International Review of Science

Steroids

Organic Chemistry
Series Two
Volume 8

Consultant Editor
D H Hey FRS
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Edited by **W. F. Johns**
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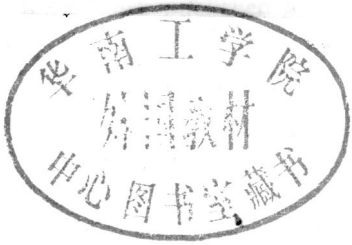

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Publisher's Note

The International Review of Science is an important venture in scientific publishing presented by Butterworths. The basic concept of the Review is to provide regular authoritative reviews of entire disciplines. Chemistry was taken first as the problems of literature survey are probably more acute in this subject than in any other. Biochemistry and Physiology followed naturally. As a matter of policy, the authorship of the Review of Science is international and distinguished, the subject coverage is extensive, systematic and critical.

The Review has been conceived within a carefully organised editorial framework. The overall plan was drawn up, and the volume editors appointed by seven consultant editors. In turn, each volume editor planned the coverage of his field and appointed authors to write on subjects which were within the area of their own research experience. No geographical restriction was imposed. Hence the 500 or so contributions to the Review of Science come from many countries of the world and provide an authoritative account of progress. The publication of Organic Chemistry Series One was completed in 1973 with ten text volumes and one index volume; in accordance with the stated policy of issuing regular reviews to keep the series up to date, volumes of Series Two will be published between the middle of 1975 and early 1976; Series Two of Physical Chemistry will be published at the same time, while Inorganic Chemistry Series Two was published during the first half of 1975. Volume titles are the same as in Series One but the articles themselves either cover recent advances in the same subject or deal with a different aspect of the main theme of the volume. In Series Two an index is incorporated in each volume and there is no separate index volume.

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Consultant Editor's Note

The ten volumes in Organic Chemistry in the Second Series of the biennial reviews in the International Review of Science follow logically from those of the First Series. No major omissions have come to light in the overall coverage of the First Series. The titles of the ten volumes therefore remain unchanged but there are three new Volume Editors. The volume on Structure Determination in Organic Chemistry has been taken over by Professor Lloyd M. Jackman of Pennsylvania State University, that on Alicyclic Compounds by Professor D. Ginsburg of Technion-Israel Institute of Technology, and that on Amino Acids, Peptides and Related Compounds by Professor H. N. Rydon of the University of Exeter. The international character of the Series is thus strengthened with four Volume Editors from the United Kingdom, two each from Canada and the U.S.A., and one each from Israel and Switzerland. An even wider pattern is shown for the authors, who now come from some sixteen countries. The reviews in the Second Series are mainly intended to cover work published in the years 1972 and 1973, although relevant results published in 1974 and 1975 are included in some cases, and earlier work is also covered where applicable.

It is my pleasure once again to thank all the Volume Editors for their helpful cooperation in this venture.

London

D. H. Hey

Preface

The strong, continuing interest in steroid chemistry reflects the important position these compounds have been accorded in both academic and industrial research. The substantial commercial significance of steroids, based on the essential endocrine properties of natural steroidal hormones, is stimulating research to find more potent, long-acting derivatives possessing sharply focused pharmacological properties. As a result, a wide variety of steroids have been prepared containing a great array of substituents, inverted asymmetric centres, nuclear hetero atoms, and modified ring skeletons. As these derivatives reach animal or human testing, the isolation, identification and synthesis of their metabolites becomes important. Much effort has also been devoted to the ingenious simplification of already succinct total syntheses of steroids. As a consequence, these routes have become competitive with methods starting from natural products.

Another principal subject of steroid research is based on the use of these readily available compounds as stereochemically defined and relatively rigid testing grounds for a diversity of reactions. Besides studies involving, for example, hydrocyanation, carbenoid additions and oxidation, the parameters for complex rearrangements have been studied intensively. In addition, the long-range effects of groups at specified distances from reactive centres have been investigated. The development of selective reactions and blocking groups also continues.

A third major topic of steroid papers is the identification and isolation of new natural products obtained from both plant and animal sources. Syntheses and intercorrelations of these materials have been developed in many cases.

This volume critically reviews the literature of 1972 and 1973; in some cases earlier studies are discussed to provide background information. The organisation of the contents in this text parallels that in the previous book of this series.

