Tetrahedron, 1959, Vol. 6, pp. 269 to 303. Pergamon Press Ltd. Printed in Northern Ireland

SELECTIVE REACTIONS AND MODIFICATION OF FUNCTIONAL GROUPS IN STEROID CHEMISTRY

H. J. E. LOEWENTHAL
Israel Institute of Technology, Haifa, Israel

(*Received* 2 *September* 1958)

INTRODUCTION

THE last ten years have seen a concentrated effort in the partial and total synthesis of steroids, occasioned in particular by the discovery of the adrenocortical hormones and of their physiological activity. This effort has involved conducting selective reactions on multifunctional compounds, and protection of one type of functional group against the consequence of reactions aimed at another. It seems desirable to give a review of such selective reactions and modifications; not only for the benefit of workers in the steroid field itself, but also as a guide for those working in other fields of organic synthesis, some of whom tend to assume that steroid chemistry is an exclusive domain.

This review covers the more important literature from 1948 through 1957, but it is not intended to be exhaustive. Work on tricyclic intermediates in steroid total synthesis has been included, but facts published in communication form are not dealt with unless such communications mention a modicum of experimental detail.

A. SELECTIVE REACTIONS OF C=C DOUBLE BONDS

I. *Selective catalytic reduction of* C=C *double bonds*

(a) *Isolated and* C=C *conjugated double bonds.* Apart from double bonds at the 8:14- (and hence at the 7-) position, which are reduced catalytically only under extreme conditions,[1,2] the isolated C_5 double bond is relatively the most unreactive to hydrogenation. It is unaffected when double bonds at positions 16, 17(20) and 20, or triple bonds (for instance in a 17-ethinyl group) are saturated in the presence of palladium catalysts.[3] In the presence of platinum it can be hydrogenated, usually in the presence of acids, giving an A/B-*trans*-steroid, except in the case of 3α-substituted pregn-5-enes which are reported to give normal (A/B-*cis*) pregnanes,[4] and, analogously, *epi*cholesterol, whose hydrogenation gives *epi*coprostanol.[5] The steric course of hydrogenation of Δ^4- and Δ^5-steroids in general has been explained on the basis of conformational arguments.[6]

An isolated C_{14} double bond appears to be slightly less reactive to hydrogenation than one at C_5[7] its saturation usually gives the normal 14α-configuration.

[1] J. J. Cahill, N. E. Wolff and E. S. Wallis, *J. Org. Chem.* **18**, 720 (1953).
[2] K. Tsuda, K. Arima and R. Hayatsu, *J. Amer. Chem. Soc.* **76**, 2932 (1954).
[3] E. B. Hershberg, E. P. Oliveto, C. Gerold and L. Johnson, *J. Amer. Chem. Soc.* **73**, 5073 (1951).
[4] J. H. Pierce, H. C. Richards, C. W. Shoppee, R. J. Stephenson and G. H. R. Summers, *J. Chem. Soc.* 694 (1955).
[5] J. R. Lewis and C. W. Shoppee, *Chem. & Ind.* 897 (1953).
[6] H. I. Hadler, *Experientia* **11**, 175 (1955).
[7] J. R. Billetter and K. Miescher, *Helv. Chim. Acta* **34**, 2053 (1951).

Side chain double bonds (e.g. at the 22(23)-position) are next in order of susceptibility to catalytic hydrogenation, and this can often be effected with Raney nickel catalysts in cases where the $\Delta^7 \rightarrow \Delta^{8(14)}$ shift, which occurs with palladium, and with platinum in acidic (though not in neutral) media,[8] is undesirable. The acid catalysed $\Delta^{8(14)} \rightarrow \Delta^{14}$ migration does not occur in certain cases.[9]

Double bonds at C_6 or $C_{8(14)}$ in maleic anhydride adducts of 5:7- or 7:14-dienes are not affected when a side chain double bond is hydrogenated.[10] The stepwise and selective reduction of 5α:8α-epidioxides of 5:7-dienes, of importance in the production of 5α-hydroxy ergostane- and -cholestane derivatives, has been described in detail.[11,12]

A C_7-double bond in 9βH-steroids can be catalytically reduced even before one in the side chain.[13–15] Steric influences are also evident in the behaviour of the 9(11)-double bond, which is inert to hydrogenation in A/B-*cis*-steroids,[16] but less so in A/B-*trans*-steroids.

Turning to selective hydrogenation of C=C-conjugated double bonds: a 5:7:9(11):22(23)-tetraene is generally reduced in the order: $\Delta^5 > \Delta^{9(11)} > \Delta^{22(23)} > \Delta^7(\rightarrow \Delta^{8(14)})$, using Raney nickel[17–21] or copper chromite[22] catalysts, less advantageously with palladium or platinum.[23,24] In conjugated diene systems represented by enol ethers or enol acetates of α:β-unsaturated ketones the γ:δ-double bond can be selectively hydrogenated using palladium,[25–28] giving an A/B-*trans*-junction if it is at the 5-position.

Selective catalytic reductions in unsaturated 3:5-*cyclo*steroids have been described.[1,29] (Table 1.)

(b) *Systems containing carbonyl conjugated double bonds.* Selectivity in catalytic hydrogenation in these systems depends to a large extent on the catalyst and solvent employed; and for this reason a relatively large number of examples are given.

It is reported that double bonds at C_{16} (including Δ^{16}-20-ketones), $C_{17(20)}$, C_{20}, and ethinyl groups at C_{17} can be hydrogenated with palladium catalysts under neutral or slightly alkaline conditions before a Δ^4-3-ketone is reduced.[3] In other cases the presence of pyridine favours the selective reduction of a carbonyl conjugated

[8] H. Wieland and W. Benend. *Liebigs Ann.* **554**, 1 (1943).
[9] O. Mancera, D. H. R. Barton, G. Rosenkranz and C. Djerassi, *J. Chem. Soc.* 1021 (1952).
[10] D. H. R. Barton and T. Bruun, *J. Chem. Soc.* 2728 (1951).
[11] P. Bladon, R. B. Clayton, C. W. Greenhalgh, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. Silverstone, G. W. Wood and G. F. Woods, *J. Chem. Soc.* 4883 (1952).
[12] R. B. Clayton, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 2015 (1953).
[13] (a). P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood and G. F. Woods.
(b). J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton and G. H. Thomas, *J. Chem. Soc.* 2921 (1953).
[14] A. Crawshaw, H. B. Henbest, E. R. H. Jones and A. A. Wagland, *J. Chem. Soc.* 3420 (1955).
[15] J. Elks, R. M. Evans, C. H. Robinson, G. H. Thomas and L. J. Wyman, *J. Chem. Soc.* 2933 (1953).
[16] B. F. McKenzie, V. R. Mattox and E. C. Kendall, *J. Biol. Chem.* **175**, 249 (1948).
[17] R. C. Anderson, R. Stevenson and F. S. Spring, *J. Chem. Soc.* 2901 (1952).
[18] L. F. Fieser, J. E. Herz and W. Huang, *J. Amer. Chem. Soc.* **73**, 2397 (1951).
[19] K. Heusler, H. Heusser and R. Anliker, *Helv. Chim. Acta* **36**, 652 (1953).
[20] G. D. Laubach and K. G. Brunnings, *J. Amer. Chem. Soc.* **74**, 705 (1952).
[21] See Ref. 36.
[22] W. R. Nes and E. Mosettig, *J. Org. Chem.* **18**, 276 (1953).
[23] L. F. Fieser, M. Fieser and R. N. Chakravarti, *J. Amer. Chem. Soc.* **71**, 2226 (1949).
[24] G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.* **16**, 298 (1951).
[25] H. H. Inhoffen, G. Koelling, G. Koch and I. Nebel, *Chem. Ber.* **84**, 361 (1951).
[26] H. H. Inhoffen, G. Stoeck, G. Koelling and U. Stoeck, *Liebigs Ann.* **568**, 52 (1950).
[27] W. S. Johnson, E. R. Rogier, J. Szmuczkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister and H. Wynberg, *J. Amer. Chem. Soc.* **78**, 6289 (1956).
[28] A. R. Pinder and R. Robinson, *J. Chem. Soc.* 3341 (1955).
[29] P. Karrer and H. Asmis, *Helv. Chim. Acta* **35**, 1926 (1952).

TABLE 1. EXAMPLES

Compound	Conditions	Double bond reduced at	Ref.
3β-Acetoxy 17-methyl androsta-5:16-diene and -5:17(20)-diene	Pd/C, EtOH	16 or 17(20) [17β-configuration]	30
3β-Acetoxy 17-methyl androsta-5:16-diene	Pd/C, EtOH	16 [17β-configuration]	31
3β-Acetoxy 17-keto 13-*iso* androsta-5:14-diene	Pt, HOAc	5[17-hydroxy]	7
Zymosterol [8(9):22(23)-diene]	RaNi, Benz	22	32
3β-Hydroxy cholesta-5:7-diene	RaNi, Dioxan	5	18
3-Ethylenedioxy cholesta-5:7-diene	RaNi, EtOH, Et_2O	5	33
3β:17β-Diacetoxy androsta-5:7-diene	Pt, EtOAc	5	34
3β-Acetoxy cholesta-6:8(9)-diene	Pt, EtOAc	6 (no shift of $C_{8(9)}$ double bond)	2
3β-Acetoxy 22a-spirosta-5:7-diene	Pt, EtOAc	5	9, 24
3β-Acetoxy 22a-spirosta-5:7-diene	RaNi, Dioxan	5	36
3-Ethylenedioxy 22a-spirosta-5:7-diene	RaNi	5	35
Ergosterol acetate [5:7:22(23)-triene]	RaNi, Benz.	5	17, 20, 36
Ergosterol acetate [5:7:22(23)-triene]	CuCrO	5	22
3β-Acetoxy ergosta-7:9(11):22(23)-triene	CuCrO	9	22
3β-Acetoxy ergosta-7:9(11):22(23)-triene	RaNi, Xyl.	9, 22	22
3β-Acetoxy ergosta-7:9(11):22(23)-triene	RaNi, EtOAc	9, 22	19
3β-Acetoxy ergosta-7:9(11):22(23)-triene	Pt, EtOAc	9, 22	36
3β-Acetoxy ergosta-6:8(14):22(23)-triene	RaNi, Dioxan	6	20
3β-Acetoxy ergosta-8(14):22(23)-diene	Pt, Dioxan	22	20
3β-Benzoyloxy ergosta-5:7:14:22(23)-tetraene	Pt, Et_2O, HOAc	5, 14, 22 [giving Δ-8(14)]	10
Methyl 3β-acetoxy bisnorchola-5:7-dienate	RaNi, Benz.	5	36
3β-Acetoxy 7-keto ergosta-9(11):22(23)-diene	Pd/C, EtOAc, HOAc	9, 22	37

[30] R. T. Rapala and E. Farkas, *J. Amer. Chem. Soc.* **77**, 6685 (1955).
[31] M. Heller and S. Bernstein, *J. Amer. Chem. Soc.* **78**, 1161 (1956).
[32] P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, *J. Chem. Soc.* 2402 (1951).
[33] R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.* **17**, 1341 (1952).
[34] F. Neumann, G. Rosenkranz, J. Romo and C. Djerassi, *J. Amer. Chem. Soc.* **73**, 5478 (1951).
[35] S. Bernstein, R. Littell and J. H. Williams, *J. Org. Chem.* **18**, 1418 (1953).
[36] W. V. Ruyle, E. M. Chamberlin, J. M. Chemerda, G. E. Sita, L. M. Aliminosa and R. L. Erickson, *J. Amer. Chem. Soc.* **74**, 5929 (1952).
[37] J. Elks, R. M. Evans, A. G. Long and G. H. Thomas, *J. Chem. Soc.* 451 (1954).

over an isolated double bond. Catalytic reduction of a Δ^{16}-20-ketone and reduction of a 14:16-diene-20-ketone with sodium and propanol, or lithium and liquid ammonia[38] leads to the normal 17β-configuration, but total catalytic reduction of 14:16-dienes[39,40] or of 14:15-epoxy 16-enes[39] leads to 14β:17α-steroids.

Catalytic reduction of Δ^4-3-ketones usually affords a mixture of products containing an A/B-*cis*- and A/B-*trans*-junction;[41–42] a trace of alkali increases the proportion of the former. However, hydrogenation of 11β-hydroxy and 11-oxo Δ^4-3-ketones leads to an A/B-*trans*-steroid,[41,43] and the A/B-*trans*-junction is always formed on reduction of Δ^4-3-ketones with metals in liquid ammonia, with or without a proton donor.

The resistance of the C_7-double bond to hydrogenation extends even to the case of a Δ^7-6-ketone,[44] while $\Delta^{8(9)}$-7-ketones and $\Delta^{8(9)}$-7:11-diketones can be reduced both catalytically and with zinc and acetic acid to give the normal (9αH:8βH) B/C-ring-junction.[37] This is of interest in connexion with the report that catalytic reduction of $\Delta^{8(9)}$-11-ketones gives an 8αH:9αH-steroid,[45] even in case where the C/D-ring-junction is *cis*.[46]

A number of remarkably specific catalytic hydrogenations in synthetic intermediates have been described, and some are shown in the examples given.[47–50] (Table 2.)

TABLE 2. EXAMPLES

Compound	Conditions	Double bond reduced at	Ref.
Androstane derivatives			
3β-hydroxy, 17-one, 16-methylene, 5-ene	Pd/C, EtOH	16-methylene	51
[17β-hydroxy, 17α-vinyl or -ethinyl, 3-one, 4-ene	Li/NH_3	4 in both cases (A/B *trans*)	52]
3β-acetoxy, 17-ethoxycarbonyl, 5:14:16-triene	$Pd/CaCO_3$, EtOH	14, 16 (17α, 14βH)	39
3-one, 17-ethoxycarbonyl, 4:9(11):16-triene	$Pd/SrCO_3$	4, 16 (mixture of A/B-*cis* and *trans*)	50
3-one, 17-formyl, 4:9(11):16-triene	$Pd/SrCO_3$, *i*-PrOH	16	48
Pregnane derivatives			
3α-acetoxy, 20-one, 7:16-diene	Pd/EtOAc, Piperidine	16	53
(*allo*) 3β-acetoxy, 20-one, 7:16-diene	Pd/EtOAc, Piperidine	16	54
(*allo*) 3β-acetoxy, 20-one, 8(14):16-diene	Pd/C, EtOAc	16	9

[38] H. Heusser, M. Roth, O. Rohr and R. Anliker, *Helv. Chim. Acta* **38**, 1178 (1955).
[39] H. Heusser, N. Frick and P. A. Plattner, *Helv. Chim. Acta* **33**, 1260 (1950).
[40] P. A. Plattner, L. Ruzicka, H. Heusser, J. Pataki and K. Meyer, *Helv. Chim. Acta* **29**, 942, 949 (1946).
[41] J. M. Chemerda, E. M. Chamberlin, E. H. Wilson and M. Tishler, *J. Amer. Chem. Soc.* **73**, 4052 (1951).
[42] J. Pataki, G. Rosenkranz and C. Djerassi, *J. Biol. Chem.* **195**, 751 (1952).
[43] E. P. Oliveto, C. Gerold and E. B. Hershberg, *J. Amer. Chem. Soc.* **74**, 2248 (1952).
[44] A. Zuercher, H. Heusser, O. Jeger and P. Geistlich, *Helv. Chim. Acta* **37**, 1562 (1954).
[45] C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 3496 (1953).
[46] C. Djerassi and G. H. Thomas, *Chem. & Ind.* 1228 (1954).
[47] L. B. Barkley, W. S. Knowles, M. W. Farrar, H. Raffelson and Q. E. Thompson, *J. Amer. Chem. Soc.* **76**, 5014 (1954).
[48] L. B. Barkley, W. S. Knowles, H. Raffelson and Q. E. Thompson, *J. Amer. Chem. Soc.* **78**, 4111 (1956).
[49] P. Wieland, G. Anner and K. Miescher, *Helv. Chem. Acta* **36**, 646 (1953).
[50] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. H. McLamore, *J. Amer. Chem. Soc.* **74**, 4223 (1952).

