A NEW SYNTHETIC ROUTE TO 2- AND 4-METHOXYESTRADIOLS BY NUCLEOPHILIC SUBSTITUTION *

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ABSTRACT

A new synthetic route to 2- and 4-methoxyestradiols is described. Benzo-15-crown-5 with CuI catalyzes the specific nucleophilic substitution at the carbon atom carrying a non-activated halogen on ring A of the estradiol.

INTRODUCTION

Methoxyestradiols are important derivatives of estrogens with biological activities similar to the parent steroidal diols yet having fewer side effects. Investigations on the physiological properties, clinical uses and the synthetic methods of such estrogens are among the prominent targets in steroid chemistry. However, existing methods for the synthesis of 2-methoxyestradiol are not so satisfactory (1-5). Of the myriad methods, the preferable one is the direct conversion of 2-bromoestradiol into the corresponding methoxyestradiol(5), which requires a prolonged reaction time (22 hours) with unsatisfactory yields (around 50%). There is a relative scarcity of synthetic methods for 4-methoxyestrogens (2,6). A recent report by Mitsuteru and his co-workers on a route to 4-methoxyestradiol from the 4-bromo counterpart in good yield is worth mentioning (7).

The conversion of 2- or 4-bromoestradiols into the corresponding methoxy estradiols is in essence a non-activated nucleophilic aromatic substitution. Under ordinary conditions, this type of substitution proceeds with extreme difficulty, stringent conditions being required. However, in a previous paper, we have reported an effective method for the nucleophilic substitution on ring A of 2,4-dibromoestrogens (8). As was pointed out therein, this reaction can be aided by the concordant action of the coordination of the sodium ion with benzo-15-crown-5

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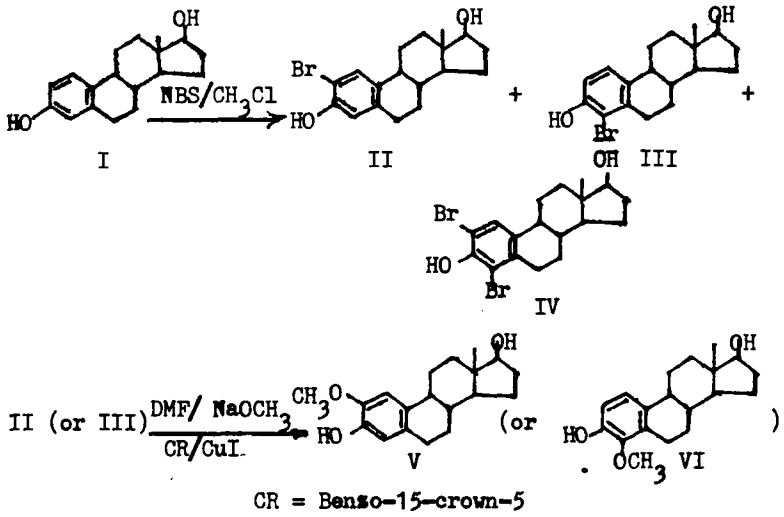
and of cuprous iodide toward aryl halide with the results that the nucleophilicity of the methoxide ion is enhanced and the carbon-halogen bond weakened. Therefore, the substitution can be effected under mild reaction conditions (5).

In the present communication, we apply the method developed by us to the direct conversion of 2- and/or 4-bromoestradiols into the corresponding methoxyestradiols.

Estradiol was brominated with N-bromosuccinimide (NBS) to give bromoestradiols (4-8), amongst which the 2- and 4-bromoestradiols were separated and subjected respectively to subsequent nucleophilic substitution of the bromo atom by methoxide ion under the catalysis of CuI (or Cu_2O)-benzo-15-crown-5 in dimethylformamide (DMF) affording 2- and /or 4-methoxyestradiols in better yield. The overall yields of final products are higher than those given in the previous literature.

The synthetic route is depicted in the following chart:



CR = Benzo-15-crown-5

EXPERIMENTAL

Melting points were determined with a microscope hot stage and are uncorrected. Infrared spectra, using pressed KBr discs, were recorded on a Perkin-Elmer Infrared Spectrophotometer. Ultraviolet spectra were determined on a SP 800 recording spectrophotometer in ethanol. Mass spectra were recorded on a Finnigan 4510 mass spectrometer. NMR spectra were determined on a JNM PMX 60S1 NMR spectrometer. TLC was performed on a SHIMADZU dual wavelength chromatogram scanner model CS-910.

2- and 4-Bromo-1,3,5(10)-estratriene-3,17β-diols (II and III)(9-15).

Estradiol (I)(3.0g, 11 mmol) was dissolved in chloroform (500 mL) to which NBS (2.1 g, 11.8 mmol) dissolved in chloroform (300 mL) was added and the mixture was refluxed for 1 h. Chloroform was removed under reduced pressure to give a solid, which was first dissolved in methanol (50 mL) and then precipitated again upon addition of water (400 mL). The solid was filtered and dried in vacuo. On crystallization from ethanol, 4-bromoestradiol (III) was separated as short needles which after recrystallization afforded the product with mp 208-209°(lit 208-210°)(15) in 42% yield (1.621 g, 4.62 mmol). IR: 3450, 3240(O-H), 610(C-Br). UV λmax: 281 nm (lit 283 nm)(9). Anal: Calcd for $C_{18}H_{23}BrO_2$ C 61.54; H 6.60, found C 62.01; H 6.74. On further evaporation of the mother liquor, 2-bromoestradiol(II) crystallized as long needles. Recrystallization twice from acetone-hexane raised the mp to 195-196°(lit 195-197.5°)(5). The yield based on the pure product is 36% (1.39 g, 3.96 mmol). IR: 3580, 3260(O-H), 620(C-Br). UV λmax: 285 nm (lit 287 nm)(9). Anal: Calcd for $C_{18}H_{23}BrO_2$ C 61.34; H 6.58. A further crop of products was obtained as the mother liquor was chromatographed over silica gel (200-260 mesh, grade IISR), benzene-dichloromethane (1:1.2 v/v) being employed as eluent. The products 2,4-dibromo, 2-bromo and 4-bromoestradiols came out in sequence. For 2,4-dibromoestradiol, the mp was 224-225°(lit 224-226°)(12). IR: 3600,3300 (O-H), 625 (C-Br). UV λ max: 289 nm (lit 291 nm) (10). Anal: for $C_{18}H_{22}Br_2O_2$ C 50.23; H 5.51, found C 49.65; H 5.03.

2- and 4-Methoxy-1,3,5(10)estratriene-3,17β diols (V and VI).

