The oxidation was carried out with several concentrations of AcOH in CH_2Cl_2 and also in pyridine. Some representative runs are shown in Table II. Estimates of ester ratios were made by glpc.

TABLE II

	% olefin	% ester	% composn 3α	% composn 3β
10 mol % acetic acid–CH_2Cl_2	28.9	60.7	65	35
100 mol % acetic acid–CH_2Cl_2	31.8	53.2	70	30
Pyridine	23.8	50.3	70	30

Registry No.—Lead tetraacetate, 546-67-8; **1**, 19640-01-8.

Acknowledgments.—The authors are grateful to Mr. G. Maciak and associates for microanalyses, to Mr. D. O. Woolf for physicochemical data, to Mr. C. Snell for gas chromatographic determinations, and to our colleagues, Dr. E. Farkas and Dr. R. T. Rapala, for helpful discussion of this work.

Tetramethyl Bismethylenedioxy Steroids. I. A Novel Protective Group

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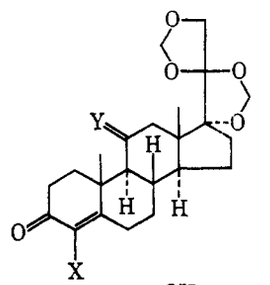
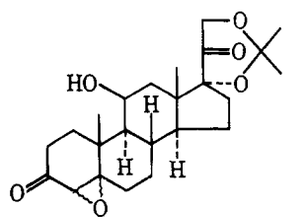
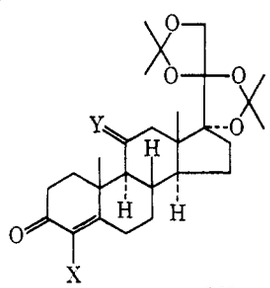
It is widely known that a bismethylenedioxy group (BMD)[3] has outstanding advantages as a protective group for the dihydroxyacetone side chain of adrenocortical hormones. Regarding the limitations, Sarett, *et al.*,[3a] noticed that a ketonic group at C_{11} retarded the BMD hydrolysis to a marked extent. We have noticed that 4-chlorohydrocortisone-BMD (**1b**), 4-chlorohydrocortisone-BMD-11-methoxy methyl ether (**1d**), and 4-chlorocortisone-BMD (**1f**) could not be hydrolyzed by acetic acid, formic acid, or perchloric acid to the corresponding 4-chlorocorticoids. This finding supports Hirschmann's observation[4] that "a variation at an even more remote position of the corticoid—for example, in the A ring—can have a marked effect on the rate of BMD hydrolysis." It may be mentioned in this connection that a chloro substituent at C_4 did not affect the hydrolysis of a 17α,21-acetonide linkage. In fact, 4-chlorohydrocortisone[5] could be prepared directly by the hydrogen chloride treatment of 4ξ,5ξ-oxido-11β-hydroxy-17α,21-isopropylidenedioxypregnane-3,20-dione (**2**). Now we have discovered that the hydrolysis of a tetramethyl bismethylenedioxy (TMBMD) group (or in other words 17,20-20,21-acetonides) is unaffected by an 11-ketone and also by a 4-chloro substituent in a steroid molecule. In fact, hydrocortisone-TMBMD (**3a**), 4-chlorohydrocortisone-TMBMD (**3b**), cortisone-TMBMD (**3c**), and 4-chlorocortisone-TMBMD (**3d**) could smoothly be hydrolyzed by acetic acid (50%) on a steam bath (3–4 hr) to the corresponding corticoids (yields, 80–90%). The faster rate of hydrolysis of the TMBMD grouping may be attributed to the hypercon-





2

1a, X = H; Y = α-OH, β-H
b, X = Cl; Y = α-OH, β-H
c, X = H; Y = α-OCH_2OCH_3, β-H
d, X = Cl; Y = α-OCH_2OCH_3, β-H
e, X = H; Y = O
f, X = Cl, Y = O