TABLE 2 (*contd.*)

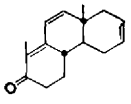
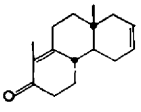
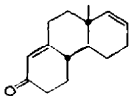
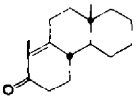
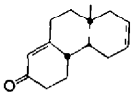
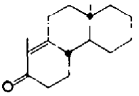
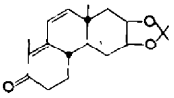
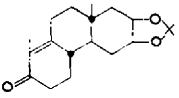
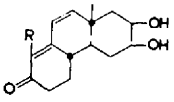
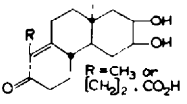
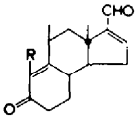
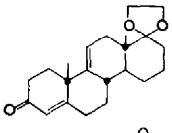
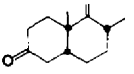
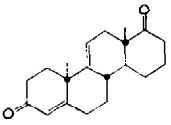
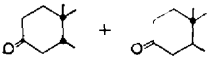
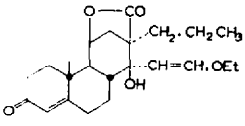
Compound	Conditions	Double bond reduced at	Ref.
(*allo*) 3β-acetoxy, 20-one, 9(11):16-diene	Pd/C, EtOAc	16	55
1β:3β-dihydroxy, 20-one, 5:16-diene	Pd/C, EtOAc	16	56
3β-acetoxy, 6-methyl, 20-one 5:16-diene	Pd/$CaCO_3$, MeOH	16	57
3β-acetoxy, 12:20-dione, 5:16-diene	Pd/$BaSO_4$, EtOAc, 45°	16	58
3β-acetoxy, 12:20-dione, 5:16-diene	Pt, HOAc	5, 16	59
21-acetoxy, 3-ethylenedioxy, 20-one, 18β → 11β-lactone, 5:16-diene	Pd/$CaCO_3$, EtOH	16	60
Ergostane derivatives			
3β-acetoxy, 7-one, 8(9):22(23)-diene	Pd/C, EtOAc	22	37
3β-acetoxy, 7:11-dione, 5:22(23)-diene	Pd/C, HOAc	5, 22	37
3β-acetoxy, 5α-hydroxy, 6-one, 7:22(23)-diene	Pd/C, dioxan, EtOH	22	44
3-one, 4:6:22(23)-triene [*iso*ergosterone]	Pd/$SrCO_3$, benz.	6	61
3-one, 4:6:22(23)-triene [*iso*ergosterone]	Pd/C, KOH, EtOH	4, 6 (A/B *cis*)	61, 62
3-one, 4:6:22(23)-triene [*iso*ergosterone]	Pd/C, KOH, EtOH (smaller concentration of OH^-)	6	62, 63
[3-one, 4:6:22(23)-triene [*iso*ergosterone]	Li/NH_3, MeOH	6	62]
3β-acetoxy, 7-one, 5:8(9):22(23)-triene	RaNi, EtOAc	5, 22	37
3β-acetoxy, 7-one, 5:8(9):22(23)-triene	Pd/C, EtOAc, HOAc	5, 8, 22	37
[3β-acetoxy, 7:11-dione, 8(9):22(23)-diene	Zn, HOAc	8	64]
3β-acetoxy, 7-one, 5:9(11):22(23)-triene	Pd/C, HOAc	5, 22	37
3β-acetoxy, 5α-hydroxy, 6-one, 7:14:22(23)-triene	Pd/$CaCO_3$, benz.	14, 22	44
3β-acetoxy, 5α-hydroxy, 6-one, 7:9(11):22(23)-triene	Pd/$CaCO_3$, benz.	9, 22	44
[3β:5α-diol, 6-one, 7:9(11):22(23)-triene	Li/NH_3	7, 9, 6-one → 6α-hydroxy 5α-hydroxy → 5α-H	44]
22a-*Spirostane derivatives*			
3-one, 4:7-diene	Pd, dioxan, KOH	4 (A/B *cis*)	53
3-one, 4:7:9(11)-triene	Pd, EtOH, KOH	4 (A/B *cis*)	65
3-one, 4:6:8(9)-triene	Pd, EtOH, KOH	4, 6 (A/B *cis*)	66
Synthetic intermediates		*Product*	
	Pd/$SrCO_3$, *i*-PrOH, NaOH		47

TABLE 2 (*contd.*)

Compound	Conditions	Double bond reduced at	Ref.
	Pd, EtOAc		49
	Pd, EtOAc		49
	$Pd/SrCO_3$, Benz.		50
	$Pd/SrCO_3$, *i*-PrOH, NaOH		48
	$Pd/SrCO_3$, *i*-PrOH,		48
	Pd, KOH		67
	Pd, KOH		67
	Pd, EtOH, Py		60

[51] F. Neumann, O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **77**, 5676 (1955).
[52] A. Bowers, H. J. Ringold and R. I. Dorfman, *J. Amer. Chem. Soc.* **79**, 4556 (1957).
[53] M. Velasco, J. Rivera, G. Rosenkranz, F. Sondheimer and C. Djerassi, *J. Org. Chem.* **18**, 92 (1953).
[54] C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.* **16**, 754 (1951).
[55] C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.* **16**, 1278 (1951).
[56] H. Lapin, *Bull. Soc. Chim.* 1501 (1957).
[57] D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4092 (1957).
[58] R. E. Marker, *J. Amer. Chem. Soc.* **71**, 2656 (1949).
[59] H. A. Walens, S. Serota and M. E. Wall, *J. Org. Chem.* **22**, 182 (1957).
[60] A. Lardon, O. Schindler and T. Reichstein, *Helv. Chim. Acta* **40**, 666 (1957).
[61] F. Johnson, G. T. Newbold and F. S. Spring, *J. Chem. Soc.* 1302 (1954).
[62] A. F. Daglish, J. Green and V. D. Poole, *J. Chem. Soc.* 2627 (1954).
[63] D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, J. E. Stafford, R. L. Pederson and A. C. Ott, *J. Amer. Chem. Soc.* **77**, 1212 (1955).
[64] E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *J. Amer. Chem. Soc.* **75**, 3477 (1953).
[65] R. Yashin, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **73**, 4654 (1951).
[66] C. Djerassi, R. Yashin and G. Rosenkranz, *J. Amer. Chem. Soc.* **74**, 422 (1952).
[67] P. Wieland, H. Ueberwasser, G. Anner and K. Miescher, *Helv. Chim. Acta* **36**, 1231 (1953).

(c) *Compounds containing acetylenic linkages.* It seems to be possible to effect partial or even total saturation of an 17-ethinyl group[3] before a 4-ene 3-ketone group is reduced. The opposite result can be achieved by metal/ammonia reduction, in which the ethinyl group is protected by its metal derivative. (Table 3.)

TABLE 3. EXAMPLES

Compound	Conditions	Group reduced	Ref.
17β-Hydroxy 3-keto 17α-ethinyl androst-4-ene	$Pd/CaCO_3$, Py	17-ethinyl [→ vinyl]	3
17β-Hydroxy 3-keto 17α-ethinyl 19-*nor*androst-4-ene	$Pd/CaCO_3$, Py	17-ethinyl [→ vinyl]	68
17β-Hydroxy 3-keto 17α-ethinyl androst-4-ene	Pd/C, dioxan	17-ethinyl [→ ethyl]	3
17β-Hydroxy 3-keto 17α-ethinyl androst-4-ene	Li/NH_3	4-ene (A/B *trans*)	52
3β-Acetoxy 17β-hydroxy 17α-ethoxyethinyl androst-5-ene	$Pd/CaCO_3$, Py	17-ethoxyethinyl [→ ethoxyvinyl]	69

(d) *Miscellaneous selective catalytic hydrogenations.* Catalytic reduction of the double bond in a Δ^4-3-ketone can be avoided by formation of its ethylene glycol ketal and resulting shift of the double bond to the 5-position,[70] for example in the catalytic debromination of a 16β:17α-bromohydrin.[71] On the other hand a Δ^4-3-ketone can be reduced catalytically to the saturated ketone (Pd, dioxan, KOH; A/B-*cis*) without affecting a 16:17α-epoxide;[72] the latter can be hydrogenolysed without saturation of an isolated double bond with sodium and an alcohol.[73]

A double bond at position 5 is unaffected during catalytic hydrogenolysis (Pd/C EtOH) of a 16α-benzyloxy group.[74]

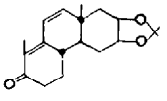
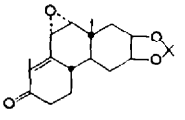
The selective catalytic hydrogenation of the γ-δ double bond in α:β:γ:δ doubly unsaturated ketones[47,48,50,61–62] is paralleled by the selective hydrogenolysis of the epoxide ring in an α-β-unsaturated γ:δ-epoxy ketone ($Pd/SrCO_3$, *i*-PrOH, KOH; or Zn, HOAc).[75]

II. *Selective epoxidation of double bonds*

Many examples of selective epoxidation have been described, particularly in work on compounds related to ergosterol in connexion with the introduction of an 11-oxygen function. The often complicated reactions attendant on and subsequent to epoxidation of 7:9(11)-dienes (with both mild and strong peracids) have been adequately reviewed.[76,77,81] Outstanding features, however, are: (i) the resistance of

[68] A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* 77, 148 (1955).
[69] H. Heusser, K. Eichenberger and P. A. Plattner, *Helv. Chim. Acta* 33, 370 (1950).
[70] E. Fernholz and H. E. Stavely, *Abstracts ACS* 102nd meeting, p. 39M (1941).
[71] E. S. Rothman and M. E. Wall, *J. Amer. Chem. Soc.* 78, 1744 (1956).
[72] A. Ercoli and P. de Ruggieri, *Gazz.* 85, 1304 (1955).
[73] B. Camerino and C. G. Alberti, *Gazz.* 85, 56 (1955).
[74] H. Hirschmann, F. B. Hirschmann and J. W. Corcoran, *J. Org. Chem.* 20, 572 (1955).
[75] W. S. Knowles and Q. E. Thompson, *J. Amer. Chem. Soc.* 79, 3212 (1957).
[76] J. W. Cornforth, *Ann. Rep. Chem. Soc.* 224 (1953).
[77] W. Klyne, *Ann. Rep. Chem. Soc.* 230–233 (1954).

TABLE 4. EXAMPLES

Compound	Conditions	Product	Ref.
Ergostane derivatives			
3:5-*cyclo*, 8(14):22-diene	Excess perbenz.	8:14α-epoxide	1
3β:5α-diacetoxy, 7:9(11)-diene	Perphthal., Et_2O 1·1 mol	9:11α-epoxide	78
3β:5α-diacetoxy, 7:9(11)-diene	Perform.	7:8α, 9:11α-diepoxide	78
3β-acetoxy, 7-one, 9(11):22-diene	Perphthal.,	9:11α-epoxide	37
3β-acetoxy, 5:7:22(23)-triene [ergosteryl acetate]	Perbenz. or perphthal:	complex mixture	87, 88
3β-acetoxy, 7:9(11):22-triene	Perbenz. or perphthal.	(successively): 9:11α-mono, 7:8α, 9:11α-di and 7:8α, 9:11α, 22:23-triepoxide	89 64, 90, 91
3β-5α-diol, 7:9(11):22(23)-triene	Perphthal.	9:11α-epoxide	92
3β-acetoxy, 5α-ol, 6-one, 7:14:22(23)-triene	Perphthal.	14:15-epoxide [low yd.]	44
3β:5α-diol, 6-one, 7:9(11):22(23)-triene	Perphthal.	9:11α- 22:23-diepoxide	44
Other compounds			
3β-Acetoxy 20-keto *allo*pregna-7:9(11)-diene	Perform.	9:11α-epoxy 7-ketone [no attack on 20-ketone]	78 93
Methyl 3α-acetoxy chola-7:9(11)-dienate	Perphthal.	9:11α-epoxide	90
Methyl 3β-acetoxy allochola-6:9(11)-dienate 5:8α-maleic ester adduct	Perphthal.	9:11α-epoxide	94
3β:5α:22-Triacetoxy bisnorchola-7:9(11):20(22)-triene	Perphthal.	9:11α-epoxide	78
3β-Acetoxy, 5α-hydroxy *allo*-spirosta-7:9(11)-diene	Perphthal.	(successively) 9:11α-epoxide and 7:8α, 9:11α-diepoxide	95
Carbonyl conjugated double bonds			
17-Formyl 3:11-diketo androsta-4:16-diene	H_2O_2, NaOH MeOH	16:17α-epoxide	80
17-Formyl 3-keto androsta-4:9(11):16-triene	H_2O_2, NaOH, MeOH	16:17α-epoxide	80
	Perphthal.		75
Enol acetates			
20-Acetoxy 3-keto-pregna-4:17(20)-diene	Perbenz.	17α-Hydroxy pregn-4-ene 3:20-dione	96
3β:11:20-Triacetoxy pregna-9(11):17(20)-diene	Perbenz.	17α-ol-20-one	82
3:20-Diacetoxy pregna-3:5:20(21)-triene	Perbenz. (1 mole)	*allo*pregnane 3:6:20-trione	84
3:20-Diacetoxy pregna-3:5:20(21)-triene	Perbenz. (2 moles)	17α-hydroxy *allo*-pregnane 3:6:20-trione	84

the 22(23)-double bond to epoxidation, and (ii) the initial formation of the 9:11α-epoxide from 7:9(11)-dienes in both A/B-*cis*- and A/B-*trans*-steroids (even in the case of a 7:9(11):20(22)-trien-22-ol acetate).[78] Examples have been chosen from cases where additional functional groups might be liable to introduce a complicating factor.

Carbonyl-conjugated double bonds are generally unaffected by electrophilic epoxidation (exception[79]), but can be epoxidised with hydrogen peroxide and alkali. It appears possible in this to differentiate between a ketone-conjugated and aldehyde-conjugated double bond,[80] the latter being more easily attacked.

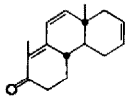
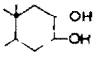
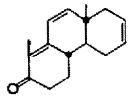
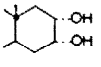
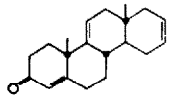
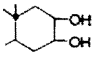
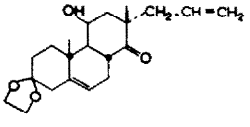
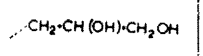
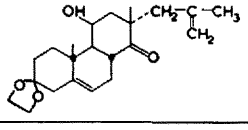
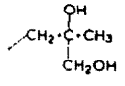
Some detailed work has been done on the selective epoxidation of compounds containing several enol acetate groupings in connexion with the introduction of the cortical side chain,[77,81] particularly such as are derived from pregnane-[82] and *allo*-pregnane-11:20-diones.[83] Of special interest are: (i) the selective epoxidation at Δ^{16} of 16:20(21)-dien-20-ol acetates,[84] (ii) the reaction of 3:5-dien-3-ol acetates with peracids[85] and (iii) the differential behaviour of 20:21-epoxy- and of 17:20-epoxy-20-ol acetates on heating or chromatography on silica.[86] (Table 4.)

