2,3-DICHLORO-5,6-DICYANOBENZOQUINONE AND ITS REACTIONS

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I. INTRODUCTION

2,3-Dichloro-5,6-dicyanobenzoquinone, hereafter referred to as DDQ, was first reported by Thiele and Günther in 1906 (229). Little interest was shown in the compound, however, until Linstead, Braude, Jackman, and co-workers (35, 146) found it to be a very superior reagent for the dehydrogenation of hydroaromatic compounds, a type of reaction known with quinones for some time (65). The reactions of DDQ were reviewed briefly by Jackman in 1960 as part of a general treatment of hydrogenation–dehydrogenation reactions (131). Since 1960, DDQ has found considerable application in the steroid field, and its use in other areas continues to grow.

II. SCOPE OF REVIEW

This review, which covers the entire literature pertaining to DDQ, was greatly facilitated by Jackman's review (131), and by the chapters contributed by Neustaedter and Owyang to a recent book edited by Djerassi (91). Literature citations to the end of 1965 have been included, along with patent references gathered from *Chemical Abstracts* up to and including page 5716 of Volume 64.

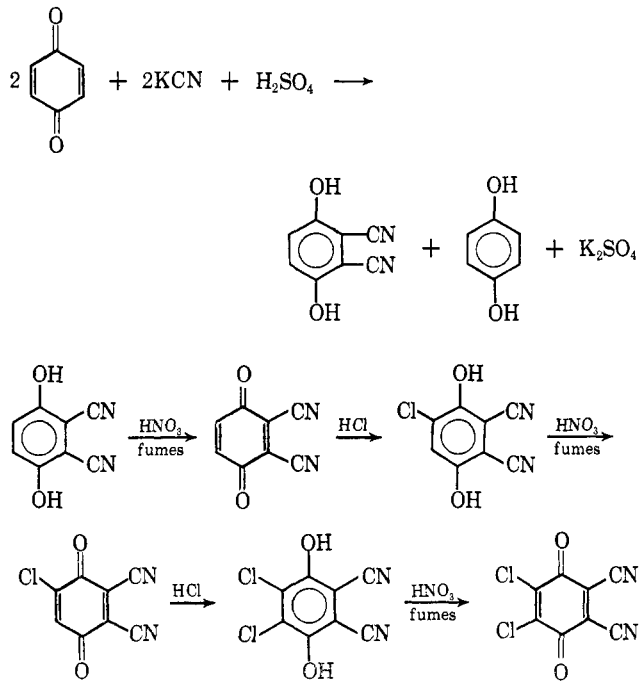
III. NOMENCLATURE

The *Chemical Abstracts* and I.U.P.A.C. nomenclature rules S-1 to S-7.5 have been used throughout this article (82).

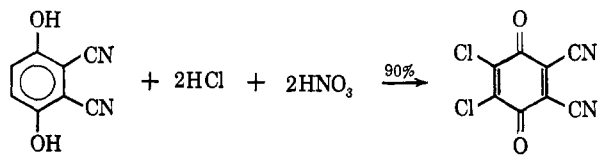
IV. SYNTHESIS

The first synthesis was described by Thiele and Günther (229) and used the following steps.

(1) Tarn Rigge, Thornbarrow Rd., Windemere, Westmorland, England.



Following the renewed interest in DDQ sparked by Linstead, Braude, Jackman, and co-workers, several improvements in the process were made. Brook (43) found that mixed nitrogen oxides were superior to nitric acid fumes. Later, Mitchell (161) showed that 2,3-dicyanohydroquinone could be chlorinated directly to 2,3-dichloro-5,6-dicyanohydroquinone in acetic acid, and that this hydroquinone could be converted to DDQ by the action of lead dioxide in aqueous ethanol containing hydrochloric acid. The over-all yield from 2,3-dicyanohydroquinone was 36.5%. DDQ has also been synthesized from chloranil using potassium cyanide, and then nitrogen tetroxide for the final oxidation (243). The over-all yield using this process was 20.2%. A single-step synthesis starting from 2,3-dicyanohydroquinone has been reported by Walker and Waugh (242), and material prepared by this procedure is now available commercially.



V. Physical Properties

A. Melting Point, Solubility, and Purification

DDQ is a brilliant yellow solid, mp 213–215°, which can be stored indefinitely in a dry atmosphere. It decomposes in the presence of water, though the rate of decomposition is considerably retarded in the presence of strong acid. DDQ may be purified by crystallization from a large volume of methylene chloride. Very crude samples of DDQ are best purified by reduction to 2,3-dichloro-5,6-dicyanohydroquinone, which material is, in turn, purified by clarifying its solution in aqueous base and precipitating with acid. The 2,3-dichloro-5,6-dicyanohydroquinone so obtained may be conveniently converted to DDQ by the standard method (242).

No information is available in the literature concerning the solubility of DDQ. It therefore seems worthwhile to give some approximate figures obtained by us in our laboratories. These solubilities were determined by slurrying excess solid with a solvent and filtering after 26 hr (DDQ results) or 5 days (2,3-dichloro-5,6-dicyanohydroquinone results). The weight of insoluble solid was deducted from the starting weight to obtain a solubility figure. The figures for DDQ should be read with caution since this quinone is known to undergo autodecomposition in various solutions (52, 107). Furthermore, with some solvents used in our solubility determinations, hydrogen cyanide was detected in the vapor standing above the liquid surface.

Table I
Solubilities of DDQ and 2,3-Dichloro-5,6-dicyanohydroquinone at 25°

Solvent	Solubility of DDQ, g/l.	Solubility of 2,3-dichloro-5,6-dicyanohydroquinone, g/l.
Methylene chloride	21	0.4
Benzene	68	0.6
Ethyl acetate	570[a]	120
t-Butyl alcohol	12[a]	38
Tetrahydrofuran	660	260
Acetic acid	65	3.5
Dioxane	180	1.8

[a] HCN detected in vapor by vapor phase chromatography (119a).

B. Spectra

The ultraviolet spectrum of DDQ is difficult to plot since the quinone undergoes autodecomposition in dilute solution. It is said, however, that concentrated solutions "undergo negligible decomposition over a period of several hours" (52). DDQ is reported to show a maximum at 390 mμ in dioxane and at 410 mμ in benzene. The maximum in benzene has been used to follow the DDQ dehydrogenation of steroidal allylic alcohols since there is no interference from 2,3-dichloro-5,6-dicyanohydroquinone, which absorbs at 362 mμ (52).

The infrared spectrum of DDQ (KBr pellet) shows a weak absorption at about 2210 cm^{-1} (CN) and strong absorptions at about 1680 (quinone) and 1555 cm^{-1} (>C=C<).

DDQ shows no esr signal when pure, but when mixed with the hydroquinone a broad radical signal, attributable to semiquinone formation, appears immediately (113).

C. OXIDATION–REDUCTION POTENTIAL

Table II gives the reduction potential of DDQ and other quinones as determined by various workers.

TABLE II
REDUCTION POTENTIALS

Quinone	E_0 (pH 0, H_2O)[a,b]	E_1 (CH_3CN)[a,c]	E_0 (95% EtOH in HCl, 25°)[d]
DDQ	1.0[f]	0.51	...
Tetrachloro-*o*-benzoquinone	...	...	0.870[e]
Chloranil	0.452[f]	0.01	0.703
Trichloro-*p*-benzoquinone	0.486[f]	−0.08	0.726
2,6-Dichloro-*p*-benzoquinone	0.475	−0.18	0.748
Chloro-*p*-benzoquinone	0.466	−0.34	0.736
Tetramethyl-*p*-benzoquinone	0.220	−0.84	0.466
Methyl-*p*-benzoquinone	0.399	−0.58	0.656
p-Benzoquinone	0.433	−0.51	0.711
1,4-Naphthoquinone	0.224	−0.71	...

[a] Potentials of quinones are in volts *vs.* sce. [b] From Clark (66). [c] One-electron reduction potentials determined by polarographic method (185). [d] By titration method (67). [e] 50% alcohol (68). [f] In ethanol.

As might be expected, results in hydroxylic systems are anomalous, and this is particularly true for the halogenoquinones. Here, general solvation changes, especially the effects produced by hydrogen bonding, contribute in an unpredictable manner. E_0 values should, therefore be interpreted with care. On the other hand, $E_1(CH_3CN)$ potentials are considered to be linearly related to the electron affinity of the molecule (185).

VI. DEHYDROGENATION

The introduction of a double bond by hydride ion abstraction and proton elimination constitutes the primary reaction of DDQ, although a few examples are recorded where radicals are produced by this quinone. The goal of this section of the review is to discuss the reactions of DDQ and the mechanisms of these reactions and to draw comparisons with other and comparable reagents.

A. DEHYDROGENATION OF STEROID KETONES

The dehydrogenation of this class of compounds has received considerable attention as a result of findings that the dehydro products of readily accessible keto steroids are frequently found to possess desirable biological activity. Furthermore, dehydro products often prove to be useful intermediates in the synthesis of other modified steroids.

The DDQ dehydrogenation method has been used particularly in the dehydrogenation of Δ^4-3-keto steroids, and here either A- or B-ring dehydro products are obtained, depending on the conditions employed.

1. Dehydrogenation of Δ^4-3-Keto Steroids

The dehydrogenation of this class of compounds with DDQ under neutral or weakly acidic conditions gives mostly $\Delta^{1,4}$-3-keto steroids, while in the presence of strong acid, $\Delta^{4,6}$-3-keto steroids are the predominant products.

a. Δ^4- to $\Delta^{1,4}$-3-Keto Steroids

The DDQ-mediated dehydrogenation of Δ^4-3-ketones is usually considered as giving $\Delta^{1,4}$-3-ketones. However, in the case of androst-4-ene-3,17-dione, Ringold and Turner (200) showed that $\Delta^{1,4}$-, $\Delta^{4,6}$-, and $\Delta^{1,4,6}$-3-ketones were produced in a ratio of 10:1:1. Since the $\Delta^{1,4}$-3-ketone was unaffected by DDQ, while the $\Delta^{4,6}$-3-ketone readily gave the $\Delta^{1,4,6}$-3-ketone, it was reasoned that the ratio of the initial C-1 to C-7 hydride ion abstraction was approximately 5:1.

It is generally understood that Δ^4-3-ketones might give rise to $\Delta^{4,6}$-3-ketones, and hence $\Delta^{1,4,6}$-3-ketones, even though most workers make no mention of such products occurring. The nature of the product depends on kinetic factors, and principally on the relative rates of formation of the two possible enols and the rates of reaction of these with DDQ (section VI, I).

The following tables list all the conversions of Δ^4-3-ketones to $\Delta^{1,4}$-3-ketones which were found in the literature: Table III for steroids of the androstane series, Table IV for steroids of the pregnane series, and Table V to cover all other types. The structures given in the tables are of the starting material. All give rise to the corresponding $\Delta^{1,4}$-3-ketones.

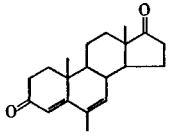
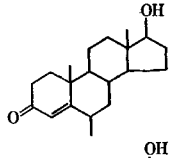
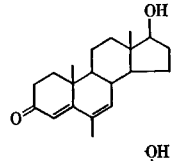
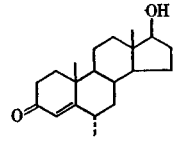
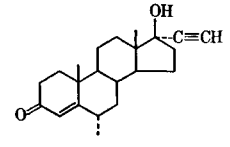
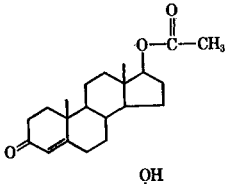
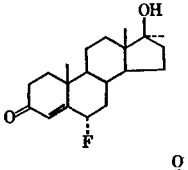
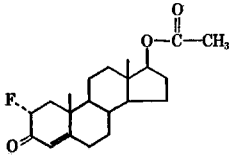
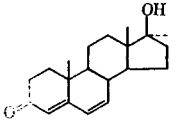
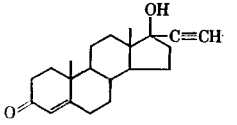
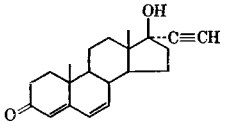
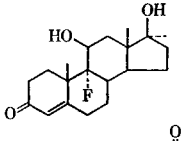
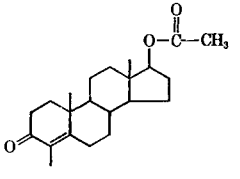
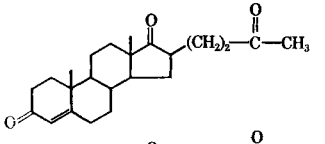
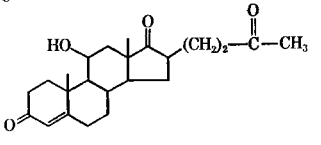
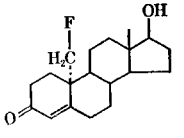
b. Δ^4- to $\Delta^{4,6}$-3-Keto Steroids

When DDQ is allowed to react with Δ^4-3-ketones in the presence of a strong acid, $\Delta^{4,6}$-3-ketones are formed. Anhydrous hydrogen chloride is most often used as the acid catalyst, though concentrated sulfuric acid has also been employed (224). The first Δ^4-3-ketones to be studied in this reaction, namely androst-4-ene-3,17-dione, testosterone, and progesterone, gave almost exclusively $\Delta^{4,6}$-3-ketones and only traces of $\Delta^{1,4}$- and $\Delta^{1,4,6}$-3-ketones (200). Coombs (69), however, has reported that testosterone acetate, with DDQ–hydrogen chloride, gave a product contaminated with about 10% of the $\Delta^{1,4}$-3-ketone.

Little investigation has been made to establish the optimum concentration of hydrogen chloride in this reaction; most workers simply bubble hydrogen chloride into the reaction mixture for an arbitrary period. In the case of 6β-methyl-9β,10α-pregn-4-ene-3,20-dione it has been shown that as little as 1 mg of HCl/ml of dioxane is sufficient to lead to some 6-dehydro product (133), though as much as 136 mg of HCl/ml of dioxane was used to convert other 6α-methylretro-Δ^4-3-ketones

TABLE III

$\Delta^4 \rightarrow \Delta^{1,4}$-3-KETOANDROSTANES

Starting material G	Starting material Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions[a]	Yield[f]	Ref
7.5		150	C_6H_6	6.2	R, 6 hr	...	50
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		...	...	...	...	...	60
0.5		6	C_6H_6	0.45	R, 8 hr	...	135
1.2		10	C_6H_6	1	R, 30 hr	80%	135
0.25		5	C_6H_6	0.25	R, 6 hr	...	252
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
1		40	Dioxane	1	R, 6 hr	...	6
1.3		...	Dioxane	1	...	...	6
0.5		10	Dioxane	0.35	R, 10 hr	...	24

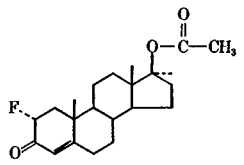
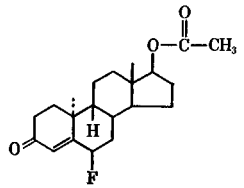
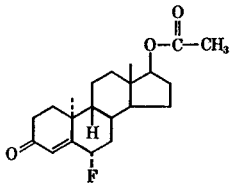
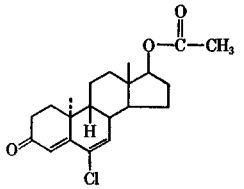
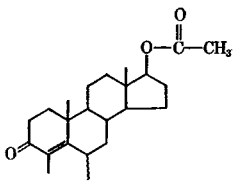
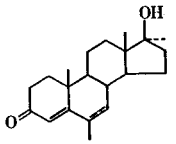
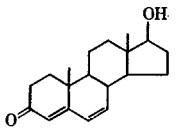
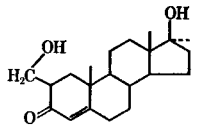
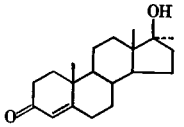
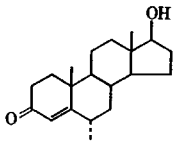
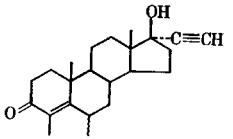
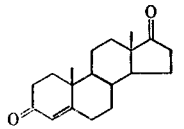
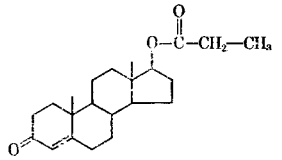
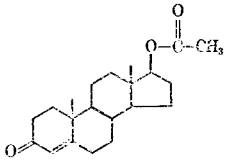
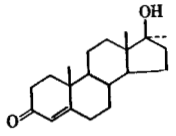
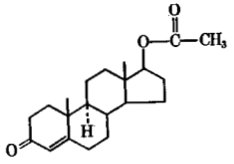
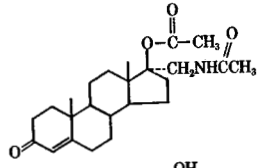
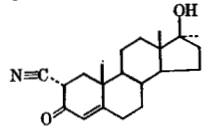
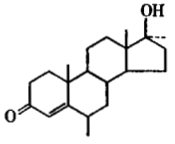
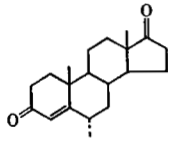
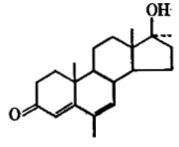
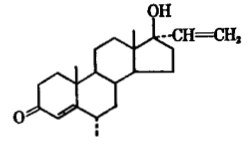
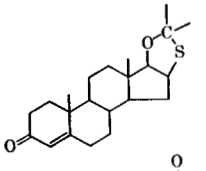
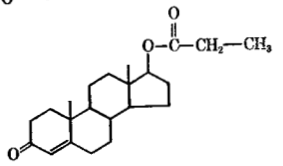
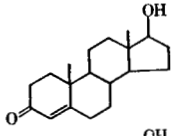
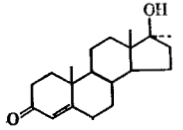
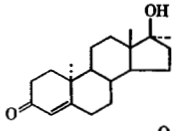
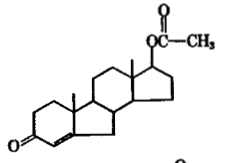
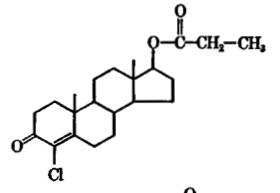
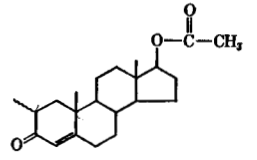
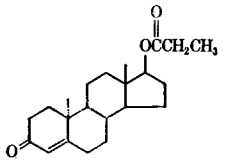
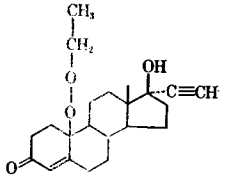
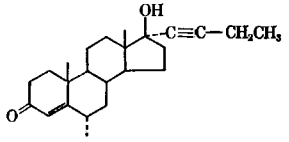
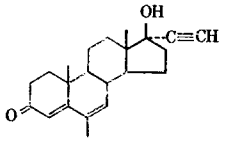
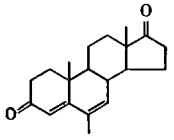
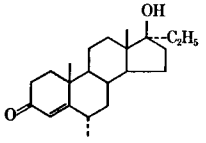
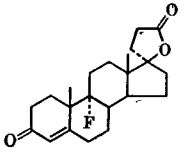
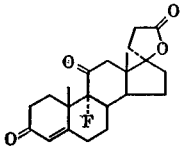
Starting material G	Starting material Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
1		10	C_6H_6	1	R, 25 hr	...	135
4		100	C_6H_6 dry	4	R,[b] 7 hr	...	251
4.9		125	Dioxane dry	6.09	R,[b] 21 hr w/N_2	1.67	188
2.72		70	Dioxane dry	2.14	R, 20 hr	...	188
...		...	C_6H_6 or dioxane	1.1 to 1.3 moles	R	...	48
...		...	C_6H_6 or dioxane	1.1 to 1.3 moles	R	...	48
3		120	Dioxane	3	R, 24 hr	...	59
1		10	Dioxane	1.1 equiv	1 min	...[a]	27
...		...	C_6H_6 or dioxane	1.1 to 1.5 moles	R	...	48
...		...	C_6H_6 or dioxane	1.1 to 1.5 moles	R	...	48
...		...	C_6H_6 or dioxane	1.1 to 1.5 moles	R	...	48
...		...	...	...	...	...	200
10		350	C_6H_6	7.3	R, 31 hr	8.42	227
4		120	C_6H_6	3.5	R, 24 hr	2.8 (70%)	240