To a solution of sodium methylate in DMF, prepared from sodium (320 mg, 1.43 mmol), methanol (15 mL) and DMF(15 mL) and then freed from methanol as much as possible, 2-bromoestradiol (500 mg, 1.44 mmol) and benzo-15-crown-5 (385 mg, 1.44 mmol) were added. The resulting mixture was heated to 100-105°. After stirring at this temperature for 6 h, the reaction mixture was poured into water, neutralised with 5% hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate extract, after drying and evaporating, was taken up in dichloromethane and chromatographed over silica gel (200 mesh). Elution with benzene-dichloromethane (9:2, v/v), gave II (Rf 0.40) and 2-methoxyestradiol(V) (Rf 0.29). Recrystallization from ethyl ether-petroleum ether (1:1, v/v) gave an analytical sample of V in 84% yield (361 mg, 1.20 mmol). IR: 3422, 3187 (O-H), 1232, 2863 (C-OCH_3). H-NMR(δ ppm): 0.75 (s, 3H, CH_3); 6.75 (s, H H-C4), 6.73 (s, H H-C1). Mass spectrum: m/e 302.2 (M^+). Anal: Calcd for $C_{19}H_{26}O_3$ C 75.46; H 8.67, found C 75.77; H 8.67.

In the same way, except that the temperature was held at 105-110°, 4-bromoestradiol (III)(429 mg, 1.43 mmol) was converted to 4-methoxyestradiol (VI) in 80% yield (343 mg, 1.14 mmol). IR: 3445, 3199 (O-H), 1235, 2860 (C-OCH_3). H-NMR (δ ppm): 0.80 (s, 3H, CH_3), 3.78 (s, 3H O-CH_3), 6.72 (D, J 9 Hz, H H-C2), 6.92 (d, J 9Hz, H-C1). Mass spectrum: m/e 302.0 (H^+). Anal: calcd for $C_{19}H_{26}O_3$ C 75.46; H 8.67, found C 75.71; H 8.85.

Effect of Reaction Conditions on the Conversion of Bromoestradiols to Methoxyestradiols.

In a set of experiments described in the following table, mixtures of the reactants were heated in the presence of catalyst to 100-105° with vigorous stirring. Portions of equal volume from each batch were taken at 1 - h intervals and quenched by pouring into water. Scanning on thin layer chromatography was employed to monitor the reactions. The results

are listed in Table 1.

TABLE 1. Effect of Reaction Conditions on the Conversion of 2-Bromoestradiol (II) to 2-Methoxyestradiol (V)*

Expt. No.	Mole Equivalents				Reaction Time(h)	Relative Yield**
	II	NaOMe	CuI(Cu_2O)	CR		
1	1	10	0.36	1	6	1.0
2	1	10	0.36	1	12	0.98
3	1	10	0.36	1	24	0.94
4	1	20	0.36	1	6	0.98
5	1	5	0.36	1	12	0.75
6	1	5	0.36	1	6	0.24
7	1	10	0.50	1	6	0.70
8	1	10	1.0	1	6	0.67
9	1	10	0.2	1	12	0.43
10	1	10	(0.50)	1	12	0.90
11	1	10	(0.50)	1	6	0.77
12	1	10	(0.36)	1	12	0.50
13	1	10	(0.2)	1	12	0.23
14	1	10	(0.7)	1	12	0.43
15	1	10	(1.0)	1	12	0.45

* Experiments were run in DMF except No. 3 where small amount of CH_3OH was added in admixture with DMF.

**Yields were determined on a SHIMADZU dual wave length chromatogram scanner model CS-910, λ_r = 520 nm, λ_s = 700 nm. The optimum yield of 84% for experiment No. 1 is designated as 1.0 for comparison.

To state the matter succinctly, with the mole ratio of the reagent to catalyst maintained in benzo-15-crown-5: nucleophile:CuI = 1:10:0.36, the reaction of 2-bromoestradiol with sodium methoxide in DMF at 100-105° for about 6 hours affords 2-methoxyestradiol in optimum yield.

Analogous set of experiments was carried out for the conversion of 4-bromoestradiol to 4-methoxyestradiol at a specifically chosen temperature, 105-110°, and the optimum ratio of reactants was found to be benzo-15-crown-5:nucleophile:CuI = 1:10:0.7, the reaction time being 13 hours.

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SYNTHESIS OF 18-HYDROXY-19-NORCORTICOSTERONE AND 18-DEOXY-19-NORALDOSTERONE. STRUCTURE DETERMINATION OF RELATED 19-NOR STEROIDS BY MEANS OF 2-D ^{1}H NMR

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ABSTRACT

The compounds named in the title have been synthesized from the di-(ethylene ketal) of 21-hydroxy-3,20-dioxo-19-norpregn-5-ene-18,11β-lactone and its 5(10)-ene isomer. Reduction of this mixture 1 with sodium aluminum bis-(methoxyethoxy)hydride furnished the 11β,18,21-triol 2a. Conversion to the 18,21-diacetate 2b, followed by deketalization to the free dione 3 and hydrolysis, afforded 18-hydroxy-19-norcorticosterone 4a which, in the solid state and probably in solution, has the 18,20-hemiacetal structure. Periodate oxidation of 4a gave 11β-hydroxy-3-oxo-19-norandrost-4-ene-17β,18-carbolactone 5a, and acid treatment of 4a or its precursor 2a yielded 18-deoxy-19-noraldosterone 6a. The structure of 5a was confirmed by mass spectrometry and ^{1}H nmr, and compared with that of its C-19 methyl homolog 5b and 19-noraldosterone-γ-etiolactone 8. In particular, 2-D nmr COSY 45 experiments, affording full ^{1}H line assignments, have rigorously established the "natural" β (axial) configuration of the C-10 hydrogen in the 19-nor lactones 5a and 8, and therefore also in the related 4a, 6a and 19-noraldosterone 7.

INTRODUCTION

Since 18-hydroxycorticosterone (18-OH-B) 4b (1), 18-hydroxy-deoxycorticosterone (18-OH-DOC), 19-nordeoxycorticosterone, 19-norcorticosterone and 18-hydroxy-19-nordeoxycorticosterone (2) are naturally occurring mineralocorticoids of considerable importance, preparation of the still unknown 18-hydroxy-19-norcorticosterone (18-OH-19-nor-B) 4a (Figure 1) was deemed desirable in order to establish its mineralocorticoid and hypertensinogenic properties, and to assist in determining if the compound is naturally occurring. Furthermore, it was expected that dehydration of 4a would furnish