III. *Selective hydroxylation of double bonds*

Work in this field has concentrated mainly on the hydroxylation of double bonds at C_{16} and $C_{17(20)}$, in connexion with the construction of the cortical side chain. The C_5-double bond appears to be relatively inert to the reagents generally used (osmium tetroxide or potassium permanganate), however ergosterol can be selectively hydroxylated to give a 5:6-glycol.[88] As with epoxidation, attack of hydroxylating agents is generally from the "rear" of the steroid molecule, but of interest in this connexion are: (i) the "front attack" of osmium tetroxide on a Δ^5-3-glycol ketal to give the 5β-6β-glycol[97] and on Δ^3-cholenic acid to give the 3β:4β-diol,[165] and (ii) the different *cis*-glycols obtained by the action of osmium tetroxide and the Prévost reagent (silver acetate and iodine in wet acetic acid).[47,50,98]

[78] P. Bladon, H. B. Henbest, E. R. H. Jones, G. W. Wood, D. C. Eaton and A. A. Wagland, *J. Chem. Soc.* 2916 (1953).
[79] P. L. Julian, E. W. Meyer and I. Ryden, *J. Amer. Chem. Soc.* **72**, 367 (1950).
[80] L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, *J. Amer. Chem. Soc.* **76**, 5017 (1954).
[81] G. Rosenkranz and F. Sondheimer, *Fortschr. Chem. Org. Naturstoffe* **10**, 274, Springer, Vienna (1953).
[82] T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *J. Amer. Chem. Soc.* **74**, 483 (1952).
[83] D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones and T. Walker, *J. Chem. Soc.* 747 (1954).
[84] R. B. Moffett and G. Slomp, *J. Amer. Chem. Soc.* **76**, 3678 (1954).
[85] J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.* **19**, 1509 (1954).
[86] A. H. Soloway, W. J. Considine, D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **76**, 2941 (1954).
[87] G. H. Alt and D. H. R. Barton, *J. Chem. Soc.* 1356 (1954).
[88] M. Fieser, A. Quilico, A. Nickon, W. E. Rosen, E. J. Tarlton and L. F. Fieser, *J. Amer. Chem. Soc.* **75**, 4066 (1953).
[89] E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *J. Amer. Chem. Soc.* **73**, 2396 (1951).
[90] H. Heusser, K. Eichenberger, P. Kurath, H. R. Daellenbach and O. Jeger, *Helv. Chim. Acta* **34**, 2106, (1951).
[91] H. H. Inhoffen and W. Mengel, *Chem. Ber.* **87**, 146 (1954).
[92] D. C. Burke, J. H. Turnbull and W. Wilson, *J. Chem. Soc.* 3237 (1953).
[93] C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *J. Amer. Chem. Soc.* **73**, 4496 (1951).
[94] R. H. Levin, M. M. Wesner and E. M. Meinzer, *J. Amer. Chem. Soc.* **70**, 2834 (1948).
[95] C. Djerassi, A. J. Lemin, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 2346 (1954).
[96] C. Djerassi, J. Grossman and G. H. Thomas, *J. Amer. Chem. Soc.* **77**, 3826 (1955).
[97] S. Bernstein, W. S. Allen, C. E. Linden and J. Clementi, *J. Amer. Chem. Soc.* **77**, 6612 (1955).
[98] H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.* **78**, 3749 (1956).

TABLE 5. EXAMPLES

Compound	Reagent	Product	Ref.
Pregnane derivatives			
3β-acetoxy, 20-one, 5:16-diene	OsO_4	16:17α-diol [osmate could be rearranged to D-homosteroid]	101
3β-acetoxy, 20-one, 5:16-diene	$KMnO_4$, acetone, HOAc	16:17α-diol	102
21-acetoxy 3-one, 4:17(20)-diene	H_2O_2, trace of OsO_4	20-one 17α-ol	103
3:20-dione, 4:16-diene	OsO_4	16:17α-diol	101
3β:21-diacetoxy, 20-one, 5:16-diene	$KMnO_4$, acetone, HOAc	16:17α-diol	104
3β:21-diacetoxy, 20-cyano, 5:17(20)-diene	$KMnO_4$, acetone, HOAc	20-one-17α-ol and further oxidation products	105
21-acetoxy, 3-one, 20-cyano, 9(11):17(20)-diene	OsO_4	20-one-17α-ol	106
		[In the corresp. *allo* compound, $\Delta^{9(11)}$ is also attacked]	107
21-acetoxy, 3-ethylenedioxy, 11-one, 20-cyano, 5:17(20)-diene	$KMnO_4$, acetone, piperidine	20-one-17α-ol	108
21-acetoxy, 3:20-dione, 5:9(11):16-triene	OsO_4	16:17α-diol [HOBr was then added to $\Delta^{9(11)}$]	109
21-acetoxy, 11β-ol, 3-one, 4:17(20)-diene	phenyl iodosoacetate OsO_4	20-one-17α-ol	110, 111
Other compounds			
Ergosterol	$KMnO_4$, methyl cyclohexane, water, 90–100°	5:6α-diol	88
	Silver acetate, iodine, HOAc, H_2O		48
	OsO_4		50
	Silver acetate, iodine HOAc, H_2O		47
	OsO_4		112
	OsO_4		113

Double bonds at the 9(11)-position are inert in A/B-*cis*-steroids[99] and in 5α:8α-epidioxyergostane derivatives,[100] but are hydroxylated in the A/B-*trans*-series, as is observed with epoxidation and electrophilic attack in general. (Table 5.)

IV. *Selective ozonisation of double bonds*

In contrast to peracids and hydrogen in the presence of catalysts, ozone will in most cases attack specifically a side chain, as against a cyclic, double bond. This applies both to isolated and enol acetate double bonds. Selectivity, and improved yields of resulting side chain aldehydes and -ketones have been found to be enhanced considerably by the presence of pyridine[63,114,115] and by conducting the ozonisation at as low a temperature as possible.[62,78,115,116] (Table 6.)

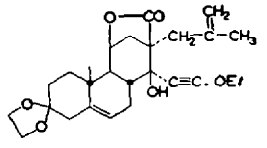
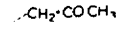
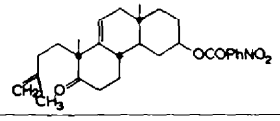
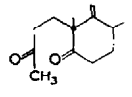
B. MODIFICATION OF DOUBLE BONDS

I. *By halogen addition*

It appears that bromine or chlorine addition to double bonds (for protection against oxidation) does not always differentiate between isolated nuclear and side chain double bonds, at least in compounds related to ergosterol, even though the selective addition of these reagents,[120] as well as of hydrogen chloride[121] to the C_5 double bond in stigmasterol has been reported. However, it seems that regeneration of double bonds from their dihalides is more selective. It has been shown[122,123] that sodium iodide (in acetone) will regenerate a nuclear double bond from its dibromide, leaving a 22:23-dihalide, from which the double bond is regenerated only with zinc in acetic acid. 22:23-Dihalides are stable also to catalytic hydrogenation conditions,[15] though not in the presence of alkali.[124]

[99] D. Gould, E. L. Shapiro, H. L. Herzog, M. J. Gentles, E. B. Hershberg, W. Charney, M. Gilmore, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *J. Amer. Chem. Soc.* **79**, 502 (1957).
[100] R. B. Clayton, A. Crawshaw, H. B. Henbest, E. R. H. Jones, B. J. Lovell and G. W. Wood, *J. Chem. Soc.* 2009 (1953).
[101] G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.* 4377 (1955).
[102] G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.* 4373 (1955).
[103] K. Miescher and J. Schmidlin, *Helv. Chim. Acta* **33**, 1840 (1950).
[104] B. Ellis, F. Hartley, V. Petrow and D. Wedlake, *J. Chem. Soc.* 4383 (1955).
[105] J. Heer and K. Miescher, *Helv. Chim. Acta* **34**, 259 (1951).
[106] R. P. Graber, A. C. Haven and N. L. Wendler, *J. Amer. Chem. Soc.* **75**, 4722 (1953).
[107] R. Hirschmann, C. S. Snoddy and N. L. Wendler, *J. Amer. Chem. Soc.* **75**, 3252 (1953).
[108] G. I. Poos, R. M. Lukes, G. E. Arth and L. H. Sarett, *J. Amer. Chem. Soc.* **76**, 5031 (1954).
[109] S. Bernstein, R. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *J. Amer. Chem. Soc.* **78**, 5693 (1956).
[110] J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson, *J. Amer. Chem. Soc.* **77**, 4436 (1955).
[111] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *J. Amer. Chem. Soc.* **78**, 6213 (1956).
[112] G. I. Poos and L. H. Sarett, *J. Amer. Chem. Soc.* **78**, 4100 (1956).
[113] L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth, *J. Amer. Chem. Soc.* **75**, 2112 (1953).
[114] J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta* **40**, 1438 (1957).
[115] G. Slomp and J. L. Johnson, *Abstracts ACS* 129th meeting, 30N (1956).
[116] P. Bladon, H. B. Henbest, E. R. H. Jones, G. W. Wood and G. F. Woods, *J. Chem. Soc.* 4890 (1952).
[117] R. B. Moffett and D. I. Weisblatt, *J. Amer. Chem. Soc.* **74**, 2183 (1952).
[118] F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.* **72**, 2617 (1950)
[119] G. Stork, H. J. E. Loewenthal and P. C. Mukerdji, *J. Amer. Chem. Soc.* **78**, 501 (1956).
[119a] D. H. Hey, J. Honeyman and W. J. Peal, *J. Chem. Soc.* 2881 (1950).
[120] H. Q. Smith and E. S. Wallis, *J. Org. Chem.* **19**, 1628 (1954).
[121] E. M. Chamberlin, E. Tristram, T. Utne and J. M. Chemerda, *J. Amer. Chem. Soc.* **79**, 456 (1957).
[122] J. A. McEwan and F. S. Spring, *J. Chem. Soc.* 3646 (1952).
[123] J. Paterson and F. S. Spring, *J. Chem. Soc.* 325 (1954).
[124] R. Budziarek, R. Stevenson and F. S. Spring, *J. Chem. Soc.* 4874 (1952).

TABLE 6. EXAMPLES

Compound	Conditions	Product	Ref.
Fucosterol		24-ketocholesterol	119a
Stigmasta-4:22-dien-3-one	Py (1 mole), methylene chloride, −78°	side chain aldehyde	115
Ergosta-4:22-dien-3-one	methylene chloride, Py −70°	side chain aldehyde	63
Ergosta-6:9(11):22-triene, 5:8-maleic anhydride	2 equivs. O_3	side chain acid	94
3β:5α-Diacetoxy 9:11α-epoxy ergosta-7:22-diene	EtOAc, −70°	side chain aldehyde	78
3β-Acetoxy 5:8α-epidioxy- ergosta-9(11):22-diene	EtOAc, −70°	side chain aldehyde and -acid	116
Enol acetates			
3β:21-Diacetoxy pregna-6:9(11):20(21):triene 5:8-maleic ester adduct	Methylene chloride	17-carboxylic acid	117
Mixture of enol acetates from 3-keto bisnorchol-4-en-22-al	$CHCl_3$	Progesterone	118
Enol acetate of			
3β:5α-Diacetoxy 9:11α-epoxy bisnorchol-7-en-22-al	EtOAc, −70°	20-ketone	78
3β-Acetoxy 5:8α-epidioxy bisnorchol-9(11)-en-22-al	EtOAc, −70°	20-ketone	116
3β-Acetoxy bisnorchol-5-en-22-al	$CHCl_3$	20-ketone	118
Miscellaneous			
	Py, $CHCl_3$		114
	Methylene chloride, −20°		119

Complications may ensue in the presence of ketone or α:β-unsaturated ketone groups. A carbonyl-conjugated double bond adds bromine less readily than an isolated double bond, especially in the presence of acetate ion,[105,125–128] but in the presence of a saturated 20-ketone α-keto bromination appears to be unavoidable.[120,130]

[125] R. K. Callow and D. A. H. Taylor, *J. Chem. Soc.* 2299 (1952).
[126] H. Heusser, E. V. Jensen, N. Frick and P. A. Plattner, *Helv. Chim. Acta* **32**, 1326 (1949).
[127] H. H. Inhoffen, F. Blomeyer and K. Brueckner, *Chem. Ber.* **87**, 593 (1954).
[128] B. Loeken, S. Kaufmann, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 1738 (1956).
[129] P. L. Julian and W. J. Karpel, *J. Amer. Chem. Soc.* **72**, 362 (1950).
[130] J. Romo and A. Romo de Vivar, *J. Amer. Chem. Soc.* **79**, 1118 (1957).

II. *By other methods*

Reversible 3:5-*cyclo*steroid formation, applicable to 5-ene-3-ols, has been used occasionally to protect both the 3β-hydroxy group and the C_5-double bond against oxidation and epoxidation, usually in the form of 6-methoxy *i*-steroids.[57,79,131–134]

Nitration of the C_5-double bond in stigmasterol has been used for its protection during ozonolysis of the side chain double bond; the nitroethylene group was subsequently reduced to the 6-ketone.[120]

It has been suggested[98] that a suitable form of protection of a double bond might be the diester or acetonide of a *cis*-glycol, which may be reconverted to the olefin by treating its ditosylate or dimesylate with sodium iodide. This sequence has been employed in 2:3-dihydroxysapogenins,[98,135–137] where it appears that the last step is applicable to the dimesylates of 2α:3α- and 2α:3β-diols, but not 2β:3β- or 2β:3α-diols.[98]

The double bond in α:β-unsaturated ketones can be protected as the epoxide (formed with hydrogen peroxide and alkali) from which its regeneration is possible by mild reduction with chromous ion.[138] The possibility of protecting other types of double bonds as epoxides and their regeneration by reaction with triphenylphosphine[139] is attractive but as yet unexplored.

C. SELECTIVE REACTIONS OF CARBONYL GROUPS

I. *Selective reduction*

The order of selective reduction of steroid ketones by metal hydrides, in particular sodium borohydride, has been summarised and exemplified by a number of authors.[140–142] It is stated to be: 3- > 17- or 20- > Δ^4-3- > 11-ketones, both in A/B-*cis*- and A/B-*trans*-steroids. It has been pointed out that this order is paralleled by that of decreasing oxidation potentials of simple alicyclic analogues of such ketones.[141]

However, a relatively minor change in general stereochemistry may affect this sequence: the selective sodium borohydride reduction of 8-*iso*androst-4-ene 3:17-dione was unsuccessful.[143]

Selectivity in reductions with borohydrides appears to be substantially increased in the presence of pyridine.[72,142,144,145]

Catalytic reduction, at any rate with nickel catalysts, appears to follow the same order as with borohydrides, though selectivity is generally less and dependent on the

[131] D. H. Hey, J. Honeyman and W. J. Peal, *J. Chem. Soc.* 4836 (1952).
[132] P. L. Julian, E. W. Meyer and H. C. Printy, *J. Amer. Chem. Soc.* **70**, 887 (1948).
[133] W. J. Peal, *J. Chem. Soc.* 3801 (1957).
[134] B. Riegel, E. W. Meyer and J. Beiswanger, *J. Amer. Chem. Soc.* **65**, 325 (1943).
[135] C. Djerassi and J. Fishman, *J. Amer. Chem. Soc.* **77**, 4291 (1955).
[136] C. Djerassi, T. T. Grossnickle and L. B. High, *J. Amer. Chem. Soc.* **78**, 3166 (1956).
[137] N. L. Wendler, H. L. Slates and M. Tishler, *J. Amer. Chem. Soc.* **74**, 4894 (1952).
[138] W. Cole and P. L. Julian, *J. Org. Chem.* **19**, 131 (1954).
[139] G. Wittig, *Experientia* **12**, 41 (1956).
[140] E. Elisberg, H. van der Haeghe and T. F. Gallagher, *J. Amer. Chem. Soc.* **74**, 2814 (1952).
[141] J. K. Norymberski and G. F. Woods, *J. Chem. Soc.* 3426 (1955).
[142] A. H. Soloway, A. S. Deutsch and T. F. Gallagher, *J. Amer. Chem. Soc.* **75**, 2356 (1953).
[143] C. Djerassi, H. Bendas and A. Segaloff, *J. Org. Chem.* **21**, 1056 (1956).
[144] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 1286 (1953).
[145] O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **74**, 3711 (1952).

state of the catalyst.[146] Platinum or palladium catalysts seem to have been employed only when one of the ketone groups is highly hindered, this is illustrated by some interesting work on tricyclic intermediates.[147,148] Meerwein-Ponndorf reduction appears to affect only saturated and unhindered ketones.[149,150] Wolff-Kischner reduction reduces all except 11-ketones under the ordinary Huang-Minlon conditions;[89,151–153] the 11-keto group can be reduced by a special procedure involving a completely anhydrous environment.[154]

The stereospecificity of the reduction of ketones to alcohols has been studied in detail. An earlier review[149] has generalised that with metal hydrides an unhindered ketone gives the equatorial and a hindered ketone the axial alcohol; Meerwein-Ponndorf reduction yields a larger proportion of the axial epimer,[155,156] while catalytic reduction gives the axial alcohol in acidic and the equatorial alcohol in neutral or basic media. Later work has led to the following conclusions: Reduction with sodium borohydride follows "steric control" to give a greater proportion of the axial epimer (in this connexion the formation of the 7α-alcohol from 7-keto cholanic acid[157] is of interest), while with lithium aluminium hydride "product control" giving the equatorial epimer predominates.[158] A comparison of products obtained by lithium aluminium hydride and catalytic reduction has also been made: with 4-, 6-, 7- and 11-ketones the same epimer ratio is obtained by both methods; with 2-, 3-, or 12-ketones it may vary according to the method used.[159]

11-Ketones on reduction with metal hydrides give mainly the 11β-(axial)alcohol,[160] though with lithium borohydride some of the 11α-epimer is formed;[161] this is given preponderantly on reduction with sodium and alcohols or with alkali metals and liquid ammonia in the presence of a proton donor.[160,162,163] From 20-ketones the 20β-alcohol is the main product of reduction by nearly all methods; the 20α-epimer is obtained on reduction of Δ^{16}-20-ketones or 16α:17α-epoxy-20-ketones with sodium and alcohols or with lithium aluminium hydride.[164]

In the borohydride reduction of keto esters in alcoholic solution ester exchange is always a possibility.[165] (Table 7.)

