# 18,21-ANHYDROALDOSTERONE AND DERIVATIVES

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ABSTRACT

18,21-Anhydroaldosterone 8, 18,21-anhydro-19-noraldosterone 9, and 3α,5β-tetrahydro-18,21-anhydro-19-noraldosterone 13, which may be present in acid-processed urine, were prepared by cleaving their 20-ketal derivatives 2, 3, and 12 with hot mineral acid. Compounds 8 and 9 were also made by direct dehydration of aldosterone 5 and 19-noraldosterone 10 in good yield. The reverse ring opening of 8 to 5 could be carried out in moderate yield with an acetic acid-acetic anhydride-perchloric acid mixture, while an analogous ring opening of 9 gave only a poor yield of 10.

## INTRODUCTION

Treatment of aldosterone under various acidic conditions was first studied 35 years ago by Simpson et al (1) who found that 18,21-anhydroaldosterone 8 is the main product. Later work indicated that aldosterone-γ-etiolactone 4 (2) and dimers of aldosterone (3,4) are acid-catalyzed products of aldosterone as well. Ergo, acid hydrolysis of urine, designed to split conjugates of aldosterone and its reduced derivatives, can lead to production of 18,21-anhydro compounds. In order to facilitate their identification, preparation of 8, 18,21-anhydro-19-

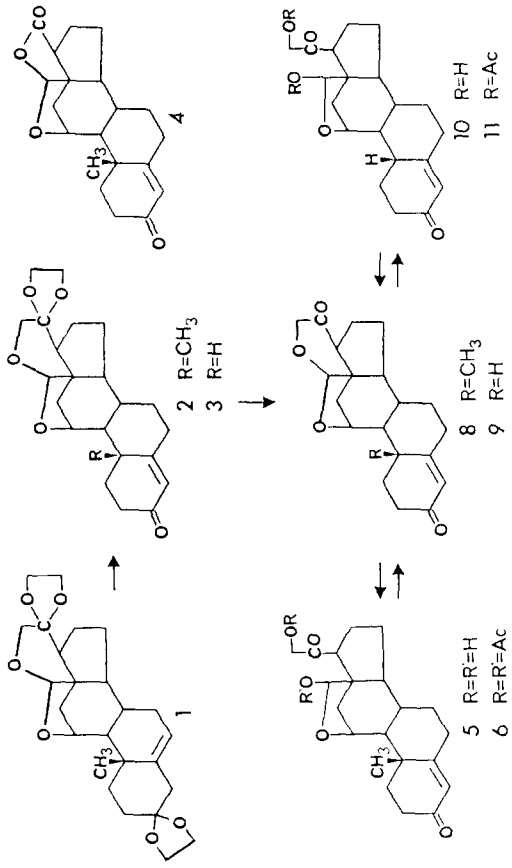


Figure 1. Preparation and ring-opening of 18,21-anhydroaldosterones.

noraldosterone 9 and 3α,5β-tetrahydro-18,21-anhydro-19-noraldosterone 13, was desirable.

17α-Hydroxy-18,21-anhydroaldosterone has been prepared by Akhtar et al (5) and its 18,21-anhydro ring opened by a well-controlled acid-catalyzed procedure to give the 17,18,21-triacetate of 17α-hydroxyaldosterone. Due to the fact that the 17-deoxy cyclic compound 3 is formed as a useless by-product in an appreciable yield in the final step of the synthesis of 19-noraldosterone 10 (6), our next goal, following the preparation of the 18,21-anhydro compounds, was the utilization of 3 by its conversion into 10, employing Akhtar's procedure. Toward this end, the transformation of 8 into aldosterone 21-acetate 7 was examined first.

## EXPERIMENTAL

E. Merck silica gel (mesh 70-230) was used in column chromatography. TLC was performed on silica gel plates (Merck F254, 0.2 mm) which 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. Mass spectra were recorded with a Finnigan 4020 quadrupole spectrometer equipped with a data system: source temperature 230 C, electron energy 30-40 eV. IR spectra were taken with a Perkin-Elmer 297 spectrometer.