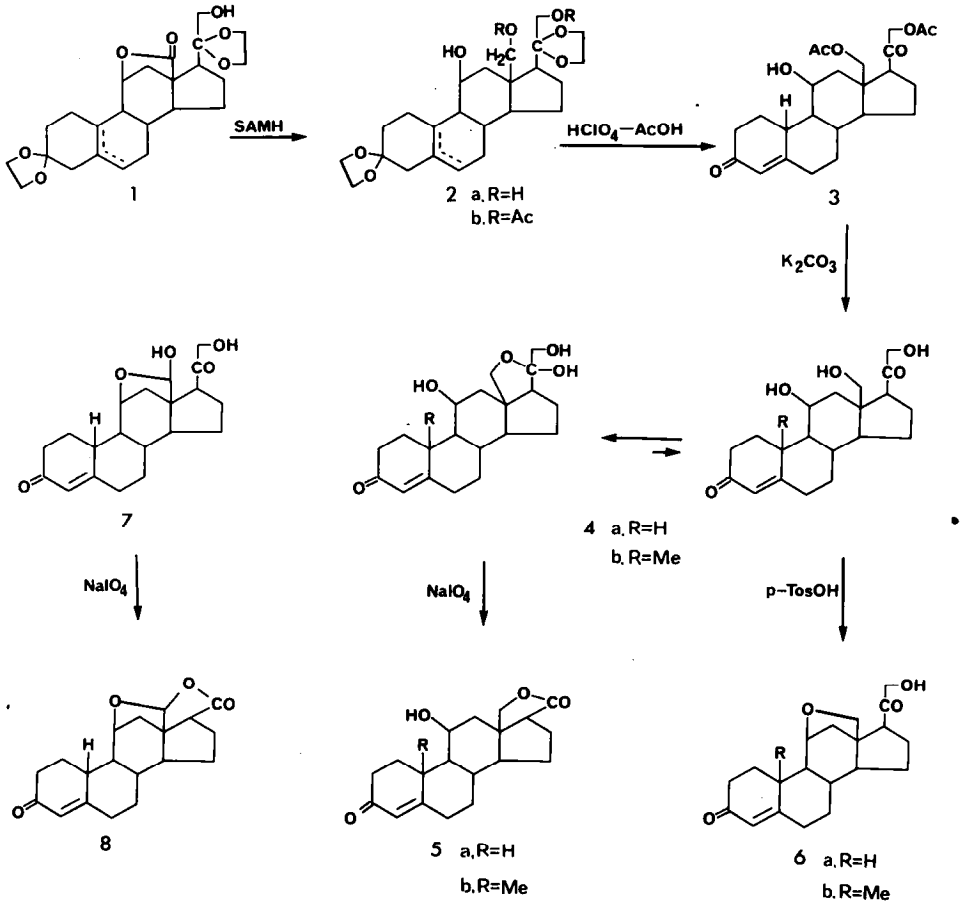

Figure 1. Synthesis of 18-OH-19-nor-B 4a, lactone 5a and 18-deoxy-19-noraldosterone 6a.

18-deoxy-19-noraldosterone 6a, a yet unreported compound, which, like 18-deoxyaldosterone 6b, may be an antagonist of aldosterone (3). Knowledge of the mineralocorticoid properties of 6a will be of considerable interest, bearing in mind that 19-noraldosterone 7 is a potent mineralocorticoid (4,5).

EXPERIMENTAL

E. Merck silica gel (mesh 70-230) was used in column chromatography. Tlc was performed with acetone-hexane or $CHCl_3$-ethanol mixtures, and the plates (silica gel Merck F254, 0.2 mm) were sprayed with 10% H_2SO_4 in ethanol before heating. ^1H nmr spectra (in $CDCl_3$ with TMS as internal standard) were obtained with a Bruker AM-360 spectrometer equipped with an ASPECT 3000 computer operating at 360.1 MHz. 2-D H-H chemical shift correlation experiments were performed in C_6D_6 with 90° ^1H pulses of 10.2 μsec (peak temperature 300°K) employing a "COSY 45" sequence. A 1-sec recycle delay was allowed between each pulse sequence. Quadrature detection was applied in both dimensions using the 16 step phase cycling for N-type peak selection. Ir spectra were recorded with a Perkin-Elmer 297 spectrometer. Mass spectra were recorded with a Finnigan 4020 quadrupole spectrometer equipped with a data system. Ionizing conditions for EI were 19-25 eV, for CI (isobutane) 57 eV, emission current 0.25 mA, electron multiplier 1.7 kV, source temperature 270°C, inlet temperature 240-270°C. Melting points were determined with the Electrothermal apparatus and are uncorrected. The following abbreviations are used: dichloromethane, MDC; sodium aluminum bis-(methoxyethoxy)-hydride, SAMH; petroleum ether bp 60-80°C, PE.

Mixture 2a of 11β,18,21-trihydroxy-19-norpregn-5-ene-3,20-dione-di-(ethylene ketal) and its 5(10)-ene isomer. A solution of 860 mg of the amorphous, chromatographed mixture 1 of 21-hydroxy-3,20-dioxo-19-norpregn-5-ene-18,11β-lactone-di-(ethylene ketal) and its 5(10)-ene isomer (ratio 3:2) (4) in 70 mL of benzene was treated with 18 mL of a 70% SAMH solution in benzene and refluxed for 1 h. The ice-cooled, magnetically stirred reaction mixture was diluted with 100 mL of benzene, quenched with 200 mL of aqueous 10% NaOH solution, and the aqueous phase was reextracted with 3 x 60 mL portions of benzene. The combined extracts were dried and evaporated in vacuo at 35°C. Scratching with ether furnished 658 mg of the crystalline mixture 2a exhibiting in tlc (10% ethanol in $CHCl_3$) two close spots; δ (CD_3OD + $CDCl_3$) 5.67 (brd, J=4, 6-H), 4.11 (m, 11α-H), 3.97 (m, 2H), 3.75 (m, 2H) and 1.00 (dt, J=2.5; 11, 9α-H); CI: m/z 437 (MH^+; 0.59%), 405 (MH^+–CH_3OH; 0.99) and 375 (MH^+–CH_3OH–HCO; 100). The mother liquor A (103 mg) could be used for the preparation of 18-deoxy-19-noraldosterone 6a.

18-Hydroxy-19-norcorticosterone 18,21-diacetate 3.

a. Acetylation of 2a. A solution of 510 mg of the mixture 2a of triols

in 3.5 mL each of pyridine and acetic anhydride was stored overnight at 23°C. The solvents were removed at 40°C with a stream of N_2 and the residual gum was scratched with ice-water for several h until it solidified. The water-washed product (612 mg), consisting of at least 5 components, contained the mixture 2b of 11β,18,21-trihydroxy-19-norpregn-5-ene-3,20-dione-di-(ethylene ketal) 18,21-diacetate and its 5(10)-ene isomer, and was deketalized as described below.

b. Treatment with perchloric-acetic acids. A solution of 611 mg of the crude mixture of acetates in 12 mL of a mixture (prepared by dissolving 1.7 mL of 70% perchloric acid in 18.3 mL of acetic acid) was kept for 10 min at 23°C, whereupon it was diluted with 300 mL of MDC and 300 mL of saturated aqueous $NaHCO_3$. After equilibration the aqueous phase was reextracted with 3 x 50 mL of MDC, the combined extracts were dried with Na_2SO_4 and the solvent was evaporated at 35°C. The oily residue was chromatographed on a column of 55 g of silica gel, eluting with 1% ethanol in $CHCl_3$ containing a trace of triethylamine. The diacetate 3 was obtained in fractions 15-24 (25 mL each) as a glass, pure by tlc, 165 mg; δ 5.81 (brs, 4-H), 4.69 (s, 21,21'-H_2), 4.47 (d, J=11, 18-H), 4.20 (brs, 11α-H), 3.88 (d, J=11, 18'-H), 2.10, 1.94 (s,s, 18,21-OAc) and 0.95 (dt, J=2.5; 12, 9α-H coupled with 10β-H); EI: m/z 433 (MH^+; 3%), 414 (M^+-H_2O; 26), 372 ($M^+-H_2O-CH_2CO$; 78) and 317 ($M^+-CH_2CO-CH_2OAc$; 100).

