Selective Oxidation of Allylic Alcohols with Active N-Halogen Compounds. I. Synthesis of Testosterone and of 4-Pregnen-20β-ol-3-one[1]

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Treatment of allylic, propargylic and benzylic alcohol with manganese dioxide at room temperature has been shown to be an effective method for the selective oxidation of these alcohols[2]. It seems necessary, however, to search other reagents for the reactions, since recent studies indicate that in some cases even under mild conditions the oxidation of saturated primary and secondary alcohols may occur[3].

Lecompte and his colleagues[4] reported the oxidation reactions of a large number of alcohols containing benzene rings with *N*-bromoacetamide. It should be noted that hydroxyl groups in positions adjacent to the aromatic systems in the alcohols are easily oxidized to carbonyl groups, whereas hydroxyl groups in other positions are unaffected under similar conditions. Thus, 1-hydroxy-1, 2, 3, 4-tetrahydronaphthalene[4a], benzhydrol and benzyl alcohol[4b] are easily oxidized to corresponding carbonyl compounds, while the oxidation of 2-hydroxy-1,2,3,4-tetrahydronaphthalene[4a], 1,3-diphenyl-2-propanol and 2-phenylethanol[4b] does not occur. Lieberman and Fukushima[5] reported that the reaction of 5-cholestene-3β, 4β, 7α-trial 3-monoacetate with *N*-bromoacetamide gave 5-cholestene-3β,4β-diol-7-one 3-monoacetate in a quantitative yield*. These observations suggest that the active *N*-halogen compounds such as *N*-bromoacetamide may be effective

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[1] Steroids Part XXII; Part XXI, This Bulletin, **31**, 347 (1958).

[2] G. Rosenkranz et al., *J. Chem. Soc.*, **1954**, 1226, 2189; *J. Am. Chem. Soc.*, **75**, 5930, 5932 (1953) and literatures cited there.

[3] H. Bruderer, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 858 (1956) and literatures cited there.

[4] a) J. Lecomte and C. Dufour, *Compt. rend.*, **234**, 1887 (1952); b) J. Lecomte and H. Gault, ibid., **238**, 2538 (1954).

[5] S. Lieberman and D. K. Fukushima, *J. Am. Chem. Soc.*, **72**, 5211 (1950).

* Cf. M. A. Romero, *J. Org. Chem.*, **22**, 1267 (1957).

TABLE I

SYNTHESIS OF TESTOSTERONE FROM A MIXTURE OF 4-ANDROSTENE-$3\alpha,17\beta$- AND -$3\beta,17\beta$-DIOLS BY TREATMENT WITH ACTIVE *N*-HALOGEN COMPOUNDS

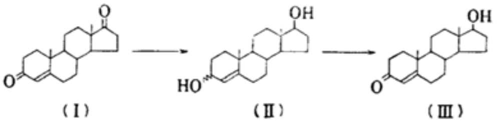
No.	andro-stenediol (mg.)	*N*-hlogene compounds	(mg.)	(equiv.)	solvents (ml.)	conditions (°C)	(hr.)	yields of testosterone (wt.%)
1	147.6	NBA,	(76.2)	(1.09)	Bu, 10; Py, 0.5; W, 0.3	20~21,	17	45
2	151.1	NBA,	(77.1)	(1.07)	Bu, 10; Py, 1; W, 1	15~17,	19	52
3	151.4	NBA,	(77.5)	(1.08)	Bu, 1; Py, 0.5	20~21,	17	71
4	152.0	NBA,	(78.6)	(1.09)	Bu, 0.5; Py, 1	20~21,	17	69
5	152.8	NBA,	(75.9)	(1.05)	Bu, 10; Py, 1	15~17,	19	68
6	151.5	NBA,	(79.5)	(1.10)	Bz, 2; Py, 1	20~21,	17	74
7	152.9	NBA,	(76.4)	(1.05)	Bz, 3; Py, 0.5	16~18,	41	57
8	151.9	NBA,	(75.9)	(1.05)	Bz, 8; Py, 0.1	16~18,	23	45
9	151.1	NBA,	(76.0)	(1.06)	Chf, 2; Py, 1	20~21,	17	47
10	152.6	NBA,	(74.0)	(1.02)	E, 4; Me, 10; Py, 0.3; W, 0.3	15~17,	19	38
11	152.2	NBS,	(97.1)	(1.03)	Bu, 0.5; Py, 1	15~17,	19	56
12	148.3	NBS,	(100.1)	(1.1)	E, 4; Me, 10; Py, 0.3; W, 0.3	15~17,	19	39
13	250.7*	NBS,	(163.0)	(1.06)	E, 5; Me, 1; 3%$KHCO_3$aq., 0.3	29	18	33
14	151.0	62% ICB,	(116.8)	(1.14)	Bz, 5; Py, 2	49~51,	1	71
15	155.5	62% ICB,	(103.0)	(0.98)	Bz, 10; Py, 0.3	50~52,	1	55
16	149.4	72% ICB,	(91.3)	(1.05)	Bu, 2; Py, 2	60~63,	1	73
17	175.6*	83% ICB,	(98.6)	(1.1)	Bu, 2; Py, 0.3; W, 0.3	60~65,	1	64

Bu=*tert*-Butanol, Py=Pyridine, W=Water, Bz=Benzene, Chf=Chloroform, E=Ether, Me=Methanol, NBA=*N*-Bromoacetamide, NBS=*N*-Bromosuccinimide, ICB=Isocyanur bromide.

