effect against anoxia is observed. No significant prolongation of the survival time was observed either 20 min or 4 hr after dosing. It should be pointed out that after intravenous administration of meclofenoxate, the brain levels of dimethylaminoethanol and *p*-chlorophenoxyacetic acid were more than several times higher than those after administration of the constituents.[3] Therefore, the protective effect of meclofenoxate against anoxia is closely related to its penetration into the central nervous systems due to the high permeability of the ester to blood-brain barrier.

Results obtained here strongly support the view that the penetration of meclofenoxate into brain is primarily important to exhibit its protective effect against anoxia. It may be likely that the effect is closely related to the cerebral metabolism of dimethylaminoethanol, since the effects observed 20 min and 4 hr after administration were conceivably exerted by different mechanisms. The present system adopted to test the tolerance of mice against anoxia is convenient, since it is very simple and easy to be carried out, using a commonly available laboratory glass jar with a lid by measuring the survival time of a paired mice. However, the statistical analysis is essential for the evaluation of the results.

Acknowledgement We wish to thank Drs. Y. Nakanishi and M. Shimizu for their valuable advises and Drs. H. Takamatsu and H. Kaneko for their support.

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Hydrogenolysis of Allylic Alcohols with Mixed Hydride Reagent of Lithium Aluminum Hydride-Titanium Tetrachloride[1]

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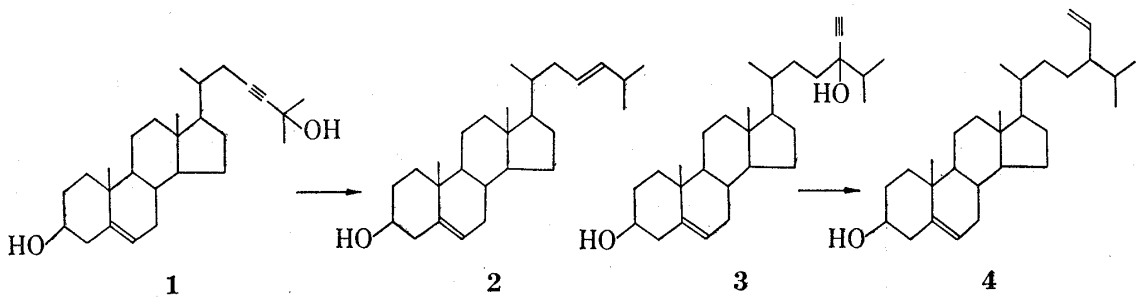
Five steroidal allylic alcohols were treated with lithium aluminum hydride–titanium tetrachloride in comparison with lithium aluminum hydride–aluminum chloride. The former reagent was found to be useful for the hydrogenolysis of allylic alcohols, especially for tertiary ones.

In the course of our synthetic studies of steroidal allenes,[3] the propargylic alcohols **1** and **3** were treated in tetrahydrofuran with an excess of a mixed hydride reagent of lithium aluminum hydride(LAH)–titanium tetrachloride($TiCl_4$) (molar ratio of 4:1). The products were not be the expected allenes, but the deoxygenated olefines **2** (78%) and **4** (50%),



1 **2** **3** **4**

Chart 1

1) This is Part 30 in the series of "Studies on Steroids." For Part 29 see ref. 3.
2) Location: *2-12-1, Ookayama, Meguro-ku, Tokyo, 152 ,Japan.*