For comparison, data for 18-OH-B 18,21-diacetate are as follows: δ 5.81 (brs, 4-H), 4.66 (s, 21,21'-H_2), 4.38 (d, J=11.4, 18-H), 4.36 (brs, 11α-H), 3.94 (brd, J=11, 18'-H), 2.08, 1.91 (s,s, 18,21-OAc), 1.34 (s, 19-CH_3) and 0.97 (dd, J=2.9; 11.1, 9α-H); EI: 447 (MH^+; 0.49%), 386 ($M^+-CH_2CO-H_2O$; 18), 331 ($M^+-CH_2CO-CH_2OAc$; 42) and 301 ($M^+-CH_2CO-CH_2OAc-H_2CO$; 100).

18-Hydroxy-19-norcorticosterone 4a. A solution of 160 mg of the chromatographed diacetate 3 in 10 mL of a solution (prepared by dissolving 1 g of anhydrous K_2CO_3 in 30 mL of H_2O and diluting with 115 mL of methanol) was stored for 20 min at 24°C, whereupon it was extracted with 150 mL and then 2 x 30 mL portions of MDC. The dried extracts containing a trace of triethylamine were evaporated *in vacuo* at room temperature, and the residue was induced to crystallize by addition of 2 mL of ether. The product was collected and washed with ether to yield 74 mg of crystalline 4a, mp 148-155°C (dec), pure by tlc ($CHCl_3$-ethanol 30:4). An additional 8 mg of slightly less pure 4a could be obtained from the filtrate. In hplc (C_{18} reversed phase column) using 22% acetonitrile in H_2O 4a had a retention time of 12.3 min, while 18-OH-B 4b had a retention time of 18.8 min; λKBr/max 2.90 and 6.10 μ; δ 5.91 (brs, 4-H), 4.26 (d, J=9.7, 18-H), 4.24 (brs, 11α-H), 3.82 (d, J=11, 21-H), 3.79 (d, J=9.7, 18'-H), 3.64 (d, J=11, 21'-H) and 1.00 (dt, J=2.6; 10.8, 9α-H coupled with 10β-H); for EI mass spectrum and fragmentation pattern see Figures 2 and 5; CI: m/z 349 (MH^+; 4.5%), 331 (MH^+-H_2O; 100) and 313 (MH^+-2H_2O; 3).

For comparison, data for 18-OH-B 4b are as follows: δ 5.71 (s, 4-H), 4.41 (brd, J=2.5, 11α-H), 4.26 (d, J=9.8, 18-H), 3.82 (d, J=11.3, 21-H), 3.79 (d, J=9.8, 18'-H), 3.64 (d, J=11.3, 21'-H), 1.41 (s, 19-CH_3) and 1.00 (dd, J=11.0; 2.5, 9α-H); for EI mass spectrum and fragmentation pattern see Figures 2 and 5; CI: m/z 363 (MH^+;

0.53%), 362 (M^+; 5), 345 (MH^+-H_2O; 100) and 327 (MH^+-2H_2O; 15).

11β-Hydroxy-3-oxo-19-norandrost-4-ene-17β,18-carbolactone 5a. A solution of 8 mg of compound 4a in 0.8 mL of methanol was treated with a solution of 56 mg of $NaIO_4$ in 0.8 mL of H_2O and allowed to stand at 24°C for 20 min. The mixture was concentrated in vacuo at room temperature and extracted with 3 x 7 mL portions of MDC. Drying (Na_2SO_4), evaporation and crystallization from ethyl acetate-PE furnished 5 mg of the lactone 5a, mp 215-8°C. In hplc (C_{18} reversed phase column) using 27% acetonitrile in H_2O, 5a had a retention time of 19.5 min, while the C-10 methyl homolog 5b had a retention time of 29.9 min. λKBr/max 2.83, 2.98, 5.70 and 6.00 μ; for nmr data see Table 1; for EI mass spectrum and fragmentation pattern see Figures 3 and 5. Isolation of 5a could also be effected by preparative tlc on a silica gel plate (0.2 mm), development with $CHCl_3$-ethanol 60:2.

11β-Hydroxy-3-oxoandrost-4-ene-17β,18-carbolactone 5b. The compound was prepared as above starting with 18-OH-B 4b. The product had mp 272-4°C (methanol) (reported 272-4°C (6); 270-2°C (7)). For EI mass spectrum and fragmentation pattern see Figures 3 and 5.

18-Deoxy-19-noraldosterone 6a.

a. From the mixture of diketals 2a. A solution of 122 mg of 2a (from filtrate A, vide supra) and 75 mg of p-toluenesulfonic acid monohydrate in 40 mL of MDC was refluxed for 30 min. The solution was washed with aqueous $NaHCO_3$, the aqueous phase was back-washed with MDC, and the combined and dried MDC solutions were evaporated. Chromatography of the gummy residue on 15 g of silica gel, using 1% ethanol in $CHCl_3$, furnished in fractions 15-20 (10 mL each) a gum which crystallized on contact with ether to give 45 mg of 6a, mp 190-3°C, by tlc ($CHCl_3$-ethanol 30:1) over 95% pure; λKBr/max 2.96, 5.82 and 5.98 μ; δ 5.86 (brs, 4-H), 4.40 (d, J=4.5, 11α-H), 4.24 (s, 21,21'-H_2), 3.72 (d, J=8.5, 18-H), 3.39 (d, J=8.5, 18'-H), 3.06 (t, J=9.1) and 0.98 (brt, J=10, 9α-H coupled with 10β-H); for EI mass spectrum and fragmentation pattern of 6a and 18-deoxyaldosterone 6b see Figures 4 and 5.

b. From 18-hydroxy-19-norcorticosterone 4a. When identical conditions were used 6a was obtained in 90% yield.

RESULTS AND DISCUSSION

The diketal 1, a mixture of the 5-ene and the 5(10)-ene isomers employed as an intermediate in a recent synthesis of 19-noraldosterone 7 (4), was the starting material in the present work (Figure 1). Reduction with SAMH was patterned after a corresponding reaction in a synthesis of 18-OH-B 4b (8) and gave a high yield of the triol 2a which consisted mostly of the 5-ene isomer, as judged by the intensity of the C-6 proton. For further conversion into 18-OH-19-nor-B

4a, the circuitous route employed by Swiss workers for the synthesis of 18-OH-B (9) was used since direct treatment of 2a with acid caused dehydration (vide infra). Acetylation of 2a with excess acetic anhydride in pyridine provided a mixture containing the diacetate 2b. The overall product was directly treated with a solution of perchloric acid in acetic acid, and the diacetylated dione 3 was isolated by chromatography as a glass in 32% overall yield from 2a. As expected, the nmr spectrum of 3 is similar to that of 18-OH-B 18,21-diacetate except for the absence of the C-19 singlet. The EI mass spectrum exhibits a fragment (414, 26%) obtained by loss of water, while a corresponding fragment is missing in the spectrum of the C-19 methyl homolog.

