2. E. Ts. Chukovskaya, R. G. Gasanov, I. I. Kandror, and R. Kh. Freidlina, Zh. Vses. Khim., 24, 161 (1979).
3. M. A. Moskalenko, A. B. Terent'ev, and R. Kh. Freidlina, Izv. Akad. Nauk SSSR, Ser. Khim., 637 (1981).
4. N. S. Ikonnikov and A. B. Terent'ev, Izv. Akad. Nauk SSSR, Ser. Khim., 371 (1975).
5. A. B. Terent'ev, N. S. Ikonnikov, and V. I. Dostovalova, Izv. Akad. Nauk SSSR, Ser. Khim., 1546 (1983).
6. N. A. Rybakova, L. N. Kiseleva, and I. V. Laputina, Izv. Akad. Nauk SSSR, Ser. Khim., 863 (1983).
7. M. R. Bendell, D. M. Doddrell, and D. T. Pegg, J. Magn. Reson., 44, 23 (1981).

OXIDATION OF SUBSTITUTED OLEFINS BY MOLECULAR OXYGEN ACTIVATED BY A DIVALENT MANGANESE – PORPHYRIN COMPLEX

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It is known that Mn(II) porphyrin complexes, obtained in situ by reducing the corresponding Mn(III) complexes, activate O_2 and catalyze the oxidation of olefins [1-3] to ketones, alcohols, epoxides, and allyl compounds [1, 2]. The formation of allyl compounds occurs by a radical autooxidation mechanism (the induction period is the only process in the absence of a reducing agent), and can be suppressed by adding a radical inhibitor [1]. The mechanism of the formation of saturated alcohols and ketones, however, has not been established. It has been suggested [1] that the oxidation of cyclohexene to cyclohexanol by the system O_2–tetra-p-methoxyphenylporphyrin manganese chloride (TPPMnCl)–$NaBH_4$ proceeds via epoxycyclohexane. According to [2], however, in the oxidation of olefins by the very similar O_2–TPPMnCl–$N(n\text{-}Bu)_4BH_4$ system no epoxides were detected, the primary reaction products being the ketones corresponding to the olefins, these being partially or completely reduced under the conditions of the reaction to the alcohols by excess hydride.

We have investigated the mechanism and the preparative possibilities of the oxidation of olefins to the corresponding alcohols (or the ketones or epoxides) by the system O_2–TPPMnCl–$NaBH_4$. The compounds selected for study were androst-5-en-3β-ol (I), cholesterol (cholest-5-en-3β-ol) (II), and several aliphatic olefins. The choice of the steroidal olefins (I) and (II) was due to the great importance in steroid chemistry of the oxidation of the 5,6-double bond, and the marked tendency of cholesterol (II) to underto autoxidation [4].

TABLE 1. Oxidation of Steroidal Olefins in the Presence of TPPMnCl–$NaBH_4$

Steroid	Solvent	TPPMnCl, M·10⁴	$NaBH_4$, M·10²	Steroid, M·10²	Yields of diol (III) or (IV), %	
					on steroid	on TPPMnCl
Androst-5-en-3β-ol (I)	DMF	4,8	10	7	–	–
	Benzene–ethanol, 1:1	2,4	10	7	78	22 000
Cholesterol (II)	DMF	2,4	8	5	80	17 000
	Benzene–ethanol, 1:1	2,4	10	7	82	23 000

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TABLE 2. Results of the Oxidation of Olefins (0.5 M) with Oxygen in the Presence of the System TPPMnCl–$NaBH_4$ (0.05 M)

