THE OXIDATION OF PROGESTERONE UNDER GoAgg^{III} CONDITIONS*

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This article is dedicated with affection and respect to the memory of Professor František Šorm — a very distinguished chemist and a brave and courageous man.

The oxidation of pregn-4-ene-3,20-dione (progesterone) by the GoAgg^{III} system (aqueous hydrogen peroxide, ferric chloride, picolinic acid in pyridine–acetic acid solution) has been investigated. Two tri-keto derivatives were isolated and identified as pregn-4-ene-3,6,20-trione and pregn-4-ene-3,12,20-trione. The third major product isolated was identified as the unstable 5α-formyl-A-nor-pregnane-3,20-dione, which deformylated spontaneously to A-nor-5β-pregnane--3,20-dione. A mechanism for the A-ring contraction is proposed, based upon the participation of a carbon–Fe(V) intermediate.

The selective oxidation of saturated hydrocarbons is a topic of current interest[1]. One approach involves porphyrin models of P_{450} enzymes,[2] where an iron-oxo species is present which behaves like an alkoxy radical.[3] As a result the selectivity order is tertiary > secondary > primary.

A different approach is embodied in the Gif family of systems.[4-7] These have the interesting characteristic of substituting secondary positions faster than tertiary or primary in the order secondary > tertiary ≧ primary. Thus oxidation affords mainly ketones. For nearly all hydrocarbons radical chemistry is a minor component of the observed reactivity.

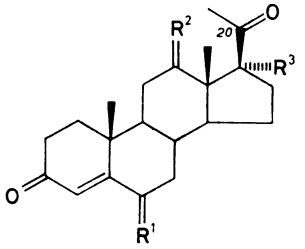
A convenient form of the Gif-type oxidations systems is GoAgg^{III}, which involves pyridine–acetic acid as solvent, iron(III) chloride as catalyst, picolinic acid as added ligand (or other ligand as specified) and hydrogen peroxide (30% aqueous) as primary oxidant. The addition of the picolinic acid increases the reaction rate up to fifty fold[8].

In previous papers[9-13] we reported on the oxidation of a variety of cholestane derivatives by the Gif system. As a rule, the major oxygenated products that we isolated were the corresponding 20-ketones which result from the industrially important side-chain cleavage. In this paper we wish to report our results on the oxidation of progesterone (*I*) by the GoAgg^{III} system and discuss the mechanism of an A-ring contraction in terms of our theory of a carbon–Fe(V) intermediate.

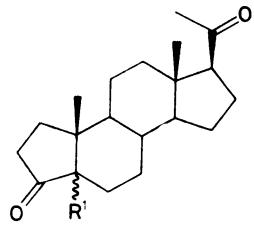
* Part XVIII in the series The Functionalization of Saturated Hydrocarbons; Part XVII: Tetrahedron *46*, 3753 (1990).

RESULTS AND DISCUSSION

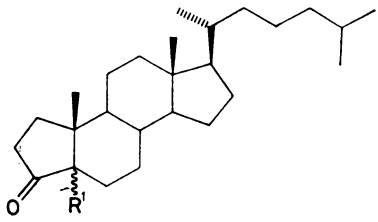
The structures and the yields of isolated oxidation products are presented in Scheme 1 and Table I, respectively. Products *II*, *III*, *VI*, *VII*, *VIII*, and *IX* were identified by



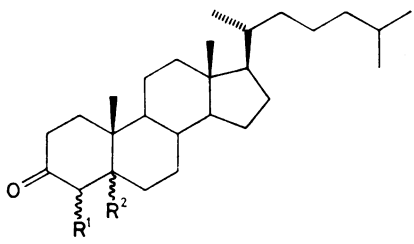
I, $R^1 = R^2 = H_2$; $R^3 = H$
II, $R^1 = O$; $R^2 = H_2$; $R^3 = H$
III, $R^1 = H_2$; $R^2 = O$; $R^3 = H$
VII, $R^1 = R^2 = H_2$; $R^3 = OH$



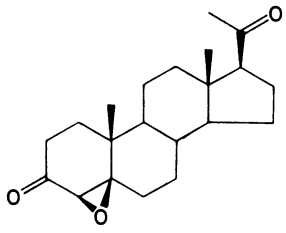
IV, $R^1 = \alpha$-CHO
V, $R^1 = \beta$-H



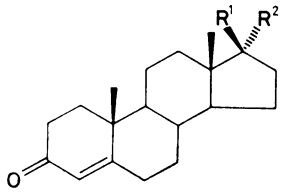
X, $R^1 = \beta$-H
XII, $R^1 = \alpha$-CHO



XI, R^1, $R^2 = \Delta^4$
XIII, R^1, $R^2 = \alpha$-epoxide
XIV, R^1, $R^2 = \beta$-epoxide
XV, R^1, $R^2 = \Delta^4$-4-hydroxy



VI



VIII, R^1, $R^2 = O$
IX $R^1 = H$; $R^2 = COCH_3$

SCHEME 1

comparison of physical (m.p.) and/or spectroscopic (^{1}H and ^{13}C NMR, IR, MS) properties with authetic samples (see Experimental).