3a, X = H; Y = α-OH, β-H
b, X = Cl; Y = α-OH, β-H
c, X = H; Y = O
d, X = Cl; Y = O

jugation effect of the acetonide methyl groups. The nmr spectrum ($CDCl_3$) of the TMBMD compounds showed signals which supported the presence of six methyl groups (τ 8.2–9.1) and one OCH_2 group (5.9–6.0). **3a** and **3c** also showed the vinyl proton (τ 4.3–4.35). The ultraviolet (uv) absorptions of the 4-chloro derivatives (**1b**, **1d**, **1f**, **3b**, and **3d**) were in the region of 254–255 mμ. The TMBMD compounds showed absorptions at 1370–1390 (*gem*-dimethyl) and 1220–1230 cm^{-1} (asymmetric C—O—C stretching) in addition to the symmetric stretching around 1070 cm^{-1}. The BMD derivatives, on the other hand, exhibit only symmetric C—O—C stretching at 1100 cm^{-1}.[3a] The chlorine substituent at C_4 of the corticoids and their derivatives (BMD and TMBMD) makes significant shifts (20–25 cm^{-1}) of Δ^4-3-keto band toward higher and C=C band toward lower frequencies. Satisfactory elemental analyses were obtained for all the new compounds.

In the preparation of the TMBMD compounds, steroids were dissolved in dry acetone, a few drops of perchloric acid (70%) were added, and the solution was stirred overnight at room temperature (yield 60–65%). Chlorination of the corticoid derivatives was effected

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(2) Recipient of a Roswell Park Memorial Institute summer fellowship from The National Institute of Health, Training Grant CA06183, 1967.

(3) (a) R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961), and other papers in this series; (b) *ibid.*, **26**, 2426 (1961); (c) *J. Amer. Chem. Soc.*, **81**, 1235 (1959); (d) *ibid.*, **82**, 170 (1960).

(4) See ref 7 on p 2423 of ref 3a.

(5) H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956).

either by epoxidation followed by acidification (HCl)[5] or by sulfuryl chloride treatment in pyridine solution.[6]

Experimental Section

Melting points (uncorrected) were determined on Fisher-Johns apparatus. The uv spectra (measured on a Cary 14 instrument) are for 95% EtOH solution unless otherwise stated. Infrared (ir) spectra were obtained with a Beckman IR-9 instrument. Microanalyses were carried out by Galbraith Laboratories, Inc. Nuclear magnetic resonance (nmr) spectra are for deuteriochloroform solutions, with tetramethylsilane as internal reference on a Varian A-60 instrument. R_f values were calculated from thin layer chromatographic mobilities on glass plates coated with silica gel G (0.25 mm). Mixtures of chloroform–acetone (9:1) (solvent system A) or chloroform–benzene–ethyl alcohol (9:1:1) (solvent system B) were used for developing. Aqueous solution of orthophosphoric acid (50%) and ethanolic solution of phosphomolybdic acid (1.5%) were used as spray reagents.

Hydrocortisone-BMD (1a), Hydrocortisone-BMD-11-methoxy Methyl Ether (1c), and Cortisone-BMD (1e).—These were prepared by the method of Sarett, *et al.*[3a]

4-Chlorohydrocortisone-BMD (1b).—**1a**, on epoxidation,[5] followed by hydrochloric acid treatment,[5] gave **1b**. **1a** (2 g), mp 220–222° (lit.[3a] mp 220–223°), was dissolved in methanol (100 ml) and cooled to 0°. The solution was successively treated with hydrogen peroxide (12 ml, 30%) and cold aqueous sodium hydroxide (5 ml, 10%). After stirring for 20 hr at 0°, the solution was neutralized by acetic acid (1:1) to pH 7. Concentration of the solution *in vacuo* below 40° gave a mixture of epoxides (1.7 g) which was dissolved in acetone (25 ml) and treated with concentrated hydrochloric acid (1 ml, 37%). The solution was stirred for 45 min at room temperature. Crushed ice was added to turbidity and the mixture was chilled overnight. The solid material (1.72 g), isolated by filtration on recrystallization from methanol–chloroform mixture, afforded **1b** (1.6 g): mp 243–245°; uv max (MeOH) 254.5 mμ (ε 14,320); ir (KBr) 3590 (11-OH), 1685 (3-keto), 1575 (C=C), and 1090 cm^{-1} (C—O—C); R_f 0.56 (solvent system A).