TABLE III (*Continued*)

Starting material G	Starting material Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
19.9		400	Dioxane	19.9	R, 24 hr	...	61
0.2		...	...	0.5	R, 8 hr	...	64
...		...	...	...	...	...	71
10		50	Dioxane	10	90°, 4 hr	1.9	180
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		10	*t*-BuOH	...	R, 4 hr	...	257
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
2		...	C_6H_6	1.7	R, 7 hr	1.36	191
...		...	Dioxane	...	R	...	34
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252

Starting material G	Starting material Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
27.6		1200	C_6H_6 dry	21.8	R, 23–30 hr	14.6	141
1		10	Dioxane	1	R, 1 hr	...	210
...		30	C_6H_6	0.2	R 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
...		30	C_6H_6	0.2	R, 12 hr	...	134
30–35		2400	Dioxane	20	R, overnight	...	44
30–35		2400	Dioxane	20	R, overnight	...	44

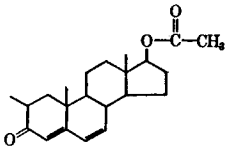
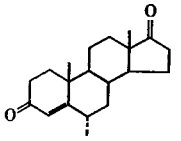
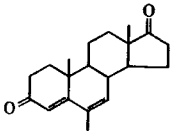
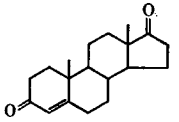
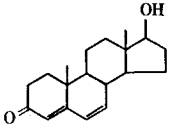
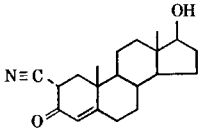
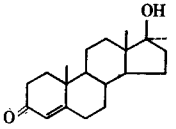
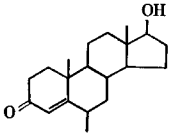
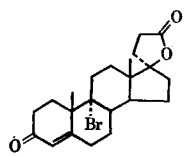
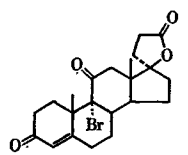
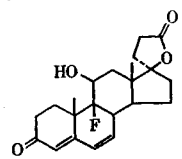
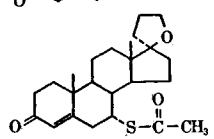
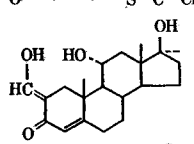
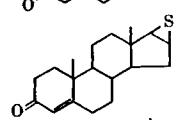
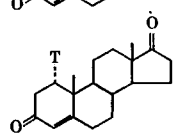
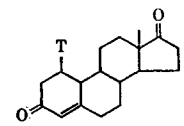
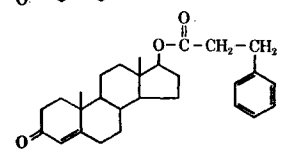
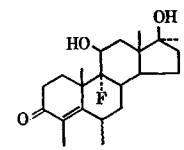
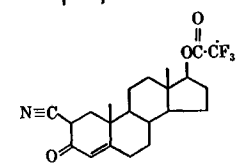
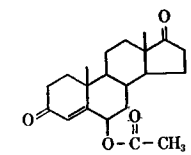
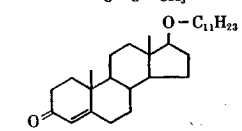
Starting material G	Starting material Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
3		30	Dioxane	3	R, 3 hr	...	50
5		50	C_6H_6	4	R, 12 hr	...	50
0.2		30	C_6H_6	0.2	R, 12 hr	...	134
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
9		60	Dioxane	8	90°, 2 hr	2.0	180
2		160	C_6H_6	2	R,[d] 20 hr	1.3	181
...		...	C_6H_6 or dioxane	1.1 to 1.5 moles	R	...	48

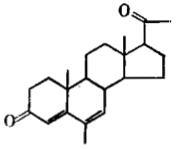
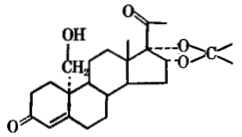
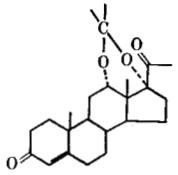
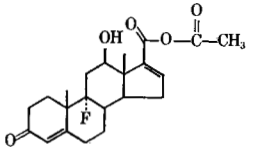
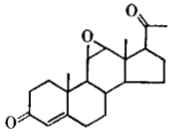
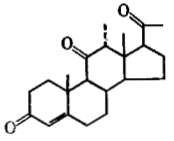
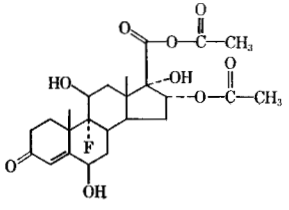
TABLE III (*Continued*)

Starting material G	Starting material Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
30–35		2400	Dioxane	20	65°, 4 hr	...	44
30–35		2400	Dioxane	20	65°, 4 hr	...	44
30–35		2400	Dioxane	20	65°, 4 hr	...	44
3		35	C_6H_6	2.75	R, 8 hr w/N_2	...[c]	160
1		40	Dioxane	0.7	2 hr	...	56
0.502		30	C_6H_6	0.234	R, 15 hr	0.385	256
...		...	Dioxane	...	...	...	42
...		...	Dioxane	...	...	...	42
12.4		200	PhMe	14	R, 6 hr	...	154
...		...	C_6H_6 or dioxane	1.1 to 1.5 moles	R	...	48
0.17		25	Dioxane	0.171	R, 18 hr	...	137
0.5		25	C_6H_6	0.395	R, 48 hr	0.308	94
6.6		50	C_6H_6	4	R, 10 hr w/N_2	6.4	62

[a] Product contains a 2-CHO group. [b] *p*-Nitrophenol used as catalyst. [c] Product contains 7-SH group. [d] 3,5-Dinitrobenzoic acid used as catalyst. [e] R = reflux. [f] In grams unless specified otherwise.

Table IV

$\Delta^4 \rightarrow \Delta^{1,4}$-3-Ketopregnanes

Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions[a]	Yield[c]	Ref
5		75	C_6H_6	5	R, 4 hr	...	50
0.5		10	Dioxane	0.35	R, 10 hr	...	77
0.1		4	Dioxane	0.065	R, 6 hr w/N_2	...	86
1		50	Dioxane	0.7	R, 7 hr	...	85
1		50	Dioxane	0.7	R, 6 hr w/N_2	...	88
0.1		10	Dioxane	0.06	R, 6 hr w/N_2	...	90
2.7		45	Dioxane	7.74	R, 20 hr	0.22	96

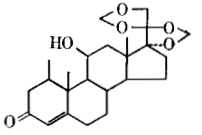
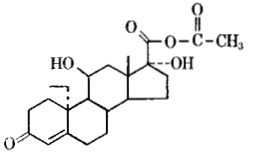
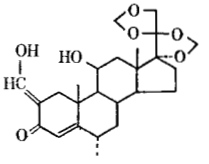
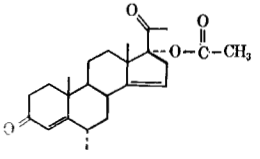
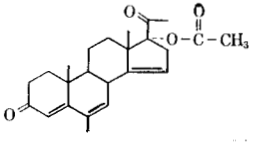
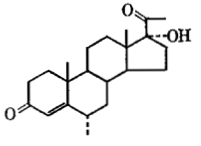
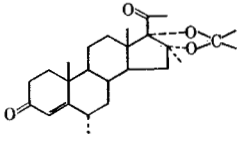
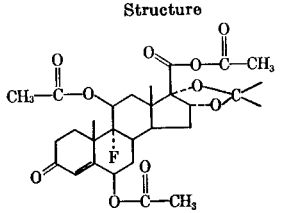
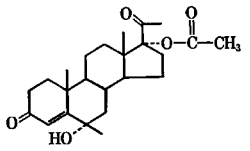
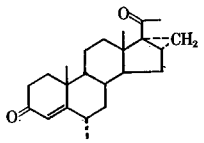
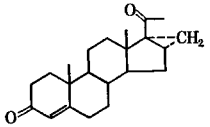
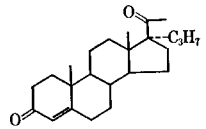
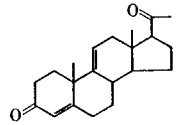
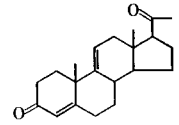
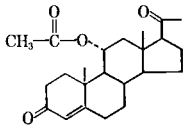
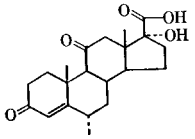
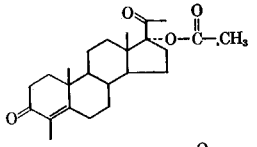
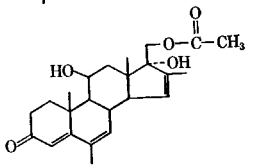
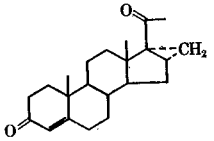
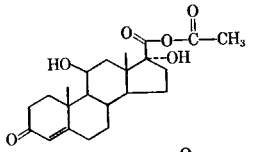
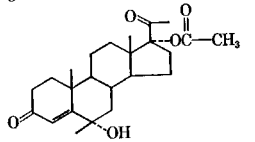
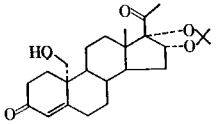
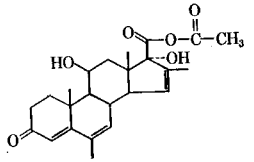
Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions[a]	Yield[c]	Ref
418		4	Dioxane	...	R	0.184	20
0.5		10	Dioxane	0.35	R, 10 hr	...	22
2		50	Dioxane	2	20°, 2 min	...	28
2		28	C_6H_6	2	R, 19 hr	...	41
0.5		...	C_6H_6	0.5	R, 19 hr	...	41
1 *M*		...	C_6H_6 or dioxane	1.1 to 1.5 *M*	R	...	48
1 *M*		...	C_6H_6 or dioxane	1.1 to 1.5 *M*	R	...	48

TABLE IV (*Continued*)

Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
0.9		15	Dioxane	0.64	R, 24 hr	0.032	96
0.3		25	Dioxane	0.3	R, 20 hr	0.165	98
1.5		100	Dry C_6H_6	1.5	R, 20 hr	0.4	47
...		...	...	...	R, 12 hr	...	55
...		...	...	...	..	...	290
20		400	Dioxane	14	R, 10 hr	...	222
...		...	...	...	...	...	223
0.375		5	Dioxane	0.28	R, 10 hr w/N_2	0.184	232
1 *M*		...	C_6H_6 or dioxane	1.1 to 1.5 *M*	R	...	48
1.2		10	Dioxane	1	R, 10 hr	...	49
5		75	Dioxane	4.8	R, 20 hr	...	157
1.5		20	Dry C_6H_6	1.7	R, 25 hr	0.5	47
1 *M*		...	Dioxane or C_6H_6	1.1 to 1.5 *M*	R	...	48
0.3		25	Dioxane	0.3	R, 20 hr	...	98
0.5		10	Dioxane	0.35	R, 10 hr	...	77
...		...	Dioxane	...	R, 20 hr	...	248

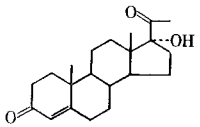
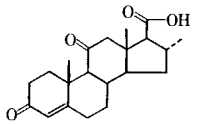
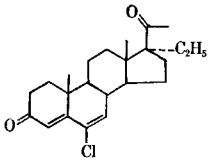
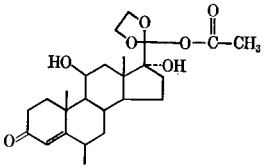
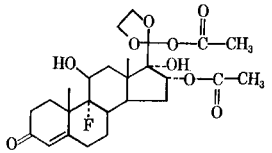
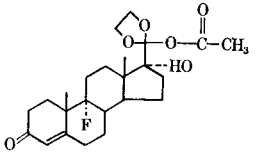
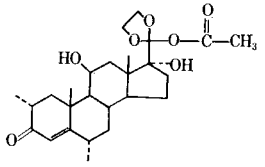
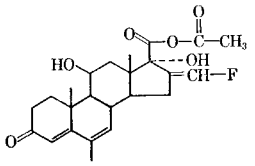
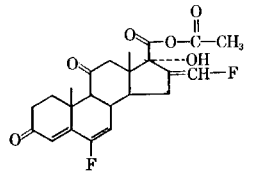
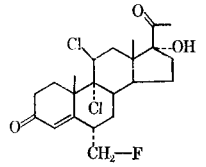
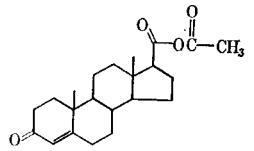
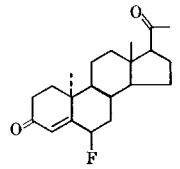
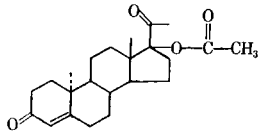
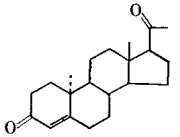
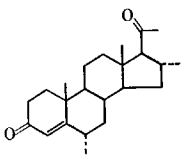
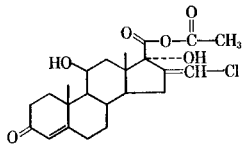
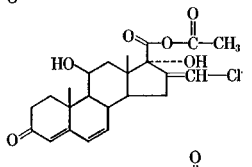
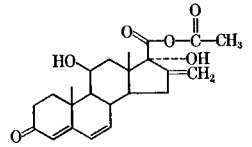
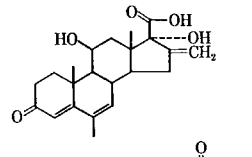
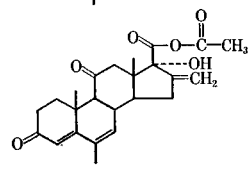
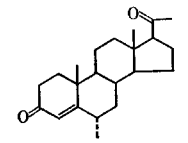
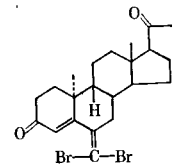
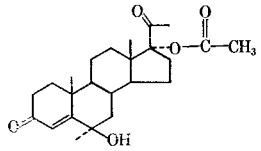
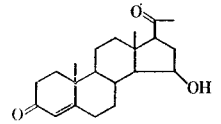
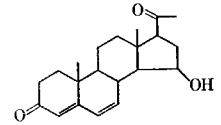
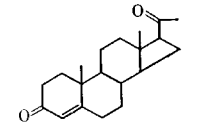
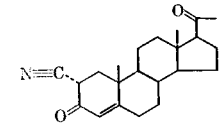
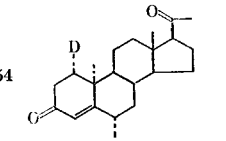
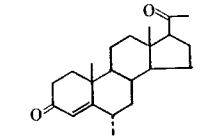
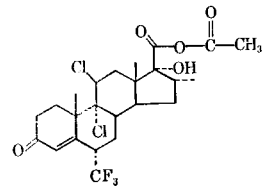
Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
0.25		5	C_6H_6	0.25	R,[b] 6 hr	...	252
...		...	...	...	...	...	205
0.4		10	Dioxane	0.264	...	0.138	247
0.2		100	Dioxane	0.8	R, 5 days	0.71	246
0.51		200	Dioxane	0.35	R, 50 hr	0.46	246
0.464		40	Dioxane	0.342	R, 5 days	0.138	246
0.025		3	Dioxane	0.017	R, 3 days	...	246
5		75	Dioxane	4.8	R, 20 hr	...	158
3.5		70	Dioxane	3.5	R, 6 hr	...	158
1		20	Dioxane	0.7	R, 24 hr	...	25
1.18		600	C_6H_6	3.17	...	8.8	141
4		100	C_6H_6	4	R,[b] 7.5 hr	...	191
4		200	C_6H_6	2.7	R, 15 hr	...	191
5		250	C_6H_6	4	R, 7 hr	2.14	191

TABLE IV (*Continued*)

Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
1.1 *M*		...	C_6H_6 or dioxane	1.1 to 1.5 *M*	R	...	48
3.5		70	Dioxane	3.5	R, 6 hr	...	153
...		...	...	...	...	...	153
5		75	Dioxane	4.8	R, 20 hr	...	156
...		...	Dioxane	...	R	...	155
...		...	Dioxane	...	R	...	155
0.1		...	C_6H_6	0.09	R,[b] 6 hr	...	134
2.65		...	Dioxane	4.34	HCl (cat.)	73%	133
0.3		25	Dioxane	0.3	R, 20 hr	...	98
5.17		62	Dioxane	4.1	R, 5.5 hr	...	235
5.17		62	Dioxane	4.1	R, 5.5 hr	...	235
...		...	...	...	...	...	194
0.17		25	Dioxane	0.171	R, 18 hr	0.141	137
0.054		10	Dioxane	0.125	R	0.0206	122
0.65		30	Dioxane	0.5	R,[b] 12 hr	...	134
0.5		10	Dioxane	0.35	R, 18 hr	...	26