Brief hydrolysis of the diacetate 3 with K_2CO_3 at room temperature (9) afforded 18-OH-19-nor-B 4a, crystallizing on addition of ether, mp 148-155°C (dec), in 64% yield. In the solid state it exhibits no saturated carbonyl in the ir spectrum, which points to the presence of only the cyclic hemiacetal form of 4a. The nmr spectra show that in $CDCl_3$ solution compounds 4a and 4b exist mainly in one form, probably as one isomer at C-20 of the hemiacetal structure. The CI mass spectrum of 4a exhibits the molecular peak (MH^+=349) which upon loss of water furnishes the base peak, in analogy with the CI spectrum of 4b. The EI spectra (Figures 2 and 5) show a facile elimination of H_2O and CHO in 4a to give the base peak 301, in this respect resembling the spectrum of 18-OH-DOC (10); while in 4b the base peak (285) is formed by the loss of the fragment $C_2H_5O_3$ representing the whole side chain including the C-18 oxygen atom.

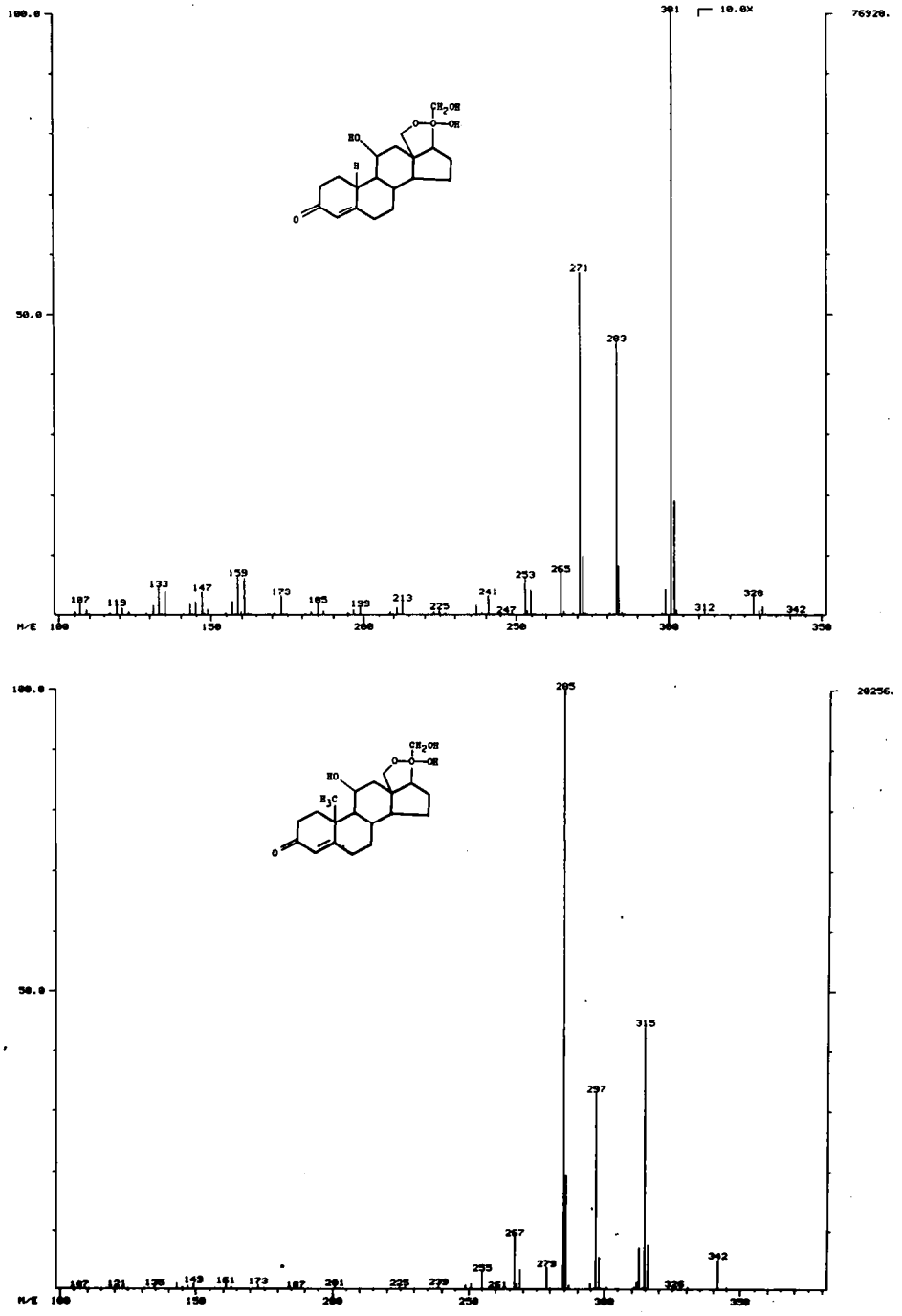

Figure 2. EI mass spectra: upper, 4a; lower, 4b.