Conversion of 11β,18;18,21-diepoxypregn-5-ene-3,20-dione-bisethylene ketal 1 into aldosterone 21-acetate 7. A solution of 105 mg of 1, mp 252-256 C (reported (7) 265-267 C for the racemic product), in 6 mL of dioxan was treated with 7.6 mL of an 8% (v/v) aqueous $H_2SO_4$. Shortly thereafter a solid started to precipitate. After 3 h at room temperature the mixture was diluted with 40 mL of water and extracted with 3 portions of dichloromethane, which was then washed with aqueous $NaHCO_3$. Evaporation furnished 11β,18;18,21-diepoxypregn-4-ene-3,20-dion-

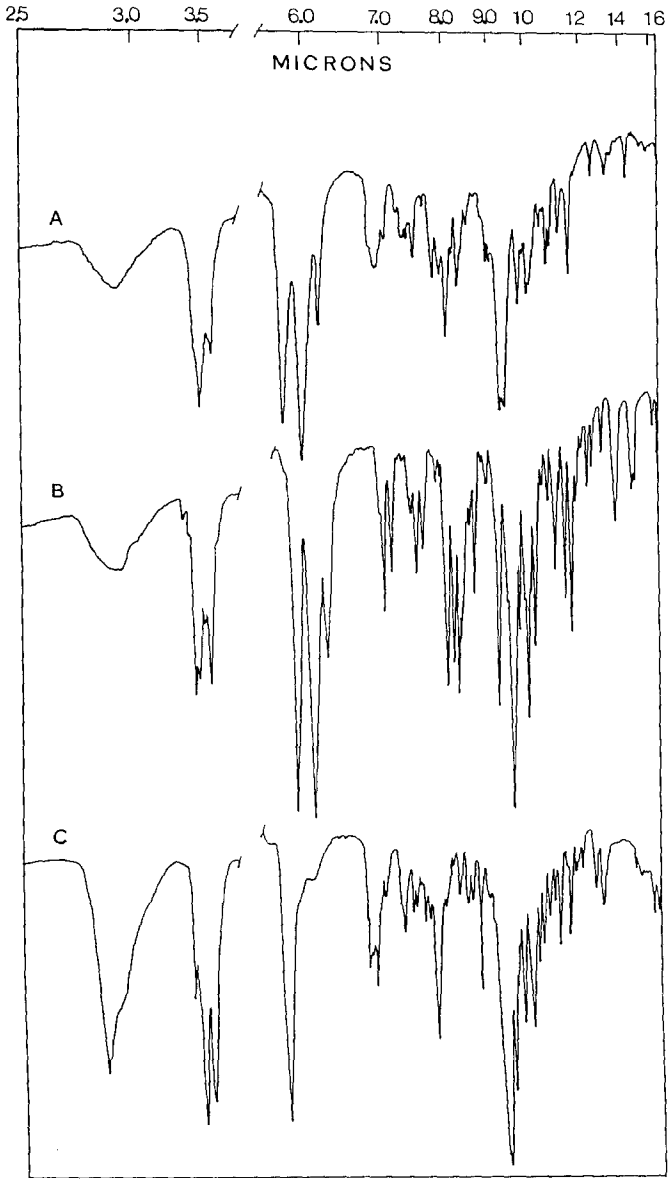


Figure 2. Infrared spectra (KBr). A, 8; B, 9; C, 13.

20-ethylene ketal 2 which was washed with a little ether, mp 284-286 C; $\lambda$KBr/max 5.94μ; δ 1.01 (d, J=10.8, 9-H?), 1.16 (dq, J=4.1, 12.0, 1H), 1.24 (d, J=11.2, 12-H eq?), 1.29 (s, 19-$CH_3$), 2.50-1.40 (m, 13H), 2.70 (dd, J=11.2, 6.2, 12-H ax?), 3.45 (dd, J=12.4, 1.8, 21-H), 3.48 (d, J= 12.4, 21-H'), 3.89 (t, J=6.2, 2H, dioxolane), 4.03 (m, 2H, dioxolane), 4.62 (d, J=6.2, 11-H), 4.74 (s, 18-H), and 5.72 (brs, 4-H); MS-EI 386 ($M^+$; <0.5%), 356 ($M^+$-$CH_2O$; 100), 328 ($M^+$-$CH_2O$-CO; 65), 286 ($M^+$-$C_4H_4O_3$; 36), 285 ($M^+$-$C_4H_5O_3$; 62), 284 ($M^+$-$CH_2O$-CO-$C_2H_4O$; 58), 269 ($M^+$-$CH_2O$-CO-$C_2H_3O_2$; 29), 266 ($M^+$-$C_4H_8O_4$; 25), and 131 ($C_{10}H_{11}^+$; 61); MS-CI (methane) 415 ($MC_2H_5^+$; 7%), 387 ($MH^+$; 100%), 369 ($MH^+$-$H_2O$; 12), 357 ($MH^+$-$CH_2O$; 4), and 301 ($MH^+$-$C_4H_6O_2$; 10).