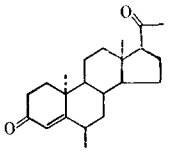
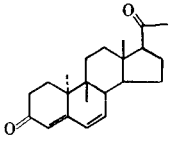
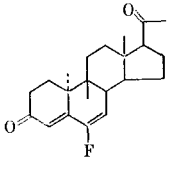
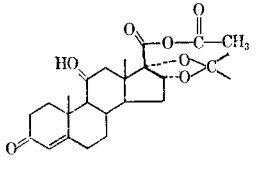
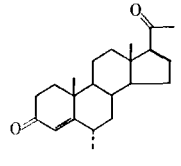
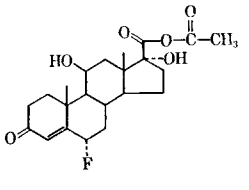
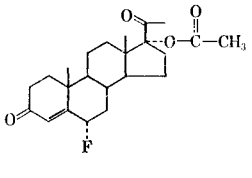
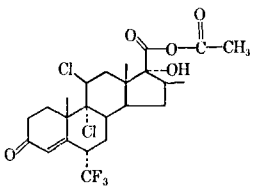
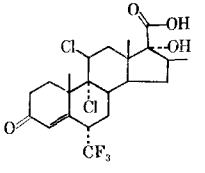
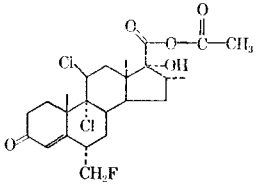
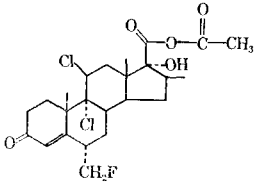
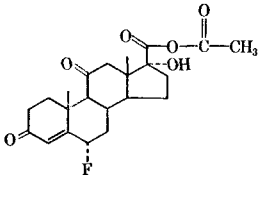
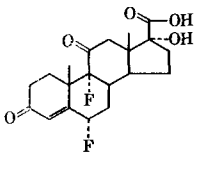
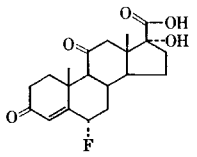
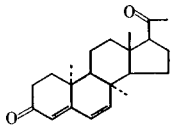
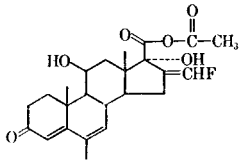
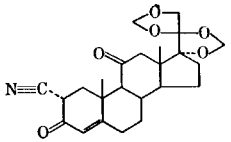
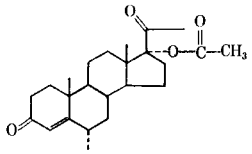
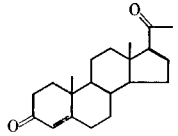
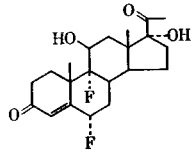
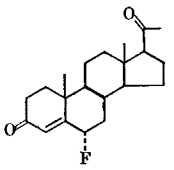
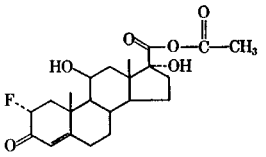
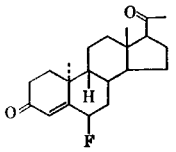
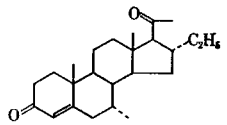
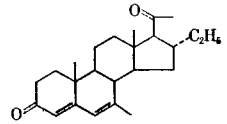
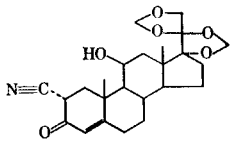
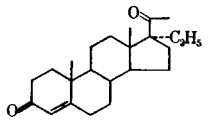
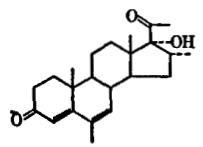
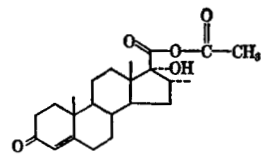
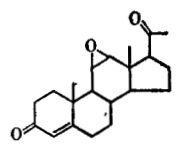
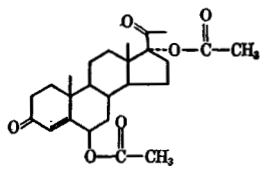
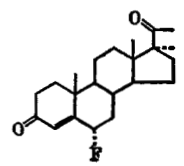
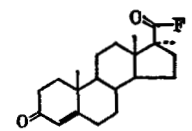
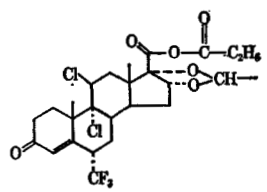
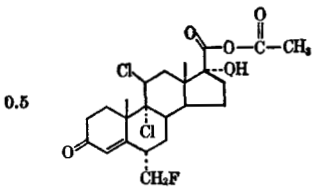
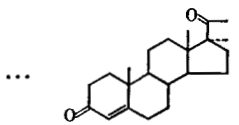
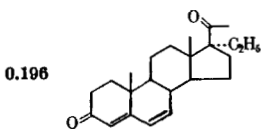
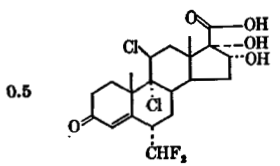
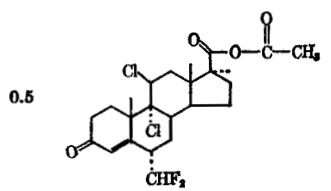
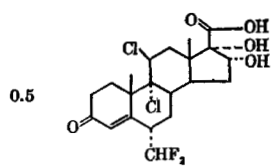
Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
2.65		...	Dioxane	4.35	...	...	133
5		150	Dioxane	4.55	R, 1.5 hr w/HCl (cat.)	3.22	250
5		150	Dioxane	4.55	R, 1.5 hr	58%	250
1		10	Dioxane	0.7	R, 20 hr	0.295	120
0.047		10	Dioxane	0.125	R, 7.5 hr	0.0179	122
0.4		4	Dioxane	0.4	R, 8 hr	...	135
0.5		6	C_6H_6	0.45	R, 8 hr	...	135
0.5		10	Dioxane	0.35	R, 18 hr	...	26
0.5		10	Dioxane	0.35	R, 18 hr	...	26
0.5		10	Dioxane	0.35	R, 18 hr	...	26
0.5		10	Dioxane	0.35	R, 18 hr	...	26
0.4		4	C_6H_6 dry	0.4	R, 8 hr	...	135
0.4		4	C_6H_6 dry	0.4	R, 8 hr	...	135

TABLE IV (*Continued*)

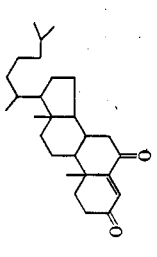
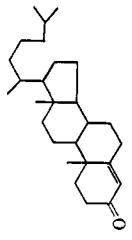
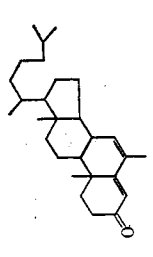
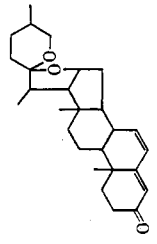
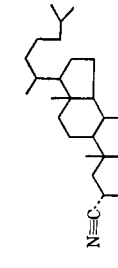
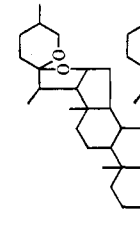
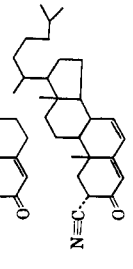
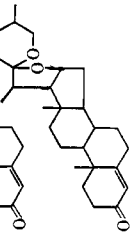
Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
0.4		4	C_6H_6 dry	0.4	R, 8 hr	...	135
1.2		60	C_6H_6 dry	1.2	R, 7 hr	...	163
5		75	Dioxane	4.8	R, 20 hr	...	159
1.69		30	Dioxane	1.7	R, 6 hr	0.371	180
1 *M*		...	C_6H_6 or dioxane	1.1 to 1.5 *M*	R	...	48
0.26		200	C_6H_6	1.22	R, 18 hr w/N_2	...	207
0.4		4	C_6H_6	0.4	R, 8 hr	...	135

Starting compound G	Starting compound Structure	Solvent M	Solvent Type	DDQ, g	Conditions	Yield	Ref
0.4		4	C_6H_6	0.4	R, 8 hr	...	135
0.4		5	Dioxane	0.4	R, 15 hr	...	135
4		100	C_6H_6 dry	4	R,[b] 7 hr	...	251
1		20	Dioxane	1	R, 10 hr	0.35	170
1		20	Dioxane	1	R, 10 hr	0.31	170
4		50	Dioxane	3	R, 6 hr 4 g $PhCO_2H$	2.3	180
1		20	Dioxane	0.72	R, 3 hr	...	209

Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions[a]	Yield	Ref
0.95		50	C_6H_6	1	R, 5 hr	...	115
0.58		30	C_6H_6 dry	0.7	R, 48 hr w/N_2	0.3	128
1		50	Dioxane	0.7	R, 6 hr w/N_2	...	89
0.82		20	Dioxane	0.65	R, 20 hr	0.371	97
0.32		66	C_6H_6	0.86	R, 18 hr 0.033 g TSA	...	83
0.347		12	Dioxane	0.25	R, 3–5 hr 0.019 g TSA	...	83
0.5		10	Dioxane	0.35	R, 18 hr	...	26
0.5		10	Dioxane	0.35	R, 18 hr	...	26
...		...	...	...	...	...	209
0.196		3	Dioxane	0.193	R, 20 hr	...	209
0.5		10	Dioxane	0.35	R, 18 hr	...	26
0.5		10	Dioxane	0.35	R, 18 hr	...	26
0.5		10	Dioxane	0.35	R, 18 hr	...	26

[a] R = reflux. [b] *p*-Nitrophenol used as catalyst. [c] In grams unless specified otherwise.

TABLE V. $\Delta^4 \rightarrow \Delta^{1,4}$-3-KETOCHOLESTANES AND SPIROSTANES

Starting compound			Solvent							
G	Structure	Ml	Type	DDQ, g	Conditions	Yield	Ref	G	Structure	Ml	Type	DDQ, g	Conditions	Yield	Ref
3		20	Dioxane	2	R, 7 hr	...	50	7.69		400	C_6H_6 dry	5.44	R, 25–30 hr	4.89	141
5		50	Dioxane	4	R, 4 hr	...	50	2		...	C_6H_6	...	R, 10 hr	1.55	130
...		...	Dioxane	...	R, 5 hr	...	84	13.3		800	C_6H_6	10	R, 33 hr	52%	206
...		...	Dioxane	...	R	...	84	...		...	C_6H_6	...	R	...	141

to the $\Delta^{4,6}$-3-ketones. Westerhof and Hartog (250) have used 0.1–1.0 mg of HCl/ml of solvent to catalyze the conversion of Δ^4-3-ketones to $\Delta^{1,4}$-3-ketones, and have stated that hydrogen chloride concentrations of 35 mg/ml or higher lead predominantly to 6-dehydrogenation.

Table VI lists all the conversions of Δ^4-3-ketones to $\Delta^{4,6}$-3-ketones which were found in the literature. The conversions of $\Delta^{3,5}$-enol ethers to $\Delta^{4,6}$-3-ketones are also tabulated. The use of wet acetone as the solvent should be noted. Under anhydrous conditions, in benzene or acetone, $\Delta^{3,5}$-enol ethers gave predominantly $\Delta^{1,4,6}$-3-ketones (189). In the cases where tetrahydrofuran is employed as the solvent, it must be presumed that some water is also present.

2. *Dehydrogenation of Saturated 3-Keto Steroids*

The results of work carried out in this area are summarized in Table VII. It is noteworthy that Δ^1-, Δ^4-, or $\Delta^{1,4}$-3-ketones can be obtained. In the case of the introduction of one double bond, the structure of the starting material frequently determines which hydrogen atoms are removed. Thus, steroidal 3-ketones carrying a 5α-hydrogen atom generally give Δ^1-3-ketones as the major product. One exception to this is provided by 17α-ethyl-17β-acetoxy-5α,9β,10α-androstan-3-one, which gives the Δ^4-3-ketone (125). On the other hand, the dehydrogenation of steroidal 3-ketones carrying a 5β hydrogen usually gives rise to Δ^4-3-ketones.

3. *Dehydrogenation of Other Keto Steroids*

Two types of reaction are collected under this heading, namely the dehydrogenation of 2-formyl-3-keto steroids and the dehydrogenation of 19-acetoxy-Δ^4-3-ketones.

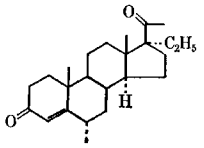
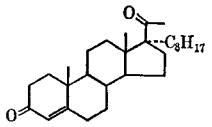
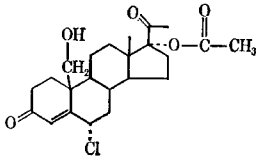
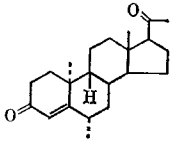
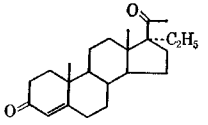
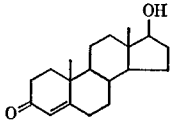
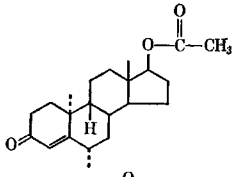
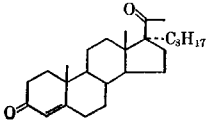
a. 2-Formyl-3-keto Steroids

Edwards, Bowers, Orr, and co-workers (27, 101, 102) reasoned that, since α-formyl ketones exist largely in their enol form, a form of an aldehyde or ketone well known for its reactivity toward DDQ (see section VI, I), 2-formyl-3-keto steroids might be readily dehydrogenated by DDQ to 2-formyl-Δ^1-3-ketones. This prediction was realized and the examples in Scheme I are given. The reactions were best run in dioxane with a slight excess of DDQ (1.1–1.5 molar equiv per mole of steroid).

Acetone, methylene chloride, tetrahydrofuran, and acetonitrile were not as satisfactory as dioxane, since either DDQ or the starting material was less soluble in these solvents. Increasing the amount of DDQ was found to make little difference to the yield. The most critical factor proved to be the reaction time: 1 to 5 min was usually sufficient to complete the reaction.

Table VI

$\Delta^{4,6}$-3-Keto Steroids from Δ^{4}-3-Ketones and $\Delta^{3,5}$-Enol Ethers

Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
0.5		...	Dioxane	0.34	Dry HCl 1 hr, room temp	...	3
7.7		...	...	...	Dry HCl	7.74	3
1.5		100	*t*-BuOH	4	R, 2 hr	1.01	63
5		450	Dioxane	4.32	0.61 g, HCl at 8° for 20 min	2.65	133
1.03		30	Dioxane	0.75	HCl gas 0.5 hr	...	209
5		200	Dioxane	5	HCl, 15 min	2.65	59
5		450	Dioxane	4.32	0.6 g HCl at 8° for 20 min	2.65	133
...		...	Dioxane	...	HCl gas	33%	247

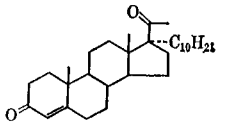
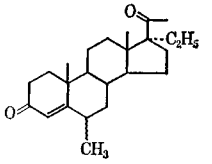
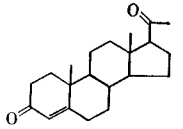
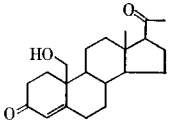
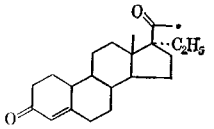
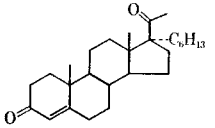
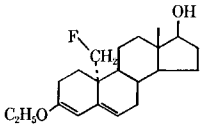
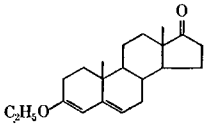
Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
...		...	Dioxane	...	HCl gas	80%	247
...		...	Dioxane	...	HCl gas	51%	247
...		...	Dioxane	...	HCl, room temp	...	200
3		200	Dioxane	2.8	Room temp, 60 sec, dry HCl, stand 1.5 hr	...	224
20.94		650	Dioxane	15.3	HCl gas	14.6	247
...		...	Dioxane	...	HCl gas	46%	247
1		20	THF	1.05 equiv	30 min at 0°, 0.1 g *p*-TSA	...	24
0.05		10	C_6H_6	0.082	A few min, room temp	6%	189

TABLE VI (*Continued*)

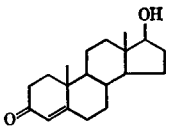
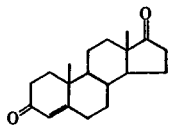
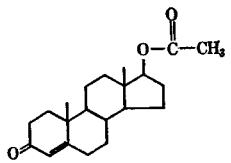
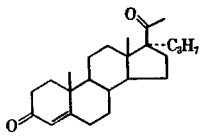
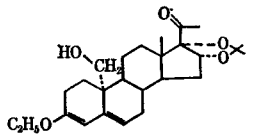
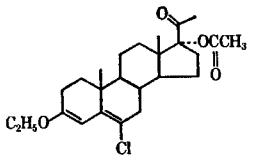
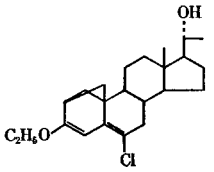
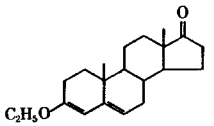
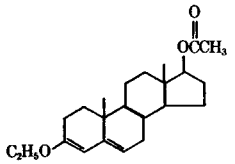
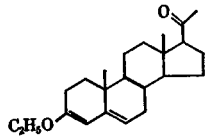
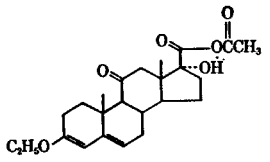
Starting compound G	Starting compound Structure	Solvent Ml	Solvent Type	DDQ, g	Conditions	Yield	Ref
...		...	Dioxane	...	Anhyd HCl, 30 min	...	200
0.2		10	Dioxane	0.175	HCl gas few sec, 30-min reaction	0.14	200
...		...	*t*-BuOH	...	...	...	69
...		...	Dioxane	...	HCl gas	30%	247
1		20	THF	1.05 equiv	0.5 hr at 0°, 0.1 g TSA	...	77
1		20	THF	1.05 equiv	0.5 hr at 0°, 0.1 g TSA	75%	226
...		...	THF	...	...	...	74
0.025		8	Wet acetone	0.019	A few min, room temp	0.018	189
0.05		6	Wet acetone	0.034	A few min, room temp	0.04	189
0.1		12	Wet acetone	0.065	A few min, room temp	0.063	189
0.104		12	Wet acetone	0.065	A few min, room temp	0.069	189

Table VII

Dehydrogenation of Saturated 3-Keto Steroids

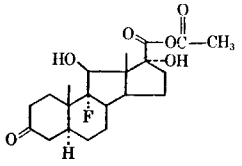
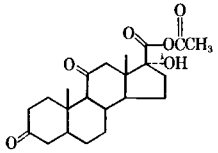
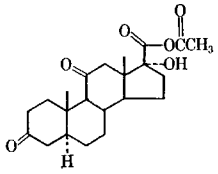
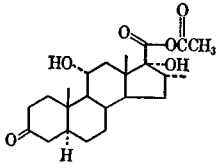
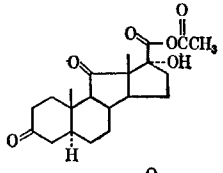
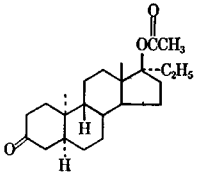
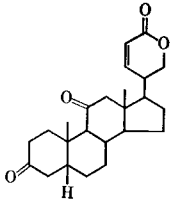
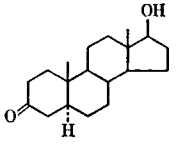
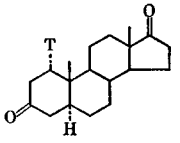
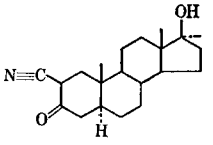
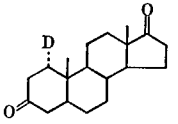
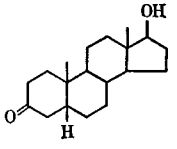
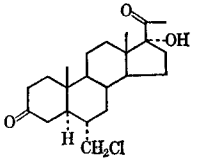
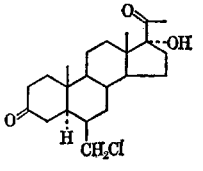
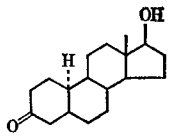
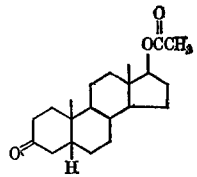
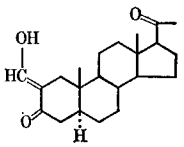
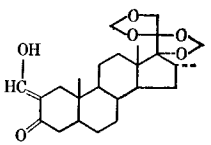
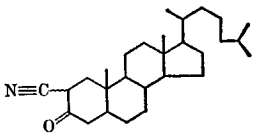
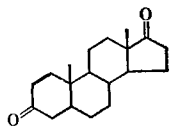
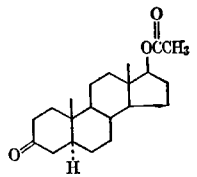
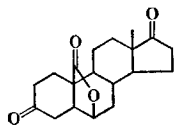
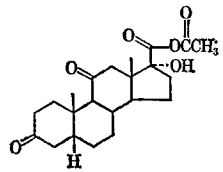
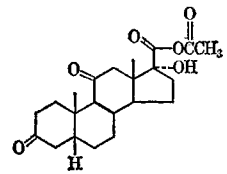
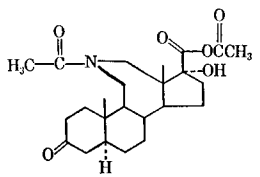
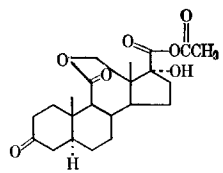
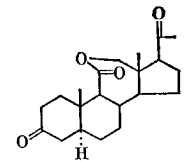
Starting saturated 3-keto steroids G	Structure	Solvent Ml	Type	DDQ, g	Conditions[d]	Yield[e]	Ref
0.3		5.5	Dioxane	0.6	R, 16 hr		174
1		...	Dioxane	...	R, 12 hr	0.51[c]	169
10		150	Dioxane	20	R, 12 hr	5.8[c]	169
5		...	Dioxane	...	R, 12 hr	2.78[c]	169
0.3		5.5	Dioxane	0.6	R, 16 hr	0.12[c]	21
0.2		10	Dioxane or C_6H_6	0.15	Room temp, 40 min, 29 mg HCl	[b]	125
0 45		18	Dioxane	0.7	R, 16 hr w/N_2	[c]	19
0.1		10	Dioxane	1.1 equiv	R		200
...		...	Dioxane	...	...	[a]	42
5		475	Dioxane	4	R, 10 min	0.96	180
...		...	Dioxane	...	R, 19 hr	[a]	196
0.1		10	Dioxane	1.1 equiv	...		200
0.5		20	*t*-BuOH	0.5	R, 40 hr		99
0.5		20	*t*-BuOH	0.5	R, 40 hr		99