Anal. Calcd for $C_{23}H_{31}O_6Cl$: C, 62.92; H, 7.12. Found: C, 62.40; H, 7.04.

4-Chlorohydrocortisone-BMD-11-methoxy Methyl Ether (1d).—Chlorination of **1c** at C_4 was effected by the method of Mori.[6] Freshly distilled sulfuryl chloride (1.4 ml) was added dropwise to an ice-cooled (5°) solution of **1c** (1 g) in dry pyridine (10 ml). The solution was stirred for 1 hr. The contents were poured onto crushed ice and the solid (1.02 g) obtained was purified by column chromatography on neutral alumina (20 g). Elution of the column with benzene (80 ml) afforded **1d** (0.85 g, 80%): mp 162–164°; uv max 255 mμ (ε 14,940); ir ($CHCl_3$) 1695 (3-keto), 1592 (C=C), 1090 (C—O—C), and 1050 cm^{-1} (11-ketal); R_f 0.81 (solvent system A).

Anal. Calcd for $C_{25}H_{35}O_7Cl$: C, 62.17; H, 7.30. Found: C, 62.27; H, 7.18.

4-Chlorocortisone-BMD (1f).—Cortisone-BMD (**1e**, 1 g) was dissolved in dry pyridine (10 ml). Freshly distilled sulfuryl chloride (1.2 ml) was added to the solution dropwise at 5° over a period of 5 min. Stirring was continued for an additional 1 hr. The reaction mixture was poured onto crushed ice and the precipitate was collected, washed with water, dried, and crystallized from aqueous acetone to yield **1f** (0.83 g, 77%): mp 290–295°; uv max 254 mμ (ε, 15,670); ir (KBr) 1700 (11- and 3-keto), 1585 (C=C), and 1100 cm^{-1} (C—O—C); R_f 0.82 (solvent system A).

Anal. Calcd for $C_{23}H_{29}O_6Cl$: C, 63.23; H, 6.70. Found: C, 63.19; H, 6.86.

4ξ,5ξ-Oxido-11β-hydroxy-17α,21-isopropylidenedioxypregnane-3,20-dione (2).—A methanolic solution (100 ml) of 17α,21-acetonide of hydrocortisone (2 g) [mp 184–186° (lit.[7] mp 194–195°); ir ($CHCl_3$) 3610 (11-OH), 1720 (20-keto), 1665 (3-keto), 1622 (C=C), 1372 and 1385 (*gem*-dimethyl), and 1225–1230 cm^{-1} (asymmetric C—O—C)], on treatment with aqueous NaOH (6 ml, 10%) and hydrogen peroxide (14 ml, 30%), for 20 hr at 0°, gave an epoxide mixture (**2**, 1.6 g, 78%) which on recrystallization from aqueous acetone had mp 118–122°; ir ($CHCl_3$) 3610 (11-OH), 1718 (20- and 3-keto), and 1225–1230 (asymmetric C—O—C); R_f 0.47 (solvent system A) (R_f of hydrocortisone-17α,21-acetonide, 0.34).

Hydrochloric Acid Treatment of 2.—A solution of **2** (1 g) in acetone (18 ml) was treated with hydrochloric acid (1 ml, 37%) for 45 min. Water was added to turbidity and the mixture was allowed to stand overnight at 5°. The residue on recrystallization from an acetone–benzene mixture afforded 4-chlorohydrocortisone (0.71 g, 75%): mp 224–226° (lit.[5] mp 225–227°); uv max 254 mμ (ε 14,280); ir (KBr) 3400–3470 (11-, 17-, and 21-OH), 1712 (20-keto), 1685 (3-keto), and 1575 cm^{-1} (C=C); R_f 0.42 (solvent system B).