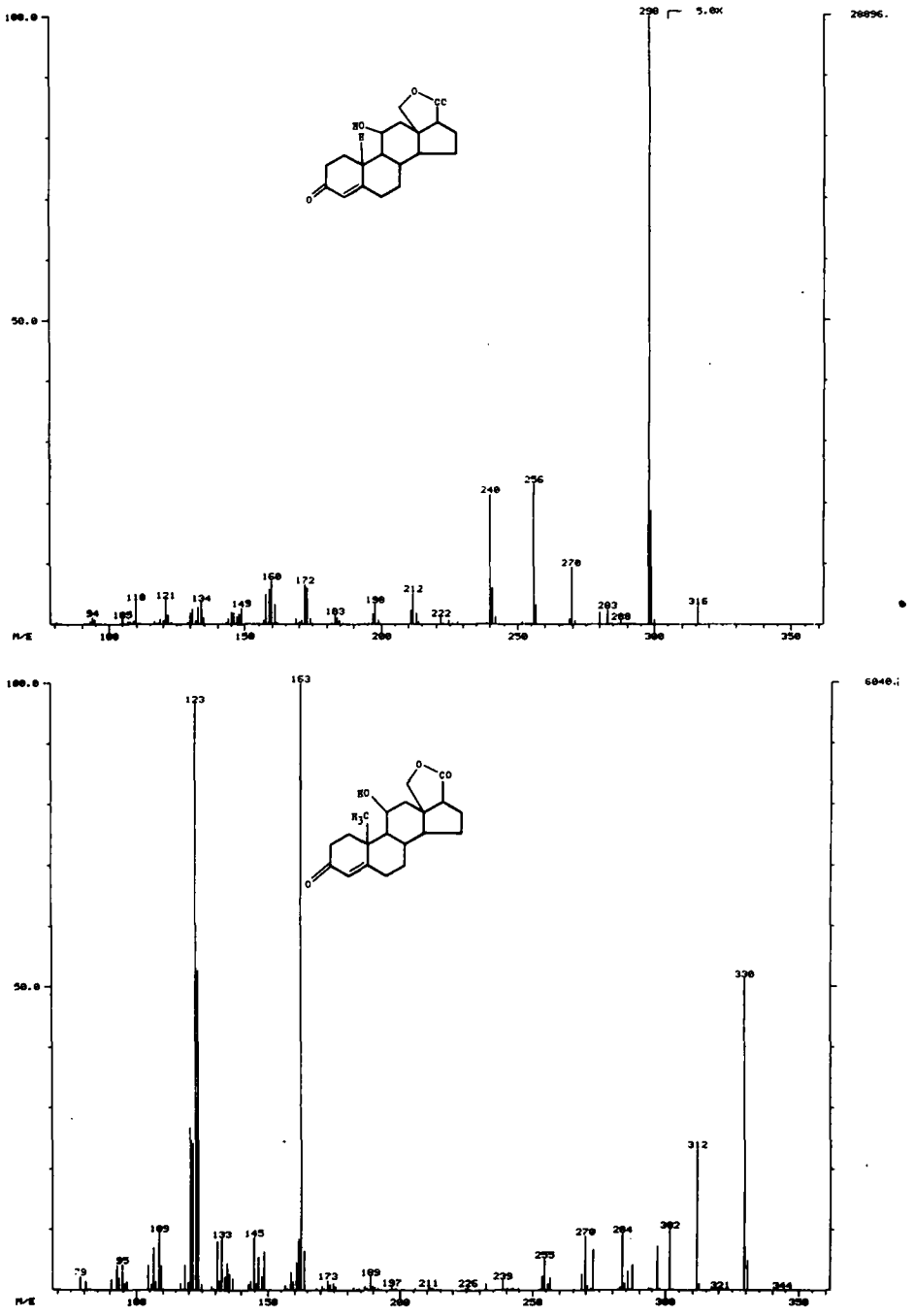

Figure 3. EI mass spectra: upper, 5a; lower, 5b.

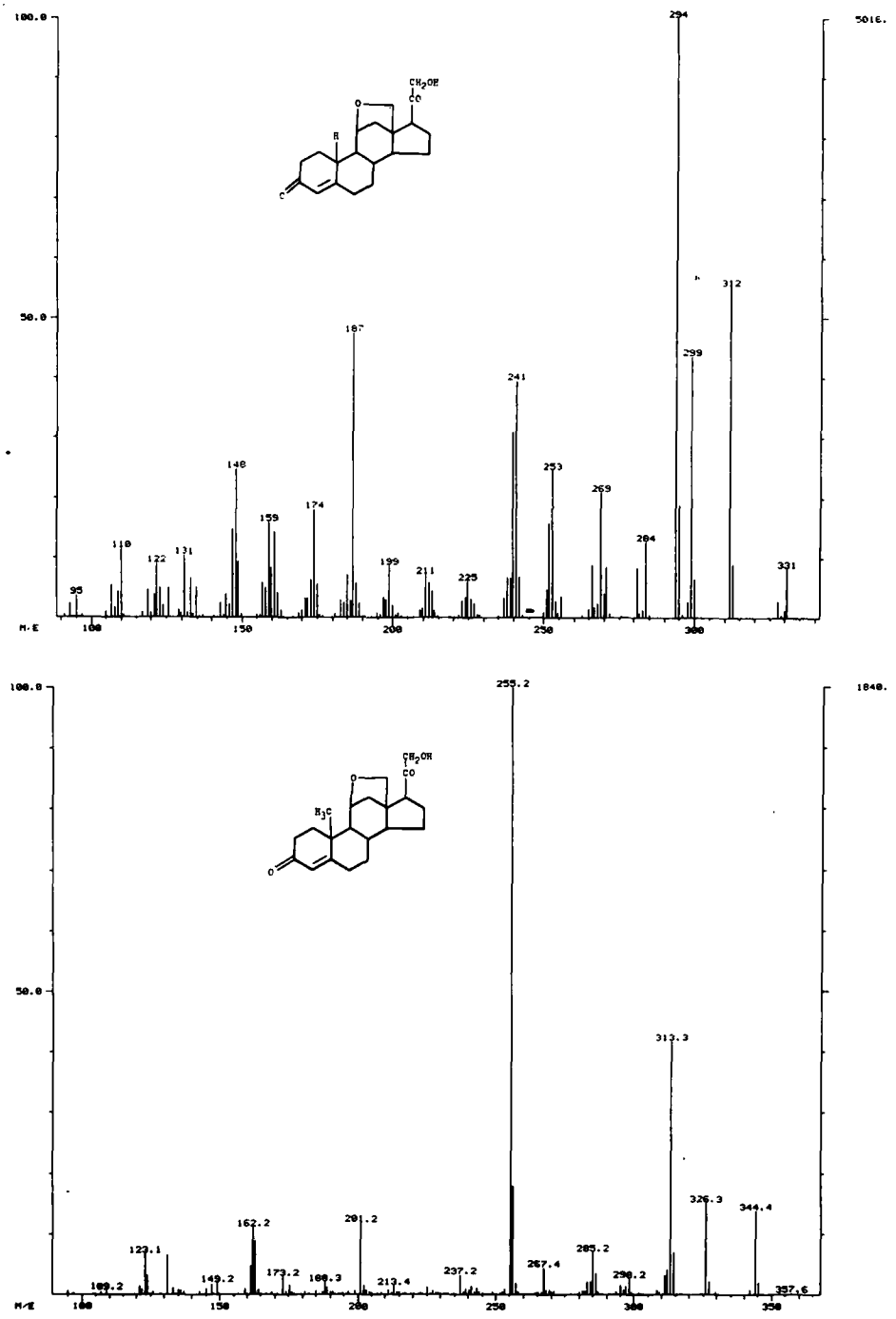

Figure 4. EI mass spectra: upper, 6a; lower, 6b.