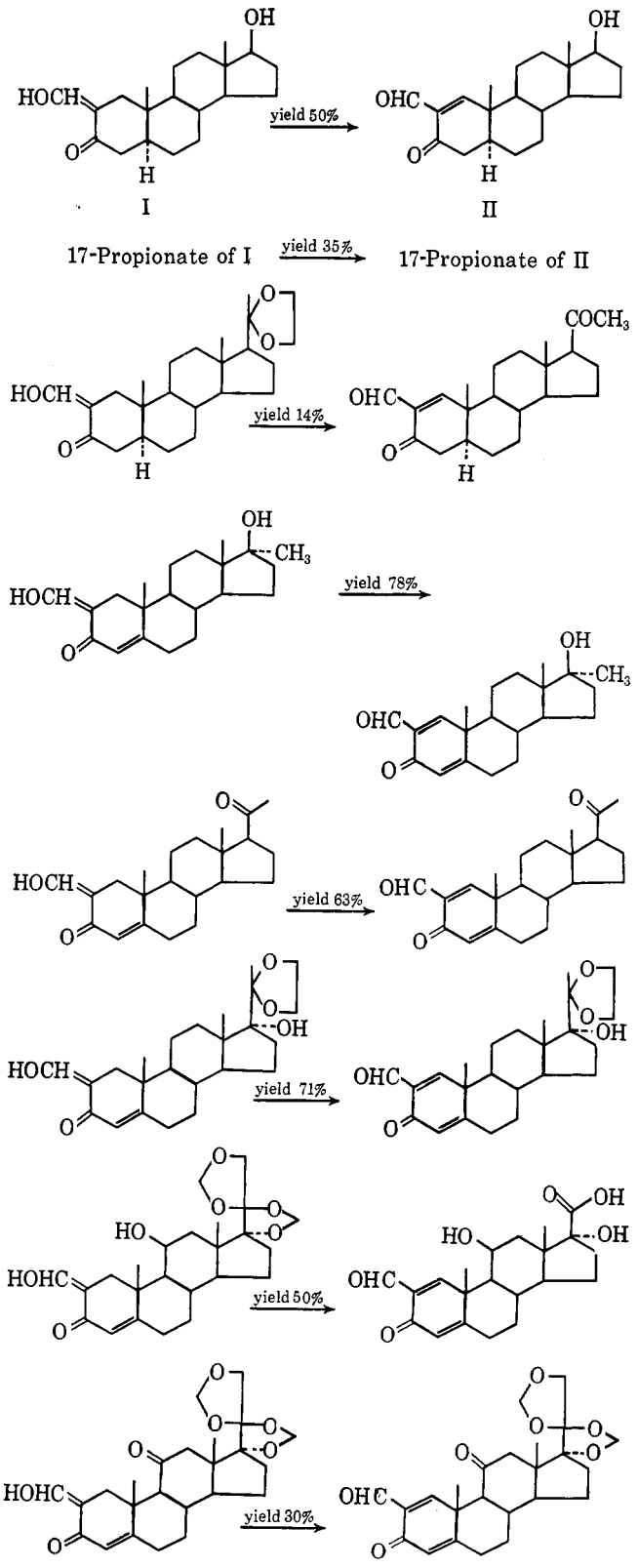
TABLE VII (*Continued*)

G	Starting saturated 3-keto steroids Structure	Solvent Ml	Type	DDQ, g	Conditions[d]	Yield	Ref
1		20	Dioxane	0.7	R, 10 hr		76
0.3		15	Dioxane	0.615	R, 16 hr	[c]	142
...		...	...	...	...	[a]	177
...		...	...	...	...	[a]	177
...		...	Dioxane	...	R, 5 hr		84
...		...	Dioxane	...	R, 12 hr		169
0.3		15	Dioxane	0.615	R, 16 hr	[c]	142

G	Starting saturated 3-keto steroids Structure	Solvent Ml	Type	DDQ, g	Conditions[d]	Yield[e]	Ref
1		50	Dioxane	5	R, 24 hr		195
0.2		10	Dioxane	0.35	R, 6 hr		142
0.2		10	Dioxane	0.35	R, 16 hr	50%[c]	164
0.2		4	Dioxane	0.31	R, 20 hr		259
0.09		...	Dioxane	...	R, 20 hr	0.04[c]	259
0.18		...	Dioxane	...	R, 20 hr	0.075[c]	259

[a] Denotes Δ^1 products. [b] Denotes Δ^4 products. [c] Denotes $\Delta^{1,4}$ products. [d] R = reflux. [e] In grams unless specified otherwise.

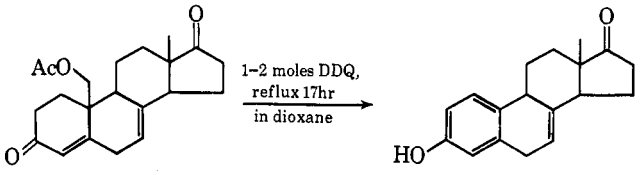
SCHEME I



When times of 10 min or longer were used, substantially lower yields were obtained. The reaction mixtures were worked up by quenching with methylene chloride and pouring down an alumina column. A few other similar examples have been described in a patent (177).

b. 19-Acetoxy-Δ^4-3-ketones

Only one example of the DDQ dehydrogenation of this class of compounds has been described (10).



4. Dehydrogenation Reaction Conditions

As indicated in Tables III–VII, there is a widespread preference for dioxane or benzene as the solvent in DDQ dehydrogenations of keto steroids. There is considerable variation in the concentration at which DDQ reactions are run in these solvents, anywhere from 5 to 100 parts of solvent being used per part of steroid. There is an added advantage to using benzene or dioxane since the 2,3-dichloro-5,6-dicyanohydroquinone produced is reasonably insoluble and may be filtered (see Table I).

Dehydrogenation reactions are most frequently run at reflux using 1.1 to 2 moles of DDQ per mole of Δ^4-3-ketone; however, larger excesses are also used without giving rise to $\Delta^{1,4,6}$-3-ketones (see section VI, J, 3). Reaction times vary from a few hours to extended periods, though in the case of the conversion of Δ^4-3-ketones to $\Delta^{4,6}$-3-ketones, in the presence of hydrogen chloride, short times at room temperature are usually sufficient.

Other solvents have been used in DDQ dehydrogenations of steroids, *e.g.*, tetrahydrofuran (226), *t*-butyl alcohol (63, 99), acetic acid (134), and mixtures of ethyl acetate and trichloroethylene (181).

Acid catalysts have been used in the dehydrogenation of Δ^4-3-ketones to $\Delta^{1,4}$-3-ketones. The one principally employed by the British Drug Houses group is *p*-nitrophenol. Use of this material probably stems from work by Braude, Jackman, and Linstead (36), who showed that acid catalysts have a marked accelerating effect on the dehydrogenation of 1,4-dihydronaphthalene by the thymoquinone in phenetole as the solvent. The best three catalysts were *p*-nitrophenol (0.058 *M*), thymoquinol (0.12 *M*), and picric acid (0.058 *M*). Other acid catalysts have been used in the dehydrogenation of Δ^4-3-ketones, *e.g.*, maleic acid, trichloroacetic acid, oxalic acid, and 3,5-dinitrobenzoic acid (181). *p*-Toluenesulfonic acid has also been shown to accelerate this dehydrogenation reaction, though with 2 equiv of acid considerable $\Delta^{4,6}$-3-ketone was formed (200). Δ^4-3-Ketones with anhydrous hydrogen chloride or sulfuric acid (224) give $\Delta^{4,6}$-3-ketones almost exclusively, except at very low concentrations of hydrogen chloride (250), where $\Delta^{1,4}$-3-ketones are formed. In converting $\Delta^{3,5}$-enol ethers to

$\Delta^{4,6}$-3-ketones, *p*-toluenesulfonic acid is the preferred catalyst.

A nitrogen blanket is frequently used during DDQ dehydrogenation reactions, probably as a precaution, since no study has been published establishing the necessity of this procedure (see Tables III–V).

Many different methods are employed in working up DDQ dehydrogenation reactions. Most workers do not trouble to destroy excess DDQ, although this may be done conveniently using sodium bisulfite or sodium hydrosulfite (191). The latter can be used on the basic side, thus aiding in the removal of the 2,3-dichloro-5,6-dicyanohydroquinone. The most generally used method of work-up, however, is to filter the 2,3-dichloro-5,6-dicyanohydroquinone at the end of the reaction, often after drowning with ether, methylene chloride, benzene, ethyl acetate, or some other solvent. Base-soluble materials are removed from the product by extraction and a final purification effected by chromatography, usually on alumina. Other adsorbents such as silica (133), magnesium silicate (120), and florisil (97) are also used. The product, if an alcohol, is sometimes acetylated before alumina chromatography.

5. *Limitations to the Dehydrogenation of Steroid Ketones*

Tables III–VII clearly indicate that many types of groups may be present during DDQ-mediated dehydrogenations of steroid ketones.

Apart from the unexpected dehydrogenation of 3α,-17α-dihydroxy-21-acetoxy-5β-pregnane-11,20-dione to the $\Delta^{1,4}$-3-ketone (164) and the isolation of some androsta-1,4,6-triene-3,17-dione in the dehydrogenation of 17β-hydroxyandrosta-4,6-dien-3-one (59), there appears to have been no mention of side reactions with groups substituted in the steroid. However, there are a few such reactions implied. It seems advisable, for instance, to protect groups which might be oxidized as well as nucleophilic substituents which might otherwise enter into replacement reactions with DDQ. Thus, Burn, Kirk, and Petrow (48) reported that higher yields of dehydro products resulted when steroid alcohols were acetylated prior to carrying out the dehydrogenation reaction. Again, it may be significant that 17-aminomethyl-17-hydroxy-Δ^4-3-ketones were acetylated before reaction with DDQ (71). Such precautions seem understandable in view of the knowledge that DDQ does react with such nucleophiles as water, methanol, and other solvents (see section V, A), although, as pointed out in section VI, J, 3, other often ill-defined factors, such as solvent effects, reaction rate, charge-transfer complex formation, and the nature of intermediates and transition states, have to be considered in assessing the possible importance of side reactions.

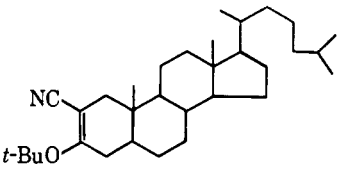
In regard to the solvent effect, DDQ is known to undergo autodecomposition in several solvents at dilutions used for running ultraviolet spectra (see section V, B and ref 52) and there is one report (107) that a benzene solution of DDQ undergoes 30% decomposition on standing 24 hr at room temperature. Benzene is, however, still widely used as a solvent, indicating that under real dehydrogenating conditions, that is, with a steroid present, the possibility of rapid reaction with the steroid, even if only to form a new or benzene-modified charge-transfer complex, may radically alter the situation prevailing in a simple benzene solution of DDQ. So, because DDQ may undergo autodecomposition in a given solvent, it does not necessarily follow that that solvent would be unsuitable under real dehydrogenation conditions.

In spite of the tremendous amount of work published on the DDQ-mediated dehydrogenation of steroid ketones, there is very little information available concerning the detailed fate of all the starting materials. The report by Pradhan and Ringold (189) showing that the DDQ moiety can enter into the steroid molecule (see section VI, I) is a strong hint that such reactions may, in fact, be more common than indicated in the literature. Indeed, the immovable spots frequently found at the source in fully developed thin layer chromatograms of DDQ dehydrogenation products might be generally attributable to compounds formed from steroids and DDQ, or 2,3-dichloro-5,6-dicyanohydroquinone anion. The presence of such strongly adsorbed substances is certainly the major reason for purifying DDQ-dehydrogenation products by alumina chromatography or base extraction. Probably the two major ways in which the DDQ moiety can incorporate into the steroid are *via* Michael additions of 2,3-dichloro-5,6-dicyanohydroquinone anion, as described by Pradhan and Ringold (189), or by Diels–Alder reactions. This last type of reaction has not yet been observed with a steroid, even with a $\Delta^{4,6}$-3-ketone or a $\Delta^{3,5}$-enol ether.

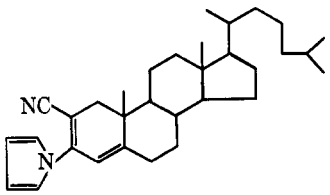
Another limitation to the DDQ-mediated dehydrogenation of steroids may be introduced by the need for an acid catalyst in certain dehydrogenation reactions; this would be particularly true, for instance, of the dehydrogenation of Δ^4-3-keto steroids to $\Delta^{4,6}$-3-keto steroids, which conversion requires the presence of excess anhydrous hydrogen chloride. Other apparent limitations may not be real. For example, the complex work-up procedures sometimes employed following DDQ dehydrogenations may induce changes in the product or cause yield losses, both of which may give false impressions as to what goes on in the actual DDQ reaction.

When used prudently, DDQ really seems to have few disadvantages as a method of introducing Δ^1-double bonds into Δ^4-3-keto steroids, although, as shown by

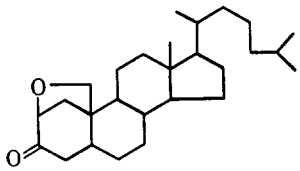
Ringold and Turner (200), some conversion to $\Delta^{4,6}$- and thence $\Delta^{1,4,6}$-3-ketones might be expected. The necessity for an acid catalyst for converting Δ^4-3-ketones to $\Delta^{4,6}$-3-ketones may limit the utility of this particular reaction; however, this disadvantage disappears when one starts with the $\Delta^{3,5}$-enol ether of the Δ^4-3-ketone. Nevertheless, DDQ sometimes fails to do the expected dehydrogenation reaction. Thus, the following compounds could not be dehydrogenated.



(84)



(84)

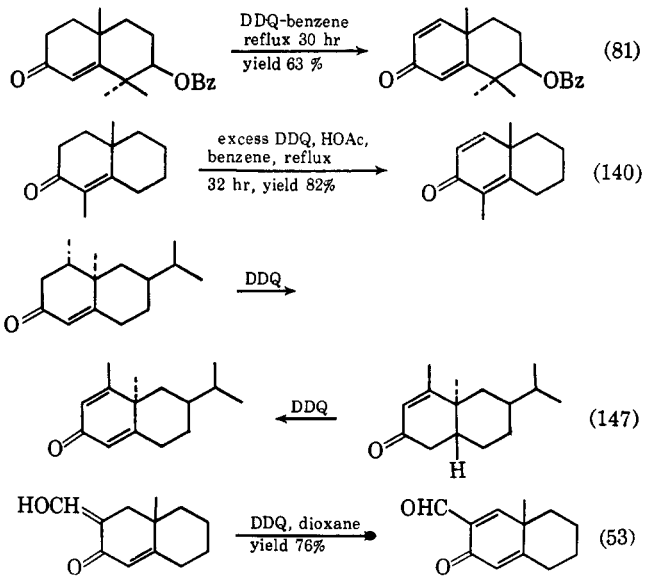


(254)

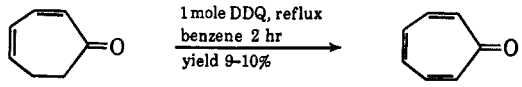
In the last case, it was reasoned that steric deformation induced by the bridge prevents the formation of unsaturated derivatives. It is pertinent to note, however, that 2β-hydroxyandrost-4-ene-3,17-dione undergoes very little dehydrogenation with DDQ because the normal *trans*-diaxial elimination of 1α,2β hydrogens is blocked (see section VI, I).

B. DEHYDROGENATION OF NONSTEROID KETONES

A number of polyhydronaphthalenes containing an α,β-unsaturated ketone group have been dehydrogenated with DDQ. The examples known are all strikingly similar to dehydrogenations of Δ^4-3-keto steroids.



Tropone has been prepared from 2,4-cycloheptadienone in low yield (228).



C. DEHYDROGENATION OF ALCOHOLS

Quinones have long been known to dehydrogenate alcohols to aldehydes and ketones in the presence of light (40) although up until a few years ago it was generally believed that saturated alcohols would not undergo measurable dehydrogenation by quinones in the absence of light. On the other hand, olefinic primary and secondary alcohols, including 3-hydroxycholest-4-ene, were shown to be easily dehydrogenated to the corresponding aldehyde or ketone by the action of tetrachloro-*o*-benzoquinone (40). This paper also described the use of DDQ in oxidizing cinnamyl alcohol to cinnamaldehyde.

DDQ was first used for the dehydrogenation of steroidal allylic alcohols by the British Drug Houses group (41), and since that time this reaction has been widely employed in the steroid field. The reaction is conveniently followed spectrophotometrically (52). Table VIII summarizes the reactions reported thus far, and includes the six examples described by Neustaedter in his review (165).

It is of interest to note that 3β,6β-dihydroxycholest-4-ene is selectively converted to 6β-hydroxycholest-4-en-3-one in good yield. This result is entirely analogous to that obtained with manganese dioxide (220).

An account of solvent effects on the dehydrogenation rates of steroidal allylic alcohols has been given by Burstein and Ringold (52). The rate of dehydrogenation of 3β,17β-dihydroxyandrost-4-ene in various solvents followed the following sequence: *t*-butyl alcohol > 2-methyl-1-propanol > nitrobenzene > acetone–benzene > dioxane > acetic acid. The slow rate in acetic acid was attributed to hydrogen bonding between acetic acid and the 3-hydroxyl group of the steroid, which caused development of a slight positive charge on the oxygen, thereby inhibiting removal of the 3α hydrogen as a hydride ion.

Since the conditions employed in the dehydrogenation of allylic alcohols are generally mild, the product, even when this is a Δ^4-3-ketone, is not usually dehydrogenated further. The rate of allylic alcohol dehydrogenations is far greater than the rate of dehydrogenation of Δ^4-3-ketones (52).