Table I. Reaction of Allylic Alcohols with LAH–$TiCl_4$ and LAH–$AlCl_3$

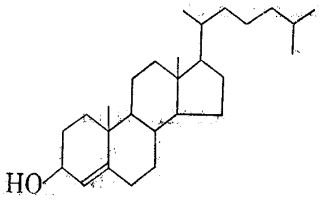
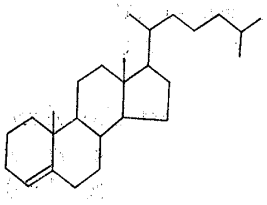
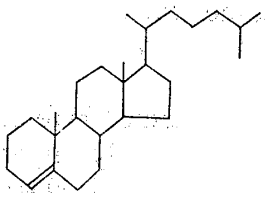
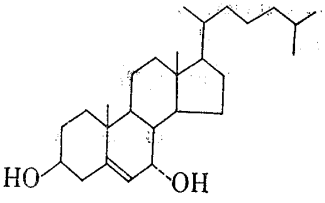
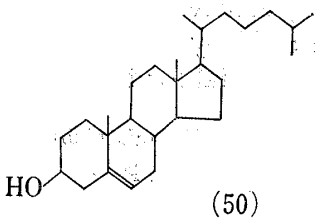
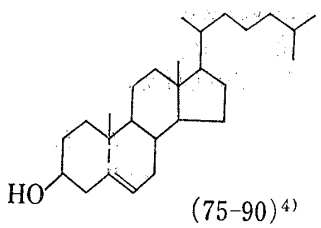
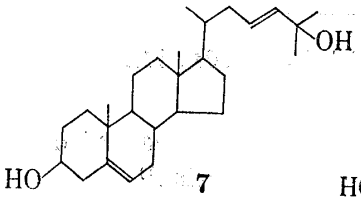
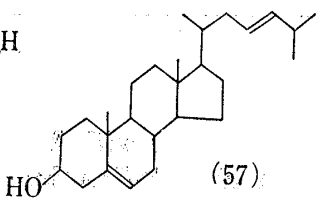
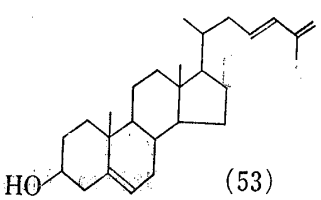
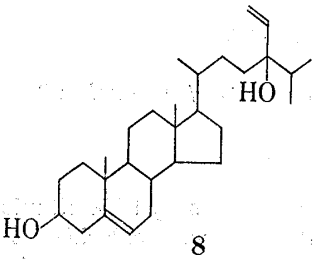
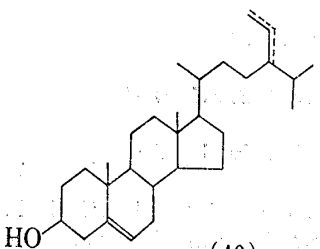
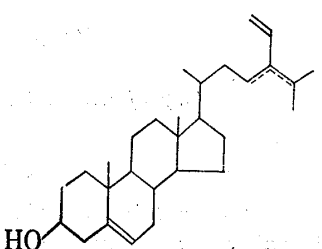
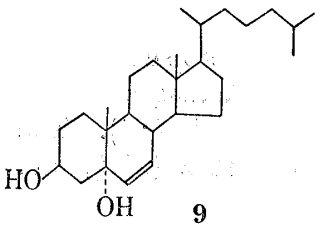
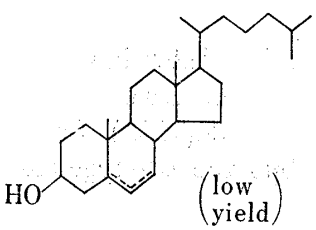
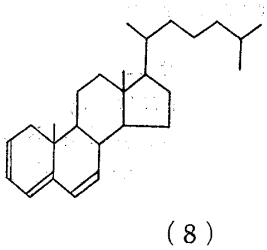
Substrate	Major products on treatment with LAH–$TiCl_4$ (% yield)	LAH–$AlCl_3$ (% yield)
 5	 (65)	 (80)
 6	 (50)	 (75–90)[4]
 7	 (57)	 (53)
 8	 (40)	 (50)
 9	 (low yield)	 (8)

Table II. Reaction of Cholest-4-en-3β-ol (1 mmole) with LAH–$TiCl_4$

$LiAlH_4$ (mmole)	$TiCl_4$ (mmole)	Solvent	Temperature	Time	Product (GLC analysis)	
					Cholest-4-ene	Cholesta-3,5-diene[a]
10	1	tetrahydrofuran	reflux	3 hr	72%	3%
4	1	tetrahydrofuran	reflux	3 hr	73	2
4	1	tetrahydrofuran	20°	24 hr	17	6
2	1	tetrahydrofuran	reflux	3 hr	24	6
1	1	tetrahydrofuran	20°	24 hr	—	15
1	1	ether	0°	10 min	—	94
1	4	ether	0°	10 min	—	98

a) H.E. Stavely and W. Bergman, *J. Org. Chem.*, **1**, 567 (1937)

respectively. These reactions appear to proceed through the allylic alcohols **7** and **8**. To clarify this, five steroidal allylic alcohols **5**—**9** (Table I) have now been subjected to reduction with LAH-$TiCl_4$. In comparison, the same substrates were treated with LAH–aluminum chloride($AlCl_3$) (molar ratio of 1: 4) by the method of Cunningham and Overton.[4] The latter reagent has been known[5] to be effective for hydrogenolysis of some of allylic alcohols.