II. *Selective enol acetate formation*

Enol acetylation affects mainly α:β-unsaturated and unhindered ketones, roughly in that order. A further degree of selectivity is provided by the use of different

[146] C. Djerassi, A. J. Manson and M. Gorman, *J. Amer. Chem. Soc.* **77**, 4925 (1955).
[147] P. A. Robins and J. Walker, *J. Chem. Soc.* 642 (1952).
[148] P. A. Robins and J. Walker, *J. Chem. Soc.* 3960 (1954).
[149] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).
[150] P. Wieland, H. Ueberwasser, G. Anner and K. Miescher, *Helv. Chim. Acta* **36**, 376 (1953).
[151] L. F. Fieser, W. Huang and J. C. Babcock, *J. Amer. Chem. Soc.* **75**, 116 (1953).
[152] Huang-Minlon, *J. Amer. Chem. Soc.* **71**, 3301 (1949).
[153] F. Sondheimer, E. Batres and G. Rosenkranz, *J. Org. Chem.* **22**, 1090 (1957).
[154] D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.* 2056 (1955).
[155] J. Elks and G. H. Phillips, *J. Chem. Soc.* 4320 (1956).
[156] H. R. Nace and G. L. O'Connor, *J. Amer. Chem. Soc.* **73**, 5824 (1951).
[157] E. H. Mosbach, W. Meyer and F. E. Kendall, *J. Amer. Chem. Soc.* **76**, 5799 (1954).
[158] W. G. Dauben, E. J. Blanz, J. Jiu and R. A. Micheli, *J. Amer. Chem. Soc.* **78**, 3752 (1956).
[159] W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Amer. Chem. Soc.* **78**, 2579 (1956).
[160] F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **75**, 1282 (1953).
[161] E. P. Oliveto, C. Gerold and E. B. Hershberg, *J. Amer. Chem. Soc.* **76**, 6111 (1954).
[162] H. L. Herzog, M. Jevnik and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 269 (1953).
[163] H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, *J. Amer. Chem. Soc.* **74**, 4470 (1952).
[164] E. L. Shapiro, D. Gould and E. B. Hershberg, *J. Amer. Chem. Soc.* **77**, 2912 (1955).
[165] K. Yamasaki, V. Rosnati, M. Fieser and L. F. Fieser, *J. Amer. Chem. Soc.* **77**, 3308 (1955).

TABLE 7. EXAMPLES

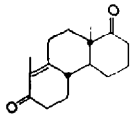
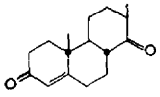
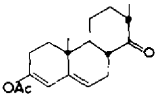
Functional groups	Method	Product	Ref.
Androstane derivatives			
3:17-dione	$NaBH_4$	3β-ol	140
5β-H, 3:17-dione	$NaBH_4$	3α-ol	140
3:17-dione	Deactivated RaNi	3α-(50%) and 3β-(34%) ol	146
5β-H, 3-ethylenedioxy, 11:17-dione	Pt, Py	17β-ol	166
Pregnane derivatives			
(*allo*) 3:20-dione	$NaBH_4$/Py	3β-ol	142
3:20-dione	$NaBH_4$	3α-ol	4
3α-acetoxy, 11:20-dione	Pt	20β-ol	168 169
3α-hydroxy, 11:20-dione	Pt	20-ol (both epimers)	170
(*allo*) 20β-acetoxy, 3:16-dione	Pt	3β-ol	171
11α-acetoxy, 3:20-dione	$NaBH_4$	3α-ol [kinetics studied]	172
3α:17α-diol, 11:20-dione	Pt, Py	20β-ol	166
3α-acetoxy, 17α-ol, 11:20-dione	Pt, HOAc	20β-ol	173
3α:17α-diol, 11:20-dione	$NaBH_4$	20β-ol	174
3β:17β-diol, 11:20-dione	$NaBH_4$, reflux	11β:20β-diol	174
3α-ol, 21-benzylidene, 11:20-dione	KBH_4	3α:20β-diol	161
3α-ol, 21-benzylidene, 11:20-dione	$LiBH_4$	3α:11β:20α-triol and 3α:11α:20α-triol	161
3α-ol, 21-benzylidene, 11:20-dione	$LiAlH_4$	21-benzyl 3α:11β:20α-triol	161
(*allo*) 11β:17α-diol, 21-acetoxy, 3:20-dione	RaNi, dioxan	3β-ol	42
3:11:20-trione	$NaBH_4$, Py	3α-ol	142, 144, 145
3:11:20-trione	$NaBH_4$, EtOH	3α-20β-diol	145
(*allo*) 3:11:20-trione	RaNi	3β-ol	175, 176
(*allo*) 3:11:20-trione	$NaBH_4$, Py	3β-ol	142
17α-ol, 3:11:20-trione	$NaBH_4$, aq. Py	3α-ol	72
21-acetoxy, 17α-ol, 1:4-diene, 3:11:20-trione	$NaBH_4$	20β-ol	177
Other compounds			
3β-Acetoxyergosta-22-ene 7:11-dione	Meerwein-Ponndorf	7β-ol	155
3β-Acetoxyergosta-22-ene 7:11-dione	Alc. KOH	7α-ol	155
Allo-22a-Spirost-8(9)-ene 3:7:11-trione	RaNi	3β-ol	178
Synthetic intermediates			
	Meerwein-Ponndorf		179
	$LiAlH_4$ (on enol ether of unsatd. ketone)		150

TABLE 8. EXAMPLES

Functional groups	Conditions	Product	Ref.
Pregnane derivatives			
3α-ol, 11:20-dione	Ac_2O, sulphosalicylic acid, toluene, 12 hr	17(20)-ene, 3:20-diacetate	184
3α-ol 11:20-dione	Ac_2O, sulphosalicylic acid, toluene, 25 min	3α-acetate only	184
3α-ol, 11:20-dione	Ac_2O, TsOH, no solvent	9(11):17(20)-diene 3α:11:20-triacetate	184 185, 186
(*allo*) 3β-acetoxy, 11:20-dione	Ac_2O, CCl_4, $HClO_4$	17(20)-ene 20-acetate	83
3β-acetoxy, 8(9)-ene, 7:20-dione	*iso*Propenyl acetate, TsOH, Benz.	7(8):9(11)-diene 7-acetate	187
(*allo*) 21-acetoxy, 17α-ol, 3:20-dione	Ac_2O, sulphosalicyclic acid, toluene	2-ene 3-acetate	188
21-acetoxy, 17α-ol, 3:11:20-trione	Ac_2O, sulphosalicyclic acid, toluene	3-ene 3-acetate	188
Other compounds			
Methyl 3α-acetoxy 7:12-diketo cholanate	Ac_2O, TsOH	6-ene 7-acetate	181, 182
3β-acetoxy 11-oxo bisnor*allo*cholanal	Ac_2O, NaOAc	20(22)-ene 22-acetate	180
3β-acetoxy 11-oxo bisnor*allo*cholanal	Ac_2O, $HClO_4$, CCl_4	(aldehyde diacetate)	180
Bisnorcholan-22-al-3-one	Ac_2O, NaOAc	20(22)-ene 20-acetate	62
	AcCl, Ac_2O		189

[166] H. L. Herzog, M. Jevnik, P. L. Perlman, A. Nobile and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 266 (1953).
[168] D. K. Fukushima, A. D. Kemp, R. Schneider, M. B. Stokem and T. F. Gallagher, *J. Biol. Chem.* **210**, 129 (1954).
[169] L. H. Sarett, *J. Amer. Chem. Soc.* **70**, 1690 (1948).
[170] S. Liebermann, D. K. Fukushima and K. Dobriner, *J. Biol. Chem.* **182**, 299 (1950).
[171] H. Hirschmann, F. B. Hirschmann and M. A. Daus, *J. Biol. Chem.* **178**, 751 (1949).
[172] E. R. Garett and D. A. Little, *J. Amer. Chem. Soc.* **75**, 6051 (1953).
[173] M. Finkelstein, J. von Euw and T. Reichstein, *Helv. Chim. Acta* **36**, 1266 (1953).
[174] E. P. Oliveto and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 488 (1953).
[175] C. Djerassi, O. Mancera, J. Romo and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 3505 (1953).
[176] G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **73**, 3556 (1951).
[177] S. A. Szpilfogel, P. A. v. Hemert and M. S. de Winter, *Rec. Trav. Chim.* **75**, 1227 (1956).
[178] C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *J. Amer. Chem. Soc.* **74**, 1712 (1952).
[179] P. Wieland, G. Anner and K. Miescher, *Helv. Chim. Acta* **36**, 1803 (1953).
[180] A. F. B. Cameron, J. S. Hunt, J. F. Oughton, P. A. Wilkinson and B. M. Wilson, *J. Chem. Soc.* 3864 (1953).
[181] R. Hirschmann, M. Brown and N. L. Wendler, *J. Amer. Chem. Soc.* **73**, 5373 (1951).
[182] R. Hirschmann and N. L. Wendler, *J. Amer. Chem. Soc.* **75**, 2361 (1953).
[184] H. V. Anderson, E. R. Garett, F. H. Lincoln, A. H. Nathan and J. A. Hogg, *J. Amer. Chem. Soc.* **76**, 743 (1954).
[185] C. W. Marshall, T. H. Kritchevsky, S. Liebermann and T. F. Gallagher, *J. Amer. Chem. Soc.* **70**, 1837 (1948).
[186] E. P. Oliveto, C. Gerold, R. Rausser and E. B. Hershberg, *J. Amer. Chem. Soc.* **77**, 3564 (1955).
[187] C. Djerassi, O. Mancera, M. Velasco, G. Stork and G. Rosenkranz, *J. Amer. Chem. Soc.* **74**, 3321 (1952).
[188] R. B. Moffett and H. V. Anderson, *J. Amer. Chem. Soc.* **76**, 747 (1954).
[189] H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and (Sir) R. Robinson, *J. Chem. Soc.* 361 (1953).

reagents: *iso*propenyl acetate is milder than acetic anhydride in the presence of sulphonic acid catalysts, but in general results appear to be capricious or dependent on small variations in experimental technique. The course of enol acetylation of 20-keto steroids, of importance in the construction of the cortical side chain, has been adequately described.[81]

In many cases lack of selectivity in enol acetylation is compensated for by selectivity in subsequent epoxidation (see section A.II).

More detailed quantitative studies have shown that *iso*propenyl acetate reacts mainly with α:β-unsaturated ketones as against saturated 20-ketones.[93] The selective enol acetylation at the 20-keto group of an *allo*pregnane 11:20-dione has been examined in detail (in this case carbon tetrachloride, acetic anhydride and 50% perchloric acid as catalyst have been found to be optimum conditions).[83]

Aldehyde groups are converted into enol acetates even with acetic anhydride in the presence of sodium acetate.[62,180] The enol acetate of a 7-ketone has the double bond at C_8.[181,182] The 12-ketone group does not give an enol acetate.[117] (Table 8.)

The $\Delta^{3:5:17(20)}$-dienol acetate of progesterone reacts selectively at the 5-double bond with N-iodo succinimide;[96] from the resulting 6-iodo 4-ene 3-ketone the 17(20)-en-20-ol acetate could be obtained by reduction with sodium bisulphite.

III. *Reaction at α-keto carbanions*

Progesterone can be dialkylated in the 4-position (methyl iodide, potassium *tert.* butoxide), without affecting the 20-ketone group.[190]

On the other hand, acylations by esters occur preferentially at anions of saturated ketone groups. Thus, progesterone with one molar equivalent of ethyl oxalate gives only the 21-oxalyl ester,[190] the same is observed with 11-keto progesterone[110,111] (in the latter case excess of acylating ester gave the 2:21-dioxalyl ester, in which, after bromination, a Favorskii rearrangement was obtained only in the side chain). An 11- or potential 11-ketone group (as in synthetic intermediates) is unaffected when ketone groups at other positions are acylated.[191,192] Of interest are two examples of tricyclic synthetic intermediates, in which acylation occured next to an unsaturated, rather than a saturated ketone group.[179,193]

IV. *Nucleophilic attack on ketone groups*

Unsaturated ketone groups appear to be less attacked by sodium or potassium acetylides than saturated ketones[194] though protection of the former by enol ether or ketal formation is advantageous in this reaction.[195] The selective Knoevenagel reaction at a 3-ketone group with cyanoacetic ester in the case of ethyl dehydrocholate has been reported.[196] The 11-keto group in methyl 3α-acetoxy 11-keto cholanate is inert to Grignard reagents, to the extent that Barbier-Wieland degradation of the ester group is possible without complications.[64]

[190] W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb and B. Sturgeon, *J. Chem. Soc.* 4490 (1956).
[191] A. Wettstein, K. Heusler, H. Ueberwasser and P. Wieland, *Helv. Chim. Acta* **40**, 323 (1957).
[192] R. M. Lukes, G. I. Poos, R. E. Beyler, W. F. Johns and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 1707 (1953).
[193] A. L. Wilds, J. W. Ralls, D. A. Tyner, R. Daniels, S. Kraychy and M. Harnik, *J. Amer. Chem. Soc.* **75**, 4878 (1953).
[194] F. Sondheimer, M. Velasco and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 5673 (1955).
[195] H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 2477 (1956).
[196] F. Smith and M. Webb, *J. Chem. Soc.* 1358 (1948).

V. *Electrophilic attack on ketone groups*

In 11:17-diketones the 17-keto group can be attacked selectively by peracids, to give a single or mixture of ring D lactones.[197–199] In *allo*pregn-16-ene 12:20:dione peracids give the C-lactone 16:17α-epoxide;[200] 11-ketone groups are inert to peracids while 12-ketones appear to give only a single ring C lactone.[201] The selective formation of bis-hydroperoxides of 3- and 12-ketones, by the action of dry hydrogen peroxide, has been described.[202]

VI. *Selective halogenation of ketones*

The selective bromination of ketone groups appears to be governed mainly by their accessability. Thus, 3-ketones in both the normal and *allo* series can be mono- and even dibrominated before 11-ketones,[43,64,82,203] 12-ketones,[204–206] 17-ketones[143,166,207,208] or 20-ketones[82,203,209–212] are affected. The course of bromination of 3-ketones in A/B-*cis*- and *trans*-steroids has been described in detail.[25,213] 20-Ketones on dibromination give the 17α:21-dibromo derivatives.[129,203,209]

Oestrone can be selectively iodinated in the aromatic ring, using iodine and mercuric acetate in acetic acid.[214] α-Keto bromination in this case,[215] and in the case of ketones containing an isolated double bond[117] is best done through the enol acetate. In fact, where selective direct formation of a α-halo ketone fails, addition of hypohalous acid to the double bond of a selectively formed enol acetate (see Section B.II) may be successful.