A few examples are recorded where saturated steroid alcohols are dehydrogenated. Thus, 3α,17α-dihydroxy-21-acetoxy-5β-pregnane-11,20-dione was dehydrogenated, in 30% yield, to 17α-hydroxy-21-acetoxypregna-1,4-diene-3,11,20-trione, by refluxing with excess DDQ in dioxane for 16 hr (164). Similarly, the

TABLE VIII

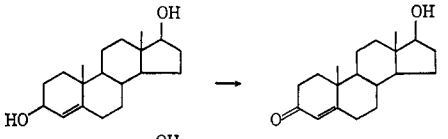
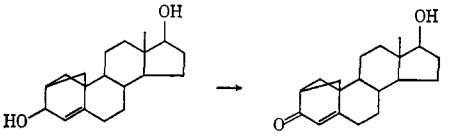
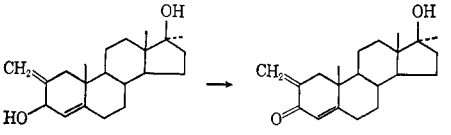
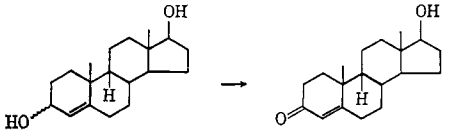
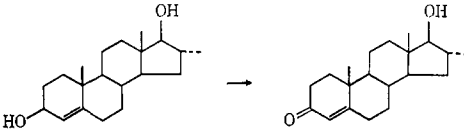
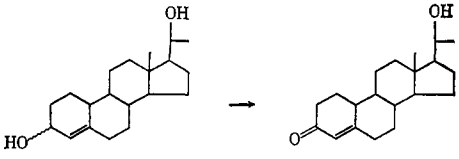
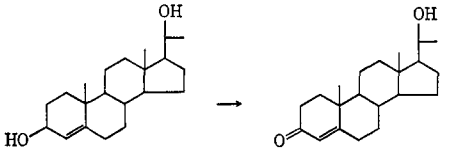
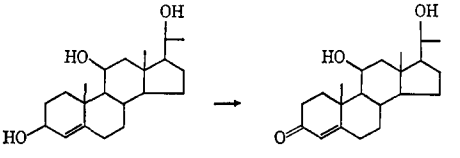
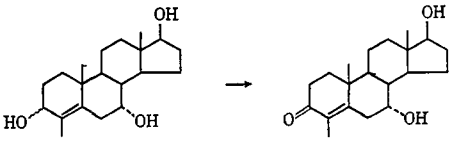
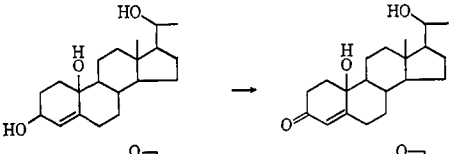
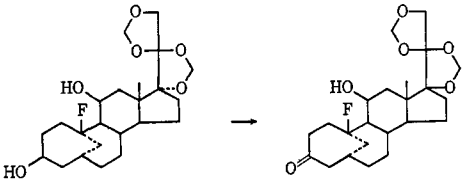
Steroid alcohols: G	Steroid alcohols: Reactions	Solvent: Ml	Solvent: Type	DDQ, g	Conditions	Yield	Ref
...		...	Dioxane	Xs	Room temp 5–15 hr	70%	51
1		20	Dioxane	1.1 equiv	3 hr at room temp	...	75
13		1000	Dioxane	10.4	18 hr at room temp	4.9 g	100
3.3		150	THF	3.3	18.5 hr at room temp	1.65 g	249
...		...	Dioxane	...	R, 16 hr at room temp	66%	30
1 equiv		...	Dioxane	1.1 equiv	3 hr at room temp	...	33
...		...	Dioxane	Xs	Room temp 5–15 hr	70%	51
...		...	Dioxane	Xs	Room temp 5–15 hr	...	51
...		...	Dioxane	...	13 hr	...	136
1		20	Dioxane	1.1 equiv	Room temp 3 hr	...	74
1		20	Dioxane	1.1 equiv	Room temp 3 hr	...	138

TABLE VIII (*Continued*)

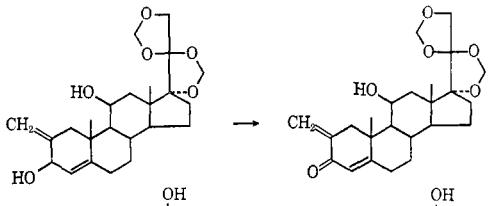
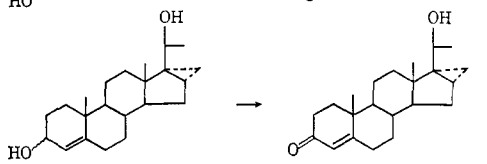
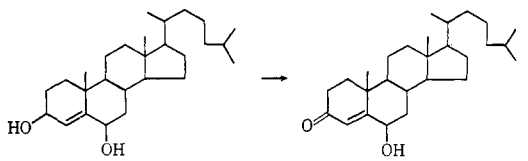
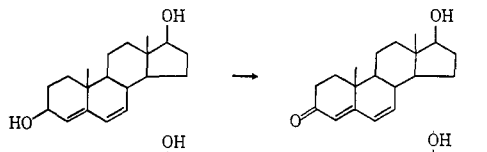
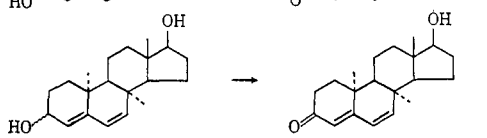
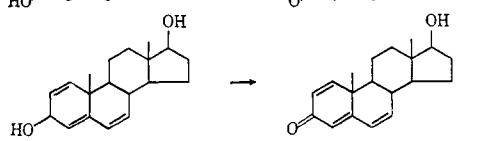
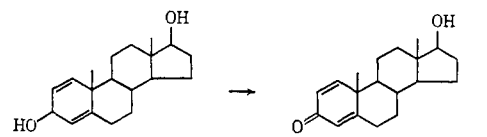
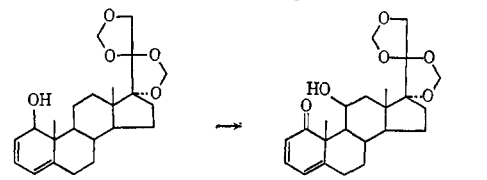
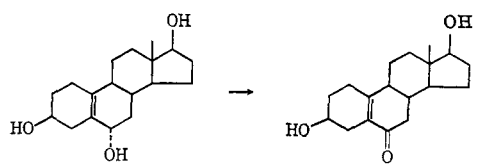
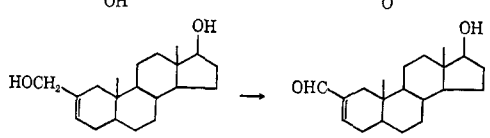
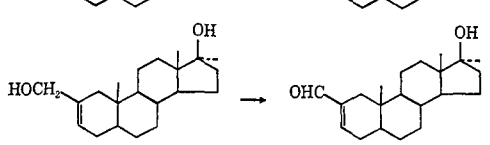
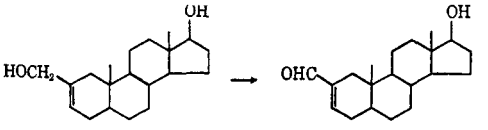
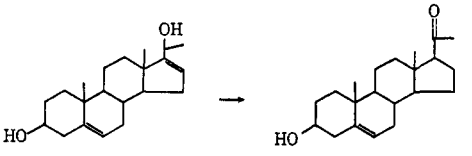
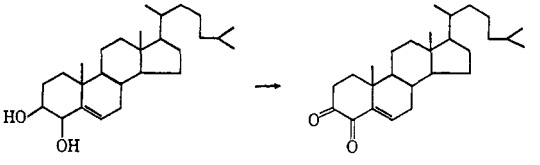
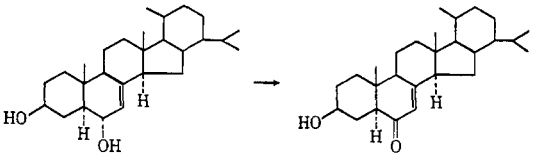
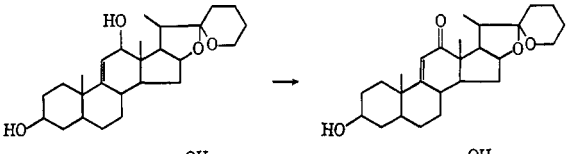
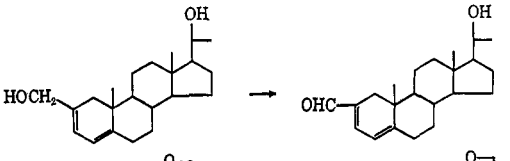
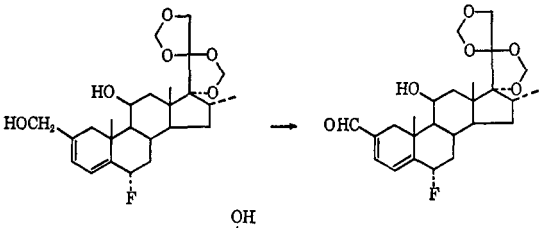
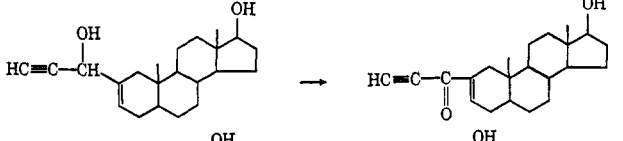
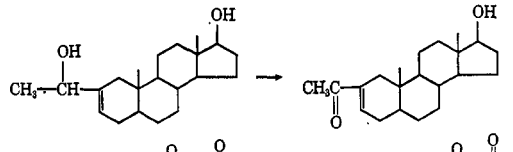
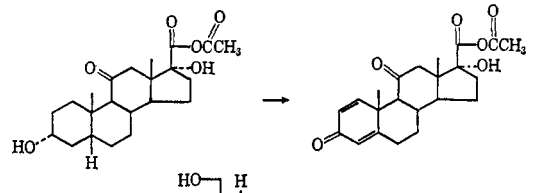
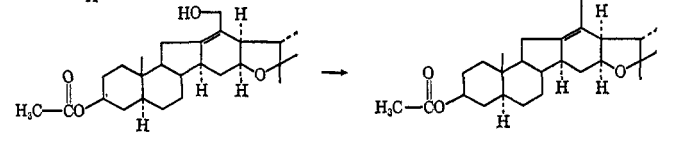
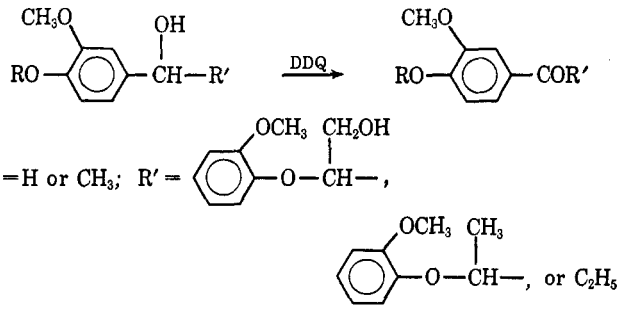
Steroid alcohols Reactions		Solvent					
G		Ml	Type	DDQ, g	Conditions	Yield	Ref
4.2		...	Dioxane	3.2	R, 6 hr	...	100
10.5		400	Dioxane	10.5	18 hr at room temp	8.0 g	47
...		...	Dioxane	Xs	5–15 hr	60%	51
...		...	Dioxane	Xs	5–15 hr	70%	51
...		60	C_6H_6	1.2	R, 7 hr	...	163
...		...	Dioxane	Xs	5–15 hr	50%	51
...		...	Dioxane	Xs	5–15 hr	45%	51
2		40	Dioxane	1.1 equiv	Room temp 3 hr	...	31
1		20	Dioxane	1.1 equiv	Room temp 3 hr	...	23
...		...	...	...	...	...	178
...		...	...	...	...	...	178

TABLE VIII (*Continued*)

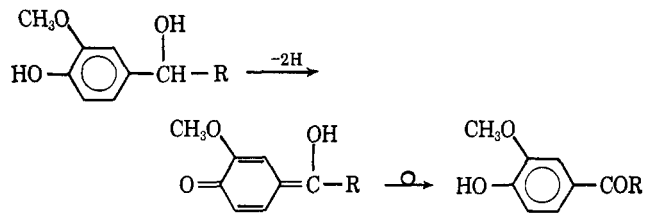
Steroid alcohols — G	Reactions	Solvent — Ml	Type	DDQ, g	Conditions	Yield	Ref
1.05		30	Dioxane	0.95	Room temp overnight	...	179
...		...	Dioxane	Xs	5–15 hr	75%	51
...		...	Dioxane	Xs	5–15 hr	75%	51
0.78		20	Dioxane	0.9	20 hr at room temp	0.42 g	92
...		...	Dioxane	Xs	5–15 hr	70%	51
1		20	Dioxane	1.1 equiv	3 hr at room temp	...	33
1		20	Dioxane	1.1 equiv	3 hr at room temp	...	32
...		...	Dioxane	...	3 hr at room temp	...	176
1		30	Dioxane	0.8	3.5 hr at room temp	...	179
0.2		10	Dioxane	0.35	R, 16 hr	30%	164
0.398		5	Dioxane	0.4	20°, 18 hr	...	70

dehydrogenation of 17β-hydroxyandrosta-4,6-dien-3-one with excess DDQ by refluxing in dioxane for 24 hr gave, in addition to the expected 17β-hydroxyandrosta-1,4,6-trien-3-one, a small amount of androsta-1,4,6-triene-3,17-dione (59). The importance of these reactions has been stressed in section VI, A, 5. There is one report of DDQ failing to dehydrogenate a steroidal allylic alcohol (93).

Only one paper has appeared concerned with the oxidation of nonsteroidal alcohols by DDQ (17). In general, the reaction may be written

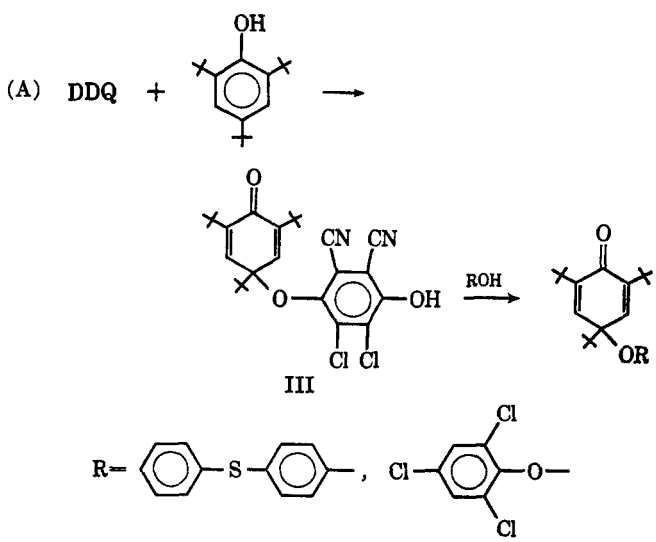


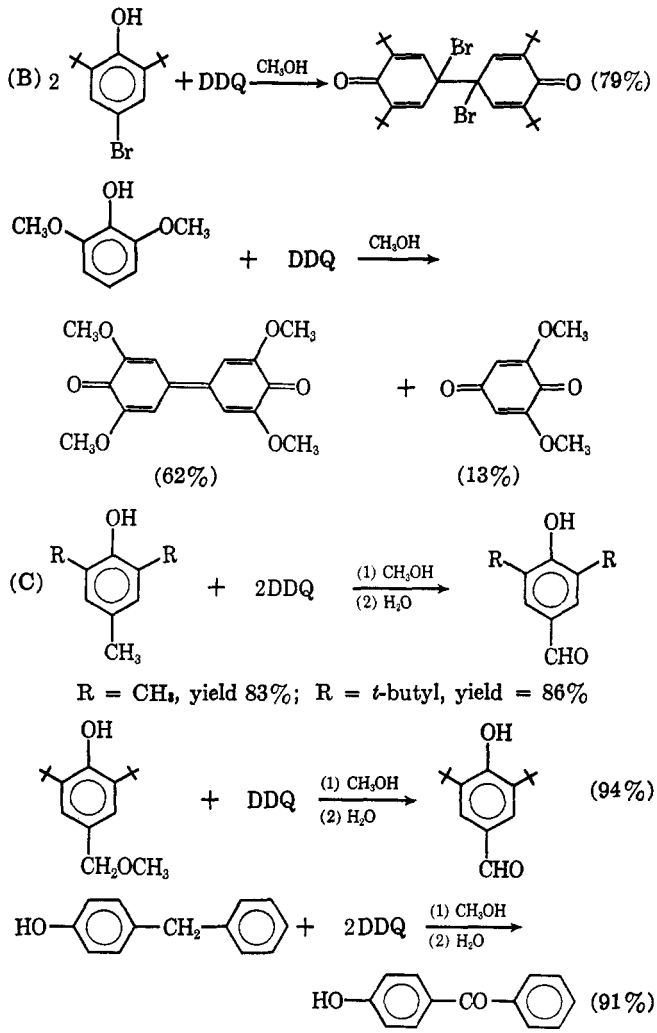
In the case of the free phenol (R = H), a quinone methide intermediate is postulated (16).



D. DEHYDROGENATION OF PHENOLS

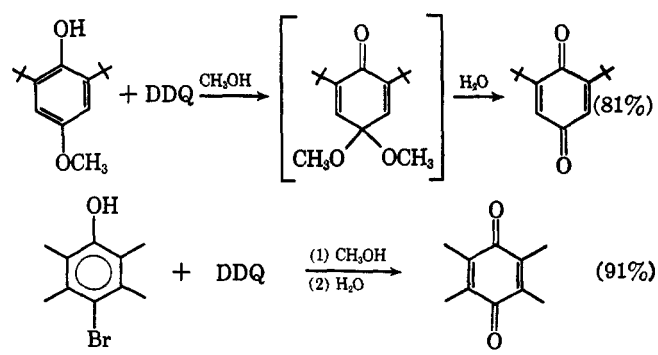
The action of DDQ on a wide variety of hindered phenols has been studied by Becker (14). All the reactions described proceeded at room temperature in methanol solution. The products obtained depended on the structure of the starting phenol, and several different types of reaction were discovered. In all cases, the products were considered to stem from radical intermediates. Three reaction types (A–C) were shown to occur.



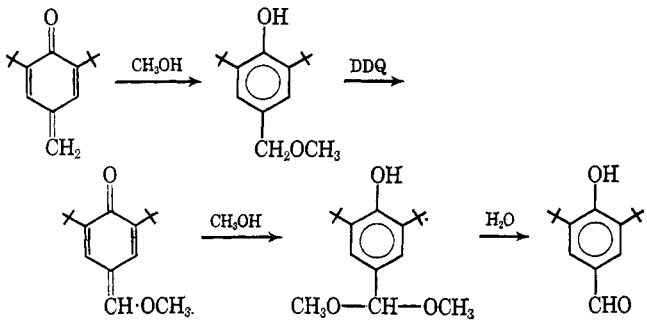


A similar preparation of an analogous structure to III (A) from 2,6-di-*t*-butyl-4-methylphenol was described. Other reactions of this type (yield of final product in parentheses) are shown in Scheme II.

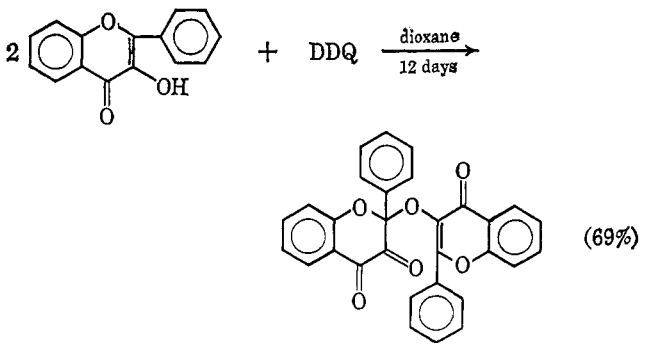
SCHEME II



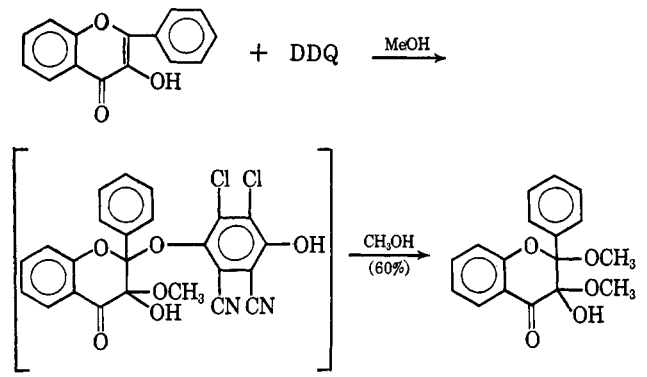
The last reactions (C) were believed to depend on the formation of quinone methides and the reaction of these with methanol, thus



Flavonol has also been reported to react with DDQ in dioxane (15). A dimer is produced.

