STEROIDS WITH FUNCTIONAL SULFUR GROUPS II. 11 β -THIOCYANO- AND 11 β -THIO-3 α ,9 α -EPOXYHEMIKETALS

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It has been shown previously that thiocyanic acid readily converts 9α ,ll α -epoxy-5 β -pregnane-17 α ,21-diol--3,20-dione acetate to 11 β -thiocyano-3 α ,9 α -epoxy hemiketal³. Since further elaboration of the thiocyano function is made more difficult by the presence of the sensitive 17-ketol side chain, it was thought that the corresponding 5 β -androstane derivatives would be a more suitable choice as starting materials.

 $\Delta^{4,9(11)}$ -androstadiene-3,17-dione (II) was prepared according to Bernstein's⁴ procedure by chromic acid oxidation of $\Delta^{4,9(11)}$ -pregnadiene-17 α ,21-diol-3,20-dione (I), but a better yield (ca. 65%) was realized by oxidation with sodium bismuthate⁵. The epoxidation of II with perbenzoic acid proceeded smoothly to yield 9 α ,11 α -epoxy-- Δ^4 -androstene-3,17-dione (III). By catalytic hydrogenation over palladium-charcoal in ethyl acetate III was







H









Č II S



XIII a R=R'=H b R=H, R'=CH₃ c R=R'=CH₃ d R=H, R'= CH₂=CH converted into a mixture which was separated by chromatography on alumina into 9α , 11α -epoxy-5 β -androstane-3, 17--dione (IV)^{6a} and the corresponding 5α -isomer (V)^{6a}, b, c. As expected from the presence of an 11α -substituent⁷, the reduction afforded the 5 β -isomer in predominance.

Treatment of IV with thiocyanic acid gave 3α , 9α --epoxy-3\beta-hydroxy-11\beta-thiocyano-5\beta-androstane-17-one (VIa) in a 79% yield. The appearance of a strong and very sharp absorption band at 4.64µ in the infrared spectrum supports the assumption of a thiocyano group rather than that of an isothiocyano function⁸. The 3β --hydroxyl group was very readily etherified to VIb in the presence of an acid catalyst. Due to the marked lability of the llβ-thiocyano group in the epoxy hemiketal (VI)⁹, weak base, even prolonged chromatography on alumina, led to the regeneration of the parent epoxide, IV. However, attempts at direct hydrolysis of VIa in acidic media also gave either starting material or crystalline matter containing no sulfur atom. In 1882 Chanlaroff reported that the interaction of ethyl thiocyanate with thiolacetic acid yielded acetyl dithiourethane and that the latter easily hydrolyzed to ethyl mercaptan¹⁰. Since it was known that the lability of the 11β -substituent in 3α , 9α -epoxy hemiketal varied according

to the nature of the substituent¹¹, it was thought, perhaps, that if the 11β-thiocyano group in VI was converted to the 11β-acetyl dithiocarbamato function it might hydrolyze to the 11β-thiol with alkali. Accordingly VIb was subjected to the reaction with thiolacetic acid in boiling benzene. The reaction proceeded smoothly and gave 3α , 9α -epoxy-3β-methoxy-11β-acetyl dithiocarbamato-5β-androstan-17-one (VII) in a yield of about 78%. The presence of an acetyl dithiocarbamato group in VII was supported by elemental analysis and the spectral similarities exhibited between VII and acetyl dithiourethane as shown below:

| | S | | | |
|-------------|---|--|--|--|
| | и С ₂ н ₅ -S-C-NHCOCH ₃ | VII | | |
| | Acetyl dithiourethane | | | |
| U.V.(mμ, ε) | 258.5 (11,290) 309 (9,710) 402 (38) | 266 (15,670) 316 (11,060) 402 (78) | | |
| I.R.(µ) | 3.18 5.91 6.60 | 3.14 5.78 6.66 | | |

The hydrolysis of VII in methanolic potassium hydroxide solution gave 3α , 9α -epoxy- 3β -methoxy- 11β -thiol-- 5β -androstan-17-one (VIII) in a yield of 84%. The compound gave a positive thiol color reaction, but exhibited no definite absorption maximum in the 2550 cm⁻¹ region (KCl disc). The lack of this absorption band can be attributed to the axial configuration of the $ll\beta$ -thiol group¹².

 3α , 9α -Epoxy- 3β -methoxy- 11β -thiocyano- 5β -pregnane-- 17α , 21-diol-20-one acetate (IX) was also converted to the 11β -acetyl dithiocarbamato derivative (X) with thiolacetic acid, but its further hydrolysis was not investigated.