* Eight grams of alumina were used.

reagents for selective oxidation of allylic alcohols.

The reduction of 4-androstene-3, 17-dione (I) with sodium borohydride gave a mixture of 4-androstene-$3\alpha,17\beta$-diol and the corresponding $3\beta,17\beta$-diol. The mixture, m.p. 95~145°C[6], was oxidized with about 1.05 equivalents of *N*-bromoacetamide, *N*-bromosuccinimide or isocyanur bromide[10] in various solvents, and the products were separated by chromatography. The results are shown in Table I. It is clear that (1) water disturbs* this reaction especially when used with *N*-bromosuccinimide or *N*-bromoacetamide, (2) *N*-bromoacetamide and isocyanur bromide are superior to *N*-bromosuccinimide as the reagents of this reaction. In the best conditions testosterone (III) was obtained in 70~74% overall yield from 4-androstene-3, 17-dione (I). (No. 3, 4, 6, 14 and 16)



(I) (II) (III)

Progesterone (IV) was reduced with sodium borohydride to give a mixture of 4-pregnene-$3\alpha,20\beta$-diol and the corresponding $3\beta,20\beta$-diol. The mixture, m.p. 147~168°C[11], was oxidized with *N*-bromoacetamide in benzene-pyridine. 4-Pregnen-20β-ol-3-one (VI) was obtained in

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[6] Sondheimer et al.[7] reported that the reduction of compound I with lithium aluminum hydride furnished a mixture of the 3α, 17β-diol and the 3β, 17β-diol and the mixture melted at 165~171°C. Presumably the difference in the melting points of both mixtures is due to difference in the proportions of 3α and 3β alcohols[8], since the C_{17} carbonyl group was exclusively reduced to the β-hydroxyl group on reduction with sodium borohydride[9].

[7] F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5930 (1953).

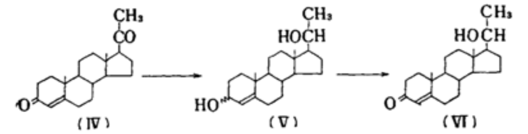
[8] For sodium borohydride reduction of 4-ene-3-ketosteroids see, W. W. Zorbach, ibid., **75**, 6344 (1953); B. Camerino and C. G. Alberti, *Gazz. chim. ital.*, **85**, 51 (1955); S. Bernstein, S. M. Stolar and M. Heller, *J. Org. Chem.*, **22**, 472 (1957).

[9] H. J. Ringold, B. Loeken, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 816 (1956); K. Miescher and C. Meystre, U. S. Pat. 2,679,502; *Chem. Abst.*, **49**, 6325^i (1955).

[10] K. Morita, This Bulletin, **31**, 347 (1958).

[11] Reduction of progesterone with lithium aluminum hydride gives a mixture with m. p. 162~172°C[7].

76 % overall yield from progesterone (IV). The 20β configuration was deduced from α_D values of compound VI, +85°, and of its acetate, +130°, which were quite similar to the reported[7,12-14]. Sondheimer et al.[7] reported that the reduction of progesterone (IV) with lithium aluminum hydride and the succeeding oxidation of the resulted diols with manganese dioxide yielded compound VI in 66 % overall yield.



Manganese dioxide attacks preferably unhindered hydroxyl groups such as primary[3] or equatorial hydroxyl[15]. On the other hand, active *N*-halogen compounds attack rather hindered hydroxyl groups[16,17]. The rate-determining step of the latter reaction is known to be the abstraction of the hydrogen atom bonded to the carbinol carbon. *N*-Halogen compounds might be serviceable for selective oxidation of polyhydroxyl compounds carrying primary or equatorial and allylic hydroxyl groups to α,β-unsaturated ketones with unaffected primary or equatorial hydroxyl groups. Such selective oxidation is probably difficult[3] when manganese dioxide is employed. Examples will be reported soon.

Experimental[18]

General Procedure of Synthesis of Testosterone (III) from 4-Androstene-3,17-dione (I).—A mixture of 1 g. of 4-Androstene-3,17-dione (I) with m.p. 165~169°C in 10 ml. of methanol and 1 g. of sodium borohydride in 1 ml. of water was heated under reflux for 1 hour. After cooling, the suspension was poured into dilute hydrochloric acid. Solid was collected by filtration and well washed with water. It melted at 95~145°C, and was presumably essentially a mixture of 4-androstene-3α,17β- and 3β,17β-diols and gave no 2,4-dinitrophenylhydrazone.