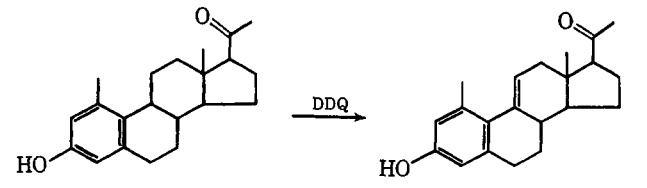


In methanol as solvent, the reaction took a different course.



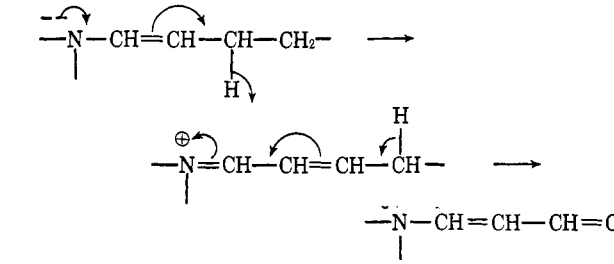
Radicals were thought to be involved in both of these reactions.

One patent has appeared describing the DDQ-mediated dehydrogenation of a phenolic steroid (222).



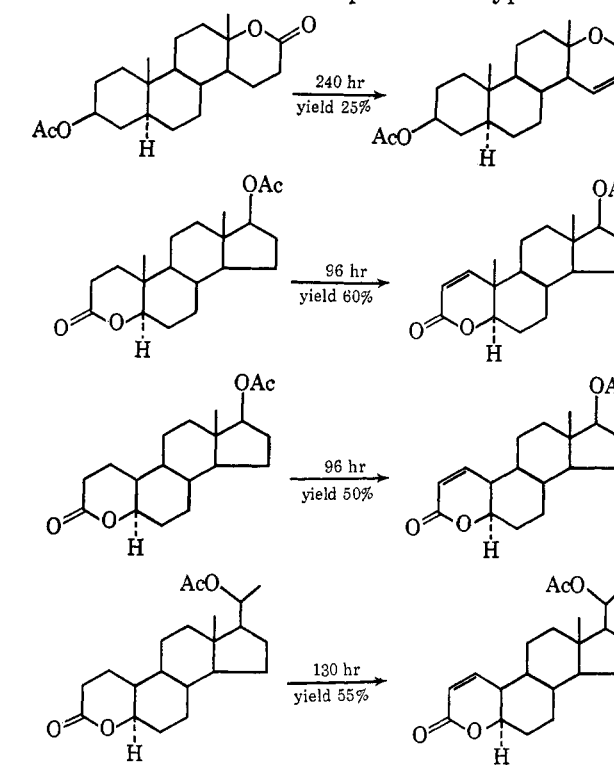
E. DEHYDROGENATION OF MISCELLANEOUS STEROIDS AND HETEROCYCLIC COMPOUNDS

This section covers the dehydrogenation of steroid lactones and steroid pyrazoles as well as other heterocyclic compounds. In the case of heterocyclic compounds, Jackman (131) has suggested that the removal of a hydride ion is assisted by a lone pair of electrons on the heteroatom.



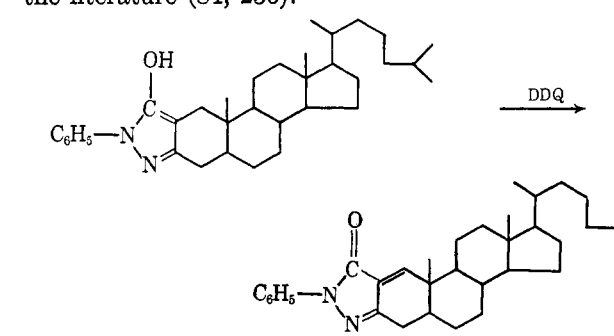
1. *Steroid Lactones*

Saturated steroid δ-lactones have been converted to α,β-unsaturated lactones by prolonged exposure to excess DDQ in dioxane (18). The following examples were described. A recent patent to Syntex Corp. (225) lists these and further examples of this type.

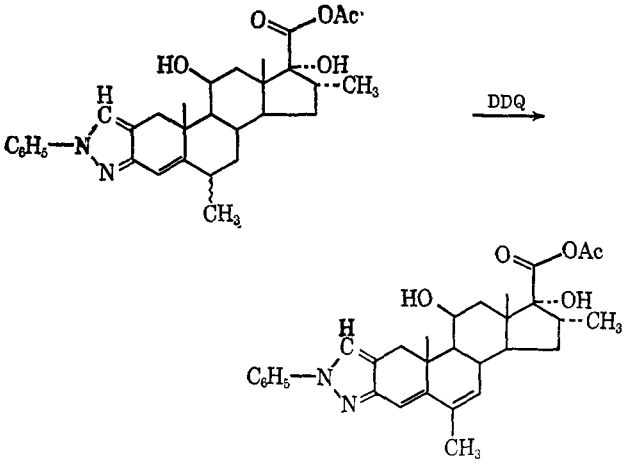


2. *Steroid Pyrazoles*

A few interesting examples have been recorded in the literature (84, 230).

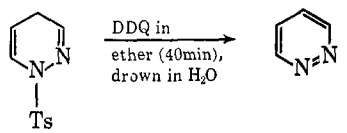


The 4-dehydro analog reacts similarly.

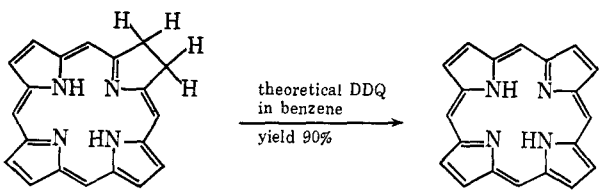


3. *Other Heterocyclic Compounds*

The following conversion has been described by Lemal and Rave (145).



DDQ has also been extensively used in the dehydrogenation of hydrogenated porphines (107).



chlorine porphine

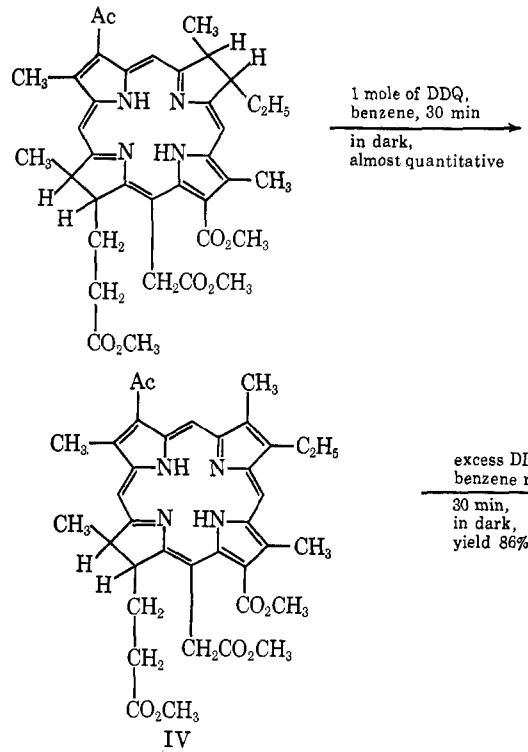
Similarly, octaethylchlorine gave a 64% yield of octaethylporphine (105). In another study (104), octaethylhexahydroporphine and octaethyloctahydroporphine were dehydrogenated with varying amounts of DDQ in benzene.

The hexahydro compound with 0.5 and 1.0 molar equiv of DDQ gave a mixture of starting material, octaethyltetrahydroporphine, and octaethylchlorine. With 2 molar equiv of DDQ, a quantitative yield of the chlorine was obtained. Three molar equivalents of DDQ gave an approximately 80% yield of octaethylporphine.

The octahydro compound with 1 or 2 molar equiv of DDQ gave a complex mixture containing the tetrahydro compound and the chlorine. When 3 molar equiv of DDQ was used, octaethylchlorine was obtained quantitatively. Use of 4 molar equiv afforded octaethylporphine in 80% yield.

Linstead and co-workers (114) have also described the dehydrogenation of bacteriochlorin e_6 trimethyl ester to a dihydro ester with 1 molar equiv of DDQ.

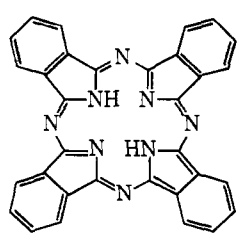
When the dihydro compound was heated with excess DDQ, removal of the other two hydrogens occurred.



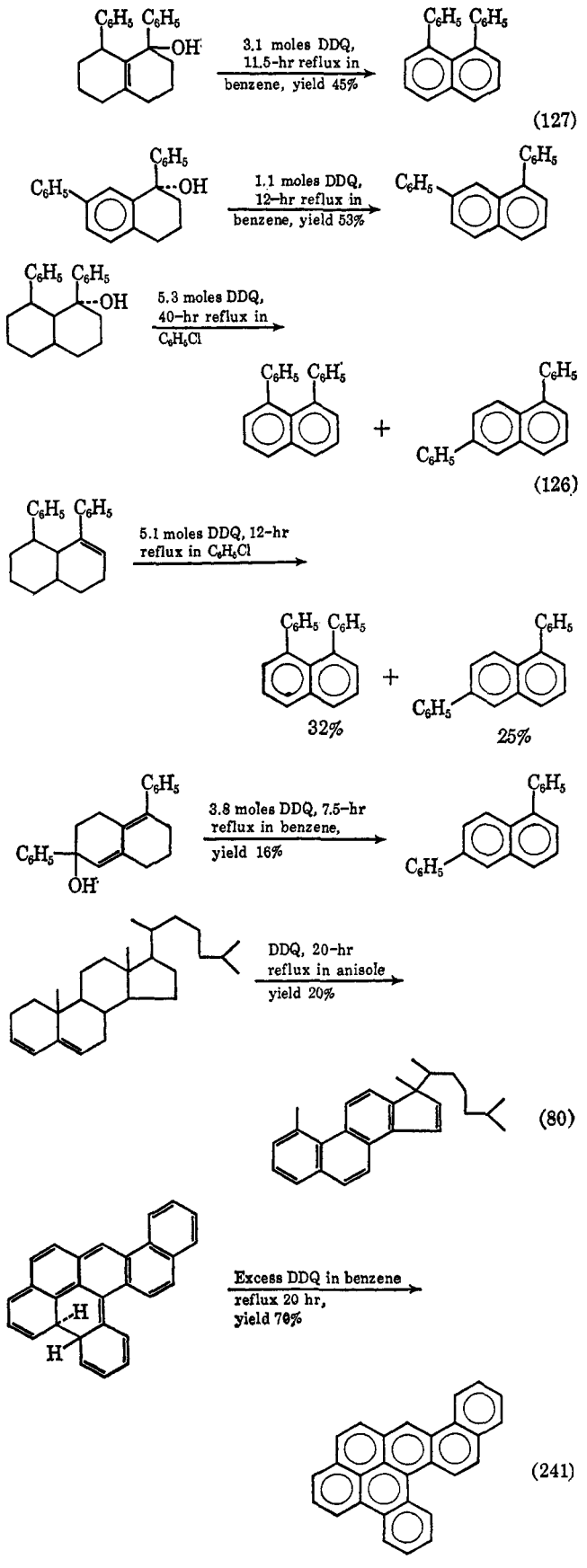
IV

Compound IV was the sole dihydro product produced, indicating a remarkably selective removal of hydrogen.

The dehydrogenation of hydrotetrazaporphines has been studied in *o*-dichlorobenzene solution in the absence of light (108). Tetrahydrooctamethyltetrazaporphine was 50% dehydrogenated by 1 molar equiv of DDQ. With 2 molar equiv of DDQ, octamethyltetrazaporphine was formed in 90% yield. The dehydrogenation of tetrahydrotetracyclohexenotetrazaporphine and tetracyclohexenotetrazaporphine with excess DDQ gave the phthalocyanine.



SCHEME III



With lesser amounts of DDQ, mixtures of compounds with incompletely aromatized rings were obtained.

F. DEHYDROGENATION OF HYDROAROMATIC COMPOUNDS

A few examples of the dehydrogenation of hydroaromatic compounds with DDQ have already been given under sections VI, A, 3 (A-ring aromatization of 19-acetoxyandrosta-4,7-dien-3-one), VI, E (aromatization of hydrogenated heterocyclic compounds), and VI, G (preparation of charged species containing $(4n + 2)$ π electrons), and these will not be discussed further.

The dehydrogenation of "hydroethylenic" systems (this term, due to Braude, Brook, and Linstead (35), covers aliphatic systems which are readily converted into ethylenic systems, *e.g.*, the conversion of dibenzyl to stilbene) will also be treated in this section. Much of the early work on dehydrogenations with DDQ was carried out, on hydroaromatic compounds, by Braude, Jackman, Linstead, and co-workers. The work by the Imperial College group is summarized in Table IX.

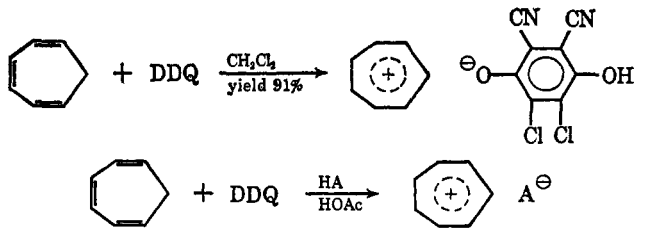
DDQ was also found to react with cyclohexene and ethylbenzene; 2,3-dichloro-5,6-dicyanohydroquinone was formed in 30–50% yields, but no simple dehydrogenation products were isolated (35). Similarly (38), β-ionone propylene ketal was only partially dehydrogenated by DDQ to 4-(3-pseudocumyl)but-3-en-2-one. Likewise, the action of DDQ on 1,1,2-tri- and 1,1,2,2-tetraphenylethane gave no olefinic products, and 2,2-dimethylindane gave none of the expected 1,2-dimethylindene. In the last case, DDQ was incorporated into the indane molecule (see section VI, I).

Ring size is reported to have a profound effect on the ease of dehydrogenation (131). Nevertheless, quinone dehydrogenation frequently provides a unique method of aromatizing rings containing quaternary carbon atoms without loss of carbon. A fuller account of this type of reaction, with a variety of quinones, is given by Jackman's review (131).

In recent years, DDQ has been used to dehydrogenate other hydroaromatic compounds (Scheme III).

G. PREPARATION OF STABLE CATIONS AND RADICALS

The great hydride ion abstracting power of DDQ has been put to interesting use by Reid and co-workers (193) in the preparation of stable cations and radicals.

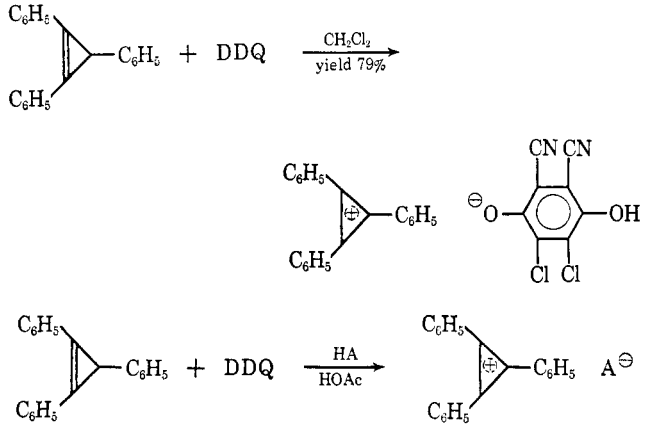


where HA = 70% w/w perchloric acid, yield of perchlorate = 92%
HA = picric acid, yield of picrate = 51%
HA = 90% orthophosphoric acid, yield of pyrophosphate = 55%

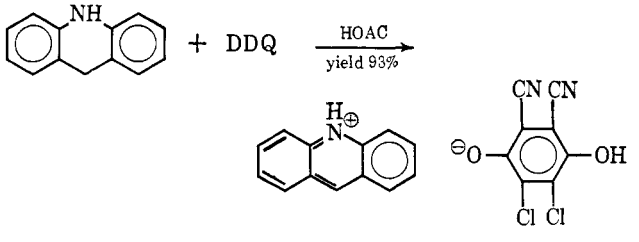
TABLE IX

Hydroaromatic compound	Moles of DDQ per mole of hydroaromatic compound	Conditions[a]	Product	Yield, %	Ref
Tetralin	4	Reflux 2 hr	Naphthalene	70	35
Acenaphthene	1	Reflux 20 hr	Acenaphthylene (79% pure)	66	35
Bibenzyl	1.06	Reflux 20 hr	Stilbene (43% pure)	50	35
1,1-Dimethyltetralin	Not given	2 hr at 80°	1,2-Dimethylnaphthalene	Almost quant.	146
1,1-Dimethyltetralin	2.2	5 hr at 80°	1,2-Dimethylnaphthalene (84% pure)	78	38
1,5,5-Trimethyl-3-methylenecyclohexene	1.2	Short time	1,2,3,5-Tetramethylbenzene	5.5[b]	38
Indane	1.09	4 hr at 80°	Indene[c]	76	38

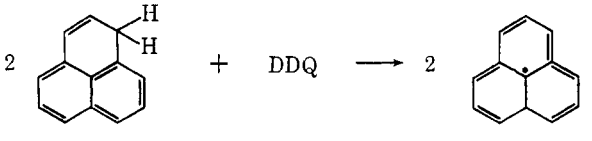
[a] Reactions carried out in benzene. [b] A Diels–Alder adduct was the major product (56%). [c] Isolated as its bromohydrin.



where HA = 70% perchloric acid, yield of perchlorate = 95%
HA = picric acid, yield of picrate = 88%



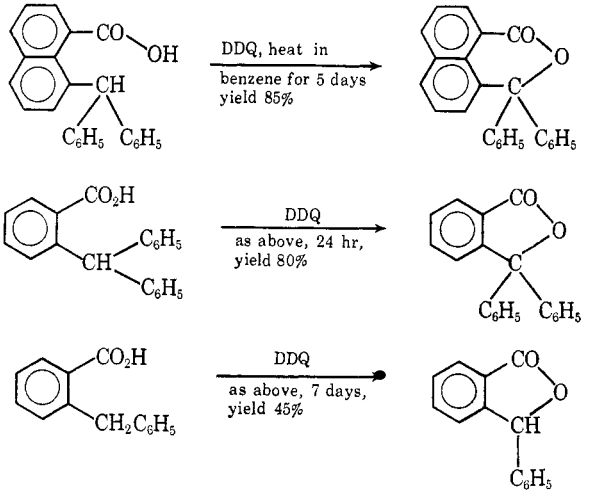
Reid and co-workers also described the preparation of the perinaphthyl radical[2] by treating perinaphthene with DDQ under neutral conditions (under acidic conditions, quinones other than DDQ gave the expected perinaphthenylium salts—DDQ was not tried under acidic conditions).



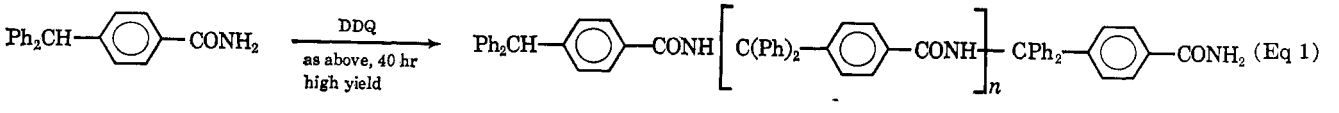
Other examples where radicals are believed to be formed as transient intermediates in DDQ reactions are given in sections D and H.

H. CYCLIZATION AND COUPLING REACTIONS WITH DDQ

A number of unusual cyclization and coupling reactions have been effected using DDQ. The following examples were reported by Creighton and Jackman (73).