The dehalogenation of halo 3-ketones[212] and of 17:21-dibromo-20-ketones[129] has been discussed in general terms.

VII. *Miscellaneous reactions*

Steroid 3-ketones can be selectively converted to 3-methoxy compounds by catalytic reduction in methanol containing hydrogen bromide.[216]

The remarkably specific action of selenium dioxide in *tert.* butanol on 3-ketones and Δ^4-3-ketones, to give 1:4-diene-3-ketones, without affecting ketone groups at other positions or the cortical side chain, has been reported by a number of

[197] D. H. R. Barton, A. S. Campos-Neves and A. I. Scott, *J. Chem. Soc.* 2698 (1957).
[198] A. Lardon, J. Schmidlin, A. Wettstein and T. Reichstein, *Helv. Chim. Acta* **40**, 662 (1957).
[199] N. L. Wendler, D. Taub and H. L. Slates, *J. Amer. Chem. Soc.* **77**, 3559 (1955).
[200] E. S. Rothman and M. E. Wall, *J. Amer. Chem. Soc.* **77**, 2228 (1955).
[201] E. S. Rothman, M. E. Wall and C. R. Eddy, *J. Amer. Chem. Soc.* **76**, 527 (1954).
[202] J. Warnant, R. Joly, J. Mathieu and L. Velluz, *Bull. Soc. Chim.* 331 (1957).
[203] C. R. Engel, *J. Amer. Chem. Soc.* **78**, 4727 (1956).
[204] C. Djerassi, A. J. Lemin, H. Martinez, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 4885 (1953).
[205] H. H. Inhoffen, G. Koelling and P. Nehring, *Chem. Ber.* **85**, 89 (1952).
[206] P. L. Julian, C. C. Cochrane, A. Magnani and W. J. Karpel, *J. Amer. Chem. Soc.* **78**, 3153 (1956).
[207] C. Djerassi, A. J. Manson and H. Bendas, *Tetrahedron* **1**, 22 (1957).
[208] C. Meystre and A. Wettstein, *Helv. Chim. Acta* **32**, 1978 (1949).
[209] C. R. Engel, *J. Amer. Chem. Soc.* **77**, 1064 (1955).
[210] B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.* **184**, 393 (1950).
[211] E. P. Oliveto, C. Gerold, E. B. Hershberg, L. Weber, H. E. Jorgensen and R. Rausser, *J. Amer. Chem. Soc.* **75**, 5486 (1953).
[212] G. Rosenkranz, S. Kaufmann, J. Pataki and C. Djerassi, *J. Amer. Chem. Soc.* **72**, 1046 (1950).
[213] C. Djerassi and G. Rosenkranz, *Experientia* **7**, 93 (1951).
[214] A. Hillmann-Elies, G. Hillmann and U. Schiedt, *Z. Naturf.* **8b**, 436 (1953).
[215] W. S. Johnson and W. F. Johns, *J. Amer. Chem. Soc.* **79**, 2005 (1957).
[216] J. C. Babcock and L. F. Fieser, *J. Amer. Chem. Soc.* **74**, 5472 (1952).

workers,[174,217,218] though some of their results have been disproved to a certain extent.[219]

D. MODIFICATION OF CARBONYL GROUPS

I. *By glycol ketal formation*

Protection of ketonic groups by ketal formation with ethylene or other glycols is one of the important aspects of steroid chemistry. Such ketals are stable to practically every kind of basic environment, including Huang-Minlon reduction[220] and the strongly alkaline conditions needed to hydrolyse a tertiary ester group,[221] (where the presence of a free ketone group led to the destruction of the molecule). They are however cleaved by base yielding ethylene glycol enol ethers in cases where they become part of a vinylogous β-diketone system.[222,223]

By choosing appropriate mild conditions ketal groups are ordinarily unaffected by acylating agents in pyridine, such as acetic anhydride,[224] acetyl chloride,[225] *p*-toluenesulphonyl chloride,[225,226] methanesulphonyl chloride;[227] and by dehydrating agents such as phosphorus oxychloride[108,228–230,233] and thionyl chloride (generally below 0°).[231,232] They are stable to organic peracids under suitable conditions,[111,233] to osmium tetroxide,[97,225,235] and to periodic acid in the presence of pyridine.[113,225,226,235]

Suitable conditions (usually with oxalic acid) have been found for the selective cleavage of enol ethers, such as obtained by Birch reduction of aromatic ethers,[234,236] and even for the rearrangement of an ethoxyethinyl carbinol (with dilute mineral acids in the presence of tetrahydrofuran or dioxan as Lewis bases),[237] without affecting a ketal group. It has been reported[236] that the 3-ethylene glycol ketal of 16-methoxycarbonyl androst-4-ene 3:17-dione was cleaved by aqueous dioxan at 200°; in this case the β-keto ester could be decarbomethoxylated (without affecting the ketal) by heating in *p*-cymene.

Ketals have been shown to be reasonably stable to conditions used for enol lactone formation (refluxing in acetic anhydride),[48,67] and to N-bromosuccinimide, preferably in the presence of potassium carbonate.[33,222,238] Even mercuric acetate dehydrogenation in acetic acid[35] and oxidations with *tert.* butyl chromate (entailing

[217] C. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta* **39**, 734 (1956).
[218] H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.* **21**, 239 (1956).
[219] K. Florey and A. R. Restivo, *J. Org. Chem.* **22**, 406 (1957).
[220] H. B. Kagan and J. Jaques, *Bull. Soc. Chim.* 699 (1957).
[221] C. R. Engel, K. F. Jennings and G. Just, *J. Amer. Chem. Soc.* **78**, 6153 (1956).
[222] R. H. Lenhard and S. Bernstein, *J. Amer. Chem. Soc.* **78**, 989 (1956).
[223] P. N. Rao and P. Kurath, *J. Amer. Chem. Soc.* **78**, 5660 (1956).
[224] S. Bernstein, M. Heller and S. M. Stolar, *J. Amer. Chem. Soc.* **77**, 5327 (1955).
[225] G. E. Arth, G. I. Poos and L. H. Sarett, *J. Amer. Chem. Soc.* **77**, 3834 (1955).
[226] W. F. Johns, R. M. Lukes and L. H. Sarett, *J. Amer. Chem. Soc.* **76**, 5026 (1954).
[227] W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.* **78**, 3223 (1956).
[228] S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard and W. S. Allen, *J. Amer. Chem. Soc.* **79**, 4555 (1957).
[229] S. Bernstein, R. Littell and J. H. Williams, *J. Amer. Chem. Soc.* **75**, 4830 (1953)
[230] S. Bernstein, R. Lenhard and J. H. Williams, *J. Org. Chem.* **19**, 40 (1954).
[231] W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.* **77**, 1028 (1955).
[232] S. Bernstein and R. Lenhard, *J. Amer. Chem. Soc.* **77**, 2233 (1955).
[233] R. Littell and S. Bernstein, *J. Amer. Chem. Soc.* **78**, 984 (1956).
[234] A. J. Birch and H. Smith, *J. Chem. Soc.* 4909 (1956).
[235] G. I. Poos, W. F. Johns and L. H. Sarett, *J. Amer. Chem. Soc.* **77**, 1026 (1955).
[236] W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *J. Amer. Chem. Soc.* **78**, 6354 (1956).
[237] G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, *J. Amer. Chem. Soc.* **76**, 1717 (1954).
[238] R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *J. Org. Chem.* **17**, 1369 (1952)

treatment with acetic and oxalic acids)[223] can be carried out in their presence. If hindered (for example as the 3-monoketal of a 4-chloro-3:20-diketopregnane) they can survive bromination (at C_{21}) with bromine in chloroform.[239,240] They are unaffected by the chromic acid-pyridine complex.[113,119,195]

Apart from their obvious use as protecting groups ketals have found use in shifting the easily reducible double bond in a Δ^4-3-ketone to the difficultly reducible C_5-position.[71] An interesting use is described in the synthesis of 14-*iso*oestrone methyl ether, during which a 16-bromo 17-ketone was dehydrobrominated after ketalisation of the ketone group to prevent destruction of the resulting *cyclo*-pentenone group by the base employed.[215] Finally ketalisation has been employed to prevent hemiketal formation between a ketone and a suitably disposed incipient hydroxyl group.[119]

(a) *Selective ketal formation.* Most procedures for ketalisation with ethylene glycol follow the original method of Salmi:[399a] refluxing the ketone in benzene or toluene with excess glycol in the presence of an acid catalyst, with azeotropic removal of the water formed. Some works have used boron trifluoride etherate as catalyst.[241–243] Similar results are reported with propylene glycol.[240]

In general, ease of ketalisation appears to be in the following order: 3-ketone or Δ^4-3-ketone > 17-ketone > 12-ketone > 20-ketone > 17α:21-dihydroxy 20-ketone > 11-ketone and 21-acetoxy 20-ketone.

Among hindered ketones, 4-chloro-3-ketones can still be ketalised[240] while 4:4-dimethyl-3-ketones are reported to be inert.[190] 11-Ketals can be formed in moderate yields by prolonged reaction.[244] In cases where acid sensitive tertiary hydroxyl groups are present ketalisation has been carried out in the glycol in the absence of solvent at 80° with removal of the water formed *in vacuo*.[245,246]

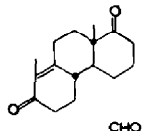
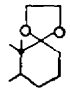
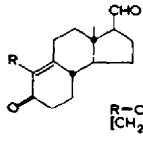
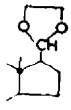
The experimental conditions for ketalisation have been studied in detail in the case of androst-4-ene 3:17-dione:[247] with a low acid catalyst/diketone ratio the 3-ketal is formed preponderantly, while higher ratios favour formation of the 17-ketal.

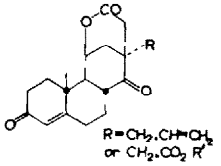
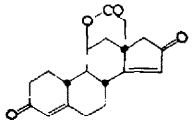
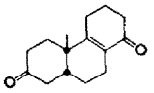
Increased selectivity of ketalisation is possible by using the method of exchange ketalisation between a steroid ketone and the ketals of acetone or 2-butanone in the presence of acid catalysts.[248] Order of ketalisation by such procedures is quoted as: 3- or 20-ketones > Δ^4-3-ketones > 2- or 4-bromo-3-ketones; no reaction being shown by 17-ketones or 2:4-dibromo-3-ketones. This was found to depend partly on the exact experimental procedure employed, such as: refluxing the ketone with the aliphatic ketal with or without removal (by fractionation) of the aliphatic ketone formed; and with or without the use of additional solvent.

As is well known, ketalisation of a Δ^4-3-ketone causes a shift of the double bond

[239] R. H. Levin, B. J. Magerlein, A. V. McIntosh, A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M. Searcy, M. A. Scheri and E. S. Gutsell, *J. Amer. Chem. Soc.* **75**, 502 (1953).
[240] R. H. Levin, B. J. Magerlein, A. V. McIntosh, A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M. Searcy, M. A. Scheri and E. S. Gutsell, *J. Amer. Chem. Soc.* **76**, 546 (1954).
[241] W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 2298 (1954).
[242] W. J. Adams, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 297 (1956).
[243] D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.* 1046 (1957).
[244] B. J. Magerlein and R. H. Levin, *J. Amer. Chem. Soc.* **77**, 1904 (1955).
[245] W. S. Allen, S. Bernstein and R. Littell, *J. Amer. Chem. Soc.* **76**, 6116 (1954).
[246] J. von Euw, R. Neher and T. Reichstein, *Helv. Chim. Acta* **38**, 1423 (1955).
[247] H. L. Herzog, M. Jevnik, M. E. Tully and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 4425 (1953).
[248] H. J. Dauben, B. Loeken and H. J. Ringold, *J. Amer. Chem. Soc.* **76**, 1359 (1954).

TABLE 9. EXAMPLES

Compound	Method	Ketal formed at position	Ref.
Androstane derivatives			
4-ene, 3:17-dione	Exchange	3	248
5β-H, 8(9):14-diene, 3:16-dione		3	193
3:6:17-trione	Exchange, 2-butanone ketal: 5 min	3	250
	Exchange, 2-butanone ketal: 30 min	3, 6	250
	Exchange, 2-butanone ketal: 5 hr	3, 6, 17	250
5β-H, 3:11:17-trione	Azeotropic	3, 17	163
5β-H, 3:11:17-trione	Azeotropic (1 mole glycol)	3 [50% yd.]	166
5β-H, 17-carboxyl, 3:11-dione	Glycol, methylene chloride, SeO_2, room temp.	3	251
Pregnane derivatives			
4-ene, 3:20-dione	Exchange (10 min)	3 (25% yd.)	252
4:16-diene, 3:20-dione	Exchange	3	252
3α-acetoxy, 11:20-dione	Azeotropic	20	253
(*allo*) 3β-acetoxy, 12:20-dione	Glycol, BF_3/Et_2O	12	243
4-ene, 21-hydroxy, 3:20-dione	Glycol at 80°, no solvent	3 (and some 3:20-bisketal)	246
4-ene, 21-acetoxy, 3:20-dione	Azeotropic	3	238
5-ene, 4:4-dimethyl, 3:20-dione		20	190
4-ene, 21:21-dibenzyloxy, 3:20-dione	Exchange	3	255
(*allo*) 3β:17α-dihydroxy, 12:20-dione	Glycol, BF_3/Et_2O	12	241
4-ene, 11α:17α:21-trihydroxy, 3:20-dione	Glycol at 80°, no solvent	3, 20	245
4-ene, 3:11:20-trione	Azeotropic	3, 20	256
(*allo*) 17α-hydroxy, 3:12:20-trione	Azeotropic	3, 12	241
4-ene, 21-acetoxy, 3:11:20-trione	Exchange (mesityl oxide ketal)	3	257
4-chloro, 17α-hydroxy, 3:11:70-trione	Azeotropic (ethylene and propylene glycols)	3, 20	240
4-ene, 17α-hydroxy, 21-acetoxy, 3:11:20-trione	Exchange	3	258, 259
Other compounds		*Product*	
	Azeotropic	 (No yds. given)	150
 R—CH_3 or $[CH_2]_2 \cdot CO_2R'$	Azeotropic		48

Compound	Method	Product	Ref.
	Azeotropic or Exchange	"3"-ketal	260
	Azeotropic Exchange	3-ketal 3,16-bisketal	260 260
	No conditions given		193

to the C_5-position,[70] but no such shift is observed on ketalisation of Δ^{16}-20-ketones.[249] The ketalisation of unsaturated ketones at other positions does not appear to have been investigated in this respect. (Table 9.)

(b) *Selective cleavage of ketals.* The order of cleavage of glycol ketals appears to be analogous to their order of formation. Thus 3-ketals and Δ^5-3-ketals are those cleaved by the mildest conditions (glacial acetic acid, *p*-toluenesulphonic acid in acetone at room temperature); ketals at other positions are succesively cleaved with aqueous acetic acid, mixtures of acetic and mineral acids and mineral acids in aqueous alcohols. Sometimes ketal cleavage, being more carefully controllable from the point of pH of the medium employed, may be more selective than ketal formation. Occasionally mild conditions have had to be used to prevent elimination of an 11β- or 17α-hydroxyl group.[240,261] (Table 10.)