A weighed sample from the above solid in a mixed solvent as described in Table I was treated with *N*-bromoacetamide, *N*-bromosuccinimide or isocyanur bromide in the dark. When a solid appeared, it was filtered off. The solution or filtrate was diluted with a mixture of 30 ml. of ether and 10 ml. of benzene and washed successively with 10 % aqueous sodium bisulfite, with 10 % aqueous sodium hydroxide, with water, with dilute sulfuric acid and again with water, and dried over anhydrous sodium sulfate. The solvent was evaporated under a reduced pressure. The oily or crystalline residue was dissolved in 10 ml. of benzene and adsorbed on a column of alumina (5 g.).

The elution of products was carried out with the following solvent systems[19].

Fraction No.	benzene (ml.)	ether (ml.)
1	12	2
2	14	4
3	6 4	4 6
4	6	14
5	4	16
6	2	18
7	0	20
	aceton (ml.)	ether (ml.)
8	2	18
9	4	16
10	6	14
11	8	12
12	methanol 30 ml.	

The earlier fractions gave 4-androstene-3,17-dione (I) or an oil. The dione, collected from all the experiments and recrystallized from acetone-*n*-hexane, exhibited m. p. 168~169°C, $\lambda_{\max}$ 240mμ, log ε 4.23. Identity was established by a mixed melting point determination.

From middle fractions testosterone (III) with m. p. 148~153°C and mixed m. p. above 149°C was obtained in yields shown in Table I. Testosterone from all the experiments was brought together and recrystallized from acetone-*n*-hexane to show m. p. 152~153°C; $[\alpha]_D^{19}$ +102 (c, 1.40 in dioxan); $\lambda_{\max}$ 241 mμ, log ε 4.21.

From later fractions the starting material or an oil was obtained. Some oily fractions showed positive Beilstein test. Such oily fractions increased when water and/or *N*-bromosuccinimide was used.

4-Pregnene-20β-ol-3-one (VI) from Progesterone (IV).—A mixture of 1.5 g. of progesterone with m. p. 125~127°C in 30 ml. of methanol and 1 g. of sodium borohydride in 1.5 ml. of water was heated under reflux for one hour. After

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[12] P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

[13] J. Romo, M. Romo, C. Djerassi and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951).

[14] R. B. Turner and D. M. Voitle, ibid., **73**, 2283 (1951).

[15] C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, **1954**, 1226; also see footnote 16 of Ref. 3.

[16] The oxidation of primary alcohols with *N*-bromoacetamide is difficult. Cf. R. E. Jones and F. W. Kocher, *J. Am. Chem. Soc.*, **76**, 3682 (1954); T. H. Krichevsky, D. L. Garmaise and T. F. G. Gallagher, ibid., **74**, 483 (1952).

[17] Axial hydroxyl groups are more easily oxidized to carbonyl than equatorial ones. Cf. W. Klyne, "Progress in Stereochemistry" **1**, Butterworths Scientific Publications, London (1954), p. 63.

[18] All melting points are uncorrected. Ultraviolet absorption spectra were measured in 95% ethanol solution with a Hitachi Photoelectric Spectrophotometer Model EPU-2.

[19] The chromatographic separations were carried out in part by Mr. T. Iwama to whom author's thanks are due.

cooling a few drops of acetic acid were added and the solution was poured into an excess of water. The solid was collected by filtration and well washed with water. The mixture of 4-pregnene-3α, 20β- and 3β, 20β-diols melted at 147~168°C. Yield 1.5 g.

A solution of 499.1 mg. of above solid in 3 ml. of benzene and 5 ml. of pyridine was treated with 265.7 mg. of *N*-bromoacetamide (1.22 equiv.) at 18~19°C for two hours. After treated as usual, the crystalline residue was dissolved in 15 ml. of benzene and adsorbed on a column of alumina (3 g.). The elution with benzene-ether (1 : 1) and recrystallization from ether-*n*-hexean gave needles with m. p. 169~171°C, $[\alpha]_D^{19}$+85 (c, 1.05 in chloroform), λ_{max}242 mμ, log ε 4.22. Yield 378 mg. or 76 % of the theoretical. Identity was established by a mixed[7] melting point determination. Reported m. p. 171~172°C, $[\alpha]_D$+84[12]; m. p. 169~171°C, $[\alpha]_D$+83, λ_{max}242 mμ, log ε 4.31[13]; m. p. 174~175°C, $[\alpha]_D$+90[14]; m. p. 174~175°C, $[\alpha]_D$+86, λ_{max}240 mμ, log ε 4.23[7].

The acetate, recrystallized from acetone-*n*-hexane, exhibited m. p. 159~160°C, $[\alpha]_D^{18}$+130 (*c*, 0.368 in chloroform). Reported m. p. 159~160°C, $[\alpha]_D$+140[12], m. p. 159~161°C, $[\alpha]_D$+137[13], m. p. 161~162°C, $[\alpha]_D$+129[14], m. p. 161~162°C, $[\alpha]_D$+134[7].

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