I would like to acknowledge the excellent cooperation offered me by each of the authors of this volume, the encouragement from Dr. P. D. Klimstra in my portion of this endeavour, and the secretarial assistance of Mrs. Beverly Laurence.

Chicago

W. F. Johns

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1
General Synthetic Transformations

D. N. KIRK
Westfield College, University of London

1.1 INTRODUCTION

The arrangement of this chapter is essentially the same as in Series One of this review, the material being classified according to the type of reaction. Again a comprehensive survey of the literature was impossible within the space available. This chapter therefore presents the author's own selection of those reactions deemed likely to be of wide interest.

1.2 REDUCTION

1.2.1 Hydrogenation

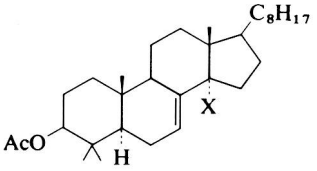
The selective hydrogenation of steroidal 5,7-dienes to give Δ^7-unsaturated compounds is usually accompanied by partial isomerisation of the Δ^7- to the $\Delta^{8(14)}$-unsaturated isomer; this complication is avoided by use of Raney nickel in the presence of triethylamine[1]. Hydrogenation of Δ^6-unsaturated steroids of the 5β series is non-stereospecific, as revealed by use of deuterium[2]. 5α-Androstan-17-one is reduced over platinum in acidified methanol to give 17β-methoxy-5α-androstane[3], suggesting a convenient and possibly general route to methoxy-steroids. Further studies of hydrogenation with soluble catalysts include the tritiation of 17β-hydroxyandrosta-4,6-dien-3-one with chlorotris(triphenylphosphine)rhodium in dioxan, which afforded the 6β,7β-[$^3H_2$] derivative with high specificity[4]. Androsta-1,4-diene-3,17-dione is reduced selectively at the 1 and 2 positions by hydrogenation in presence of any of a series of dichlorotris(triarylphosphine)ruthenium derivatives, with a variety of *p*-substituents in the phenyl rings. The rate of reaction is increased by the presence of triethylamine or diethylamine[5].

1.2.2 Hydride donors

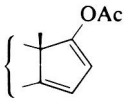
$LiAlH_4$ reduces an ergostan-23-one to give the 23*S*- and 23*R*-alcohols in the ratio 7 : 3, in accordance with Cram's rule, but the 22-one gave the 22*S*- and 22*R*-alcohols in the ratio 7 : 1, contrary to Cram's rule[6]. It was concluded that steric restraints affecting the side-chain must enforce a conformation in the vicinity of C-22 which causes the reduction to occur in the sense contrary to prediction.

A 32-nitrile (1) is incompletely reduced by $LiAlH_4$, giving the 32-aldehyde

(2) after hydrolysis, although the aldehyde can then be further reduced to give the 32-alcohol (3)[7]. The $\Delta^{14,16}$-dien-17-ol acetate (4) is reduced by $NaBH_4$ to give the Δ^{14}-en-17β-ol (5)[8]; since the dienol acetate is readily obtained in three steps (bromination, dehydrobromination, enol acetylation) from the saturated 17-ketone[9], this sequence affords a convenient route to androst-14-ene derivatives.



(1) X = CN
(2) X = CHO
(3) X = CH_2OH



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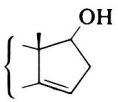

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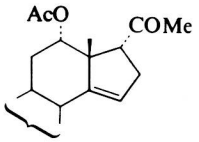
Several novel applications of sodium cyanoborohydride ($NaBH_3CN$) are reported. Its stability to weak acids permits the reduction of ketones in acidified THF as solvent, presumably by hydride transfer on to the protonated ketone. Pronounced differences in reactivity permit the selective reduction of a 3-oxo group in the presence of either a 17-oxo or a 20-oxo function[10]. αβ-Unsaturated ketones may be reduced by $NaBH_3CN$ with either 1,2- or 1,4-addition of hydrogen, the resulting proportions of allylic alcohol and saturated ketone depending on the pH of the solution, and on the particular enone being reduced[11]. Reductive amination of 3-oxo steroids can be achieved by the action of $NaBH_3CN$ in the presence of an ammonium (or alkylammonium) salt[12]. The ammonium salt converts the ketone reversibly into an iminium ion, which is reduced more rapidly than the ketone, giving mainly the 3β-amino (or alkylamino) derivative. Again 17-oxo or 20-oxo groups are inert, allowing selective amination at C-3.