Cortisone-TMBMD (3c).—Perchloric acid (1.25 ml, 70%) was added to a solution of cortisone (5.8 g) in dry acetone (340 ml). The solution was stirred for 20 hr at room temperature. The resulting yellow solution was neutralized by aqueous potassium carbonate (20 ml, 2%) until the solution was colorless. The solution was concentrated *in vacuo* when **3c** (4.78 g, 65%) separated. Recrystallization from aqueous acetone led to an analytical sample of **3c**: mp 250–252°; uv max 241 mμ (ε 16,540); ir (KBr) 1705 (11-keto), 1675 (3-keto), 1618 (C=C), 1370 and 1385 (*gem*-dimethyl), 1225–1230 (asymmetric C—O—C), and 1070 cm^{-1} (symmetric C—O—C); nmr ($CDCl_3$) τ 4.3 (s, 1 H), 6.0 (s, 2 H), and 8.2–9.1 (complex, 18 H); R_f 0.79 (solvent system A) (R_f of cortisone-BMD, 0.71).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.78; H, 9.00.

Hydrocortisone-TMBMD (3a).—Treatment of hydrocortisone (6.2 g) as above, with dry acetone (400 ml) and perchloric acid (1.28 ml, 70%) for 20 hr followed by recrystallization from aqueous acetone, furnished **3a** (4.65 g, 60%): mp 235–238°; uv max 241 mμ (ε 15,820); ir (KBr) 3405 (11-OH), 1660 (3-keto), 1620 (C=C), 1375 and 1382 (*gem*-dimethyl), 1225–1230 (asymmetric C—O—C), and 1070 cm^{-1} (symmetric C—O—C); nmr ($CDCl_3$) τ 4.35 (s, 1 H), 5.95 (s, 2 H), and 8.2–9.1 (complex, 18 H); R_f 0.65 (solvent system A) (R_f of hydrocortisone-BMD, 0.46).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.57; H, 9.05.

4-Chlorocortisone-TMBMD (3d).—A solution of cortisone-TMBMD (**3c**, 0.85 g) in dry pyridine (9.5 ml) was treated with freshly distilled sulfuryl chloride (0.9 ml) and worked up as described in the preparation of **1f**. The solid material, isolated by filtration, on recrystallization from a chloroform–methanol mixture, afforded **3d** (0.68 g, 75%): mp 252–255°; uv max 254 mμ (ε, 16,240); ir (KBr) 1710 (11-keto), 1700 (3-keto), 1595 (C=C), 1375 and 1390 (*gem*-dimethyl), 1225–1230 (asymmetric C—O—C), and 1080 cm^{-1} (symmetric C—O—C); nmr ($CDCl_3$) τ 5.95 (s, 2 H) and 8.2–9.1 (complex, 18 H); R_f 0.89 (solvent system A).

Anal. Calcd for $C_{27}H_{37}O_6Cl$: C, 65.91; H, 7.58; Cl, 7.00. Found: C, 65.17; H, 7.63; Cl, 7.22.

4-Chlorohydrocortisone-TMBMD (3b).—Treatment[6] of a methanolic solution of hydrocortisone-TMBMD (1.2 g in 75 ml of methanol) with aqueous sodium hydroxide (3 ml, 10%) and hydrogen peroxide (8 ml, 30%), for 20 hr at 0°, gave an epoxide mixture (0.94 g, 76%): mp 215–230°; ir (KBr) 3440 and 3470 (11-OH), 1705 and 1720 (3-keto), 1375 and 1380 (*gem*-dimethyl), 1225–1230 (asymmetric C—O—C), and 1080 cm^{-1} (symmetric C—O—C); R_f 0.75 and 0.81 (solvent system A). Reaction of the epoxide mixture (0.65 g) with acetone (60 ml) and hydrochloric acid (0.6 ml, 37%) for 45 min at room temperature yielded **3b** (0.53 g, 80%): mp 283–285°; uv max 254 mμ (ε 14,990); ir (KBr) 3500 (11-OH), 1690 (3-keto), 1590 (C=C), 1225–1230 (asymmetric C—O—C), and 1075 cm^{-1} (symmetric C—O—C); nmr ($CDCl_3$) τ 5.95 (s, 2 H) and 8.2–9.1 (complex, 18 H); R_f 0.76 (solvent system A).

Anal. Calcd for $C_{27}H_{39}O_6Cl$: C, 65.63; H, 7.95; Cl, 6.97. Found: C, 65.34; H, 7.80; Cl, 7.01.