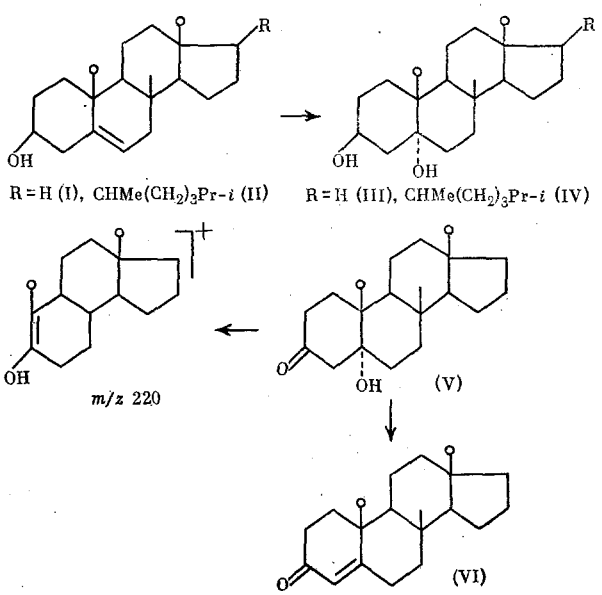
Expt. No.	Olefin	Solvent	Conc. of TPPMnCl, $\cdot 10^3$ M	Product	Yield* on TPPMnCl, %
1	Ethylene	DMF†	9	EtOH	167
2	Propylene	DMF†	9	MeCOMe *i*-PrOH	222 333
3	1-Hexene‡	DMF	5	*n*-BuCOMe *n*-BuCHOHMe	975 325
4	1-Hexene	C_6H_6 – EtOH	9	*n*-BuCOMe *n*-BuCHOHMe *n*-BuCH—CH_2 (O)	110 420 28
5	2Z-Hexene	DMF	5	*n*-BuCOMe *n*-PrCOEt *n*-BuCHOHMe *n*-PrCHOHEt	600 600 150 150
6	2Z-Hexene	C_6H_6 – EtOH	9	*n*-BuCOMe *n*-PrCOEt *n*-BuCHOHMe *n*-PrCHOHEt *n*-PrCH—CHMe (O)	26,6 26.6 287 287 40

* Calculated from extent of reaction of olefin and product ratio by GLC.

† In C_6H_6–EtOH, oxidation was slight.

‡ For stoichiometry: one mole of $NaBH_4$ gives 2 moles of the alcohol or 4 moles of the ketone or epoxide.

Scheme 1



The oxidation of the steroidal olefins (I) and (II) with atmospheric oxygen in the presence of 1-2 mole % of TPPMnCl and 1.5-2.2 mole-equiv. of $NaBH_4$ was quite rapid (reaction complete in 3 h), giving (III) and (IV) in yields (after chromatographic separation) of 80% (Table 1).

The PMR spectrum of (III) contained no signals for vinyl protons, but additional carbinol protons as compared with the original (I). The elemental composition of (III) was $C_{19}H_{32}O_2$, corresponding to hydration of the double bond in (I). The molecular formula, together with the tertiary nature of the new OH group in (III), was confirmed by the chemical, chromatographic, and mass spectral behavior of the compound. The mass spectrum

of (III), even when the sample was introduced directly into the ion source, showed only a very weak molecular ion peak (m/z 292). The trimethylsilylated derivative of (III) was identical in respect of its GLC mobility and mass spectrum to the trimethylsilyl ether of (I), and Johnson oxidation gave a mixture of androst-4-en-3-one (VI) and a compound $C_{19}H_{30}O_2$ (m/z 290), the structure of which (androstan-5α-ol-3-one (V)) was confirmed by the formation of the unsaturated ketone (VI) on partial thermal dehydration under GLC conditions and the presence in its mass spectrum of a strong ion with m/z 220, formed by fission of ring A, a reaction characteristic of 3-keto-5-hydroxysteroids [5].

The product (IV) obtained by oxidation of cholesterol (II) had similar properties. Its constants agreed with those given in the literature for cholestan-3β,5α-diol [4], also confirming the 5α-configuration of the latter. This configuration for (III) and (IV) was confirmed by their PMR spectra, the form of the signals for the 3β-carbonyl protons (a multiplet with $W_{1/2}$ 30 Hz) corresponding to trans-fusion of rings A and B in these steroids.

The rapid and selective oxidation of the steroidal olefins (I) and (II) could be due to the dependence of the reaction rate and the course of the TPPMnCl–catalyzed oxidation of the olefins on the extent of substitution of the double bond. To resolve this point, we examined the oxidation of ethylene, propylene, and 1- and 2-hexenes (Table 2). It was found that the rate of oxidation of the olefins (as determined from the sums of the yields of products) was directly related to the extent of substitution of the double bond, increasing in the sequence ethylene, propylene, 1-hexene, and 2-hexene. The unsymmetrically substituted olefins(propylene and 1-hexene) gave only ketones and secondary alcohols, i.e., the reaction was characterized by the formation of the products of oxidation of the more highly substituted carbon atom. In the light of these findings, the oxidation of the trisubstituted steroidal olefins (I) and (II) naturally occurs rapidly and regioselectively to give the 5-oxidized products (III) and (IV). The stereospecificity of the oxidation is a consequence of the general rule for the preferential attack on the steroid molecule from the unhindered α-side [6], particularly by bulky reagents, amongst which TPPMn(II) and its derivatives must undoubtedly be included.