II. *Dimethyl and diethyl ketals*

The formation of these, by the action of the corresponding alcohols in the presence of acid catalysts, appears to be highly specific to ketones at C_3. Using selenium dioxide as catalyst it has been shown[263] that only saturated 3-ketones form ketals; Δ^4-3-ketones, 11-ketones and 17- or 20-ketones being unaffected. On heating 3:3-dimethyl ketals are reported to form enol ethers.[263] Their formation has been

[249] S. Bernstein, M. Heller and S. M. Stolar, *J. Amer. Chem. Soc.* **76**, 5674 (1954).
[250] G. Rosenkranz, M. Velasco and F. Sondheimer, *J. Amer. Chem. Soc.* **76**, 5024 (1954).
[251] E. P. Oliveto, H. Q. Smith, C. Gerold, R. Rausser and E. B. Hershberg, *J. Amer. Chem. Soc.* **78**, 1414 (1956).
[252] F. Sondheimer, M. Velasco and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 192 (1955).
[253] G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.* **17**, 290 (1952).
[254] G. Rosenkranz, O. Mancera, F. Sondheimer and C. Djerassi, *J. Org. Chem.* **21**, 520 (1956).
[255] O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **77**, 5669 (1955).
[256] B. J. Magerlein and R. H. Levin, *J. Amer. Chem. Soc.* **75**, 3654 (1953).
[257] J. M. Constantin, A. C. Haven and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 1716 (1953).
[258] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.* **18**, 70 (1953).
[259] F. Sondheimer, O. Mancera and G. Rosenkranz, *J. Amer. Chem. Soc.* **76**, 5020 (1954)
[260] K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta* **40**, 787 (1957).
[261] G. I. Poos, *J. Amer. Chem. Soc.* **77**, 4932 (1955).
[262] E. P. Oliveto, H. Q. Smith, C. Gerold, L. Weber, R. Rausser and E. B. Hershberg, *J. Amer. Chem. Soc.* **77**, 2224 (1955).
[263] E. P. Oliveto, C. Gerold and E. B. Hershberg, *J. Amer. Chem. Soc.* **76**, 6113 (1954).

TABLE 10. EXAMPLES

Compound	Conditions of cleavage	Ketal cleaved at position	Ref.
Pregnane derivatives			
4-bromo, 11β-17α-dihydroxy, 3:20-bisketal	HCl, acetone	20	262
5-ene, 11α:17α-dihydroxy, 3:20-bisketal	TsOH, acetone, room temp.	3	160
5-ene, 11α-17α-dihydroxy 3:20-bisketal	TsOH, acetone, room b.p.	3, 20	160
5:16-diene, 11β:21-dihydroxy, 3:20-bisketal	HOAc	3	231
5:16-diene, 11β:21-dihydroxy, 3:20-bisketal	HOAc, H_2O or H_2SO_4, MeOH	3, 20	231
5-ene, 17α:21-dihydroxy, 11-ketone, 3:20-bisketal	HOAc, H_2O	3	258
5-ene, 21-acetoxy, 17α-hydroxy, 11-ketone, 3:20-bisketal	HOAc, H_2O	3	258
5-ene, 21-acetoxy, 11β:16α:17α-trihydroxy, 3:20-bisketal	HOAc, H_2O	3	228
5-ene, 21-acetoxy, 11β:16α:17α-trihydroxy, 3:20-bisketal	H_2SO_4, H_2O	3, 20	228
4-chloro, 17α-hydroxy, 11-ketone, 3:20-bisketal	H_2SO_4, acetone	20	240

utilised in the bromination at C_{21} of a pregnane 3:20-dione without affecting ring A.[262]

III. *Enol ethers*

Enol ethers, usually prepared by the reaction of ketones with orthoformates in the presence of traces of acid, appear to be selectively formed from α:β-unsaturated ketones, in particular Δ^4-3-ketones.[264–266] They are stable to all basic reaction conditions, for example reactions of other ketonic groups with lithium aluminium hydride, Grignard reagents, reduction with sodium and alcohols, Claisen condensations, and to the very strongly alkaline conditions needed for hydrolysing a tertiary ester.[267] An interesting use of enol ethers of Δ^4-3-ketones is that involving selective catalytic reduction of their C_5-double bond, the product rearranging to a 2-en-3-ol ether with an A/B *trans*-junction.[25,27,43] Their cleavage can be effected under very mild acidic conditions, sometimes even by dissolution in technical chloroform.[268]

IV. *Thioketals*

Thioketals of ketones formed with ethane- or propanedithiols in the presence of mild acid catalysts have been used more as intermediates for reduction of such ketones to methylene groups, rather than as protecting groups. Their formation is

[264] S. Bernstein, R. Lenhard and J. H. Williams, *J. Org. Chem.* **18**, 1166 (1953).
[265] P. L. Julian, E. W. Meyer, W. J. Karpel and W. Cole, *J. Amer. Chem. Soc.* **73**, 1982 (1951).
[266] A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 4117 (1953).
[267] C. R. Engel and G. Just, *Canad. J. Chem.* **33**, 1515 (1955).
[268] D. K. Patel, V. Petrow, R. Royer and I. A. Stuart-Webb, *J. Chem. Soc.* 161 (1952).

often very selective. Boron trifluoride ether complex has been suggested as a very suitable catalyst,[269] its action being mildest in acetic acid solution, while use of the complex itself as solvent gives a more vigorous reaction; thus cholestane 3:6-dione gives the 3-thioketal under the former and the 3:6-*bis*thioketal under the latter conditions. Other catalysts that have been used include zinc chloride and methanolic hydrogen chloride. The use of propanedithiol has been reported to give improved yields.[270] The idea of forming thioketals by exchange with dimethyl dithiolan is said to fail.[271] It has been demonstrated that no shift of the double bond occurs on forming thioketals of Δ^4-3-ketones.[272]

While thioketals appear to be stable to alkali,[273] they are reported to be attacked in certain cases by lithium aluminium hydride.[274] Like glycol ketals they can be cleaved to the original ketone with acids, but non-hydrolytic conditions (cadmium carbonate or mercuric chloride) can also be used.[273]

Specificity of thioketal formation depends not only on the position of the ketone group but also on the type of thiol used. 6-, 7- and 12-ketones form thioketals only with dithiols, 3-, 16- and 17-ketones also with monothiols.[275] (Table 11.)

TABLE 11. EXAMPLES

Compound	Conditions	Thioketal formed at	Ref.
Androst-4-ene 3:17-dione	ethanedithiol, TsOH, HOAc	3	276
Androst-4-ene 11β-ol 3:7-dione	ethanedithiol, TsOH, HOAc	3	276
Androst-4-ene 3:11:17-trione	ethanedithiol, TsOH, HOAc	3	276
Pregn-4-ene 3:20-dione	ethanedithiol, TsOH, HOAc	3	276
Pregnane 3:11:20-trione	ethanedithiol, no solvent, HCl, $-15°$	3, 20	277
3β:17β-Diacetoxyandrostane 7:11-dione	ethanedithiol, no solvent, HCl, 0°	7	278
3β-Acetoxycholestane 7:11-dione	ethanedithiol, no solvent, HCl, 0°	7	278
3β-Acetoxyergost-22-ene 7:11-dione	ethanedithiol, no solvent, HCl, 0°	7	278
Methyl 3α-hydroxy 11:12-diketo cholanate	propanedithiol, MeOH, HCl	12	279
3α-Acetoxy 22a:5β-spirostane 7:11-dione	ethanedithiol, HOAc, HBr	7	280

[269] L. F. Fieser, *J. Amer. Chem. Soc.* **76**, 1945 (1954).
[270] H. Hauptmann and M. Moura-Campos, *J. Amer. Chem. Soc.* **72**, 1405 (1950).
[271] C. Djerassi and M. Gorman, *J. Amer. Chem. Soc.* **75**, 3704 (1953).
[272] H. Hauptmann, *J. Amer. Chem. Soc.* **69**, 562 (1947).
[273] L. Norymberska, J. Norymberski and A. Olalde, *J. Amer. Chem. Soc.* **70**, 1256 (1948).
[274] R. H. Mazur and E. A. Brown, *J. Amer. Chem. Soc.* **77**, 6670 (1955).
[275] H. Hauptmann and M. Moura-Campos, *J. Amer. Chem. Soc.* **74**, 3179 (1952).
[276] J. W. Ralls and B. Riegel, *J. Amer. Chem. Soc.* **76**, 4479 (1954).
[277] A. Ruff and T. Reichstein, *Helv. Chim. Acta* **34**, 70 (1951).
[278] H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger and O. Jeger, *Helv. Chim. Acta* **35**, 295 (1952).
[279] S. Archer, T. R. Lewis, C. M. Martini and M. Jackman, *J. Amer. Chem. Soc.* **76**, 4915 (1954).
[280] G. Rosenkranz, M. Velasco, C. Djerassi and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 4430 (1953).

V. *Thioenol ethers*

Formation of these, generally with benzyl thiol, appears as with enol ethers to be specific to α-β unsaturated ketones.[179] As catalyst pyridine hydrochloride has been suggested.[281] 1:4-addition of the thiol may occur if the conjugated double bond is not sterically hindered (as with cholest-1-ene-3-one,[281,282]) and may happen exclusively with basic catalysts (e.g. piperidine).

Sulphoxides formed by hydrogen peroxide oxidation of thioenol ethers have been suggested as acid-stable modifications of the ketone group;[281] from these the thioenol ether can be regenerated by reduction with lithium aluminium hydride. However, little use seems to have been made of this method of ketone protection.

VI. *Hemithioketals*

Some interesting work has been done on this type of ketone group modification. Like glycol ketals, hemithioketals can be prepared by azeotropic removal of water on reaction of the ketone with mercaptoethanol or mercaptopropanol, or by exchange with the corresponding acetone hemithioketal.[271] In 4-ene-3-ketones a shift of the double bond to the 5-position is said to be probable.

Hemithioketals are stable to basic reaction conditions and to the action of lithium aluminium hydride.[274,283] Raney nickel does not cause hydrogenolysis but regenerates the original ketone, this affording a method of ketone protection not involving acid conditions for cleavage.[284]

Hemithioketal formation appears to be less subject to steric hindrance than ethylene glycol ketalisation; this is exemplified by dehydrocholic acid[274] from which a tris-hemithioketal can be formed successfully.

VII. *Enamine formation*

This is another method for the protection of carbonyl groups which is specific to α:β-unsaturated ketones, particularly at C_3,[285–287] depending somewhat on the secondary amine used. Thus: androst-4-ene-3:11:17-trione gave the 3-monoenamine with morpholine and the 3:17-*bis*enamine with pyrrolidine.[288] Aldehyde groups are converted to enamines in preference even to Δ^4-3-ketones.[63,289]

Enamines are usually formed by refluxing the ketone with a secondary cyclic amine in benzene solution and azeotropic removal of the water formed. A catalyst is not necessary. Their stability to lithium aluminium hydride (even in the case of an enamine from a 1:4-diene 3-ketone,[111,285,290,291]) to Grignard reagents[286] and to strong acids[291] makes them attractive alternatives to ketals for ketone protection. They are easily cleaved by aqueous alkali.

[281] J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *J. Amer. Chem. Soc.* 73, 1528 (1951).
[282] P. A. Plattner, A. Fuerst and H. Els, *Helv. Chim. Acta* 37, 1399 (1954).
[283] J. Romo, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* 73, 4961 (1951).
[284] C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *J. Amer. Chem. Soc.* 74, 3634 (1952).
[285] M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.* 75, 5927 (1953).
[286] M. E. Herr, J. A. Hogg and R. H. Levin, *J. Amer. Chem. Soc.* 78, 500 (1956).
[287] F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.* 75, 1918 (1953).
[288] F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.* 77, 488 (1955).
[289] M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.* 74, 3627 (1952).
[290] J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal and J. Korman, *J. Amer. Chem. Soc.* 77, 4438 (1955).
[291] J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Amer. Chem. Soc.* 78, 430 (1956).

Enamines have also seen use in view of the preferential oxidisability of their C=C double bond (e.g. in the degradation of *bis*-nor aldehydes,[63]) and as intermediates in a new method for the monoalkylation of ketones.[292]

VIII. *Semicarbazones and other hydrazones*

Semicarbazones have seen use as protecting groups in view of their stability to metal hydride reduction, e.g. with lithium aluminium hydride,[293] sodium- or potassium borohydrides[99,294–296] and lithium borohydride[297–300] and to Oppenauer oxidation conditions[301,302] where they have been employed to prevent reduction and self-condensation of a free ketone group.

The selectivity of semicarbazone formation appears to be less pronounced than that of ketalisation, even though the 11-keto group is inert in all cases. 3-Ketones and 4-enc-3-ketones react preferentially;[99,297,303] 20- and 17α-hydroxy 20-ketones also react reasonably rapidly but Δ^{16}-20-ketones are less reactive.[304] 21-Acetoxy-20-ketones are reported to be more prone to semicarbazone than to ketal formation[293,294,296,298,303,305] in spite of earlier reports to the contrary.[300] In a special case selective semicarbazone formation has been studied with regard to reaction temperature and solvent employed.[306]

Cleavage of semicarbazones has been effected mainly by exchange with pyruvic acid;[294,299,307,308] but other reagents such as nitrous acid[293,295] and acetic anhydride/pyridine[309] have also seen use. At this point the use of semicarbazones for the formation of Δ^4-3-ketones from 4-bromo-3-ketones in the pregnane series should be noted[82,210,303] this can be done in the presence of a 21-bromo 20-ketone grouping.[310] Originally 2:4-dinitrophenylhydrazones,[311] and more recently ethoxycarbonylhydrazones,[312] have been used for this conversion.

Other derivatives which have been explored for ketone protection include oximes[293,305] and hydrazones,[293] but their cleavage to the original ketone appears to be more difficult.