Ketal hydrolysis at C-20 was effected by heating 76 mg of 2 with 6 mL of 8% (v/v) aqueous $H_2SO_4$ for 2 h at 90-92 C. Workup as above gave 60 mg of 18,21-anhydroaldosterone 8, mp 190-200 C (reported (1) 196 C); for IR spectrum see Figure 2; δ 1.30 (s, 19-$CH_3$), 2.596 (dd, 12-H), 2.827 (dd, 12-H'), 3.975 (brd, J=16.2, 21-H), 4.080 (d, J=16.2, 21-H'), 4.683 (d, J=6.1, 11-H), 4.964 (s, 18-H), and 5.727 (s, 4-H); MS-EI 342 ($M^+$; 21%), 298 ($M^+$-$CO_2$; 6.3), 284 ($M^+$-$C_2H_2O_2$; 100; 269 ($M^+$-$C_5H_3O_2$; 37), 266 ($M^+$-$CH_2CO$-$H_2O$; 23), 255 ($M^+$-$C_3H_3O_3$; 31), and 131 ($C_{10}H_{11}^+$; 10).

A solution of 60 mg of 8 in 10 mL of acetic acid and 6 mL of acetic anhydride was cooled in ice and treated dropwise with 1.2 mL of 70% perchloric acid. After 90 min at 0 C the dark product was poured onto a mixture of 30 mL of concentrated ammonia and 150 g of ice, and swirled for 10 min. Extraction with dichloromethane, drying with $Na_2SO_4$ and evaporation gave crude aldosterone 18,21-diacetate 6, 85 mg. This material was best purified by heating at 55 C in 90% acetic acid (8) to afford 35 mg of aldosterone 21-acetate 7, identical with an authentic sample.

Acid-catalyzed conversion of aldosterone 5 and 19-noraldosterone 10 into their 18,21-anhydro derivatives 8 and 9. A solution of 4.3 mg of 5 in 2 mL of dioxan was treated with 1.2 mL of 18% HCl and stored at 20 C for 24 h until TLC ($CHCl_3$-methanol 60:1) showed 90% conversion. Addition of aqueous $NaHCO_3$ and thorough extraction with dichloromethane produced a gum which crystallized on scratching with ether to give 2 mg of 8.

In another preparation, 189 mg of 5 in 50 mL of dioxan was treated with 24 mL of 20% (v/v) aqueous $H_2SO_4$. After 22 h at 24 C the reaction mixture was worked up by shaking with 300 mL each of saturated aqueous $NaHCO_3$ and dichloromethane, followed by three extractions with 100 mL of dichloromethane. The combined

extracts were dried and evaporated to furnish a crystalline residue containing a small amount of a slightly more polar impurity. Chromatography on 22 g of silica gel (elution with $CHCl_3$) and washing of the product with ether gave 118 mg of pure, and 11 mg of somewhat contaminated, 8.

Similarly, treatment of 51 mg of 10 in 10 mL of dioxan with 6 mL of 18% HCl and storing at 24 C for 43 h gave rise to a gum which after chromatography on 8 g of silica gel gave 23 mg of pure, ether-washed, 18,21-anhydro-19-noraldosterone 9, mp 191-200 C, by TLC slightly more polar than 8; for IR spectrum see Figure 2; δ 2.619 (dd, 12-H), 2.879 (dd, 12-H'), 4.017 (dd, J=16.2, 1.5, 21-H), 4.103 (d, J=16.2, 21-H'), 4.668 (d, J=6.3, 11-H), and 4.976 (s, 18-H); MS-EI 328 ($M^+$; 36%), 310 ($M^+-H_2O$; 33), 300 ($M^+-CO$; 3.5), 282 ($M^+-CH_2O_2$;18), 270 ($M^+-C_2H_2O_2$; 100), 252 ($M^+-C_2H_2O_2-H_2O$; 25), 241 ($M^+-C_2H_2O_2-HCO$; 83), 213 ($M^+-C_2H_2O_2-HCO-CO$; 12), and 199 ($M^+-C_2H_2O_2-HCO-CH_2CO$; 20).

Conversion of 11β,18;18,21-diepoxy-19-norpregn-4-ene-3,20-dion-20-ethylene ketal 3 into 19-noraldosterone 10. A solution of 387 mg of 3 (6) in 35 mL of dioxan was treated with 35 mL of 8% (v/v) aqueous $H_2SO_4$ and heated at 92-94 C for 2 h. Dilution with 300 mL of $H_2O$ and extraction with 3 x 100 mL of dichloromethane, followed by washing with 100 mL of saturated aqueous $NaHCO_3$ and evaporation, gave the gummy dione 9 exhibiting a single spot by TLC (hexane-acetone 3:1). Without further purification the material was dissolved in 25 mL of acetic acid and 15 mL of acetic anhydride, and with ice-cooling treated dropwise with 3 mL of 70% perchloric acid. After 1.5 h at 0 C the mixture was poured onto 100 mL of concentrated ammonia and 500 g of ice. Workup with dichloromethane gave 570 mg of grossly impure gum containing 19-noraldosterone 18,21-diacetate 11. Sixty six milligrams of this product was dissolved in 5 mL of 0.1N $K_2CO_3$ in 80% aqueous methanol. After 15 min 20 mL of $H_2O$ was added, the mixture was extracted with 3 x 20 mL of dichloromethane, the organic phase was washed with 10 mL of $H_2O$ and the solvent was evaporated. The gummy residue was chromatographed on 5 g of silica gel: elution with 2% ethanol in $CHCl_3$ afforded 5.1 mg of 10 (6), of about 85% purity (IR and TLC).