Attempted Bismethylenedioxy Group Hydrolysis of 1b, 1d, and 1f.—A BMD derivative (**1b** or **1f**, 250 mg) was heated in 20 ml of 50% acetic acid at 100° for 6 hr. When the solvent was evaporated to dryness in an atmosphere of nitrogen, only the starting material was obtained in almost quantitative yield (220–230 mg). Attempts to remove the BMD group by formic acid (60%) or glacial acetic acid were also futile. Prolonged acetic acid treatment or use of perchloric acid along with acetic acid gave some decomposed material and the parent compound.

1d, on similar treatment, afforded a mixture of **1b** and **1d** but no 4-chlorocortisone.

Facile Tetramethyl Bismethylenedioxy Group Hydrolysis of 3a, 3b, 3c, and 3d.—Cortisone-TMBMD (**3c**, 540 mg) was heated with acetic acid (16 ml, 50%) at 95° for 3 hr. The contents, on removal of solvent, were crystallized from aqueous methanol to

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(7) R. Gardi, R. Vitali, and A. Ercoli, *J. Org. Chem.*, **27**, 668 (1962).

give cortisone (235 mg, 88% yield): mp 223–225°; R_f 0.61 (solvent system B).

4-Chlorocortisone-TMBMD (**3d**, 500 mg) on heating with acetic acid (40 ml, 50%) at steam-bath temperature for 4 hr afforded 4-chlorocortisone (340 mg, 85% yield): mp 212–214° (lit.[5] mp 210–212°; uv max 254 mμ (ε 15,220); ir (KBr) 3500 and 3520 (17- and 21-OH), 1700 and 1710 (11- and 20-keto), 1685 (3-keto), and 1590 cm^{-1} (C=C); R_f 0.64 (solvent system B).

Hydrocortisone-TMBMD (**3a**, 400 mg) was heated with acetic acid (30 ml, 50%) at 90° for 3 hr. The reaction mixture was then taken to dryness *in vacuo*. The residue was crystallized from aqueous ethanol to give hydrocortisone (282 mg, 90% yield): mp 220–221°; R_f 0.37 (solvent system B).

Hydrolysis of 4-chlorohydrocortisone-TMBMD (**3b**, 370 mg) with aqueous acetic acid (50 ml, 50%) for 4 hr as in previous examples, followed by crystallization from benzene–acetone, gave 4-chlorohydrocortisone[5] (245 mg, 83% yield): mp 224–225°; R_f 0.42 (solvent system B). The identity of the material with that prepared by hydrochloric acid treatment of **2** was shown by mixture melting point and uv and ir spectral comparisons.

Registry No.—**1b**, 19551-06-5; **1d**, 19551-07-6; **1f**, 19551-08-7; **2**, 19594-74-2; **3a**, 19551-09-8; **3b**, 19581-61-4; **3c**, 19551-10-1; **3d**, 19551-11-2.

Acknowledgment.—The authors desire to extend their sincere thanks to Dr. W. Roy Slaunwhite, Jr., Research Director of this institute, for his keen interest in the work.

Catalytic Hydrogenation of 17β-Hydroxyde-A-androst-9-en-5-one, (±)-17β-Hydroxy-18-methylde-A-androst-9-en-5-one, and (±)-17β-Hydroxy-18-methylde-A-D-homoandrost-9-en-5-one

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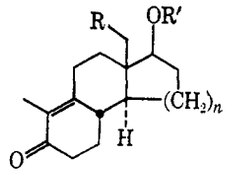
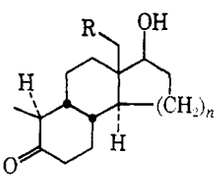
This Note describes the preparation of 17β-hydroxy-9β,10β-de-A-androstan-5-one (**2a**), (±)-17β-hydroxy-9β,10β-18-methylde-A-androstan-5-one (**2b**), and (±)-17β-hydroxy-9β,10β-18-methylde-A-D-homoandrostan-5-one (**2c**) by catalytic hydrogenation of the title compounds (**1a**, **1g**, and **1k**)[3] and their derivatives (Chart I). These compounds were required for our total synthesis of retro steroids (*i.e.*, 9β,10α steroids).[4]

Previous work reported from these laboratories[5] indicated that rhodium on alumina in ethanol–hydrochloric acid would favor formation of **2a** from **1a**, the major by-product being **3a**[6] which has the 9α,10α configuration. The best ratio of **2a**:**3a** obtainable by us under these conditions is shown in Table I (expt 1).