Ketones may be deoxygenated to the corresponding saturated hydrocarbons by reducing their tosylhydrazones with $NaBH_3CN$ in acidified DMF–sulpholane. Most other functional groups (e.g. esters, amides, nitriles) are inert to this reagent system[13].

Diborane reduces the pyrrolidyl enamines of 3-oxo steroids to give saturated 3α- and 3β-pyrrolidino-steroids; the products are initially formed as amine–borane adducts, but these can be decomposed by methanol to liberate the amine[14].

Pregna-14,16-dien-20-ones have been reduced selectively at the Δ^{16}-unsaturated bond by triethylsilane to give the 14-en-20-one, but only with the inconvenience of reaction in a sealed tube. The same result is achieved more conveniently by use of one of the less volatile compounds $Et_2(EtO)SiH$ or $(Me_2SiH)_2O$ [15]. The alternative reagent Ph_3SnH has been used for the same purpose, but in the presence of a 12α-acetoxy substituent gave the 17α-pregn-14-en-20-one derivative (6) accompanied by the unusual lactone (7)[16].



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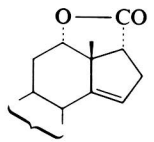


(7)

Reduction of ketones to axial alcohols by propan-2-ol containing chloroiridic acid and trimethyl phosphite (Henbest's procedure) is not as specific for 3-oxo steroids as had been thought[17]; 5α-androstan-12-one[18] and a 2-oxo-5α-steroid[19] were reduced to give the corresponding axial alcohols. Added NaOH enhances reactivity, a 17-oxo steroid then being reduced to give the 17β-alcohol. Chlorotris(triphenylphosphine)rhodium is said to be superior even to the iridium reagent for selective reduction of 3-oxo steroids to give axial alcohols[19].

Iron pentacarbonyl with NaOH, in a moist solvent, generates a hydrido–iron complex which can be used *in situ* for the selective reduction of cholest-4-en-3-one to give 5β-cholestan-3-one, or by use of D_2O to give the 5β-deuterio-ketone[20].

Benzyl alcohol is an effective hydride donor for the transfer-hydrogenation of reactive olefinic or acetylenic bonds[21]. A 1-en-3-one gives the saturated ketone, but a 1,4-dien-3-one or a 4,6-dien-3-one afford the 4-en-3-one as the main product. 3β-Hydroxypregna-5,16-dien-20-one is reduced selectively at the Δ^{16}-bond, and 17α-ethynylandrost-5-ene-3β,17β-diol was reduced to give the 17α-ethylandrostenediol. The benzyl oxide anion can also apparently function as a hydride donor for reduction of the olefinic bond in a 1-en-3-one, but the basic conditions seemingly promote condensation of the resulting benzaldehyde and saturated ketone, for the product was the 2-benzylidene-3-ketone[22].

1.2.3 Metals and their compounds

5α-Cholest-8(14)-en-7-one is reduced stereospecifically by either Li–NH_3 or Zn–HOAc to give the unusual 5α,14β-cholestan-7-one[23]. Alcohols or ketones may be deoxygenated to give saturated products by forming their esters or enol esters, respectively, with the reagents $(Me_2N)_2POCl$ or $(EtO)_2POCl$, and reducing these esters with Li–$EtNH_2$; an 11α-hydroxy steroid, for example, is deoxygenated by this reaction sequence[24]. The Clemmensen reduction, modified by use of Zn–Ac_2O–HCl in a hydrocarbon solvent, converts ketones, enones or α-acetoxy ketones efficiently into hydrocarbons[25].

The reduction of αβ-epoxy-ketones with chromium(II) acetate has been extended to 4α,5α-epoxy and 4β,5β-epoxy-3-oxo steroids, giving the corresponding 5-hydroxy-3-ketones; a 6α,7α-epoxy-4-en-3-one similarly gave the 7α-hydroxy-4-en-3-one[26]. Yields are *ca.* 50%, the reactions being accompanied by elimination to give the 4-en-3-one or 4,6-dien-3-one, respectively, but the use of chromium(II) acetate rather than the salt of a stronger acid minimises the extent of the elimination reaction. Lithium dimethylcuprate

($LiCuMe_2$) has reducing properties, thought to depend on an initial electron transfer from the Me_2Cu^- ion. A 4β,5β-epoxy-ketone is reduced selectively to give the 5β-hydroxy-3-ketone[27]; α-acetoxy- or α-bromo-ketones are converted into the corresponding unsubstituted ketones[28].