The results are summarized in Table I. As evident, the secondary allylic alcohols **5** and **6** showed comparable behavior toward LAH–$TiCl_4$ as observed with LAH–$AlCl_3$, affording the corresponding hydrogenolysis products in fair yields. However, when the tertiary allylic alcohols **7**—**9** were treated with LAH–$AlCl_3$, dehydration reactions predominated instead of hydrogenolysis. In contrast, the expected hydrogenolysis occurred in the case of reaction with LAH–$TiCl_4$, to give cholesta-5,23-dien-3β-ol, stigmasta-5,28-dien-3β-ol and cholest-6-en-3β-ol. The side-products, namely fucosterol and isofucosterol from **8** and cholesterol from **9** may be produced *via* reductive S_N2' reaction. Thus, C-29 of **8** and C-7 of **9** seem to be much less hindered than C-24 and C-5 respectively, and therefore the hydride will attack on these former carbons with a concomitant migration of double bond.

The effects of solvent, temperature and the ratio of LAH/$TiCl_4$ were examined with cholest-4-en-3β-ol and the results are shown in Table II. These reactions appear to be rather sensitive to the reaction conditions and the optimum ones giving the required hydrogenolysis are described in experimental section.

This report shows that LAH–$TiCl_4$ is an useful reagent for hydrogenolysis of allylic alcohols, especially for the tertiary ones.

Experimental

A general procedure of LAH–$TiCl_4$ reduction is as follows. To a stirred solution of $TiCl_4$ (165 μl, 1.5 mM) in anhydrous tetrahydrofuran (10 ml) was added LAH (190 mg, 5 mM) in argon atmosphere under cooling with ice-bath. To the resulting black mixture a solution of sterol (200 mg, 0.5 mM) in anhydrous tetrahydrofuran (5 ml) was added, and the mixture was refluxed for 3 hr. Excess of reagents were decomposed by addition of a moist ether and the organic layer was washed with 1N HCl, saturated sodium bicarbonate solution and water. The residue obtained by evaporation of solvent was chromatographed on silica gel (Wako-gel C-200. The yield is listed in Table I.

Cholest-4-en-3β-ol (**5**)[4] was treated with LAH–$TiCl_4$ and LAH–$AlCl_3$, respectively, to give cholest-4-ene.

Cholest-5-ene-3β,7α-diol (**6**)[4] gave cholesterol by reaction with both reagents.

Cholesta-5,23-diene-3β,25-diol (**7**)[3] gave cholesta-5,23-dien-3β-ol[3] by treatment with LAH–$TiCl_4$. Gas chromatography–mass spectrometry analysis of the crude product indicated the copresence (3%) of desmosterol. Cholesta-5,23-diene-3β,25-diol (**7**) was treated with LAH–$AlCl_3$ to give, after acetylation, cholesta-5,23,25-trien-3β-ol acetate, mp 104—105°, λ_{max} (ε) 225(15400), 230(21500) and 239 nm (20100), δ($CDCl_3$) 1.80(3H, bs, 27-Me), 4.84 (2H, bs, 26-H_2) and 6.02(1H, t, J=11 Hz, 23-H).

Saringosterol (**8**)[3,6] was treated by LAH–$TiCl_4$ to give a mixture of cholesta-5,28-dien-3β-ol (**4**),[3] fucosterol and isofucosterol in a ratio of 42: 49: 9 which was revealed by gas–liquid chromatography (GLC) analysis of trimethylsilyl ether of the product. Compound (**8**) gave a mixture of trienes by reaction with LAH–$AlCl_3$, and the main component was identified with stigmasta-5,24,28-trien-3β-ol.[7]

Cholest-6-ene-3β,5α-diol (**9**)[8] was treated with LAH–$TiCl_4$ to give a complex mixture. One of the components was identified with cholesterol by GLC analysis. Nuclear magnetic resonance and ultraviolet spectra of the crude product of LAH-$AlCl_3$ reduction showed the substantially pure cholesta-2,4,6-triene,[9] but it was rapidly decomposed on standing at room temperature or by silica gel chromatography, causing the low isolated yield.