The structure of compound *IV* was assigned from its ^{1}H NMR spectrum (formyl resonance at δ 9·50 ppm), its ^{13}C NMR spectrum (three carbonyl resonances, three aliphatic quaternary carbons) and its spontaneous transformation to compound *V*. The A–B *trans* ring junction (stereochemistry 5α) was assigned taking into account the lack of NOE enhancement between methyl-19 and the formyl hydrogen atom, and the ^{13}C NMR chemical shift of C-19 (16·59 ppm), typical of a 5α-substitution.[14]

The structure of compound *V* was deduced from its spectroscopic properties and from its preparation by $BF_3.OEt_2$-catalysed rearrangement of 4β,5β-epoxy-pregnane--3,20-dione (*VI*).[15] The A–B *cis* ring junction (5β-stereochemistry, more stable of both C-5 epimers[16]) is assigned from the ^{13}C NMR resonance for C-19 (21·94 ppm)[14] and by comparison of the ^{1}H NMR methyl-19 chemical shift with the one corresponding to A-nor-5β-cholestan-3-one (*X*).[17]

In early experiments we observed the formation of 17-isoprogesterone (*IX*), arising by enolisation of the starting material. The formation of this by-product was supressed by lowering the amount of acetic acid present in the $GoAgg^{III}$ system to a value still compatible with the oxidation process. When no acetic acid was present, the amount of oxidation was negligible.

From the selectivity figures in Table I it follows that for all the possibilities of attack on the pregnane nucleus only four are the major pathways: (i) ketonization at C-6 (allylic position), (ii) ketonization at C-12, (iii) A-ring contraction, and (iv) 17α-hydroxylation (enolisable position).

TABLE I

Yields of products isolated from $GoAgg^{III}$ oxidation of pregn-4-ene-3,20-dione (*I*)

Product	Isolated yield[a] %	Selectivity of oxidation[b], %
II	10·7	16·7
III	17·1	26·6
IV	19·3	37·9
V	5·0	
VI	2·1	3·2
VII	5·7	15·6
VIII	4·3	

[a] Allowing for recovered starting material. [b] Product *V* is considered to be formed by spontaneous deformylation of *IV*; product *VIII* is considered to be formed by oxidation of *VII*.

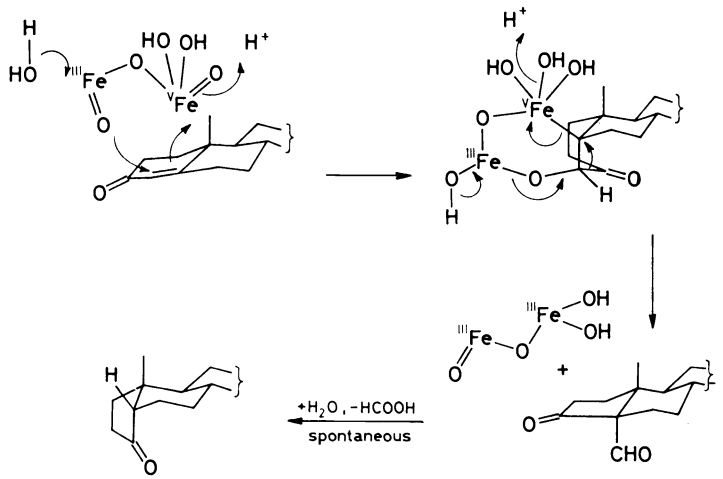
The formation of A-nor-5β-cholestan-3-one (*X*) in the Gif^{IV} oxidation of cholest--4-en-3-one (*XI*) has already been reported[9], though we did not isolate the corresponding aldehyde intermediate (*XII*). In the progesterone series aldehyde *IV* is also unstable. It decomposes to the A-nor-derivative *V* by heating in organic solvents like methylene chloride, or by purification attempts using preparative thin layer chromatography. However, using flash chromatography technique[18] it could be isolated in substantially pure form and analysed by spectroscopic methods.

This type of A-ring contraction has been reported previously[15]. It occurred by Lewis acid treatment of either 4α,5-epoxy-5α-cholestan-3-one (*XIII*) or its 4β,5β--isomer (*XIV*), and afforded, in addition to the A-nor-3-keto derivative, 4-hydroxy--cholest-4-en-3-one (*XV*). The intermediacy of the aldehyde *XII* was postulated, but it was not detected, presumably due to its spontaneous deformylation to *X*.