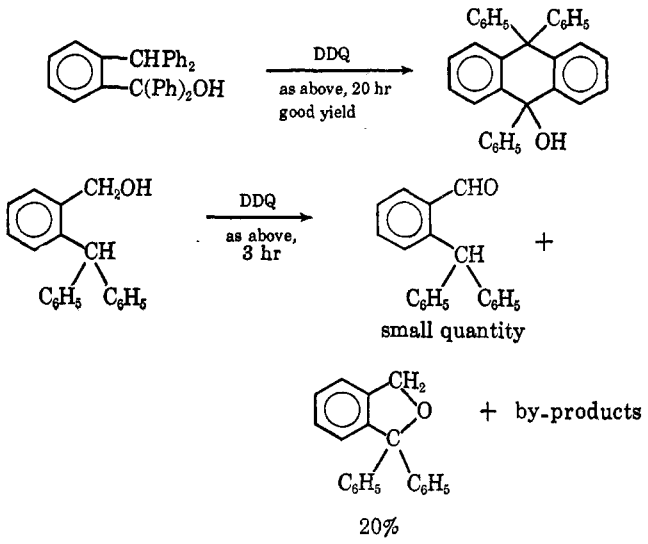


The by-products in the last experiment were identified as biphthalidyls. Tars resulted from the action of DDQ on *o*-toluic acid (Eq 1).

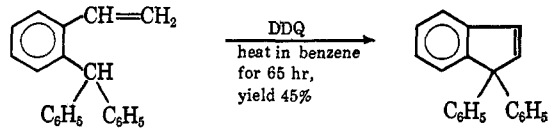


DDQ did not react with *o*-diphenylmethylbenzamide.

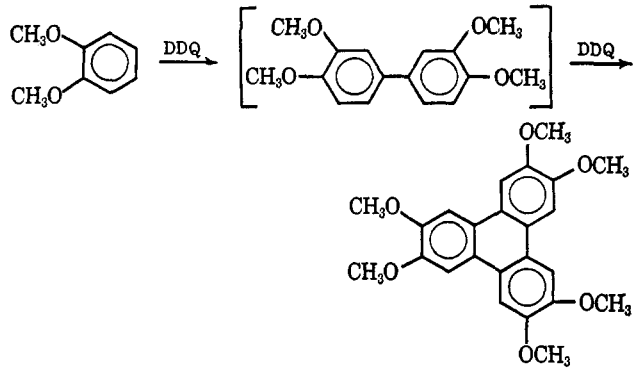
(2) The perinaphthyl radical is formulated as a [12]annulene according to the suggestion of Wolovsky and Sondheimer (255).



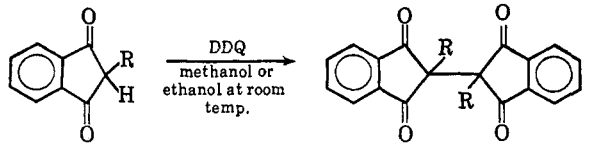
Brown and Jackman (45) have described the following conversion.



Matheson, Musgrave, and Webster (151) found that veratrole, when stood with excess DDQ in 70% v/v sulfuric acid for 10 days at room temperature, gave a triphenylene derivative in undisclosed yield. Chloranil was reported to give a somewhat better yield than DDQ in this reaction, and the yield reported with chloranil was 73%.



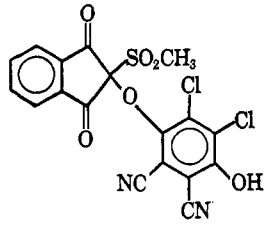
The coupling of 2-arylindane-1,3-diones using DDQ has been described by Becker (15).



where R = C_6H_5, yield = 62%; R = CH_3O—C$_6$H$_4$—, yield = 92%;

R = —C$_6$H$_4$—SO_2—C$_6$H$_4$—, yield = 94%

When R = CH_3SO_2, the product obtained (81% yield) is



The evidence available suggests that the products are formed from radical intermediates.

The DDQ-induced coupling reactions of phenols are described in section VI, D.

I. MECHANISM OF DEHYDROGENATION

Much of the early work on the mechanism of quinone dehydrogenation was carried out, on hydroaromatic compounds, by Braude, Jackman, and Linstead (36, 37). These workers found that, in the cases studied, the reactions were (i) essentially bimolecular, (ii) faster in polar than in nonpolar solvents, (iii) unaffected by radical producing agents, (iv) markedly influenced by the reduction potential of the quinone, which property is dependent on the substituent present, being enhanced, for instance, by electron-attracting substituents, and (v) catalyzed by proton donors. Charge-transfer complexes are probably formed in the initial step of the over-all reaction sequence (131).

On the basis of this evidence, a two-step heterolytic mechanism was proposed.

$$RH_2 + Q \xrightarrow{\text{slow}} RH^{\oplus} + QH^{\ominus} \xrightarrow{\text{fast}} R + QH_2$$

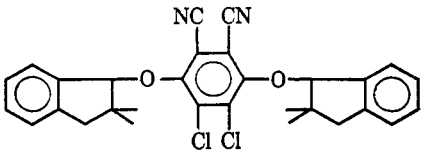
Catalysis by proton donors was explained as occurring through formation of the conjugate acid of the quinone, which species would be expected to be a far more powerful hydride ion abstractor than the neutral quinone.

$$Q + HX \overset{\text{fast}}{\rightleftharpoons} QH^{\oplus} + X^{\ominus}$$

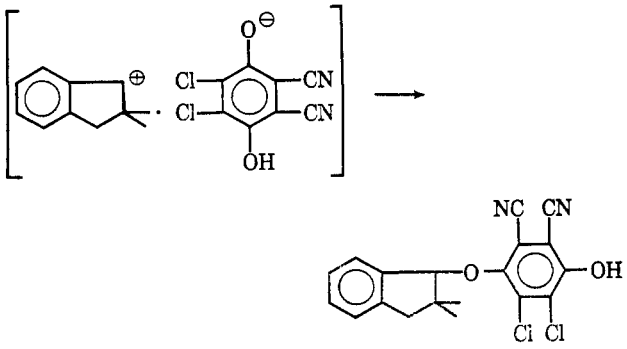
$$RH_2 + QH^{\oplus} \xrightarrow{\text{slow}} RH^{\oplus} + QH_2$$

$$RH^{\oplus} + X^{\ominus} \xrightarrow{\text{fast}} R + HX$$

It is now clear that the intermediate RH^+, or the ion pair $RH^+ \cdot QH^-$, may undergo several types of reaction. The most common is elimination of a proton to give an olefin, but a number of cases are known (38, 146) where Wagner–Meerwein-type rearrangements occur prior to loss of proton. Caution must be used in predicting which intermediates will undergo Wagner–Meerwein-type rearrangements. Thus, 2,2-dimethylindane, on treatment with DDQ, did not give the expected 1,2-dimethylindene. Instead, an ether of the following structure was obtained (38).



This product was said to arise from the monoether formed by collapse of the intermediate ion pair.

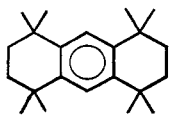


The failure of 2,2-dimethylindane to undergo rearrangement, in spite of the ready formation of the carbonium ion, was regarded (39) as striking evidence for the need of a truly diaxial conformation for maximum participation of the methyl groups.

A more complex rearrangement occurring during a DDQ dehydrogenation was observed by House and Bashe (126), who isolated a mixture of 1,8-diphenylnaphthalene and 1,6-diphenylnaphthalene from the dehydrogenation of either 1,8-diphenyl-1-hydroxydecalin or 1,8-diphenyl-$\Delta^{1,2}$-octalin.

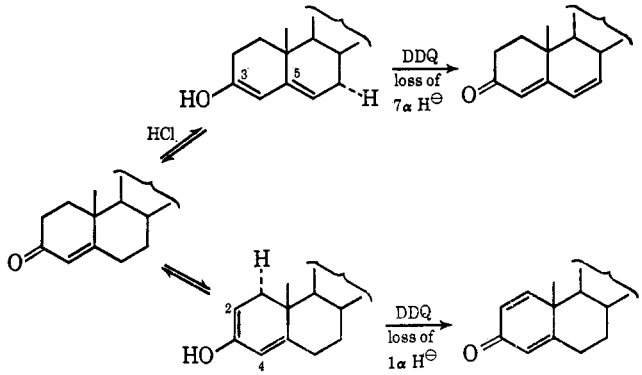
A further note of caution is introduced by the observation (38) that DDQ undergoes a Diels–Alder condensation with 1,5,5-trimethyl-3-methylenecyclohexene. In this case, dehydrogenation of the olefin to 1,2,3,5-tetramethylbenzene (isodurene) accounts for only 9% of the reaction.

In ionic dehydrogenation reactions, it is fairly clear that the hydrogen atom abstracted as a hydride ion has to be activated to some extent. Alternatively, the greater the resonance energy of the carbonium ion produced in a dehydrogenation reaction, the less is the resistance to the initial removal of a hydride ion. Braude, Jackman, Linstead, and Lowe (38) have pointed out that in the dehydrogenation of hydroaromatic compounds by quinones, a benzylic hydride ion is removed. Thus, the carbonium ion produced is the one most stabilized by resonance with the benzene ring. In accord with this statement, octahydrooctamethylanthracene of structure



fails to dehydrogenate with tetrachloro-1,2-benzoquinone.

There are many cases, particularly in the steroid field, where the hydride ion is removed from an allylic position. Steroids, and especially Δ^4-3-keto steroids, have been the subject of most study from a mechanistic viewpoint. Interestingly, Δ^4-3-keto steroids react with DDQ alone to give $\Delta^{1,4}$-3-keto steroids, while the same reaction with chloranil leads to $\Delta^{4,6}$-3-keto steroids. In the presence of anhydrous hydrogen chloride as a catalyst, DDQ also gives the $\Delta^{4,6}$-3-keto steroids. This has been explained in terms of the following scheme.



In the absence of a catalyst, the kinetically determined enol is predominantly the $\Delta^{2,4}$-enol (196, 197, 200). The rate of formation of this enol is slower than the rate of hydride ion abstraction by DDQ, with the result that $\Delta^{1,4}$-3-ketones are favored. In the presence of a catalyst, such as anhydrous HCl, formation of the thermodynamically more stable $\Delta^{3,5}$-enol is accelerated. Hydride ion abstraction from this enol gives a $\Delta^{4,6}$-3-ketone.

Further evidence for the enol dependency of the reaction was provided by a study of the DDQ dehydrogenation of $\Delta^{3,5}$-enol ethers (189, 226) (Scheme IV).

Under anhydrous conditions, abstraction of a C-7 hydride ion is followed by loss of a C-2 proton from the intermediate V and abstraction of a C-1 hydride ion from intermediate VI, while in the presence of water, hydrolysis of intermediate VII is faster than loss of proton from the C-2 position.

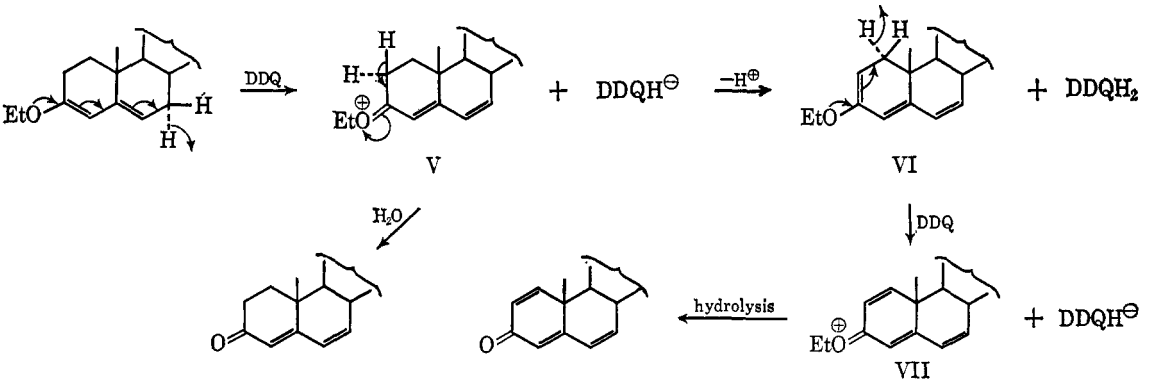
Incidentally, when the $\Delta^{2,4}$-enol is both the kinetically determined and thermodynamically favored enol, DDQ gives the same dehydrogenation product as chloranil. This occurs in the case of 2α-cyanocholest-4-en-3-one (84).

It is of some importance to note that, in anhydrous acetone as solvent, DDQ was found to incorporate into the steroid at C-1 by way of intermediate VII. Scheme V was proposed for this reaction.

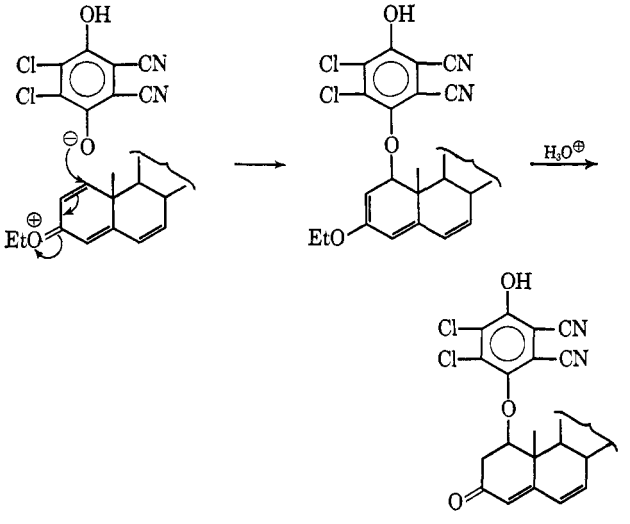
Unstable, alkali-soluble intermediates have also been obtained from the reaction of 9β, 10α-pregna-4,6-diene-3,20-dione with DDQ in the presence of a trace of hydrogen chloride (250).

The stereochemistry of the dehydrogenation reaction has been the subject of elegant work by Ringold

SCHEME IV



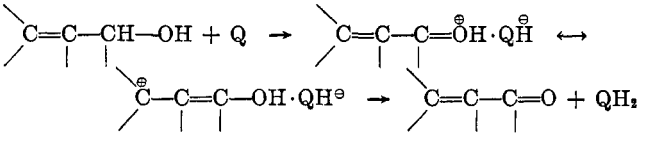
SCHEME V



and co-workers (196, 197, 200). The observation that DDQ would introduce a Δ^1-double bond into 1β-methyl-5α-androstan-17β-ol-3-one, but not into its 1α isomer, indicated the importance of the 1α-hydrogen atom in the dehydrogenation reaction. However, the most convincing evidence establishing the stereochemistry of dehydrogenation was provided by the finding that saturated steroidal 3-ketones with a 1α-deuterio substituent lost almost all their deuterium on dehydrogenation with DDQ or *Bacillus sphaericus*. Deuterium remaining in the dehydrogenated steroid was attributed to the presence of a small amount of 1β-deuterio-substituted steroid in the starting material. (It is pertinent to note that treatment of 1α-*d*-6α-methyl-10α-progesterone with DDQ gives a 1-dehydro product containing 38% deuterium. In this case, the dehydrogenation seems sterically less homogeneous than in the 10β series (122). It is known that some elimination of 1β hydrogen does occur when a normal 10β-Δ^4-3-ketone is dehydrogenated with DDQ, but not when it is dehydrogenated with *Bacillus sphaericus* (42)). The loss of the 2β-hydrogen atom was inferred from work with 2α-methyl- and 2α-hydroxytestosterone, which underwent dehydrogenation, and with 2β-hydroxyandrost-4-ene-3,17-dione, which underwent very little dehydrogenation. Furthermore, 2-deuterioandrost-4-ene-3,17-dione, in which the deuterium was primarily located at 2β, underwent a 75% loss of deuterium on dehydrogenation.

Thus, it has been established that the dehydrogenation of Δ^4-3-keto steroids, with both DDQ and *Bacillus sphaericus*, proceeds mainly by a *trans*-diaxial loss of the 1α,2β-hydrogen atoms. The dehydrogenation of $\Delta^{3,5}$-enol ethers is presumed to occur (189) by loss of the axial 7α hydrogen by analogy with the chloranil-mediated conversion of Δ^4-3-keto steroids to $\Delta^{4,6}$-3-keto steroids, which is known to involve abstraction of the axial 7α hydrogen (54).

The mechanism of the dehydrogenation of allylic alcohols by quinones has been studied by Braude and co-workers (40) and, in the steroid series, by Burstein and Ringold (52). Braude and co-workers postulated that the reaction took the following course.



Burstein and Ringold carried this study further using DDQ as the quinone and Δ^4-3-hydroxyandrostanes and -cholestanes as model compounds. They found that the reaction was bimolecular and unaffected by the addition of benzoyl peroxide, as would be expected from the above ionic reaction scheme. They also found that the 3α-deuterio steroids were subject to a large primary deuterium isotope effect (*ca.* fivefold) and that equatorial alcohols (3β) were dehydrogenated faster than axial alcohols. This latter fact was attributed to favorable σ–π overlap of the departing axial hydride ion in the case of the 3β alcohols, thus minimizing the energy of the transition states.

A few examples are known where DDQ reacts to produce radicals. Waters (244, 245) long ago suggested that quinones could abstract a hydrogen atom to give a free organic radical and a semiquinone radical. Later, Reid and co-workers (193) postulated that the ionic

mechanism of dehydrogenation by quinones may even represent a summary of two successive reactions.

$$RH_2 + Q \rightarrow RH\cdot + QH\cdot$$
$$RH\cdot + QH\cdot \rightarrow RH^{\oplus} + QH^{\ominus}$$

or, if RH· is a stable, long-lived radical, then the following reaction may occur as well.

$$RH_2 + QH\cdot \rightarrow RH\cdot + QH_2$$

The formation of semiquinone radical may even be bypassed.

$$2RH_2 + Q \rightarrow 2RH\cdot + QH_2$$

Reid and co-workers found one example of radical formation with DDQ, this being the formation of the perinaphthyl radical from perinaphthene (see section G).

More recently, Becker (14, 15) has concluded that radicals are involved in the DDQ oxidation of monohydric phenols, and in the oxidative dimerization of enols and enolizable ketones using DDQ (see sections D and H).

J. COMPARISON OF DDQ WITH OTHER REAGENTS

Since several other reagents perform similar functions to DDQ, it is tempting to draw comparisons, especially yield comparisons. Unfortunately, however, very little published information is available in which yields are compared; this is true even of industrial laboratories where interest in optimum yields is usually greatest. The following brief survey, therefore, covers only the types of reactions carried out by other and comparable reagents and is, in a sense, a guide to side reactions which might be expected in using these reagents; some attempts are made to point out the advantages and disadvantages of the various methods. It is fairly clear that in some instances the dehydrogenating agents are complementary to one another.

1. Comparison with Microbiological Methods

The action of microorganisms on organic substances has fascinated chemists for more than a century (109), and in the last 2 decades, particularly, the subject has grown enormously. Microorganisms have been used to bring about both oxidation and reduction of a wide variety of organic materials but, from the point of view of the organic chemist, one of the most exciting contributions to chemistry has been the application of fermentation processes to the preparation of modified steroids.

Microorganisms have been widely used to introduce hydroxyl groups into the steroid molecule, notably at the 11 position, using, *e.g.*, *Rhizopus arrhizus* (186), *Metarrhizium anisopliae* (155), *Curvularia lunata* (158), and *Psilocybe caerulescens var. mazatecorum* (221), to mention but a few. Various other microorganisms have been used to introduce hydroxyl groups into other positions in the molecule (29, 72, 116, 144, 150, 162, 167, 236). The position taken up by the entering hydroxyl group often depends on the structure of the starting steroid.

Microorganisms are also known to aromatize steroids (95, 148) and to form ring-D lactones from progesterones (87, 111). Again, appropriately substituted steroids, for example, 19-hydroxylated steroids, can be selectively converted to products devoid of the carbon-17 side chain, thus opening up the possibility of obtaining useful raw materials from hitherto unattractive steroid sources (ref 215 and preceding papers by Sih mentioned therein).