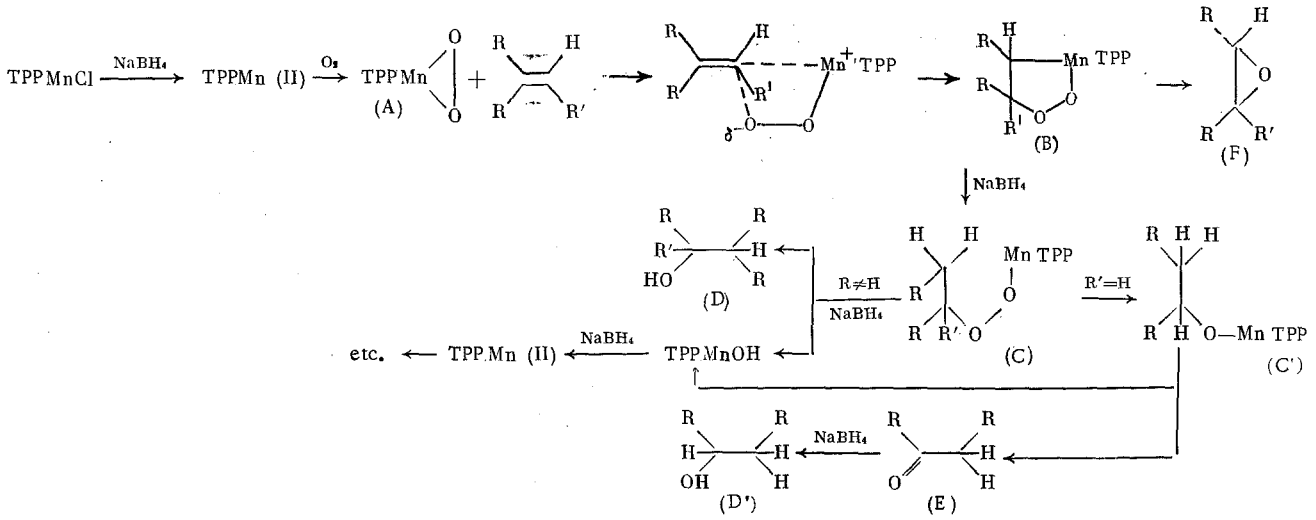
The rate of oxidation of aliphatic olefins is dependent on the medium, being greater in dimethylformamide (DMF) than in benzene–ethanol. More important, however, is the change in the product ratios. When the reaction is carried out in benzene–ethanol alcohols predominate, whereas in DMF ketones are preferentially formed, owing to the greater rate of reduction of ketones to alcohols in hydroxylic media, if ketones are the primary reaction products. In benzene–ethanol, significant amounts of the epoxides of the olefins are formed (experiments 4 and 6, Table 2), and, in agreement with [1], the preferential formation of alcohols under these conditions may be due to oxidation of the olefins to the epoxides, followed by reduction of the latter.

Neither of these mechanisms for the formation of alcohols in the TPPMnCl-catalyzed oxidation of olefins explains the formation of (III) or (IV) from the steroidal olefins (I) and (II). The formation of the tertiary alcohols (III) and (IV) cannot be due to reduction of ketones, and a painstaking search for the appropriate α-epoxide in the oxidation products of (I) by TLC failed to reveal their presence. Furthermore, the epoxide, obtained by oxidation of (I) with m-chloroperbenzoic acid, remained unchanged under the conditions of formation of the diol (III).

It appears that a mechanism must be sought which would account both for the formation of tertiary alcohols from trisubstituted olefins, and of ketones and secondary alcohols from mono- and disubstituted olefins. Such a mechanism must account both for the regioselectivity of the oxidation, and for the dependence of the rate of oxidation on the electron density at the double bond.

The initial steps in the oxidation of olefins by the system O_2–TPPMnCl–$NaBH_4$ have been studied [1]. TPPMnCl is reduced by $NaBH_4$ to TPPMn(II), which forms complex (A) with a molecule of oxygen [7] (Scheme 2). The cationoid addition of this complex to the double bond controls the regioselectivity of the reaction, giving a cyclic intermediate (B) similar to that previously considered in the literature [8]. Reductive cleavage of the C–Mn bond in the intermediate (B) may lead to the peroxide complex (C), the further reactions of which will depend on the substitution at the carbon atom bearing the peroxide radical (i.e., on the extent of substitution of the original olefin). Reduction of the O–O bond by the borohydride ion gives alcohols (D or D') and TPPMnOH, which enters a new catalytic cycle. The peroxide complex with a secondary carbon atom (C') can also disproportionate to the ketone (E) and TPPMnOH, and the ketone is further reduced by borohydride to the alcohol (D'), this being a second alternative route to the formation of secondary alcohols. The sequence of the fission of the O–O and Mn–C bonds in the cyclic intermediate (B) can also be reversed, but this does not affect the possibility of the simultaneous formation as primary manganese-free products of the ketone (E) and

Scheme 2



alcohols (D) and (D'). There is also the possibility that disproportionation of the cyclic intermediate (B) will give the epoxide (F) as a by-product in the oxidation of the olefin.