To find out if one of the epoxy-progesterones was an intermediate in the formation of *IV* and *V* from progesterone under GoAgg^{III} conditions, authentic samples were prepared by alkaline hydrogen peroxide epoxidation of compound *I* and submitted to GoAgg^{III} conditions. No rearranged product could be detected (GC-MS), showing that neither the alpha nor the beta epoxide are converted to the A-nor derivatives under the GoAgg^{III} reaction conditions.

This ketonisation of a methylene group several carbons removed from a ketone function has analogy in previous work[10–13]. The phenomenon indicates the slightly electrophilic nature of the Fe(V) oxenoid species[19].

The formation of compounds *II* and *VII* is compatible with an autoxidation of small amounts of the enolic form of the appropriate ketonic groups.



SCHEME 2

The formation of the aldehyde *IV* as a major product of the reaction is more difficult to explain. However, taking into account the recently proposed[20] theory for Gif type functionalisation we can propose the mechanism shown in Scheme 2. In this Scheme, as in our previous discussion of theory[20], we have omitted the ligands and used a convenient (OH, =O) terminology. Selective addition to the β-face of a steroidal 4,5-unsaturated 3-ketone has considerable precedent.[21]

EXPERIMENTAL

^{1}H NMR spectra were recorded at 200 MHz on a Varian XL-200-E or a Varian Gemini-200 spectrometer or at 400 MHz on a Varian XL-400 spectrometer. ^{13}C NMR spectra were recorded at 50 MHz on either of the first two spectrometers. In every case $CDCl_3$ was the solvent and the chemical shifts are expressed in ppm relative to tetramethylsilane (0·00 ppm). Where appropriate, the ^{1}H NMR signals for 18- and 19-methyl groups were calculated according to the method of Zurcher[22], and are presented as value observed (value calculated, multiplicity, integration, assignation). ^{13}C NMR spectra were assigned using a combination of DEPT pulse sequence[23] and known substituent shifts effects[14]. Assignations labelled with an asterisk might be interchangeable. The infrared spectra were recorded in $CDCl_3$, unless otherwise stated, on a Perkin–Elmer 881 spectrophotometer; only the most significant absorptions are listed, expresed in cm^{-1}. Gas chromatography–mass spectrometry analyses were carried out on a Hewlett–Packard 5790A gas chromatograph coupled to a Hewlett–Packard 5970 mass selective detector (70 eV, electron impact). Melting points were determined with a Koffer hot stage apparatus and are uncorrected. Optical rotation measurements were done using a JASCO model DIP 140 digital polarimeter. Flash chromatography was carried using esentially the technique of Still et al.[18], with silica gel Merck grade 60, mesh 230—400, 60 A. All the solvents were analytical quality and were used without further purification.

$GoAgg^{III}$ Oxidation of Progesterone (*I*)

To a pyridine (15 ml)–acetic acid (0·5 ml) solution of pregn-4-ene-3,20-dione (1·57 g, 5·0 mmol) and $FeCl_3.6\,H_2O$ (54 mg, 0·2 mmol) was added picolinic acid (73·8 mg, 0·6 mmol). The solution was stirred at room temperature for 30 min and cooled in an ice-water bath. Hydrogen peroxide (30%, 1·0 ml, 8·8 mmol) was added dropwise during 3 min. The reaction mixture was stirred at room temperature for 18 h. The dark brown solution was cooled down in an ice-water bath, acidified with H_2SO_4 (20%) and extracted with ether (3 × 50 ml). The organic extracts were washed with $NaHCO_3$ (5%), NaCl (satd. sol.) and water, dried ($MgSO_4$) and concentrated in a rotary evaporator to yield the crude oxidation mixture (1·48 g, 94%).

The solid was recrystallized from methanol, yielding 0·96 g of starting material and the mother liquor. The compounds contained in this fraction were adsorbed on silica gel and the fine solid obtained submitted to flash chromatography, eluting with hexane–ethyl acetate (80 : 20). Authentic samples of compounds *VII* and *VIII* were commercially available.

Pregn-4-ene-3,6,20-trione (II). To a stirred suspension of pregn-4-ene-3,20-dione (0·5 g, 1·6 mmol) and sodium peroxide (2·0 g, 25·6 mmol) in ethanol (25 ml), water (5 ml) was added dropwise during two hours. The yellow mixture was acidified with HCl (1 : 10) and extracted with chloroform (3 × 25 ml). The combined organic extracts were washed with $NaHCO_3$ (satd. sol.) and water, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography, yielding 310 mg (59%) of compound *II*, m.p.:

191–193°C (methanol), lit.[24] m.p.: 193–194°C. $[\alpha]_D^{20}$ +28·5 (*c* 6·74, tetrahydrofuran). ^{1}H NMR spectrum: 0·69 (0·70, s, 3 H, Me-18); 1·18 (1·15 s, 3 H, Me-19); 2·15 (s, 3 H, Me-21); 6·16 (s, sharp, 1 H, H-4). ^{13}C NMR spectrum: 35·69 (C-1); 33·96 (C-2); 199·21 (C-3); 125·74 (C-4); 160·47 (C-5); 201·54 (C-6); 45·51 (C-7); 34·05 (C-8); 50·82 (C-9); 39·71 (C-10); 20·89 (C-11); 38·20 (C-12); 43·89 (C-13); 55·58 (C-14); 24·17 (C-15); 22·89 (C-16); 63·18 (C-17); 13·26 (C-18); 17·57 (C-19); 208·74 (C-20); 31·43 (C-21). MS, *m/z* (%): 328 (M^+, 55); 313 M^+ – Me, 57); 310 (50); 300 (60); 243 (85); 137 (100). IR spectrum (CH_2Cl_2): 2 951; 1 691; 1 609.

Pregn-4-ene-3,12,20-trione (III). The authentic sample was obtained from Roussel–Uclaf, m.p.: 216–218·5°C (methanol). The compound isolated from $GoAgg^{III}$ oxidation had m.p.: 215–217°C (methanol) and $[\alpha]_D^{20}$ +26·3 (*c* 3·38, tetrahydrofuran). Mixed melting point: 215 to 218°C. ^{1}H NMR: 1·02 (1·06, s, 3 H, Me-18); 1·27 (1·30, s, 3 H, Me-19); 2·28 (s, 3 H, Me-21); 3·32 (t, J = 10 Hz, 1 H, H-17α); 5·80 (s, broad, 1 H, H-4). ^{13}C NMR spectrum: 35·42 (C-1); 33·70 (C-2); 193·64 (C-3); 124·85 (C-4); 168·20 (C-5); 32·42 (C-6); 31·37 (C-7); 34·87 (C-8); 56·45* (C-9); 38·35 (C-10); 37·43 (C-11); 211·90 (C-12); 57·81 (C-13); 55·37* (C-14); 24·13 (C-15); 22·70 (C-16); 54·15* (C-17); 13·50 (C-18); 16·89 (C-19); 209·38 (C-20); 31·00 (C-21). IR spectrum: 2 972; 1 702; 1 615. MS, *m/z* (%): 328 (M^+, 100); 313 (50); 267 (30); 243 (25); 205 (50); 124 (65).

4α-*Formyl-A-nor-pregnane-3,20-dione* (IV). ^{1}HNMR: 0·64 (s, 3 H, Me-18); 1·16 (s, 3 H,; Me-19); 2·11 (s, 3 H, Me-21); 9·50 (s, 1 H, CHO). ^{13}C NMR spectrum: 35·44 (C-1); 30·13 (C-2) 215·61 (C-3); 71·23 (C-5); 27·18* (C-6); 29·45* (C-7); 34·82 (C-8); 46·63 (C-9); 46·07 (C-10); 21·59 (C-11); 39·19 (C-12); 44·36 (C-13); 56·77 (C-14); 24·70 (C-15); 23·36 (C-16); 63·93 (C-17); 13·77 (C-18); 16·59 (C-19); 209·82 (C-20); 31·89 (C-21); 202·25 (CHO). IR spectrum: 2 975; 1 730; 1 702. MS, *m/z* (%): 330 (M^+, 15); 302 (30); 301 (10); 287 (100).

5β-A-*Nor-pregnane-3,20-dione* (V). To a solution of 4·5-epoxy-pregnan-3,20-dione (0·5 g) in benzene (25 ml) was added boron trifluoride etherate (0·1 ml). The solution was stirred at room temperature for 18 h, then diluted with ether (50 ml), washed with $NaHCO_3$ (satd. sol.), water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, affording compound *V* (80 mg, 18%), m.p.: 116–118°C (methanol). ^{1}H NMR spectrum: 0·63 (s, 3 H, Me-18); 1·16 (s, 3 H, Me-19); 2·11 (s, 3 H, Me-21); 2·50 (t, J = 10 Hz, 1 H, H-17α). ^{13}C NMR spectrum: 31·30* (C-1); 34·86* (C-2); 220·00 (C-3); 58·61 (C-5); 28·03* (C-6); 22·25 (C-7); 35·16 (C-8); 44·76 (C-9); 41·49 (C-10); 19·77 (C-11); 38·98 (C-12); 44·25 (C-13); 56·36 (C-14); 24·39 (C-15); 22·90 (C-16); 63·72 (C-17); 13·44 (C-18); 21·94 (C-19), 209·59 (C-20); 31·37 (C-21). IR spectrum: 2 936; 1 730; 1 697. MS, *m/z* (%): 302 (M^+, 70); 284 (100); 269 (35).

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