An attempted conversion of the epoxide in 9α , 11α --epoxy- Δ^7 , 22-ergostadiene-3 β -ol acetate (XI) to an episulfide with potassium thiocyanate was unsuccessful. But with thiocyanic acid in ether at room temperature the epoxide ring in XI was opened to give a sulfur containing product. The rather strongly laevorotatory compound thus obtained exhibited a very strong absorption maximum at 248.5 mu (alcohol), which shifted to 237.5 mµ in 0.1 N alcoholic potassium hydroxide. It also possessed infrared absorption bands at 3.14, 6.67 and 12.48 μ . The absence of an absorption band in the 4-5 μ region indicated that the compound had neither thiocyano nor isothiocyano group. The spectral similarities as displayed by our compound and some 2-thiooxazolidone derivatives (vide infra) together with the known fact that β -hydroxy-isothiocyano group readily cyclizes

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to a 2-thiooxazolidone ring¹³ induces us to tentatively propose the formulation (2'-thiooxazolidono-5',ll α ,4',9 α)-- Δ^7 ,22-ergostadiene-3 β -ol acetate (XII) as the structure for our new derivative.

| | XII | XIIIa ^{14a} | XIIIb ¹⁴ | XIIIc ^{14a} | XIIId ^{14b} | XIV ^{14c} |
|--------------------------------|--------------|----------------------|----------------------|----------------------|----------------------|--------------------|
| U.V. (mµ) (in alcohol) | 248.5 | | | | 240 | 256 |
| U.V. (mµ) (in basic medium) |) 237.5 | | | | 232 | |
| I.R. (µ) | 3.14 6.67 | 2.89 6.61 | 2.92 3.17 6.71 | 2.92 3.17 6.61 | 2.92 3.17 6.63 | 3.12 6.65 |

The formation of the 2-thiooxazolidone ring apparently invokes an exceptional cis axial-equatorial, 9α and 11α , opening contrary to the known trans diaxial opening of steroid epoxides in the absence of vicinal groups capable of exerting marked polar or conjugative effects. The evidence on hand also does not permit a definite assignment as to which carbon atom (C-9 or C-11) is linked to the oxygen atom of the thiooxazolidone ring; however, a C-11 linkage seems preferable since it involves the attack of thiocyanato (NCS⁻) radical at a more stable tertiary carbonium ion, A. The infrared absorption band at 12.48 μ probably indicates the retention of the original double bond at C-7.



EXPERIMENTAL 15

 $\Delta^{4,9(11)}$ -Androstadiene-3,17-dione (II). (a) With chromic_acid.⁴ To a stirred solution of 3.534 g. of I in 730 ml. of glacial acetic acid was added over a period of 1 hr. at room temperature a solution of 3.5 g. of chromic acid (dissolved in a minimum of water) in 100 ml. of glacial acetic acid. Stirring was continued for 1 hr., the mixture poured in 3 l. of water and extracted with ether. The extracts after thorough washing with water, sodium bicarbonate, water and drying left by evaporation a colorless crystalline residue. Crystallization from acetone-hexane gave 1.43 g. of colorless prisms melting at 203-206°. The yield varied from 50 to 55%. (b) <u>With sodium bismuthate</u>.⁵ To a solution of 500 mg. of I in 150 ml. of glacial acetic acid and 150 ml. of water was added 9.0 g. of sodium bismuthate, and the resulting suspension was agitated vigorously at room temperature in the dark for 24 hr. The solution was then filtered, the precipitate washed with ether, and

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the total mixture extracted with ether. The extracts after thorough washing with water, sodium bicarbonate, water and drying left by evaporation a colorless crystalline residue. Crystallization from acetone-hexane gave 193 mg. of colorless prisms melting at 195-202°. The mother liquor gave a second crop (74 mg.) of m.p. 196-198°. Total yield was about 65%.

<u> 9α ,ll α -Epoxy- Δ^4 -androstene-3,17-dione (III)</u>. II(3.93 g.) was dissolved in 1 l. of an ice-cold 0.024 M solution of perbenzoic acid in chloroform and the mixture allowed to remain in the cold room. Iodometric titration after 38 hr. indicated the consumption of 1.25 mole equivalents of perbenzoic acid. The resulting chloroform solution was washed in the order given with sodium iodide in 0.2 N sulfuric acid, dilute sodium sulfite, water, sodium bicarbonate and water. The crystalline residue from the chloroform solution upon recrystallization from acetone gave 3.38 g. (82%) of colorless elongated prisms of m.p. 278-280^o; $[\alpha]_D$ +183.5 ± 1.5^o (c 1.0); λ_{max} 237 mµ (15,600); 5.74, 6.01 µ (CO).