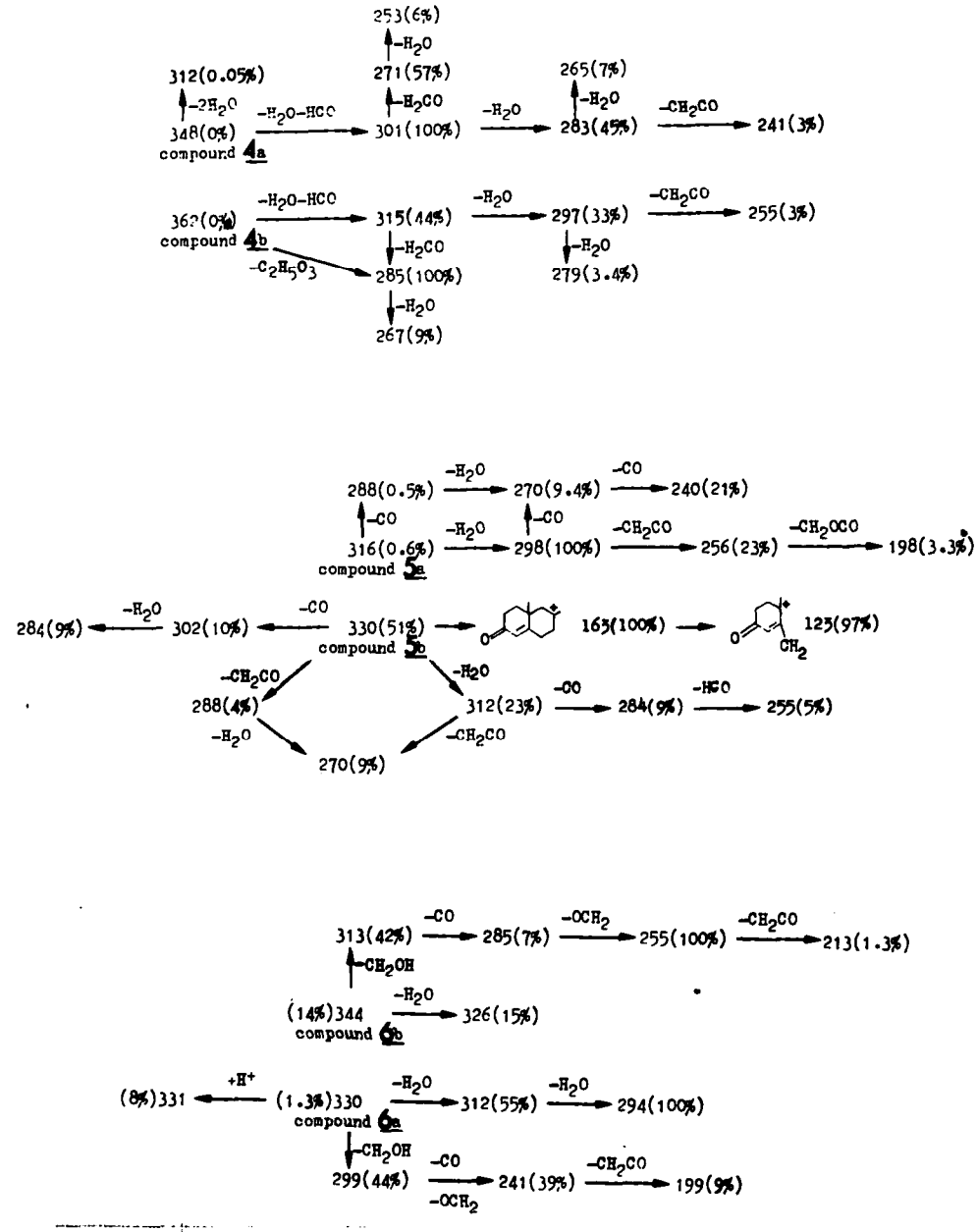

Figure 5. Fragmentation pattern of 4a, 4b, 5a, 5b, 6a and 6b.

Further confirmation of the structure 4a was obtained by periodate oxidation to the 17,18-lactone 5a, mp 215-8°C. A complete chemical shift assignment of the latter has been achieved by a COSY 2-D ^{1}H nmr experiment (see Figure 6 for the high-field part of the spectrum, and Table 1). For comparison, COSY experiments of the closely related 19-methyl analog 5b and of 19-noraldosterone-γ-etiolactone 8 (4) have also been performed. A summary of all assignments, coupling constants and H-H connectivities of compounds 5a, 5b and 8, presented in Table 1, is in full agreement with the postulated stereochemistry. Comparison of the chemical shifts of 5a with those of 5b reveals major differences at positions 1α, 1β, 2β, 6α, 8β, 11α and 12β. Most significant are the patterns of the H-1_{ax} and H-9 protons (H-1: $J_{1\alpha,1\beta}$=13.5, $J_{1\alpha,10}$=9.8, $J_{1\alpha,2\beta}$=13.5 and $J_{1\alpha,2\alpha}$=4.4, and for H-9: $J_{9\alpha,8\beta}$=10.8, $J_{9\beta,10}$=10.8 and $J_{9\alpha,11}$=2.8), clearly pointing to an axial (β) orientation of H-10 in 5a. In 5b, on the other hand, H-9, lacking the H-9/H-10 coupling, appears as a double doublet.

Comparison of 5a with 8 reveals larger differences than in the 5a/5b pair, which is to be expected due to the presence of the 11,18 ether bridge affecting a large part of the molecule. Apart from H-11 and H-18, most influenced are H-14α and H-16β, pointing to a different conformation of ring D. This finds confirmation also by comparison of the available coupling constants of this ring (e.g., of H-15α and H-17α, Table 1). Applying the same line of reasoning as above for 5a, H-10 in compound 8, and therefore also in 19-noraldosterone 7 from which it is derived, must have the "natural" β (axial) configuration.

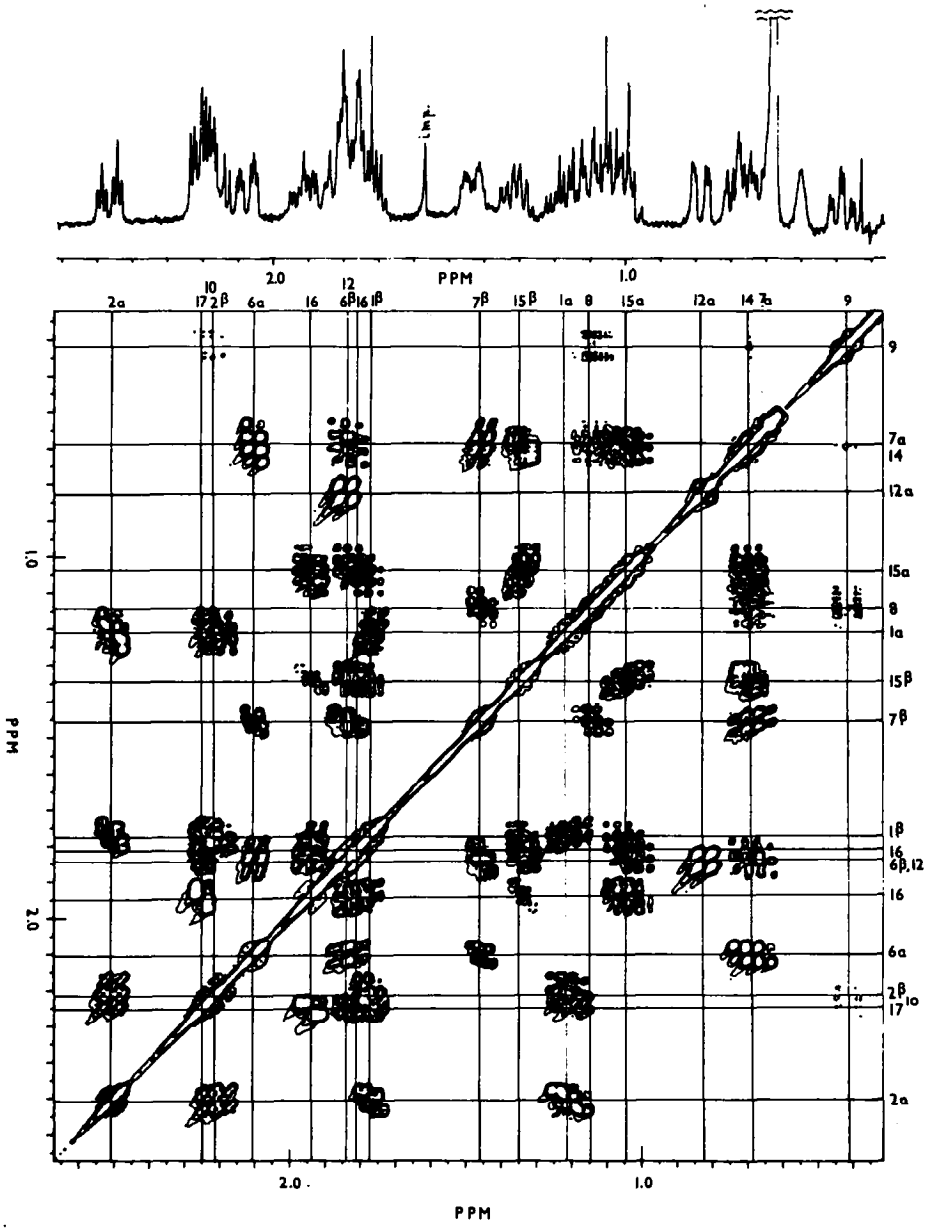

Figure 6. Partial 1-D and 2-D ^{1}H nmr spectrum of lactone 5a.