IX. *Cyanohydrins*

Cyanohydrin formation appears promising as a method for the specific protection

[292] G. Stork, R. Terrell and J. Szmuczkovicz, *J. Amer. Chem. Soc.* **76**, 2029 (1954).
[293] E. P. Oliveto, R. Rausser, L. Weber, E. Shapiro, D. Gould and E. B. Hershberg, *J. Amer. Chem. Soc.* **78**, 1736 (1956).
[294] E. M. Chamberlin and J. M. Chemerda, *J. Amer. Chem. Soc.* **77**, 1221 (1955).
[295] H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, *J. Amer. Chem. Soc.* **77**, 4781 (1955).
[296] R. Joly, G. Nominé and D. Bertin, *Bull. Soc. Chim.* 1459 (1956).
[297] Huang-Minlon and R. H. Pettebone, *J. Amer. Chem. Soc.* **74**, 1562 (1952).
[298] D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Amer. Chem. Soc.* **78**, 2912 (1956).
[299] N. L. Wendler, R. P. Graber, R. E. Jones and M. Tishler, *J. Amer. Chem. Soc.* **74**, 3630 (1952).
[300] N. L. Wendler, Huang-Minlon and M. Tishler, *J. Amer. Chem. Soc.* **73**, 3818 (1951).
[301] C. H. Gleason and G. W. Holden, *J. Amer. Chem. Soc.* **72**, 1751 (1950).
[302] A. Stoll, A. von Wartburg and J. Renz, *Helv. Chim. Acta* **36**, 1531 (1953).
[303] W. F. McGuckin and E. C. Kendall, *J. Amer. Chem. Soc.* **74**, 5811 (1952).
[304] H. Reich and R. W. Collins, *J. Amer. Chem. Soc.* **73**, 1374 (1951).
[305] R. E. Jones and S. A. Robinson, *J. Org. Chem.* **21**, 586 (1956).
[306] R. Joly, G. Nominé and J. Jolly, *Bull. Soc. Chim.* 837 (1956).
[307] E. B. Hershberg, *J. Org. Chem.* **13**, 542 (1948).
[308] D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Amer. Chem. Soc.* **79**, 452 (1957).
[309] E. P. Oliveto, H. L. Herzog, L. Weber, M. E. Tully and E. B. Hershberg, *J. Org. Chem.* **21**, 795 (1956).
[310] L. Velluz, J. Warnant, G. Nominé, R. Joly and A. Petit, *Bull. Soc. Chim.* 906 (1953).
[311] V. R. Mattox and E. C. Kendall, *J. Amer. Chem. Soc.* **70**, 882 (1948).
[312] R. Joly and G. Nominé, *Bull. Soc. Chim.* 1381 (1956).

of saturated, as against α-β-unsaturated ketone groups. A number of examples, utilising exchange with acetone cyanohydrin, have been reported.[313] Reversal to the ketone occurs with bases, but cyanohydrins are reasonably stable to acidic conditions, such as when cyanohydrin formation with a saturated ketone group is followed by ketalisation of an α-β unsaturated ketone, though in such a case it is advisable to add some acetone cyanohydrin in the latter reaction, to minimise reversal and dehydration of the steroid cyanohydrin.[314]

E. SELECTIVE REACTIONS OF HYDROXYL GROUPS

I. *Selective oxidation*

(a) *Chromic acid*, NBS, NBA *and Oppenauer oxidations.* (Table 13.) A definite order in the oxidisability of steroid hydroxyl groups, depending on their configuration and position, was recognised in the early work on the structure of the bile acids.[315,316] This order has since been put on a firmer basis by the crystallisation of modern views on conformational analysis.[149,317,318]

Regarding oxidation with hexavalent chromium; the rate-determining step generally attack on the hydrogen atom on the same carbon as the hydroxyl group, the conformational factor will nearly always determine the order of oxidation among several hydroxyl groups. Oxidation with reagents such as N-bromosuccinimide or N-bromoacetamide[319] is less clear out from the mechanistic viewpoint; it being uncertain whether this proceeds through formation of the steroid alcohol hypohalite, and if so whether the rate-determining step is formation of the hypohalite or abstraction of the α-hydrogen atom.[320] On the one hand, examples are known in which oxidation with NBS appears to follow the same order as for chromic acid.[316,321,322] With the more powerful NBA reagent, however (whose action is enhanced by the presence of *tert.* butyl alcohol[322]) selectivity seems to be governed more by accessibility of the hydroxyl groups; this decidedly is the case with Oppenauer oxidation.

Primary alcohols can in most cases be left unaffected during oxidation of other secondary alcohol groups, both with chromic acid[17,245,323,324] and with hypohalite reagents.[111,325–329]

Oxidation with *tert.* butyl hypochlorite,[239,240,330–332] N-chlorosuccinimide[332] or

[313] A. Ercoli and P. de Ruggieri, *J. Amer. Chem. Soc.* **75**, 650 (1953).
[314] G. Stork and H. J. E. Loewenthal, unpublished results.
[315] L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Reinhold, New York (1949).
[316] L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.* **71**, 3935 (1949).
[317] J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta* **38**, 1529 (1955).
[318] W. Klyne, *Progress in Stereochemistry* Vol. I. Butterworths, London (1954).
[319] H. Reich and T. Reichstein, *Helv. Chim. Acta* **26**, 562 (1943).
[320] C. A. Grob and H. J. Schmid, *Helv. Chim. Acta* **36**, 1763 (1953).
[321] L. F. Fieser and S. Rajagopalan, *J. Amer. Soc.* **71**, 3938 (1949).
[322] L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.* **72**, 5530 (1950).
[323] S. Bernstein and R. Lenhard, *J. Amer. Chem. Soc.* **77**, 2331 (1955).
[324] A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *J. Amer. Chem. Soc.* **76**, 6210 (1954).
[325] M. Ehrenstein, G. W. Barber and M. W. Gordon, *J. Org. Chem.* **16**, 349 (1951).
[326] M. Ehrenstein and M. Duennenberger, *J. Org. Chem.* **21**, 774 (1956).
[327] M. Ehrenstein and M. Duennenberger, *J. Org. Chem.* **21**, 783 (1956).
[328] K. Florey and M. Ehrenstein, *J. Org. Chem.* **19**, 1174 (1954).
[329] R. E. Jones and F. W. Kocher, *J. Amer. Chem. Soc.* **76**, 3682 (1954).
[330] J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, *J. Amer. Chem. Soc.* **75**, 3500 (1953).
[331] G. S. Fonken, J. L. Thompson and R. H. Levin, *J. Amer. Chem. Soc.* **77**, 172 (1955).
[332] A. R. Hanze, G. S. Fonken, A. V. McIntosch, A. M. Searcy and R. H. Levin, *J. Amer. Chem. Soc.* **76**, 3179 (1954).

hypochlorous acid[332] appears to be specific to the 3α- or 3β-hydroxyl group, giving the α-chloro ketone; an α-bromo ketone is formed when oxidation with NBA is allowed to proceed in the presence of hydrobromic acid.[332]

A general picture of the order of oxidation by these reagents is provided by the following rules arising out of more systematic work:

TABLE 12

Reagent	Type of compound	Order of oxidation of OH groups	Ref.
CrO_4^{--}/OAc^-	Bile acids	$7\alpha > 12\alpha$	322
$Cr_2O_7^{--}/H^+$	A/B-*trans*-steroids	$11\beta > 11\alpha > 3\beta$	333
NBS/acetone/H_2O	Bile acids,	$7\alpha > 12\alpha$	322
NBS/acetone/H_2O	Cholestane derivatives	$6\beta > 3\beta$	321
NBS/acetone/H_2O	Cholestane derivatives	$7\alpha > 3\beta$	322
NBA/acetone	A/B-*trans*-steroids	$11\beta > 3\beta > 11\alpha$	333, 334
NBA/acetone	A/B-*cis*-steroids	$3\alpha + 17\beta > 11\alpha$	162
NBA/acetone	A/B-*cis*-steroids	$3\alpha > 12\alpha > 12\beta > 17\beta$	319
NBA/acetone	A/B-*cis*-steroids	$11\beta > 11\alpha$	332
TBH	A/B-*cis*-steroids	$3\alpha > 11\alpha + 11\beta$	240, 331, 332

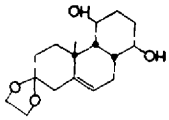
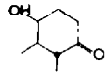
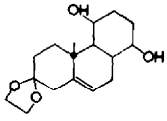
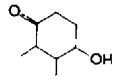
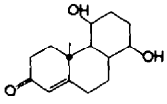
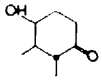
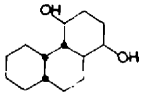
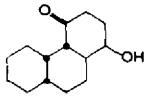
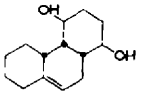
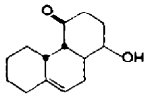
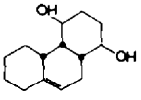
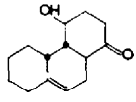
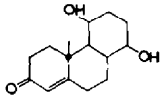
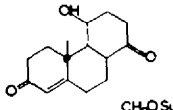
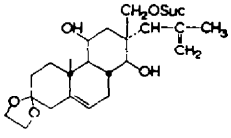
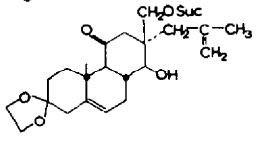
(b) *Oxidation by other methods:* (i) *Manganese dioxide oxidation.* This reagent oxidises selectively allylic as against saturated alcohol groups.[350] It has been used in particular for the synthesis of testosterone and its analogues, through selective oxidation of a suitable androst-4-ene 3:17-diol[51,143,350–354] and applies equally well to oxidation of 4-ene 3-ols in the presence of saturated hydroxyl groups at other positions.[119,252,355,356]

[333] S. G. Brooks, J. S. Hunt, A. G. Long and B. Mooney, *J. Chem. Soc.* 1175 (1957).
[334] O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Org. Chem.* **17**, 1066 (1952).
[335] L. H. Sarett, *J. Biol. Chem.* **173**, 185 (1948).
[336] M. Davis and V. Petrow, *J. Chem. Soc.* 2536 (1949).
[337] W. Schlegel, C. Tamm and T. Reichstein, *Helv. Chim. Acta* **38**, 1013 (1955).
[338] S. A. Julia, P. A. Plattner and H. Heusser, *Helv. Chim. Acta* **35**, 665 (1952).
[339] S. P. Barton, G. Cooley, B. Ellis and V. Petrow, *J. Chem. Soc.* 5094 (1957).
[340] J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 1277 (1953).
[341] W. J. Adams, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 1825 (1954).
[342] E. P. Oliveto, H. L. Herzog, M. Jevnik, H. E. Jorgensen and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 3651 (1953).
[343] W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 870 (1955).
[344] L. H. Sarett, M. Feurer and K. Folkers, *J. Amer. Chem. Soc.* **73**, 1777 (1951).
[345] Q. R. Petersen and C. T. Chen, *J. Amer. Chem. Soc.* **77**, 2557 (1955).
[346] A. S. Jones, M. Webb and F. Smith, *J. Chem. Soc.* 2164 (1949).
[347] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).
[348] H. P. Uehlinger, C. Tamm and T. Reichstein, *Helv. Chim. Acta* **40**, 2234 (1957).
[349] J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta* **40**, 1034 (1957).
[350] F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 5930 (1953).
[351] M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 4099 (1957).
[352] O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 2189 (1953).
[353] A. L. Nussbaum, G. Brabazon, E. P. Oliveto and E. B. Hershberg, *J. Org. Chem.* **22**, 977 (1957).
[354] H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.* **22**, 99 (1957).
[355] B. Camerino and C. G. Alberti, *Gazz.* **85**, 51 (1955).
[356] D. Taub, R. H. Pettebone, N. L. Wendler and M. Tishler, *J. Amer. Chem. Soc.* **76**, 4094 (1954).

TABLE 13. EXAMPLES

Compound	Method	Product	Ref.
Androstane derivatives			
5β-H, 3α-acetoxy, 11β:17α-diol	Oppenauer	17-one	335
4-ene, 17-one, 3β:6β-diol	Oppenauer	4-ene, 3:6:17-trione	336
4-ene, 17-one, 3β:6β-diol	CrO_3	4-ene, 3β-ol, 6:17-dione	336
5β-H, 17-carbomethoxy, 3β:1β-diol	NBA, *tert.* BuOH/Py, H_2O	3-one	337
5β-H, 3α:11α:17β-triol	NBA	3:17-dione	162, 163
3β:5α:17β-triol	CrO_3	17-one	338
4-ene, 3β:16α:17β-triol	Oppenauer	4-ene, 3:16-dione	242
4-ene, 17α-hydroxymethyl-ethinyl, 3β:17β-diol	Oppenauer	4-ene 3-one	339
Pregnane derivatives			
5-ene, 20-ethylenedioxy, 3β:16α-diol	Oppenauer	4-ene 3-one	249
5-ene, 3:20-bisethylenedioxy, 11α:21-diol	CrO_3/Py	11-one	323
(*allo*) 16:17α-epoxy, 20-one, 3β:11α-diol	Oppenauer	3-one	340
17(20)-ene, 20-cyano, 11-one, 3α:21-diol	NBA, MeOH/Py	3-one	329
20-one, 3α:11α:17α-triol	NBA, acetone/H_2O	3-one	341, 342
20-one, 3α:11α:17α-triol	TBH	4-chloro 3-one	240
(*allo*) 20-one, 3β:12β:17α-triol	NBA, Py/H_2O	3-one	343
(*allo*) 12-one, 3β:17α:20-triol	NBA, *tert.* BuOH/H_2O	3-one	241
(19-*nor*), 4-ene, 3:20-dione, 11β:17α:21-triol	CrO_3	11-one	324
4-ene, 6α-Me, 3:20-dione, 11β:17α:21-triol	NBA, Py	11-one	111
21-acetoxy, 20-one, 3α:12α-17α-triol	NBA, *tert.* BuOH/Py/H_2O	3-one	341
1:4-diene, 6α-Me, 3:20-dione, 11β:17α:21-triol	NBA/Py	11-one	111
5-ene, 3:20-bisethylenedioxy, 11α:17α:21-triol	CrO_3/Py	11-one	245
3α:11β:17α:20:21-pentol 20:21-acetonide	Oppenauer	3-one	344
Cholestane derivatives			
5-ene, 3β:7β-diol	Oppenauer	4-ene 3-one	345
3β:7α-diol	NBS	7-one	322
3β:5α:6β-triol	NBS	6-one	321

TABLE 13. (*contd.*)

Compound	Method	Product	Ref.
Other compounds			
*Isoallo*spirostane 3β:11β-diol	Oppenauer	3-one	333
Methyl cholate 7-acetate	K_2CrO_4, HOAc	12-one	322
Methyl cholate and -desoxy-cholate	Oppenauer	3-one	346
Synthetic intermediates			
	Oppenauer		347
	CrO_3/Py		347
	NBA		347
	CrO_3		148
	CrO_3		148
	Oppenauer		148
	CrO_3/Py		348
	1 mole CrO_3/Py		349

An interesting case is provided by 16-methylene androst-4-ene 3:17-diol;[51] here the allylic 3-hydroxy group is oxidised in preference to the "exocyclically" allylic 17-hydroxy group.

4-Ene 3:6-diols are oxidised to 6-hydroxy 4-ene 3-ketones.[85,350,357] Under vigorous conditions (in benzene solution at 72°) oxidation may proceed further in certain cases and give 4:6-diene 3-ketones from both 4-ene 3-ketones and 5-ene 3β-alcohols,[358] while cholesteryl acetate is reported to give a small amount of the 7-keto compound.[359]

The activity of manganese dioxide in this type of oxidation depends greatly on its method of preparation; the most suitable reagent being that made by precipitation from alkaline solution.[360]

(ii) *Catalytic oxidation.* Platinum oxide and oxygen, usually in ethyl acetate solution, can oxidise specifically highly accessible secondary alcohol groups (3α and 3β) in a number of hydroxy steroids,[361] but this has been reported to fail with cholesterol. This method has been employed with success in the field of highly hydroxylated compounds derived from cardiac aglycones.[362]

II. *Various selective reactions of hydroxyl groups*

11β- or 9βH-11α-^{14}Hydroxyl groups are dehydrated under conditions which do not affect tertiary 17α-hydroxyl groups.[229,233,363] The tertiary 5α-[364] and 5β-hydroxy[327,365] group is left unchanged under conditions used for dehydration of the 14β-hydroxy group (phosphorus oxychloride, pyridine).

In certain cases allylic[366] or homoallylic[367] as against saturated hydroxyl groups can be converted selectively into the corresponding chlorides.

In the 17α:21-diol-20-one cortical side chain the 17α-hydroxyl group can be removed by catalytic hydrogenolysis after formation of a 21-dibenzyl acetal.[255]

F. MODIFICATION OF HYDROXYL GROUPS

I. *Selective ester formation and hydrolysis*

(a) *General.* Formation of an ester, usually an acetate, is the most useful method of protecting a hydroxyl group against reactions proceeding under acidic conditions, such as oxidation. Selective formation of esters and their selective hydrolysis are governed by both conformational and positional factors. Acylating groups larger than acetyl, such as benzoyl or succinoyl, are usually chosen for the greater selectivity they confer both in acylation and hydrolysis.

[357] C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 1226 (1954).
[358] F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 5932 (1953).
[359] P. Meunier, G. Zwingelstein and J. Jouanneteau, *Bull. Soc. Chim. Biol.* **35**, 495 (1953).
[360] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1094 (1952).
[361] R. P. A. Sneeden and R. B. Turner, *J. Amer. Chem. Soc.* **77**, 190 (1955).
[362] R. P. A. Sneeden and R. B. Turner, *J. Amer. Chem. Soc.* **77**, 130 (1955).
[363] S. A. Szpilfogel and V. Gerris, *Rec. Trav. Chim.* **74**, 1462 (1955).
[364] H. Heusser, N. Frick, E. V. Jensen and P. A. Plattner, *Helv. Chim. Acta* **32**, 1334 (1949).
[365] M. Ehrenstein, A. R. Johnson, P. C. Olmsted, V. I. Vivian and M. A. Wagner, *J. Org. Chem.* **15**, 264 (1950).
[366] B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, *J. Biol. Chem.* **173**, 271 (1948).
[367] J. Broome, B. R. Brown and G. H. R. Summers, *J. Chem. Soc.* 2071 (1957).