Anal. Calcd. for C₁₉H₂₄O₃ : C,75.97; H,8.04. Found : C,75.95; H,8.06.

 9α , 11α -Epoxy-5 β -androstane-3, 17-dione (IV). A mixture of 4.6 g. of III and 1.4 g. of 10% palladium-charcoal in

1.4 l. of ethyl acetate was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure. After the hydrogen uptake had ceased, the catalyst was removed by filtration and washed with ethyl acetate. The residue (4.6 g.) left by evaporation of the filtrate was separated into its components by repeated chromatography on alumina. Elution with benzene-Skellysolve B (1:5) and crystallization from methanol-water gave 3.18 g. (68%) of IV, melting at 154-155°; $[\alpha]_D$ +91.9 ± 0.6° (c 1.0). Lit.^{6a}: m.p. 155-157°; $[\alpha]_D^{15}$ + 85.2 ± 6°.

Anal. Calcd. for C₁₉H₂₆O₃ : C,75.46; H,8.67. Found: C,75.73; H,8.96.

Elution with benzene and crystallization from methanol-water gave ca. 0.58 g. of 9α , 11α -epoxy- 5α --androstane-3, 17-dione (V), melting at 216-218°. Lit.^{6a}: m.p. 213-215°.

 $3\alpha, 9\alpha$ -Epoxy-3 β -hydroxy-11 β -thiocyano-5 β -androstane--17-one (VIa). A solution of 1.0 g. of IV in 21 ml. of glacial acetic acid and 21 ml. of the thiocyanic acid solution³ was allowed to stand at room temperature for 23 hr., water was added, and the mixture extracted with chloroform. The extracts after thorough washing with water and drying left by evaporation a colorless resinous residue. Crystallization from acetone-hexane gave 0.95 g.

(79%) of colorless needles, melting at 167-173°. Recrystallization from the same solvent mixture raised the m.p. to 177-178°; $[\alpha]_D$ + 121.2 ± 1.5° (c 0.5); λ_{max} 2.91 (OH), 4.64(SCN), 5.76 μ (CO).

Anal. Calcd. for C₂₀H₂₇O₃NS : C,66.46; H,7.53; N,3.88; S,8.85. Found: C,66.64; H,7.61; N,4.16; S,8.82.

 9α ,ll α -Epoxy-5 β -androstane-3,l7-dione (IV) from VIa. (a) <u>With ammonia</u>. A solution of 50 mg. of VIa in 10 ml. of methanol and 1 ml. of 28% aqueous ammonia was allowed to stand at room temperature overnight. The crystals left by evaporation of the solvent was recrystallized from methanol-water yielding IV of m.p. 151-153°.

(b) <u>With potassium carbonate</u>. A mixture of 40 mg. of VIa in 10 ml. of methanol and 1 ml. of 10% aqueous potassium carbonate solution was stirred at room temperature for 1.5 hr. The reaction mixture was acidified with acetic acid and extracted with chloroform. The chloroform solution left by evaporation IV of m.p. 150-154^o.

(c) <u>By prolonged chromatography on alumina</u>. 20 mg. of VIa(dissolved in 10 ml. of benzene) was adsorbed on a column of 0.8 g. of alumina ("Woelm" non-alkaline almost neutral aluminum oxide, Grade IV), and the resulting column allowed to stand at room temperature overnight. Elution with benzene gave IV of m.p. 154-155⁰. Invariably compound IV was obtained in very high yield. Identification was confirmed in each case by mixed m.p. and infrared spectrum.

<u> $3\alpha, 9\alpha$ -Epoxy-3\beta-methoxy-11\beta-thiocyano-5\beta-androstane-</u> <u>-17-one (VIb)</u>. To a solution of 302 mg. of VIa in 17 ml. of methanol was added 3 drops of concd. hydrochloric acid, and the mixture stirred at room temperature for 3 hr. The crystals which had deposited during the agitation were collected and recrystallized from methanol yielding 240 mg. (77%) of VIb, melting at 196-197°; $[\alpha]_{\rm D}$ +88.6 ± 0.7° (c 1.0); $\lambda_{\rm max}$ 4.67(SCN), 5.74 µ(C).

Anal. Calcd. for C₂₁H₂₉O₃NS: C,67.16; H,7.78; N,3.73; S,8.54. Found: C,67.18; H,8.06; N,3.75; S,8.41.