Although this mechanism has not been confirmed directly by experiment, all its steps have reasonable analogs, viz., disproportionation of secondary alcohols to carbonyl compounds (C–E) [9], and the borohydride reduction of the C–Mn bond (B–C) are known [10].

In conclusion, it is noteworthy that this facile, single-step preparative conversion of Δ^5-steroids to 5α-hydroxysteroids by the O_2–TPPMnCl–$NaBH_4$ system, which may be regarded as a redox Markovnikov hydration of the double bond, is the simplest preparative method for these steroids.

EXPERIMENTAL

Melting points were taken on a Boetius hot-plate (East Germany), rotations were measured on a Hilger-Watts 270-5ML, IR spectra were recorded in KBr disks on a Specord instrument, PMR spectra in $CDCl_3$ on a Tesla-487C (80 Hz), internal standard tetramethylsilane (δ = 0), and mass spectra were obtained during GLC (unless otherwise indicated) on an LKB-2091 mass spectrometer, ionizing electron energy 22.5 eV, GLC in helium on a column with 1% SE-30 phase on Gas-Chrom-Q carrier (100-120 mesh). TLC was carried out on Silufol plates (Czechoslovakia).

Benzene, ethanol, and DMF were purified by standard methods [11]. Ethylene and propylene were purified by freeze-thawing twice, and 1- and 2-Z-hexene by redistillation over sodium. Androst-5-en-3β-ol, mp 133-134°C, was obtained as described in [12], cholesterol (Koch-Light), mp 147-150°C, was used without further purification, and TPPMnCl was prepared as described in [1].

Oxidation of Aliphatic Olefins. A solution of the olefin (0.5 M) and TPPMnCl ($9\cdot10^{-3}$ M) in 5 ml of solvent (DMF or benzene–absolute ethanol, 1:1) was stirred in air until the TPPMnCl had dissolved completely (30 min), then $NaBH_4$ was added to give a concentration of $5\cdot10^{-2}$ M, and the mixture stirred for 24 h in air. GLC of the reaction mixtures was carried out on a Perkin-Elmer 452 (ethylene and propylene) or a Khrom-4 (1- and 2-Z-hexenes), columns with PEG-6000, 100°C. Identification was by comparison with authentic samples. The results are given in Table 2.

Oxidation of Steroidal Olefins (I) and (II). To a solution of 100 mg of the olefin (I) or (II) in 5 ml of a mixture of benzene and ethanol (1:1) was added 3 mg of TPPMnCl, the mixture stirred for 15 min until the TPPMnCl had dissolved completely, 20 mg of $NaBH_4$ was added, and stirring continued for 3 h. The mixture was applied to a column with 50 g of SiO_2 (100-250 mesh), and eluted with hexane–ethyl acetate (1:4) to give diols (III) and (IV).

Androstan-3β,5α-diol (III). This was obtained in 80% yield as colorless plates, mp 203-204°C (from a 1:1 mixture of hexane and ethyl acetate), $[\alpha]_D^{18}$ – 6.2° (c 2.5, $CHCl_3$), R_f 0.36 hexane–ethyl acetate, 1:4), R_f of starting material (I) 0.81; IR spectrum (ν, cm^{-1}): 3600, 3400, 3300 (OH), 1045 (CO). PMR spectrum (δ, ppm): 0.69 s (3H, $C^{18}H_3$), 0.97 s (3H, $C^{19}H_3$), 4.06 nm (1H), $W_{1/2}$ 30 Hz, HC^3O); mass spectrum (direct intro-

duction at 60°C), m/z (intensity, %): 292 (1.4, M^+), 274 (100, $M^+ - H_2O$), 259 [69, $M^+ - (Me + H_2O)$], 256 (27, $M^+ - 2H_2O$), 241 [26, $M^+ - (Me + 2H_2O)$]. Found: C 78.40, H 11.05%. Calculated for $C_{19}H_{32}O_2$: C 78.02, H 11.02%. Silylation with a mixture of $(Me_3Si_2)NH$, Me_3SiCl, and C_5H_5N (3:1:3, 20°C, 1 h) gave a compound $C_{22}H_{38}OSi$, steroid number (SN) 22.84, mass spectrum, m/z (intensity, %): 346 (100, M^+), 331 (4.6, $M^+ - Me$), 318 (9.6), 256 (7.4, $M^+ - Me_3SiOH$), 241 [8.8, $M^+ - (Me + Me_3SiOH)$], 143 (70, Me_3SiO^+) = CHOH = CHMe). Oxidation of the diol (III) by the Jones method in acetone (10 min, 20°C) gave a less polar, pure compound (V) (TLC), which under GLC underwent partial dehydration with the appearance of a peak for androst-4-en-3-one (SN 22.84), identical with an authentic sample, in addition to the base peak.