Conversion of 3α,5β-tetrahydro-18,21-anhydro-19-noraldosterone-20-ethylene ketal 12 into 3α,5β-tetrahydro-18,21-anhydro-19-noraldosterone 13. A mixture of 44 mg of 12 (9), 2 mL of dioxan and 2 mL of 8% (v/v) aqueous $H_2SO_4$ was heated for 2 h at 92-4 C. Addition of 30 mL of $H_2O$, extraction with a total of 40 mL of dichloromethane, washing with bicarbonate and evaporation of solvent gave 13, which was collected with aid of

ether: 16 mg, mp 182-193 C; for IR spectrum see Figure 2; $\delta$ 2.23 (m), 2.552 (dd, 12-H), 2.813 (dd, 12-H'), 3.653 (m, 3$\beta$-H), 3.979 (dd, J=16.1, <1, 21-H), 4.062 (d, J=16.1, 21-H'), 4.601 (d, J=6.2, 11-H), and 4.896 (s, 18-H); MS-EI 332 ($M^+$; 18%), 314 ($M^+$-$H_2O$; 10), 301 ($M^+$-$CH_2OH$; 2), 274 ($M^+$-$CH_2CO$; 49), 256 ($M^+$-$CH_2CO$-$H_2O$; 23), 245 ($M^+$-$CH_2CO$-HCO; 79), and 227 ($M^+$-$CH_2CO$-HCO-$H_2O$; 100).

RESULTS AND DISCUSSION

In the aldosterone series, the diketal 1 was converted by acid hydrolysis (7,8) into 18,21-anhydroaldosterone 8 via the monoketal 2. While ketal removal at C-3 was very facile, heat was required to eliminate completely the C-20 ketal group in 2. Alternatively, dehydration of aldosterone with hydrochloric or sulfuric acid was studied on a preparative scale in dioxan-water at room temperature, when a 66% yield of pure, column-chromatographed 8 was isolated and its structure confirmed by mass and NMR spectrometry. The filtrates contained minor amounts of more polar material which was not further examined and may have been one of the reported aldosterone dimers (3,4) or aldosterone-$\gamma$-etiolactone 4 (2).

18,21-Anhydroaldosterone 8, in an acetic acid-acetic anhydride-perchloric acid mixture according to the procedure of Akhtar et al (5), gave aldosterone 18,21-diacetate 6, best directly converted into the monoacetate 7 (8) in 50% overall yield from 8.

In the 19-nor series, hydrolysis of 3 to 9 at 92 C proceeded uneventfully. Direct cyclization of 19-noraldosterone 10 to 9

with acid at room temperature could also be readily achieved. However, treatment of 9 with the acetic acid-acetic anhydride-perchloric acid mixture gave only a low yield of 19-noraldosterone 18,21-diacetate 11 which, by brief hydrolysis with potassium carbonate, furnished 19-noraldosterone 10 (6) in 11% overall yield from 3.

Finally, 3α,5β-tetrahydro-18,21-anhydro-19-noraldosterone 13 was easily prepared by hydrolysis with hot acid of its monoketal 12, a by-product in the synthesis of 3α,5β-tetrahydro-19-noraldosterone (9).

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APPENDIX

The following trivial names for steroids are used:

17α-hydroxyaldosterone = 11β,17α,21-trihydroxy-3,20-dioxopregn-4-en-18-al
19-noraldosterone = 11β,21-dihydroxy-3,20-dioxo-19-norpregn-4-en-18-al
18,21-anhydroaldosterone = 11β,18;18,21-diepoxypregn-4-ene-3,20-dione
18,21-anhydro-19-noraldosterone = 11β,18;18,21-diepoxy-19-norpregn-4-ene-3,20-dione
17α-hydroxy-18,21-anhydroaldosterone = 11β,18;18,21-diepoxy-17α-hydroxypregn-4-ene-3,20-dione
3α,5β-tetrahydro-18,21-anhydro-19-noraldosterone = 11β,18;18,21-diepoxy-3α-hydroxy-19-nor-5β-pregnan-20-one

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