$ (100 mg) portionwise at −15° over 1 min. After allowing to stand for 2 min moist ether was added to decompose the excess reagent and acidified with 10% H_2SO_4. The organic layer was separated, washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent an oily residue obtained was submitted to the preparative TLC using hexane–AcOEt (4:1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.48) with ether and recrystallization of the eluate from aq. MeOH gave I (60 mg) as colorless prisms. mp 139—141°. $[\alpha]_D^{15}$ −41.7° (c=0.12). *Anal.* Calcd. for $C_{21}H_{33}O_3Br$: C, 61.01; H, 8.05. Found: C, 60.41; H, 7.82. NMR (5% solution in $CDCl_3$) τ: 9.24 (3H, s, 19-CH_3), 8.95 (3H, s, 18-CH_3), 7.98 (3H, s, –$OCOCH_3$), 6.15 (1H, d, J=7.6 cps, 17β-H), 5.0—5.6 (2H, broad, 3α-H, 16β-H). Usual acetylation with Ac_2O and pyridine gave the 3,17-diacetate.[3b] mp 144—145°.

16α-Bromo-17β-deuterio-5α,13α-androstane-3β,17α-diol 3-Acetate (Id)——To a solution of 3β-acetoxy-16α-bromo-5α,13α-androstan-17-one (225 mg) in anhydrous ether (30 ml) was added $LiAlD_4$ (100 mg) portionwise at −15° over 1 min. Treatment of the crude product in the same manner as in I gave Id (140 mg). mp 140—141°.[9] Disappearance of the NMR signal of proton attached to carbon bearing a hydroxyl group verified an introduction of deuterium at C-17.

16β-Bromo-17α-deuterio-5α,13α-androstane-3β,17β-diol (IId)——To a solution of 3β-acetoxy-16β-bromo-5α,13α-androstan-17-one (300 mg) in anhydrous ether (50 ml) was added $LiAlD_4$ (100 mg) portionwise at −15° over 1 min. After allowing to stand for 4 min the reaction mixture was treated in the same manner as in Id. An oily product thus obtained was dissolved in hexane and chromatographed on silica gel (11 g). Elution with benzene and recrystallization of the eluate from MeOH gave 16β-bromo-17α-deuterio-5α,13α-androstane-3β,17β-diol 3-acetate (130 mg) as colorless prisms. mp 170—171°. Elution with benzene and recrystallization of the eluate from hexane gave 16β-bromo-17β-deuterio-5α,13α-androstane-3β,17α-diol 3-acetate (50 mg) as colorless needles. mp 141—143°. Further elution with benzene–ether (50:1) and recrystallization of the eluate from hexane gave IId (80 mg) as colorless needles. mp 174—175°. Hydrolysis of the 3-acetate with 10% H_2SO_4 in acetone also gave IId. With these compounds disappearance of the NMR signal of proton attached to carbon bearing a hydroxyl group verified an introduction of deuterium at C-17.

16β-Bromo-5α,13α-androstane-3β,17β-diol (II), 16β-Bromo-5α,13α-androstane-3β,17α-diol (III), 3β-Hydroxy-5α,13α-androstan-17-one (IV)——Prepared by the methods previously reported.[3b]

General Procedure for Reduction of 3β-Hydroxy-5α,13α-androstan-17-one (IV) with Mixed Hydride——To a solution of anhydrous AlX_3 (X=Cl, Br) in ether (10 ml) was added $LiAlH_4$ (50 mg) at 0° and stirred at room

8) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were determined in $CHCl_3$ solution. Infrared spectra were obtained on Hitachi Model EPI-2 spectrophotometer. Nuclear magnetic resonance spectra were run on Hitachi Model H-60 spectrometer at 60 Mcps in $CDCl_3$ using $(CH_3)_4Si$ as an internal standard. For preparative thin-layer chromatography (TLC) silica gel H (E. Merck AG) was used as an adsorbent. Isotopic purity of lithium aluminum deuteride employed was 99% (E. Merck AG).

9) All the deuterated compounds showed no depression on admixture with the non-labelled authentic samples, respectively.

temperature for 1 hr to form the complex completely. To this solution was added a solution of IV (50 mg) in anhydrous ether (5 ml). After allowing to stand at room temperature for 4 hr moist ether was added and acidified with 10% H_2SO_4. The organic layer was separated, washed with H_2O and dried over anhydrous Na_2SO_4. Completion of the reaction was confirmed by TLC and then a mixture of the epimeric 17-hydroxylic compounds produced was submitted to gas chromatographic determination.

General Procedure for Reduction of the 16,17-Bromohydrins with $LiAlH_4$ ($LiAlD_4$)——To a solution of the 16,17-bromohydrin (100 mg) in anhydrous ether (15 ml) was added $LiAlH_4$ ($LiAlD_4$) (100 mg) at 0° and allowed to stand at room temperature for 5—20 hr. To the resulting solution was added moist ether to decompose the excess reagent and acidified with 10% H_2SO_4. The organic layer was separated, washed with H_2O and dried over anhydrous Na_2SO_4. After evaporation of solvent a crystalline residue obtained was submitted to the preparative TLC using hexane–AcOEt (5:3) as developing solvent. Elution of the adsorbent corresponding to the spots (*Rf* 0.20, 0.16) with acetone and recrystallization of the eluate from hexane-acetone gave epimeric 5α,13α-androstane-3β,17β-diol and 5α,13α-androstane-3β,17α-diol, respectively. The position and configuration of deuterium introduced were confirmed by NMR and IR spectra upon comparison with those of the authentic samples.[10]

Gas Chromatography——The apparatus used was a Shimadzu Model GC-1C gas chromatograph equipped with a hydrogen flame ionization detector and a U-shaped stainless steel column (2.625 m×3 mm i.d.). The column was packed with 2% OV-17 on a support of Chromosorb W (60—80 mesh). The detector and flash heater were kept at 240°, while the column was at 200°. N_2 was used as carrier gas at a flow rate of 45 ml/min. The relative retention times of 17α- and 17β-hydroxylic compounds to cholestane (56.0 min) were 0.71 and 0.63, respectively. The composition ratio was determined by peak-height method refering to a calibration curve.

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10) T. Nambara, H. Hosoda, M. Usui, and J. Fishman, *Chem. Pharm. Bull.* (Tokyo), **16**, 1802 (1968).