Iron pentacarbonyl exhibits selective reducing properties, converting enol acetates or vinyl chlorides into olefins, removing the acetoxy group from α-acetoxy-ketones, or decarbonylating an αβ-unsaturated aldehyde[29]. Nickel boride (Ni^{II} salt + $NaBH_4$) desulphurises a thioacetal, but gives a mixture of the corresponding saturated and unsaturated hydrocarbons. The reagent is generally less effective than Raney nickel, unless the reaction conditions are carefully chosen[30].

1.2.4 Miscellaneous reductions

A 15β,16β-epoxy-17-ketone is known to react with hydrazine to give the Δ^{16}-unsaturated 15β-alcohol, but the reaction has often proved unreliable. Use of hydrazine and toluene-*p*-sulphonic acid, with aeration, is reported to give the *saturated* 15β-alcohol in good yield, apparently by hydrogenation of the Δ^{16}-olefinic bond in the primary product through reaction with di-imide, an oxidation product of hydrazine[31]. Huang–Minlon reduction of 5α-androstane-3,11,17-trione gave the 11-hydrazone of 5α-androstan-11-one as the major product[32]; similar reduction of an 8(14)-en-7-one gave a mixture of isomeric olefins[33].

'Thiourea dioxide' in n-propanol containing sodium propoxide will reduce 3-oxo-5α-steroids selectively to give the 3β-alcohols[34]. Photoreduction occurred when a 4,5-methano-3-ketone was irradiated in propan-2-ol; the main product was the 5β-methyl 3-ketone, irrespective of the original configuration of the methano group[35]. A plausible mechanism for stereochemical inversion is proposed.

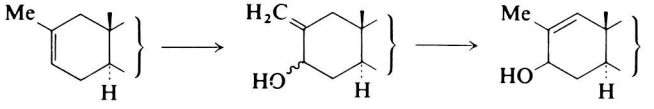
1.3 OXIDATION

1.3.1 Auto-oxidation and photo-oxidation

Several recent papers have been concerned with the auto-oxidation of cholesterol[36,37]. The main product of attack by ground-state (triplet) oxygen is the 7β-hydroperoxy derivative, probably resulting from combination of oxygen with an allylic free radical embracing C-5, C-6 and C-7, which can arise under a variety of conditions, including exposure to daylight[38]. Enzymic oxidation is apparently similar[39]. The C-20 isomeric 20-hydroperoxypregn-5-en-3β-ols have been isolated from cholesterol after ageing in air at 70 °C in the dark[40]. Photosensitised oxidation of cholesterol (singlet oxygen) gives the 5α-hydroperoxy-6-ene as major product, along with traces of the 6α- and 6β-hydroperoxy-Δ^4-isomers[41].

A detailed study of the photosensitised oxidation of 2-methyl- (8) and 3-methyl-5α-cholest-2-ene (11) has given mixtures of products (9) and (10), and (12) and (13), respectively.

The results are interpreted as evidence for a reactant-like transition state[42].



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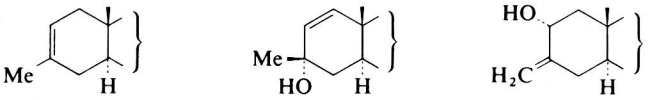
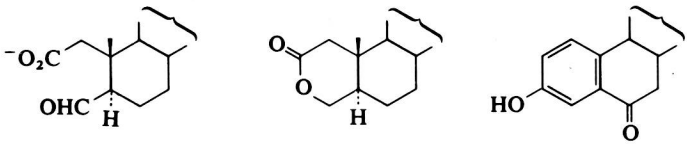


(11) (12) (13)

Oxygenation of 5α-cholestan-3-one in the presence of $KOBu^t$ causes expulsion of C-3 to give the carboxy-aldehyde (14), readily convertible into the lactone (15) by reduction ($NaBH_4$) and acidification[43]. An oestr-4-en-3-one reacts with oxygen in anhydrous DMF or DMSO containing KOAc at 120 °C to give the 6-oxo-phenolic derivative (16)[44].