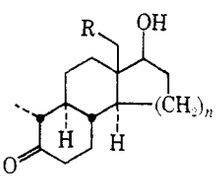
CHART I



1a, R = R′ = H; *n* = 1
b, R = H; R′ = $COCH_3$; *n* = 1[a]
c, R = H; R′ = COC_6H_{11}; *n* = 1
d, R = H; R′ = $COCH_2C(CH_3)_3$; *n* = 1
e, R = H; R′ = COH; *n* = 1
f, R = H; R′ = $C(CH_3)_3$; *n* = 1
g, R = CH_3; R′ = H; *n* = 1
h, R = CH_3; R′ = $COCH_3$; *n* = 1
i, R = CH_3; R′ = COC_6H_{11}; *n* = 1[a]
j, R = CH_3; R′ = $CO(CH_2)_2C_5H_9$; *n* = 1[a]
k, R = CH_3; R′ = H; *n* = 2
l, R = CH_3; R′ = $COCH_3$; *n* = 2



2a, R = H; *n* = 1
b, R = CH_3; *n* = 1
c, R = CH_3; *n* = 2



3a, R = H; *n* = 1
b, R = CH_3; *n* = 1
c, R = CH_3; *n* = 2

[a] Cycloalkyl derivatives.

Experiments with other solvents under neutral, acidic, or basic conditions failed to improve the ratio, and the same was true when palladium on barium sulfate or rhodium on carbon was used as the catalyst. Variation of the amount of hydrochloric acid used indicated that the best results were obtained when *ca.* 3 equiv were used. The optimum yield of **2a** proved to be 40%.

TABLE I
HYDROGENATION OF DE-A-ANDROST-9-EN-5-ONES[a]

Expt	Compd 1	Relative ratio 2a:3a
1	**a**	75–83:25–17
2	**b**	88–90:12–10
3	**c**	82:18
4	**d**	85:15
5	**e**	75:25
6	**f**	65:35[b]
		2b:3b
7	**g**	56:44
8	**h**	84:16
9	**i**	94:6
10	**j**	87:13
		2c:3c
11	**k**	67:31
12	**l**	96:4

[a] All hydrogenations were performed using 5% Rh/Al_2O_3 in EtOH–HCl. The formate **1e** hydrolyzed during hydrogenation, the acetates were saponified with KOH—MeOH, and the other esters with NaOMe–MeOH prior to vpc determination of the isomer ratio in the products. The vpc analyses used system A for the products from **1a-f** and system B for the remainder (see Experimental Section). [b] The ether group was first removed with aqueous HCl in EtOH or with *p*-toluenesulfonic acid in benzene.

An improved ratio of **2a**:**3a** was obtained by hydrogenation of acetate **1b** (expt 2), and subsequent saponification. Three other esters (**1c**, **1d**, and **1e**) were also prepared as was the *t*-butyl ether **1f**. Bulky esters **1c** and **1d** (expt 3 and 4) gave results comparable with those obtained with acetate **1b** as regards the ratio of **2a**:**3a**; but the yields of **2a** after saponification and crystallization were only *ca.* 45% as opposed to 70% obtained from **1b**. This almost certainly reflects the strenuous hydrolysis conditions (sodium methoxide in boiling

(1) Hoffmann-La Roche, Inc., Nutley, N. J. 07110.
(2) F. Hoffmann-La Roche and Co. Ltd., Basle, Switzerland.
(3) It should be noted that all the compounds with R = Me referred to in Chart I are racemic, whereas those with R = H belong to the normal steroid series. Throughout the paper steroid nomenclature is used.
(4) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967); A. M. Krubiner, G. Saucy, and E. P. Oliveto, *ibid.*, **33**, 3548 (1968).
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(6) M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*, 1312 (1962).