3) M. Morisaki, N. Awata, Y. Fujimoto, and N. Ikekawa, *J. C. S. Chem. Commun.*, **1975**, 362; Y. Fujimoto, M. Morisaki, and N. Ikekawa, *J. C. S. Perkin I*, **1975**, 2302.
4) I.M. Cunningham and K.H. Overton, *J. C. S. Perkin I*, **1974**, 2458.
5) J.H. Brewster and H.O. Bayer, *J. Org. Chem.*, **29**, 105 (1964).
6) N. Ikekawa, K. Tsuda, and N. Morisaki, *Chem. Ind.*, (London), **1966**, 1179.
7) H. Ohtaka, M. Morisaki, and N. Ikekawa, *J. Org. Chem.*, **38**, 1688 (1973).
8) G.O. Schenk, K. Gollnick, and O.A. Neumuller, *Annalen*, **603**, 46 (1957).
9) H. Schaltegger, *Helv. Chim. Acta*, **33**, 2101 (1950).

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Added in Proof (March 15, 1976) Recently several reports appeared, describing LAH-$TiCl_4$ as a characteristic reducing reagent: P. W Chun and S. T. Wilson, *Tetrahedron Letters*, **1976**, 15; Y. Watanabe, M. Shono and T. Mukaiyama, *Chem. Lett.*, **1975**, 871; T. Mukaiyama, M. Hayashi and K. Narasaka, *ibid.*, **1973**, 291.

[Chem. Pharm. Bull. 24(4) 828—831 (1976)]

UDC 547.92.04 : 547.284.04

Chemical Modifications of Androsta-1,4-diene-3,17-dione. III.[1] The Synthesis of (20*R*)-17α,20,21-Trihydroxypregna-1,4-dien-3-one and Its Derivatives

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(Received July 26, 1975)

The partial synthesis of (20*R*)-17α,20,21-trihydroxypregna-1,4-dien-3-one (its D-ring moiety is identical with that of cortisone) from androsta-1,4-diene-3,17-dione is described. This conforms a model experiment for the synthesis of adrenal steroid compounds from the latter compound without affecting its A-ring moiety.

The conversion of androstanes to pregnanes has been one of the most thoroughly examine projects for synthetic chemists in the steroid field.[3] In order to show the wide synthetic applicability of androsta-1,4-diene-3,17-dione (I) readily obtainable from cholesterol by microbiological oxidation using *Arthrobactor Simplex*, we have converted this dione to pregnane-type steroids having the dihydroxyacetone side chain characteristic of cortisone and dihydrocortisone.

The methods employed in this conversion are summarized in Chart 1.

In the present scheme, we have attempted to preserve the 1,4-dien-3-one function in the starting material throughout, because it could serve for further chemical modifications (especially at A and B rings) of both the final and the intermediate compound obtainable in the conversion.[4]

The first step in the present conversion is the addition of a two carbon fragment selectively to the 17-keto function in I, *via* the reaction with acetylene. Thus, by treatment of I with

1) Part II: H. Sakamoto, A. Sugimoto, C. Kaneko, T. Suda, and S. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 1733, (1975).
2) Location: *9-500-1, Nagareyama-shi, 270-01, Chiba.*
3) The fundamental methods for the conversion of androstanes to pregnanes were summarized recently by E.P. Oliveto, "Organic Reactions in Steroid Chemistry," edited by J. Fried and J.A. Edwards, Vol. 2, van Nostrand, Reinhold Co., 1972, pp. 129—140.
4) The successful modification of I at both A and B rings for the synthesis of androcalciferol derivatives having a hydroxyl group at either 1α- or 2β-positions was reported in the part I of this series; H. Sakamoto, A. Sugimoto, and C. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **22**, 2903 (1974).