<u>3α,9α-Epoxy-3β-methoxy-llβ-acetyl dithiocarbamato-5β-</u> <u>-androstane-l7-one (VII)</u>. To a solution of 200 mg. of VIb in 20 ml. of dry benzene was added 0.1 ml. of freshly distilled thiolacetic acid. The mixture was refluxed for 6 hr., and evaporated to dryness in vacuo. Trituration of the yellow oily residue with methanol gave 188 mg. (78%) of crystalline VII. Recrystallization from methanol gave lemon-yellow long prisms, melting at 230° dec.; $[\alpha]_{\rm D}$ +27.2 ± 1° (c 1.0); $\lambda_{\rm max}$ 266(15,670), 316(11,060), 402 mµ(78); 3.14(NH), 5.74 (CO), 5.78 (acetate), 6.66 µ(thioureide).

Anal. Calcd. for C₂₃H₃₃O₄NS₂: C,61.16; H,7.36; N,3.10, S,14.19. Found: C,61.18; H,7.56; N,3.10; S,13.91.

<u>Acetyl dithiourethane</u>.¹⁰ M.p. 121-122°; λ_{max} 258.5(11,290), 309(9,710), 402 mµ(38); 3.18, 5.91, 6.60µ.

<u>3a,9a-Epoxy-3β-methoxy-11β-thiol-5β-androstane-17-</u> -one (VIII). To a solution of 200 mg. of VII (0.443 m moles) in 16 ml of methanol was added a solution of 50 mg. of potassium hydroxide (0.891 m moles) in 4 ml. of water, and the mixture was refluxed for 12 minutes, cooled and acidified with acetic acid. Water was added and the mixture was extracted with chloroform. The residue from the washed with water and dried chlorform extracts was triturated with methanol, and the colorless crystals thus obtained recrystallized from methanol yielding 130 mg. (84%) of colorless long prisms (VIII), melting at 176-178°; $[\alpha]_D$ +74.3 ± 1° (c 1.0); λ_{max} 5.72 µ(CO); neither in nujol mull nor in a KCl pellet the SH band (3.8-4.1 µ) could be detected.

Anal. Calcd. for C₂₀H₃₀O₃S: C,68.54; H,8.63; S,9.16. Found: C,68.57; H,8.84; S,9.39.

<u> $3\alpha,9\alpha$ -Epoxy-3\beta-methoxy-ll β -acetyl dithiocarbamato-5 β --pregnane-17 $\alpha,21$ -diol-20-one acetate (X). To a solution of 2.05 g. of $3\alpha,9\alpha$ -epoxy-3 β -methoxy-ll β -thiocyano-5 β --pregnane-17 $\alpha,21$ -diol-20-one acetate (IX)³ in 100 ml. of</u> dry benzene was added to 0.75 ml. of freshly distilled thiolacetic acid. The mixture was refluxed for 6 hr., and evaporated to dryness in vacuo. The yellow resinous residue was dissolved in 50 ml. of benzene and purified by chromatography on 40 g. of florisil. The yellow residue (1.95 g., 82%) from the benzene eluate was triturated with ether giving lemon-yellow prisms (X) of m.p. 198-201°. Recrystallization from ether raised the m.p. to 204-206°; $[\alpha]_{\rm D}$ +62.0 ± 3° (c 0.48); $\lambda_{\rm max}$ 267.5(15,210), 318 (10,600), 401 mµ(56); 2.87, 3.00, 5.69, 5.78, 5.81 µ(shoulder).

Anal. Calcd. for C₂₇H₃₉O₇NS₂ : C,58.56; H,7.10; N,2.53; S,11.58. Found: C,58.69; H,7.23; N,2.94; S,11.60.

<u>2-Thiooxazolidone derivative (XII)</u>. To a solution of 300 mg. of 9α ,ll α -epoxy- $\Delta^{7,22}$ -ergostadiene-3 β -ol acetate (XI) in 25 ml. of ether was added 15 ml. of ca. 0.5 N ethereal thiocyanic acid solution¹⁶, and the reaction mixture was allowed to stand at room temperature for 72 hours. The reaction mixture was washed with water, sodium bicarbonate and water, dried and evaporated to dryness in vacuo. Crystallization of the crystalline residue from acetone gave colorless prisms (XII) of m.p. 260-263°. Recrystallization from methanol raised the m.p. to 267-269°. $[\alpha]_D$ -114.0 ± 1.3° (c 0.53); λ_{max} 248.5 mµ(23,860), in 0.1 N alcoholic alkali shifted to 237.5 mµ(15,510); 3.14, 5.83, 6.67, 12.48 µ.

Anal. Calcd. for $C_{31}H_{47}O_3NS : C,72.48; H,9.22;$

N,2.73; S,6.24. Found: C,72.27; H,9.32; N,2.99; S,6.26.

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