Androstan-5α-ol-3-one: SN 22.25; mass spectrum, m/z (intensity, %): 290 (41, M^+), 275 (31, $M^+ - Me$), 272 (100, $M^+ - H_2O$), 257 [52, $M^+ - (Me + H_2O)$], 220 (31, $M^+ - CH_2CH_2COCH_2$).

Cholestan-3β,5α-diol (IV). This was obtained in 82% yield, colorless needles, mp 225-226°C (from EtOH), $[\alpha]_D^{18}$ +17.9 (c 18, $CHCl_3$ (cf. [6])). R_f 0.30 (hexane–ethyl acetate, 1:4), R_f of starting material 0.8; mass spectrum (direct introduction at 85°C), m/z (intensity, %): 404 (M^+, 13), 886 ($M^+ - H_2O$, 100), 371 ($M^+ - Me + H_2O$, 24), 353 ($M^+ - Me + 2H_2O$, 55), 332 (14), 246 (11), 231 (29), mass spectrum of the TMS ether, m/z (intensity, %): 458 (100), 443 (4), 429 (8), 400 (2), 368 (9), 353 (7), 316 (9), 262 (10), 213 (8). PMR spectrum (δ, ppm): 0.66 s (3H, 18-Me), 0.86 d (6H, J = 6.1 Hz, 26, 27-Me_2), 0.90 d (3H, J = 5.7 Hz, 21-Me), 0.99 s (3H, 19-Me), 4.08 m (1H, $W_{1/2}$ 30 Hz, HC^3O); IR spectrum (ν, cm^{-1}): 3610, 3420, 3310 (OH), 1050 (CO). Found: C 80.31; H 11.90%. $C_{27}H_{48}O_2$. Calculated: C 80.14; H 11.96%.

CONCLUSIONS

1. The rate and extent of oxidation of olefins by molecular oxygen activated by a tetraphenylporphyrin complex of divalent manganese is directly related to the degree of substitution of the double bond. Δ^5-Steroids are oxidized to 5α-hydroxysteroids, and this reaction provides a convenient method for the preparation of these steroids.

2. A single mechanism is proposed for the formation of ketones and secondary alcohols in the oxidation of disubstituted olefins, and of tertiary alcohols in the oxidation of trisubstituted olefins, in the presence of the system O_2–TPPMnCl–$NaBH_4$.

LITERATURE CITED

1. I. Tabushi and N. Koga, J. Am. Chem. Soc., 101, 6456 (1979).
2. M. Perree-Fauvet and A. Gaudemer, J. Chem. Soc., Chem. Commun., 17, 874 (1981).
3. I. Tabushi and A. Vazari, J. Am. Chem. Soc., 103, 7371 (1981).
4. L. Fieser and M. Fieser, Steroids [Russian translation], Mir, Moscow (1964), p. 207.
5. V. Zeev, Zaretskii, Mass Spectrometry of Steroids, John Wiley and Sons, New York–Toronto (1967), p. 89.
6. J. Lifshyz, Chem. Ber., 41, 252 (1908).
7. N. S. Enikolopyan, K. A. Bogdanova, and K. Askarov, Usp. Khim., 52, 20 (1983).
8. I. Z. Portefaix and F. Figueras (eds.), Chemical and Physical Aspects of Catalytic Oxidation, Lyon (1980), pp. 15-75.
9. D. Swern (ed.), Organic Peroxides, 3 vols., Wiley (1970-1972).
10. O. A. Reutov, I. P. Beletskaya, and V. I. Sokolov, Reaction Mechanisms of Organometallic Compounds [in Russian], Khimiya, Moscow (1972), p. 301.
11. A Laboratory Manual of Organic Chemistry [Russian translation], Mir, Moscow (1965), p. 565.
12. A. Butenandt, L. Karlson-Poschman, G. Faiber, U. Shiedt, and E. Bieckert, Liebigs Ann. Chem., 575, 123 (1951).