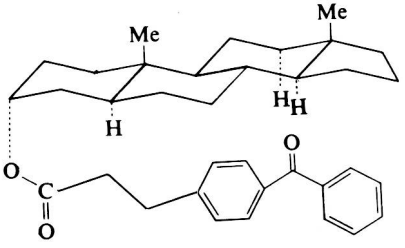


(14) (15) (16)

The photo-oxidation of ergosteryl esters to give the 5α,8α-peroxide is catalysed by either trityl tetrafluoroborate or tris-(*p*-bromophenyl)aminium-hexachloroantimonate $[(p\text{-}BrC_6H_4)_3N^+\ SbCl_6^-]$[45].

Several new examples of the introduction of substituents into non-activated positions in the steroid nucleus have been described. Irradiation of a steroid in CCl_4 or $BrCCl_3$ causes halogenation (Cl or Br, respectively) at the 9α- and 14α-positions, through a free radical mechanism. Solutions containing $C_6H_5ICl_2$ are even more effective for the photochemical introduction of 9α- or 14α-Cl substituents[46]. The products were dehydrohalogenated prior to isolation as the $\Delta^{9(11)}$- or Δ^{14}-olefinic derivatives.

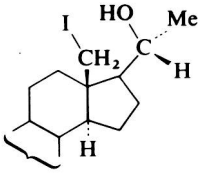
The possibilities for 'remote oxidation' by photochemically excited benzophenone derivatives, attached via an ester linkage to the steroid molecule, have been explored in detail[47]. Molecular models give useful indications of possible points of attack. 5α-Cholestan-3α-yl benzophenone-4′-propionate (17), for example, is seen to have a shape which permits the benzophenone oxygen atom to approach either the 7α-, 12α- or 14α-hydrogen atoms without undue strain, so that a mixture of products (e.g. olefins) results from abstraction of one or another of these hydrogens. Numerous examples of successful oxidations are given, along with some instances of unreactive esters (e.g. of 3β-hydroxy-5α-steroids), where molecular geometry prevents approach of the benzophenone to the body of the steroid. These and related reactions



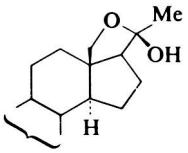
(17)

have been reviewed[48]. In a similar fashion, irradiation of 5α-androstan-3α-yl β-(*p*-nitrophenyl)propionate gave the 14α-hydroxy and a little of the 12α-hydroxy derivative, characterised after oxidation to 5α-androst-14-en-3-one and 5α-androstane-3,12-dione, respectively[49].

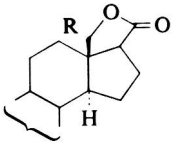
The conversion of a pregnan-20β-ol into an 18-substituted steroid is commonly achieved by irradiation with iodine and $Pb(OAc)_4$ (hypoiodite reaction). The initial product, the 18-iodo-20β-alcohol (18), has hitherto been converted without isolation into the hemiacetal (19), by oxidation followed by Ag^+- assisted hydrolysis. Superior overall yields are now claimed by the isolation of the iodo-alcohol (18), which proved fairly stable, and was obtained in 60% yield[50].



(18)



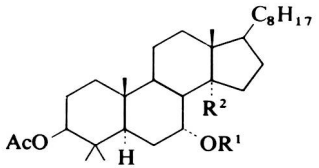
(19)



(20) R = H_2
(21) R = O

Conditions similar to the hypoiodite reaction transformed an etianic acid amide into mixtures of the lactone (20) and the acid anhydride (21), in variable proportions depending on the reaction conditions[51].

Photolysis of the 7α-nitrite (22) in the lanostane series in the absence of oxygen gives the 32-oximino derivative (23), but when oxygen was bubbled through the solution during irradiation the product was the 32-nitrate (24), which could be reduced by Zn–HOAc to afford the 7α,32-diol (25)[52]. This seems a particularly convenient and direct route for the introduction of a hydroxy function at a non-activated site.



(22) R^1 = NO, R^2 = Me
(23) R^1 = H, R^2 = CH:NOH
(24) R^1 = H, R^2 = CH_2ONO_2
(25) R^1 = H, R^2 = CH_2OH