Formates have been used because of their very facile hydrolysis under basic conditions[368,369] and because they can be formed with very hindered hydroxyl groups (e.g. at C_{11}); the same applies to trifluoroacetates.[370] They are reported to be stable to acidic conditions, to metal hydride reduction in non-hydroxylic solvents[371] and to potassium acetate in acetone.[372]

Carbonate ester formation (usually from ethyl chloroformate and the alcohol in pyridine) is reported to be highly specific to equatorial alcohol groups.[373] Carbonates are stable to acidic conditions and to the action of peracids;[201] and are of additional interest in that they are easily eliminated by pyrolysis to give olefins.[374]

Regarding *p*-toluene sulphonates and methanesulphonates; these are reasonably stable to mild basic conditions, such as during metal hydride reduction.[4,375–377] Tosylation is less affected by steric factors than acetylation[378,379] and is more selective than mesylation.[380] In all cases, a primary alcohol group will be acylated before a secondary hydroxyl group. 20-Keto 21-ols are not tosylated with *p*-toluene sulphonyl chloride and pyridine but give pyridinium salts.[381]

(b) 11-*Hydroxy groups.* 11α-Hydroxy groups are reported to be acetylated fairly easily,[254,258] 11β-hydroxyl groups only after prolonged reaction; e.g. with acetic anhydride/pyridine at 100° for 24 hours,[382] with acetic anhydride and *p*-toluenesulphonic acid,[211,353] with acetyl chloride[383] or with *iso*propenyl acetate.[384] When very vigorous conditions are used, enol acetylation of a 20-ketone group may be unavoidable but can be reversed on working up under mildly alkaline conditions.[353] Less information is available on the hydrolysis of 11β-acetates.[211] The resistance of 11-hydroxy groups to acetylation disappears in a 12:13-ene 11-ol.[385]

(c) *Tertiary hydroxyl groups.* 17α-Hydroxyl groups can be acetylated under reasonably vigorous conditions[386,387] as can 5α- (but not 5β) hydroxyl groups.[11] Such tertiary ester groups are fairly stable to alkaline conditions but their hydrolysis presents no special problems as in the case of 11β-esters.

(d) *Miscellaneous.* Acetylation can be carried out using phenyl acetate and sodium hydride to avoid mixed anhydride formation with a carboxyl group,[388] or by ester exchange with ethyl acetate in the presence of an acid catalyst[389] to prevent

[368] A. Lardon and T. Reichstein, *Helv. Chim. Acta* **37**, 388 (1954).
[369] G. B. Spero, A. V. McIntosh and R. H. Levin, *J. Amer. Chem. Soc.* **70**, 1907 (1948).
[370] A. Lardon and T. Reichstein, *Helv. Chim. Acta* **37**, 443 (1954).
[371] H. J. Ringold, B. Loeken, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 816 (1956).
[372] H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 820 (1956).
[373] L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero and T. Utne, *J. Amer. Chem. Soc.* **74**, 3309 (1952).
[374] G. L. O'Connor and H. R. Nace, *J. Amer. Chem. Soc.* **74**, 5454 (1952).
[375] M. N. Huffman, M. H. Lott and A. Tillotson, *J. Biol. Chem.* **218**, 565 (1956).
[376] J. H. Looker and D. N. Thatcher, *J. Org. Chem.* **19**, 784 (1954).
[377] C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.* 2230 (1954).
[378] F. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **75**, 2273 (1953).
[379] R. Hirschmann, C. S. Snoddy and N. L. Wendler, *J. Amer. Chem. Soc.* **74**, 2693 (1952).
[380] A. Corbellini and G. Nathansohn, *Gazz.* **86**, 1240 (1956).
[381] W. J. Leanza, J. P. Conbere, E. F. Rogers and K. Pfister, *J. Amer. Chem. Soc.* **76**, 1691 (1954).
[382] A. D. Kemp, A. Kappas, I. I. Salamon, F. Herling and T. F. Gallagher, *J. Biol. Chem.* **210**, 123 (1954).
[383] A. Crawshaw, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 731 (1954).
[384] W. S. Johnson, R. Pappo and W. F. Johns, *J. Amer. Chem. Soc.* **78**, 6339 (1956).
[385] H. L. Herzog, C. C. Joyner, M. J. Gentles, M. T. Hughes, E. P. Oliveto, E. B. Hershberg and D. H. R. Barton, *J. Org. Chem.* **22**, 1413 (1957).
[386] E. Batres, R. Gomez, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.* **21**, 240 (1956).
[387] R. B. Turner, *J. Amer. Chem. Soc.* **75**, 3489 (1953).
[388] R. Pappo, B. M. Bloom and W. S. Johnson, *J. Amer. Chem. Soc.* **78**, 6347 (1956).
[389] W. S. Johnson, E. R. Rogier and J. Ackerman, *J. Amer. Chem. Soc.* **78**, 6322 (1956).

acetylation of a phenolic hydroxy group, even though generally phenols are acylated under the usual conditions with greater difficulty than secondary alcohols.[390,391]

While esters of equatorial 3-alcohols are hydrolysed more easily than their axial epimers, the reverse may occur in the presence of a hydroxyl group at C_5.[392]

TABLE 14. SELECTIVE ESTER FORMATION

A/B-*trans*-steroids		A/B-*cis*-steroids		Δ^5-steroids		Δ^4-3-keto-steroids	
Order	Ref.	Order	Ref.	Order	Ref.	Order	Ref.
Acetates							
$3\beta > 1\alpha$	393	$3\beta > 1\beta$	395	21[a] > 3β	396	21[a] > 6β	259
$3\alpha > 1\alpha$	393	$3\alpha > 12\alpha$	185			21[a] > 11α + 17α[c]	378
$3\beta > 7\alpha$	394	$3\alpha + 7\alpha > 12\alpha$	322			21[b] > 11α	397
$3\beta > (9\beta H)11\alpha$	14	$3\alpha + 17\beta > 11\beta$	162			21[b] > 16α	398
$3\beta > 11\beta$	382	21[e] > 20α	169				
20[d] > 3α	399						
20[d] > $3\beta > 1\alpha$	399						
Carbonates		$3\alpha > 12\alpha$	400				
		$3\alpha > 12\alpha + 17\alpha$[c]	341				
		$3\alpha > 7\alpha + 12\alpha$	316				
			322				
Formates		$3\alpha > 17\alpha$[c] $- 11\beta$	186				
		$3\alpha > 12\beta$[f]	279				
Succinates							
$3\beta > 12\alpha$ or 12β	379	$3\alpha > 12\alpha$	206				
			401				
$3\beta > 11\beta$	424	$3\alpha > 7\alpha$	322				
			402				
		$3\alpha > 12\beta$	403				
Benzoates				$3\beta > 7\alpha$[f]	404		
p-*Toluenesulphonates*							
$3\beta > 6\beta$[g]	4						
	377						
	380						
Methanesulphonates							
$16\alpha > 11\beta + 17\alpha$[c]	227						

[a] 17α-hydroxy 20-keto 21-alcohol. [b] 20-keto 21-alcohol. [c] tertiary alcohol.
[d] 20-hydroxy 21-nor steroid. [e] Primary alcohol. [f] Acetylation was not selective in this case.
[g] Mesylation was not selective in this case.

[390] N. Borsel, *J. Amer. Chem. Soc.* **74**, 251 (1952).
[391] M. N. Huffman and M. H. Lott, *J. Biol. Chem.* **172**, 325 (1948).
[392] H. B. Henbest and B. J. Lovell, *Chem. & Ind.* 278 (1956).
[393] P. Striebel and C. Tamm, *Helv. Chim. Acta* **37**, 1094 (1954).
[394] D. H. R. Barton and G. F. Laws, *J. Chem. Soc.* 52 (1954).
[395] W. Schlegel and C. Tamm, *Helv. Chim. Acta* **40**, 160 (1957).
[396] K. Florey and M. Ehrenstein, *J. Org. Chem.* **19**, 1331 (1954).
[397] F. Reber, A. Lardon and T. Reichstein, *Helv. Chim. Acta* **37**, 45 (1954).
[398] E. Vischer, J. Schmidlin and A. Wettstein, *Helv. Chim. Acta* **37**, 321 (1954).
[399] F. Sallmann and C. Tamm, *Helv. Chim. Acta* **39**, 1340 (1956).
[399a] E. J. Salmi, *Ber.* **71**, 1803 (1938).
[400] R. Casanova, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 2983 (1953).
[401] E. B. Hershberg, H. L. Herzog, S. B. Coan, L. Weber and M. Jevnik, *J. Amer. Chem. Soc.* **74**, 2585 (1952).
[402] H. P. Sigg and T. Reichstein, *Helv. Chim. Acta* **39**, 1507 (1956).
[403] E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.* **177**, 951 (1949).
[404] H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 1792 (1948).

TABLE 15. SELECTIVE ESTER HYDROLYSIS

A/B-*trans*-steroids			A/B-*cis*-steroids			Δ^5-steroids			Δ^4-3-keto-steroids		
Order	Method	Ref.	Order	Method	Ref.	Order	Method	Ref.	Order	Method	Ref
Acetates											
$3\beta > 1\alpha$	F	393	$3\beta > 6\beta$	C	409	$3\beta > 1\beta$	F	411	$21^a > 11\alpha$	F	342
$3\beta > 6\beta$	C	405, 406	$3\beta > 11\alpha$	F	397	$3\beta > 17\beta$	C	412	$21^b > 11\alpha$	A	397
$3\beta > 11\alpha$	A	334	$3\alpha > 12\alpha$	B	341	$3\beta > 17\beta$	B	413	$21^b > 19^e$	A	416, 417
$3\beta > 17\beta$	B	407	$3\alpha > 17\alpha^c + 11\beta$	F	211	$3\beta > 16\beta$	A	414			
$3\beta > 20\beta + 16\alpha$		171	$3\alpha > 20\alpha$	C	410	$3\beta > 16\alpha + 20\alpha$	A	73			
$3\beta + 20^d > 1\alpha$	F	399	$3\alpha + 12\alpha > 7\alpha$		277	$19^e > 3\beta$	B	326			
$21^b + 3\beta > 11\alpha$	C	408	$17\alpha^c > 11\beta$	B	211	$21^a > 3\beta$	D	396			
			$21^b + 3\alpha > 11\alpha$	C	408	$21^d > 3\beta$	A	415			
Other esters											
3β-benz.											
$>7\beta$-benz.	D	418	3α-form.			3β-form.					
			$>21^b$-acet.	F	419	$>16\alpha$-acet.	A	74			
			21^b-form.			3β-acet.					
			$>3\alpha$-acet.	A	410	$>20\alpha$-benz.	E	420			
						3β-tos. $>16\beta$-tos.	G	421			

Conditions used for hydrolysis are indicated as follows:

HCO_3^-/MeOH ⟶ A OMe^-/MeOH ⟶ D
CO_3^{--}/MeOH ⟶ B OH^-/dioxan ⟶ E H^+/acetone ⟶ G
OH^-/ROH ⟶ C H^+/MeOH ⟶ F

[a] 17α-hydroxy 20-keto 21-ester [b] 20-keto 21-ester [c] tertiary ester [d] 21-nor 20-ester [e] primary ester

[405] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 1790 (1952).
[406] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 3361 (1952).
[407] D. L. Garmaise and C. W. Shoppee, *J. Chem. Soc.* 245 (1953).
[408] F. Sondheimer, G. Rosenkranz, O. Mancera and C. Djerassi, *J. Amer. Chem. Soc.* **75**, 2601 (1953).
[409] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 2876 (1955).
[410] L. H. Sarett, *J. Amer. Chem. Soc.* **71**, 1165 (1949).
[411] C. Sannié and H. Lapin, *Bull. Soc. Chim.* 1237 (1957).
[412] P. L. Julian, E. W. Meyer and H. C. Printy, *J. Amer. Chem. Soc.* **70**, 3872 (1948).
[413] P. Wieland and K. Miescher, *Helv. Chim. Acta* **32**, 1768 (1949).
[414] Y. Sato, H. G. Latham and E. Mosettig, *J. Org. Chem.* **22**, 1496 (1957).
[415] F. Giral, *J. Amer. Chem. Soc.* **72**, 1913 (1950).
[416] G. W. Barber and M. Ehrenstein, *J. Org. Chem.* **19**, 1758 (1954).
[417] G. W. Barber and M. Ehrenstein, *J. Amer. Chem. Soc.* **76**, 2026 (1954).
[418] H. Heymann and L. F. Fieser, *Helv. Chim. Acta* **35**, 631 (1952).
[419] J. Warnant, *Bull. Soc. Chim.* 1456 (1956).
[420] R. B. Turner and D. M. Voitle, *J. Amer. Chem. Soc.* **73**, 2283 (1951).
[421] M. N. Huffman, M. H. Lott and A. Tillotson, *J. Biol. Chem.* **222**, 447 (1956).

In view of the great number of examples in the literature both of selective acylation and of selective hydrolysis of esters, results have been given in a shortened tabular form. (Tables 14 and 15.)

II. *Ethers*

(a) *Tetrahydropyranyl ethers.* Formation of tetrahydropyranyl ("THP") ethers, by reaction of a primary or secondary alcohol group with dihydropyran in a solvent such as chloroform or methylene chloride in the presence of a trace of acid, is an excellent method for protection of the hydroxyl group under basic reaction conditions.[422,423] They are stable to conditions of oxidative cleavage[424,425] or epoxidation[426] with alkaline hydrogen peroxide, and will protect the hydroxyl group during Dieckmann cyclisation,[425] reaction with Grignard reagents,[189] lithium alkyls[422a] and reduction with metal hydrides.[194,423] They are stable at high temperatures (pyrolitic elimination of ester groups,[427]) and reasonably stable in acetic acid solution as for example during chromic acid oxidation[140] of another hydroxyl group. They have been used in the preparation of 7-hydroxy 4-ene-3-keto-steroids: Oppenauer oxidation of a free 5-ene-3:7-diol gave only a low yield of the desired compound, while carrying out the reaction on the 7-THP ether 3-acetate was successful.[428]

A disadvantage of using dihydropyran to protect secondary alcohol groups lies in the formation of an additional asymmetric centre, leading in most cases to a mixture of stereoisomeric ethers, but this does not usually detract from the value of this method.

(b) *Triphenylmethyl ethers.* The conditions of stability of these ethers are similar to those of tetrahydropyranyl ethers.[325,365,429] Their formation is specific to primary[325,365] or easily accessible secondary[189] hydroxyl groups, and like tetrahydropyranyl ethers they are easily cleaved by dilute mineral acids.

[422] W. G. Dauben and H. L. Bradlow, *J. Amer. Chem. Soc.* **74**, 559 (1952).
[422a] C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 1190 (1951).
[423] A. C. Ott, M. F. Murray and R. L. Pederson, *J. Amer. Chem. Soc.* **74**, 1239 (1952).
[424] W. S. Johnson and D. S. Allen, *J. Amer. Chem. Soc.* **79**, 1261 (1957).
[425] W. S. Johnson, B. Bannister and R. Pappo, *J. Amer. Chem. Soc.* **78**, 6331 (1956).
[426] H. J. Ringold, E. Batres, O. Mancera and G. Rosenkranz, *J. Org. Chem.* **21**, 1432 (1956).
[427] R. Hirschmann, C. S. Snoddy, C. F. Hiskey and N. L. Wendler, *J. Amer. Chem. Soc.* **76**, 4013 (1954).
[428] C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 2375 (1952).
[429] H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.* **184**, 259 (1950).