One of the most valuable uses of microorganisms in steroid chemistry is in the introduction of Δ^1-double bonds into Δ^4-3-ketones (42, 153, 154, 157, 168, 197, 205, 211, 248) or $\Delta^{4,6}$-3-ketones (155–158, 168, 248). This type of dehydrogenation is also accomplished by DDQ, as already described (section VI, A, 1), and it is only this facet of microbiological chemistry which can be compared with DDQ dehydrogenation. The microbiological dehydrogenation is most often carried out with *Bacillus sphaericus* (42, 153–155, 157, 158, 196, 197, 248) and *Arthrobacter simplex* (153, 157, 158, 168), although a great variety of other microorganisms is also claimed to introduce Δ^1-double bonds into Δ^4-3-keto steroids, for example, *Corynebacterium simplex* (155, 156, 248), *Curvularia simplex* (158), *Septomyxa affinis* (168), and many others (150, 175, 203, 237). Saturated steroidal 3-ketones may also be converted to Δ^1-3-ketones using *Bacillus sphaericus* (42, 196, 197). Yields of Δ^1-dehydro products by the microbiological method are very variable, ranging from a few per cent (111) to 45–95% (196, 197).

The chief disadvantages of the microbiological method of dehydrogenation lie in the very large dilutions which have to be employed to run the reaction, and consequent handling difficulties during work-up. Equipment costs are thus relatively high, so that until a fermentation method is available for working at much greater concentration, comparable chemical methods of dehydrogenation, such as provided by DDQ, will continue to remain the most attractive.

2. Comparisons with Inorganic Dioxides

a. Selenium Dioxide

Selenium dioxide has long been known for its extraordinary versatility as an oxidizing agent. It has been widely used for converting $-COCH_3$ groups to COCHO groups, or occasionally to $COCH_2OH$ groups (231). It has been used for converting aromatic methyl groups to aldehyde groups (213) or to carboxylic acid groups (9). It has been used for oxidizing olefins to allylic

alcohols (2, 214, 253), and cases are known (190, 202) where cyclic olefins are converted to cyclic olefinic ketones. Selenium dioxide has also been used as a catalyst, particularly with hydrogen peroxide, the oxidation of aldehydes to acids (216) and of steroidal Δ^4-3-ketones to secolactones (57, 58) being two cases in point.

All of these reactions involve the introduction of oxygen atoms, but such oxidations do not define the scope of the usefulness of selenium dioxide. It is also a powerful dehydrogenating agent and clearly similar to DDQ in many of its reactions. Thus, in recent years selenium dioxide has been employed in the dehydrogenation of arylsuccinic acids to arylmaleic anhydrides (123), in the dehydrogenation of dibenzoylethanes to dibenzoylethylenes (208), in the dehydrogenation of allylic alcohols to aldehydes (79), in the conversion of 2,4-cycloheptadienone to tropone (228), and in the aromatization of cyclohexadienes (258). It has found its most extensive use as a dehydrogenating agent in steroid chemistry, where again it does many of the same reactions as DDQ. The following types of reaction have been recorded with selenium dioxide: (a) dehydrogenation of saturated 3-ketones to Δ^1-, Δ^4-, and $\Delta^{1,4}$-3-ketones (172, 174, 183, 239); (b) dehydrogenation of Δ^4-3-ketones to $\Delta^{1,4}$-3-ketones (4, 25, 56, 132, 143, 154, 160, 168, 171, 173, 183, 191, 198, 205, 211, 237); (c) dehydrogenation of Δ^1-3-ketones to $\Delta^{1,4}$-3-ketones (56, 187); (d) dehydrogenation of $\Delta^{4,6}$-3-ketones to $\Delta^{1,4,6}$-3-ketones (158, 160, 168, 183). (e) Dehydrogenations of Δ^5-12-ketones to $\Delta^{5,9(11)}$-12-ketones, 12-ketones to $\Delta^{9(11)}$-12-ketones, 7-ketones to Δ^5-7-ketones, D-homo-17-ketones to D-homo-Δ^{15}-17-ketones, and Δ^8-steroids to $\Delta^{8,14}$-steroids have been described in the review by Owyang (183). (f) One patent (238) has described the conversion of $\Delta^{4,17(20)}$-3-ketones into 16-hydroxy-$\Delta^{1,4,17(20)}$-3-ketones.

Selenium dioxide is most often used in *t*-butyl alcohol. Sometimes acetic acid is added (4, 56, 132, 154, 158, 168, 239), and occasionally a little mercury is included (56, 132, 160). Other workers prefer the presence of a little pyridine in the *t*-butyl alcohol (103, 174, 198). Wet pyridine has also been used as the solvent (202), as have moist benzene (191, 199), acetic acid (110), *t*-amyl alcohol (211), tetrahydrofuran (238), and dioxane (110). The presence of an alkali ion-exchange resin has been claimed to improve the yields (173). Yields are very variable, ranging from a few per cent to 85%, which is not surprising in view of the polyfunctional nature of many steroids and the reactivity of selenium dioxide.

Because of the greater tendency to side reactions with selenium dioxide, DDQ would seem to be more attractive than this oxide for dehydrogenation reactions. No strictly comparative study seems to have been published, however. One great disadvantage to selenium dioxide from the point of view of drug manufacture stems from its unfortunate propensity to enter into the molecule of the material being dehydrogenated (12, 110, 154, 202). Deselenization of the oxidation products in steroid dehydrogenations has been achieved by heating with 20% aqueous ammonium sulfide (139), by treatment with Raney nickel and recycling the reduction product (154), or by heating with zinc and acetic acid (124). The physiological action of selenium dioxide, which resembles that of arsenic compounds, has been discussed by Patty (184).

b. Manganese Dioxide

Manganese dioxide has a high reduction potential [$E_0 = \sim 1.25$ v (152)] but in practice proves to be only a very mild oxidizing agent, seldom effecting aromatization reactions, although such are known (8). Manganese dioxide has been found to effect a variety of oxidation reactions (117), among the most important being the oxidation of aromatic secondary alcohols to ketones (234), certain tertiary amines to products containing carbonyl groups (78), allylic methylene groups to unsaturated ketones (121), and the oxidation of allylic alcohols to aldehydes and ketones (7, 11). This last reaction has been widely used in the steroid field and is the subject of a recent review (166). A newer use of manganese dioxide is in the conversion of steroidal $\Delta^{3,5}$-enol ethers to $\Delta^{4,6}$-3-ketones (45, 250), a dehydrogenation reaction entirely analogous to that effected by DDQ and other quinones (sections VI, A, 1b and VI, J). Yields are in the range 25–60%. Dehydrogenation of Δ^4-3-ketones to $\Delta^{4,6}$-3-ketones with manganese dioxide is unsatisfactory (219).

Where manganese dioxide proves to be a suitable oxidant, it is often sufficient simply to filter the allylic alcohol through the tube containing the oxidizing agent (121). Unfortunately, manganese dioxide is used heterogeneously, and furthermore it varies considerably in its activity from one batch to another (117, 121, 152). In addition, suitably active samples require special preparation (121, 218), and even then it often seems necessary to use large quantities. On the other hand, manganese dioxide oxidations are subject to fewer side reactions than selenium dioxide oxidations, although at high temperatures its specificity for allylic hydroxyl groups is frequently lost (219).

It seems highly probable, in view of the work of Burn, Petrow, and Weston (51) already discussed (section VI, C), that DDQ will prove to be the most convenient reagent for oxidizing allylic alcohols to the corresponding aldehyde or ketone.

3. Comparisons with Other Quinones

As is apparent from the Table VII, the reduction potential of quinone is markedly influenced by the sub-

stituent present, electron-withdrawing groups enhancing the potential and electron-donating groups weakening it. Quinones of high reduction potential are more powerful electron or anion acceptors than are those of low reduction potential, and the rates of dehydrogenation reactions with a given substrate reflect these differences. Thus, DDQ dehydrogenates chlorine to porphine at a faster rate than tetrachloro-*o*-quinone (107) and, more precisely, DDQ dehydrogenates 1,2-dihydronaphthalene 5500 times faster than chloranil at 100°, while tetrachloro-*o*-benzoquinone reacts 4200 times faster than chloranil in the same reaction under identical conditions (131). The difference between *o*- and *p*-tetrahaloquinones is striking, suggesting that the unknown dichlorodicyano-*o*-benzoquinones might be even more potent than DDQ in dehydrogenation reactions. Some useful comparisons of quinones were given by Braude, Brook, and Linstead (35) in a detailed study of the dehydrogenation of tetralin, acenaphthene, and bibenzyl. They found DDQ to be the most effective dehydrogenating agent, followed by tetrachloro-*o*-benzoquinone, tetrachloro-1,8-diphenoquinone, and chloranil. Numerous other quinones were described.

Most of the quinones generally used in dehydrogenation reactions are subject to side reactions such as Diels–Alder condensation, hydrolysis, and other group replacement reactions. DDQ, as explained in sections VI, A, 5 and VI, I, is no exception in this respect, but its extraordinarily high reduction potential, and consequent high rate of reaction, provides an advantage which frequently more than offsets other side reactions. Thus, based on the observation that DDQ gives HCN with water (229), it was once considered essential to use this quinone under anhydrous conditions (131). However, as shown in section VI, I, the presence of water is actually necessary for the conversion of enol ethers of Δ^4-3-ketones into $\Delta^{4,6}$-3-ketones (189). In this case the high rate of reaction of DDQ with the steroid is such that the slower hydrolysis of the quinone by water is a negligible side reaction. In the absence of water, the $\Delta^{1,4,6}$-3-ketone is the predominant product.

Again, with tetrahydrooctamethyltetrazaporphin (108), DDQ effects a clean dehydrogenation in high yield, while quinones of lower potential react more slowly and so allow thermal decomposition of both pigment and quinone to take place. Somewhat similar reasoning may apply to the dehydrogenation of cycloheptatriene by various quinones in a perchloric acid–acetic acid mixture (193). The yields of tropylium perchlorate obtained with a number of quinones were as follows: DDQ (92%), tetrachloro-*o*-benzoquinone (97%), chloranil (70%), and benzoquinone (30%). Different acid catalysts, however, gave different results. In the presence of picric acid, DDQ gave a 51% yield of tropylium picrate. In the presence of oxalic acid, tetrachloro-*o*-benzoquinone gave an 83% yield of tropylium tetroxalate. Similarly, DDQ dehydrogenated triphenylcyclopropene to triphenylcyclopropenium perchlorate (95% yield) in acetic acid–perchloric acid, and to triphenylcyclopropenium picrate (88% yield) in acetic acid–picric acid. Tetrachloro-*o*-benzoquinone was regarded by Reid and co-workers to be the most practical from their standpoint, since it is quite soluble in acetic acid and its quinol is soluble in ether.

Another important facet of acid catalysis in DDQ dehydrogenations has already been illustrated in connection with the preparation of steroidal $\Delta^{4,6}$-3-ketones from Δ^4-3-ketones (see sections VI, A, 1b and VI, I). In this case, while it probably speeds the rate of dehydrogenation by DDQ, the chief function of the acid is to accelerate the rate of formation of the stable $\Delta^{3,5}$-enol. This specific function thus lends a versatility to DDQ dehydrogenations of Δ^4-3-ketones, and this property has been widely exploited (see section VI, A, 1b). Incidentally, when the thermodynamically stable $\Delta^{3,5}$-enol is preformed, say as its ether or acetate, many quinones can be used for dehydrogenation (226), indicating the ease with which the 7α-hydrogen atom is removed in these cases. It is also of interest to note that 2,3-dicyanobenzoquinone (134), 2,3-dibromo-5,6-dicyanobenzoquinone (129, 204), and tetrachloro-*o*-benzoquinone (217) apparently give the same dehydrogenation products as DDQ in the dehydrogenation of steroidal Δ^4-3-ketones, and in this respect these four quinones compare with selenium dioxide and microbiological agents in their specificity.

DDQ is widely employed in the preparation of $\Delta^{1,4}$-3-ketones from Δ^4-3-ketones, while chloranil appears to be the reagent of choice for converting Δ^4-3-ketones to $\Delta^{4,6}$-3-ketones. In Table X are given a number of examples where both DDQ and chloranil have been used to dehydrogenate the same steroid.

Under normal conditions of use, DDQ does not appear to dehydrogenate $\Delta^{1,4}$-3-ketones to $\Delta^{1,4,6}$-3-ketones, even in the presence of a large excess of quinone (96, 122, 164, 200), though chloranil is reported to convert $\Delta^{4,6}$-3-ketones to $\Delta^{1,4,6}$-3-ketones in low yields using secondary amyl alcohol in place of the commonly used *t*-butyl alcohol (1).

However, $\Delta^{1,4}$-3-ketones can be converted to $\Delta^{1,4,6}$-3-ketones with chloranil (1, 25, 71, 99, 239) and $\Delta^{4,6}$-3-ketones may be readily dehydrogenated to $\Delta^{1,4,6}$-3-ketones with DDQ (155, 157, 235). Of the two methods, the last appears to be the most frequently employed.

Chloranil-mediated dehydrogenations of Δ^4-3-keto steroids are often carried out on materials carrying a 6-substituent, almost invariably in the 6α conformation (25, 41, 99, 153, 157, 158, 209, 239, 248). Steroidal Δ^4-3-ketones substituted at 6β give poor yields of $\Delta^{4,6}$-3-ketones with both chloranil and DDQ–HCl (250). Evidently, 6α-substituted Δ^4-3-ketones enolize to the

TABLE X

Starting material	Quinone[a]	Location of dbl bonds in product (yield, %)	Ref
17α-Acetoxy-6α-methyl-4,14-pregnadiene-3,20-dione	DDQ	$\Delta^{1,4,14}$	41
	Chloranil	$\Delta^{4,6,14}$	
17α-Methylprogesterone	DDQ	$\Delta^{1,4}$	209
	Chloranil	$\Delta^{4,6}$ (17)	
16β-Mercapto-17β-hydroxy-androst-4-en-3-one 16,17-acetonide	DDQ	$\Delta^{1,4}$	257
	Chloranil	$\Delta^{4,6}$ (60)	
19-Methyl-10α-pregn-4-ene-11β,-17α,21-triol-3,20-dione 21-acetate	DDQ	$\Delta^{1,4}$	22
	Chloranil	$\Delta^{4,6}$	
11β-Hydroxy-16-(3-oxobutyl)-androst-4-ene-3,17-dione	DDQ	$\Delta^{1,4}$	6
	Chloranil	$\Delta^{4,6}$	
16-Chloromethylene-4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate	DDQ	$\Delta^{1,4}$	153
	Chloranil	$\Delta^{4,6}$	
2α-Cyanocholest-4-en-3-one	DDQ	$\Delta^{1,4}$	84
	Chloranil	$\Delta^{4,6}$	
Retroprogesterone	DDQ	$\Delta^{1,4}$ (43)	
	Chloranil	$\Delta^{4,6}$ (13)	191
17α-Acetoxyretroprogesterone	DDQ	$\Delta^{1,4}$	191
	Chloranil	$\Delta^{4,6}$	
17α-Methyl-21-fluoroprogesterone	DDQ	$\Delta^{1,4}$	83
	Chloranil	$\Delta^{4,6}$	

[a] Chloranil is used in various solvents, *t*-butyl alcohol being the most popular (6, 22, 25, 69, 156, 158, 160, 191, 209). Others used are amyl alcohol (239), ethyl acetate (157), *sec*-butyl alcohol (41), dioxane (157, 158), and tetrahydrofuran (153, 156). Acid catalysts, *e.g.*, *p*-nitrophenol (41) and acetic acid (25, 157, 158, 209), are often added.

6-substituted $\Delta^{3,5}$-enols much more easily than the corresponding 6β compounds.

Since chloranil is much less reactive than DDQ, it can often be used in the presence of groups which have to be protected for reaction with DDQ. The dehydrogenation of 17α-aminomethyltestosterone provides a case in point (71). In spite of this example, however, amines, even tertiary amines, are known to react with chloranil (46). Furthermore, chloranil is also known to undergo Diels–Alder reactions (112), and one case has been recorded where chloranil opens the 16α,17α epoxide ring of a 16β-methyl steroid giving a 16-methylene-17α-hydroxy steroid (156).

Numerous quinones, including DDQ, chloranil, tetrachloro-*o*-benzoquinone, 3,3′,5,5′-tetrachlorodiphenoquinone, 2,7-dinitrophenanthrenequinone, and 2-nitrophenanthrenequinone, are known to effect extensive dehydrogenation of cholesta-3,5-diene in refluxing anisole (80), but the drastic conditions employed render it difficult to draw conclusions regarding the effectiveness of individual quinones. The work of Braude and co-workers (35), already referred to, is much more useful in assessing the relative value of quinones in dehydrogenation reactions. The advantages and disadvantages of 3,3′,5,5′-tetrachloro-4,4′-diphenoquinone, phenanthrenequinone, and 2,7-dinitrophenanthrenequinone have been discussed by Jackman (131).

It may be concluded that whenever DDQ dehydrogenations prove to be slow the importance of side reactions will necessarily increase. Clearly, the relative dehydrogenating power of quinones is not the only factor to be considered in predicting the importance of possible side reactions. One has to consider the effect of acid catalysis and also the donor ability of the material to be dehydrogenated. In addition, the nucleophilicity of the reagents and groups present needs to be taken into account, as well as the changes induced in both donors and acceptors by the formation of charge-transfer complexes or transition states.

VII. CHARGE-TRANSFER COMPLEXES AND COLOR REACTIONS

Charge-transfer complexes may be formed as the first step in many reactions involving DDQ, since this quinone is reported to be comparable with tetracyanoethylene in acceptor strength (119). As yet, however, little investigation of such complexes with DDQ has been made. The colors formed by treating solutions of DDQ, in methylene chloride or carbon tetrachloride, with aromatic hydrocarbons have been ascribed to π–π charge-transfer complexes (119, 192). Specific color reactions due to the formation of such complexes are reported to occur when nitromethane solutions of DDQ are added to dilute chloroform solutions of a number of organic compounds; these color reactions are said to be suitable for locating spots of aromatic hydrocarbons, aldehydes, amines, acids, esters, and phenols on developed paper chromatograms. The colors produced are sometimes only transitory (5). Several charge-transfer complexes of DDQ have been prepared and their physical properties measured.

The 1:1 complex formed by DDQ and durene is unstable; it shows strong electron spin resonance absorption and a melting point well above the melting points of the constituents. Other spectral characteristics and thermodynamic parameters have been determined (119).

Methylene chloride solutions of the DDQ–naphthalene complex are stable for at least 48 hr. The extinction coefficient, equilibrium constants, and heat of formation of this complex have been reported (192).

Some interest has been shown in the conductivity of 1:1 complexes of DDQ with *p*-phenylenediamine, perylene, and pyrene (182). Table XI summarizes some of the results obtained. DDQ is included for comparison.

Of the complexes cited in Table XI, only that with *p*-phenylenediamine gives an electron spin resonance signal, and, again this is the only complex whose infrared spectrum is significantly different from the superimposed spectra of the components.

TABLE XI

1:1 complex of DDQ with	Mp, °C	Resistivity at 25° in ohm-cm	Activation energy for conductivity, ev	Seebeck coeff, mv/°C
p-$C_6H_4(NH_2)_2$	Dec >300	10^6	0.37	0.24 at 30° 0.85 at 65°
Perylene	204	3×10^6	0.45	−0.36 at 30° −0.53 at 65°
Pyrene	233–234	10^{13}	0.9	−1.9 at 60°
DDQ (cryst from CH_2Cl_2)	214–215	3×10^{10}	0.6	...
DDQ (cryst from C_6H_6)	214–215	5×10^8	0.6	−1.9 at 30° −1.9 at 60°

Charge-transfer complexes are implicated in the DDQ-catalyzed polymerization of N-vinylcarbazole (212).

VIII. On Compilations and Bibliographies

It seems fitting to caution the reader regarding the completeness of the bibliography included in this review. Many mentions of DDQ are buried in chemical papers and do not appear in journal indexes or in *Chemical Abstracts*. It is fairly likely that some such references have been missed in our own search. Therefore, the remarks made by Tucker some years ago (233) provide an appropriate note on which to close: "Compilations and bibliographies are double-edged weapons; though they facilitate access to some sources of information, they usually tend to intensify the concealment of others."

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