Table 1. Chemical shifts, coupling constants and H-H correlations of lactones 5a, 5b and 8 deduced from COSY 45 experiments

	5a		5b		8	
1α	1.17 ddt (9.8, 4.4, 13.5)	1e,2e,2a,10a	1.44 m	1e,2a,2e	1.02 dddd (14, 13.2, 10, 4.4)	1e,2a,2e,10a
1β	1.75 m	1a,2a,2e,10a	1.64 dt (13.2, 4.8)	1a,2a,2e,19	1.84 m	1a,2a,2e,10a
2α	2.45 dt (16, 4.2)	1a,1e,2a,4	2.43 m ABXY	1a,1e,2a	2.38 ddt (16.0, 0.5, 3.7)	2a,1e,1a,4
2β	2.16 ddd (16, 13.5, 5)	1a, 1e,2e	2.43 m	1a,1e,2e	2.07 dt (5.0, 16.0)	2e,1a,1e
4	6.07 brs	2e,6a,10a	5.92 d (1.7)	6a	6.01 brs	2e,10a,6a
6α	2.07 ddd (14.4, 3, 2.6)	6a,7a,7e	1.84 ddd (14.5, 4.7, 2.2)	6a,7a,7e	2.04 dt (16.5, 3.7)	6a,7e,7a
6β	1.80 m	4, 6e,7a,7e	2.03 ddt (5.4, 1.7, 14.5)	4,6e,7a,7e	1.80 m	6e,7e,4
7α	0.68 m	6a,6e,7e,8a,9?	0.61 m	6e,6a,7e,8	0.73 dq (4, 11.8)	7e,6e,6a?,8a
7β	1.43 dddd (13.8, 5.6, 4.2, 3.8)	6a,6e,7a,8a	1.47 m	6e,6a,7a,8	1.34 ddt (11.5, 5.5, 2.5)	7a,6a,6e,8a
8β	1.07 m	7a,7e,9,14	1.40 m	7a,7e,9,14	0.80 m	7a,7e,9,14
9α	0.38 dt (2.8, 10.8)	8a,10,11e	0.39 dd (11.0, 2.7)	8a,11e	0.34 dd (10.5, 11.3)	8a,10a,11e
10β	2.21 m	4,1a,1e,9	1.13 s (Me, 3H)	1a	1.99 brdt (3.7, 11.3)	1e,1a,4,9a
11α	3.45 quin (~ 3)	9,12a,12e,14?	3.60 quin (3.2)	9,12a,12e	4.31 d (5.7)	9,12e,12a
12α	0.79 ddd (13.8, 1.9, 1.3)	11,12e,18'	0.77 ddd (12.5, 3.0, 1.3)	11e,12e,18'	0.81 brd (11.2)	11e,12e
12β	1.79 dd (13.8, 2.4)	11,12a	1.58 dd (13, 2.6)	11,12a	1.81 dd (11.2, 5.7)	11e,12a,18
14α	0.63 m	8,15α,15β,11?	0.58 m	8,15α,15β	1.80 m	8a,15β
15α	1.32 brdq (12, 6.3)	14,15α,16α,16β	1.35 m	14,15α,16α,16β	1.44 ddt (11.3, 5.7, 7.2)	16α,16β,15β,17α
15β	1.03 m	14,15β,16α,16β	1.02 m	14,15β,16α,16β	0.83 m	15α,16α
16α	1.79 m	15α,15β,16α,17	1.78 brdd (14, 11.8)	15α,15β,16α,17	1.80 m	15α,16α,17α
16β	1.91 dddd (13.9, 9.0, 3.6, 1.3)	15α,15β,16β,17	1.93 dddd (14, 8.7, 3.6, 1.3)	15α,15β,16β,17	0.89 m	15β,15α,16β,18
17α	2.19 dd (11.8, 3.8)	16α,16β,18?	2.21 dd (11.8, 3.6)	16α,16β	2.53 dd (8.3, 8.1)	16β,15α
18	4.83 d (9.9)	18'	4.86 d (10)	18'	5.19 s	12β,16α,17?
18'	3.76 dd (9.9, 1)	18,12a	3.76 dd (10, 1.2)	18,12a		

The EI mass spectra of 5a and 5b (Figures 3 and 5) show a basic difference in that the former easily loses water with formation of the base peak 298, while 5b gives the base peak 163 by cleavage of the molecule between rings B and C.

It is well known that 18-OH-B 4b is sensitive to acids, one of the products being 18-deoxyaldosterone 6b (9). Ulick et al found that 6b possesses 1/3 of the binding affinity of aldosterone for the cytoplasmic mineralocorticoid receptor of rat kidney and exhibits an approximate 2:1 antagonist/agonist ratio in toad bladder and adrenalectomized rat bioassays (3). Since 19-noraldosterone 7 is a strong mineralocorticoid (4,5), 18-deoxy-19-noraldosterone 6a has now been prepared for comparison. This was achieved by dehydration of 4a in high yield with p-toluenesulfonic acid in MDC (3,8), or dehydration and deketalization of 2a in one operation by similar acid treatment.

The biological properties of 18-OH-19-nor-B 4a and 18-deoxy-19-noraldosterone 6a are under investigation and will be reported at a later date.

NOTES AND REFERENCES

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APPENDIX

The following trivial names for steroids are used:

aldosterone = 11β,21-dihydroxy-3,20-dioxopregn-4-en-18-al

19-noraldosterone = 11β,21-dihydroxy-3,20-dioxo-19-norpregn-4-en-18-al

18-hydroxycorticosterone = 18-OH-B = 11β,18,21-trihydroxypregn-4-ene-3,20-dione

18-hydroxydeoxycorticosterone = 18-OH-DOC = 18,21-dihydroxypregn-4-ene-3,20-dione

19-nordeoxycorticosterone = 21-hydroxy-19-norpregn-4-ene-3,20-dione

19-norcorticosterone = 11β,21-dihydroxy-19-norpregn-4-ene-3,20-dione

18-hydroxy-19-nordeoxycorticosterone = 18,21-dihydroxy-19-norpregn-4-ene-3,20-dione

18-hydroxy-19-norcorticosterone = 18-OH-19-nor-B = 11β,18,21-trihydroxy-19-norpregn-4-ene-3,20-dione

18-deoxyaldosterone = 11β,18-epoxy-21-hydroxypregn-4-ene-3,20-dione

18-deoxy-19-noraldosterone = 11β,18-epoxy-21-hydroxy-19-norpregn-4-ene-3,20-dione