SYNTHESES AND ULTRAVIOLET ABSORPTION OF AZA-STEROIDS

M. Sharma[1] and V. Georgian
Department of Chemistry, Tufts University
Medford 55, Massachusetts

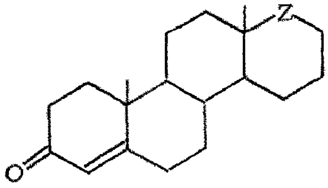
Received: 11/14/75

ABSTRACT

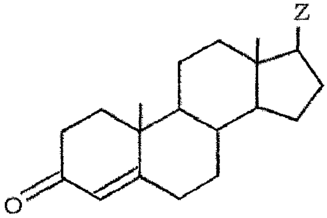
A series of aza-steroids was synthesized containing chromophoric groups, such as α, β-unsaturated ketones and doubly unsaturated conjugated and monoconjugated heteroannular dienones with the heteroatom in the D ring at the 20 and 17a positions. The effect of an appositely placed electronegative center in these molecules upon their ultraviolet absorptions was studied. In order to obtain a basis for the observed spectral changes, the corresponding carbocyclic compounds were also synthesized. The maximum absorptions of the aza-steroids were hypsochromically shifted relative to the carbocyclic compounds in all cases (n=8). The displacement caused by the electronegative center on absorption maximum of the chromophores is, however, highly dependent on its location within the molecules.

It was observed that the compounds which contain an appositely placed electronegative center absorb abnormally in the ultraviolet (2a-c). The transannular electrostatic interaction, vectorially opposed, between the polarised form of the unsaturated carbonyl system and the electronegative center within the molecules raises the energy associated with the electronic disturbances therein with a consequent hypsochromic shift. The study of the phenomenon has been confined mainly to bicyclic hetero compounds (2a-c). Studies, presented herein, were made to examine whether a similar hypsochromic shift exists in polycyclic compounds such as aza-steroids, where the distances separating the chromophores from appositely placed electronegative center are increased considerably.

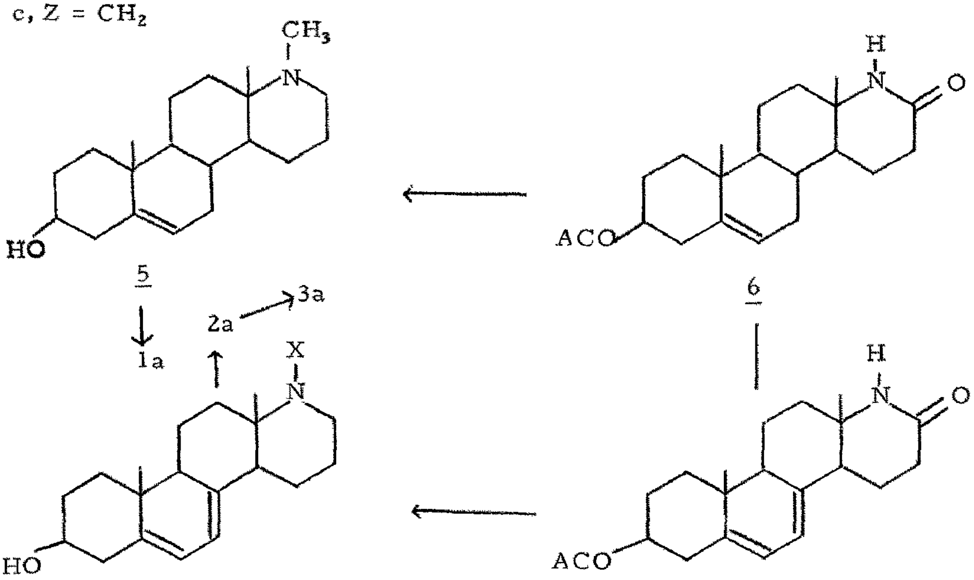
The following diagram presents the compounds synthesized for the purpose of this study.



1(a, b, c)
2(a, b, c)
3(a, b, c)
2= Δ^7-1; 3= Δ^6-1
a, Z = NCH_3
b, Z = $\overset{+}{N}(CH_3)_2ClO_4^-$
c, Z = CH_2



4(a^1, b^1, c^1)
a^1, Z = $N(CH_3)_2$
b^1, Z = $\overset{+}{N}(CH_3)_3ClO_4^-$
c^1, Z - CH_2



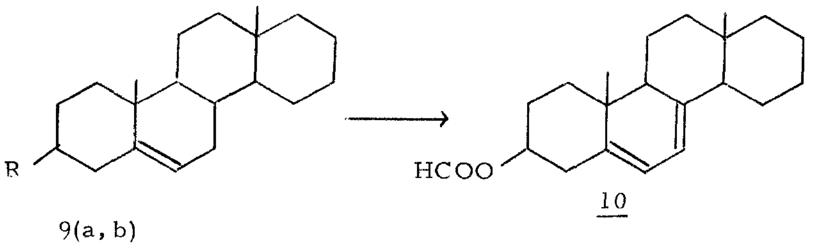
8(a, b)
a, X = H
b, X = CH_3

Reduction of the lactam 6 with lithium aluminum hydride (3) followed by methylation with a mixture of formic acid and formaldehyde gave the N-methyl amino steroid 5 which was subsequently oxidized to the α, β-unsaturated ketone 1a (4). Bromination with N-bromosuccinimide and dehydrobromination with trimethylphosphite of the lactam 6 (5) gave a crystalline product identified as the homoannular diene 7 by both elemental analyses and spectral evidence. The doubly unsaturated lactam 7 was reduced with lithium aluminum hydride to the amino steroid 8a in good yield. The amine was methylated as before to the N-methylated amine 8b in 95% yield. Both the infrared and the ultraviolet spectra of the methylated product 8b indicated that the diene system in ring B did not isomerize under the conditions of methylation. Oppenauer oxidation of the N-methyl amino steroid 8b afforded the monoconjugated dienone 2a in only fair yield. A sample of this ketone was isomerized to the conjugated dienone 3a in high yield with 3% methanolic hydrochloric acid. The N, N-dimethyl amino ketone 4a[1] was synthesized by oxidation of the corresponding 3β-ol amine which was prepared from 3β-hydroxy-5-androsten-17-one using a mixture of N, N-dimethyl formamide and 99% formic acid (6).

The quaternary iodides of the amines 1a, 2a, 3a and 4a[1] were prepared by treating a sample of corresponding amines in acetone with hydroiodic acid. As iodide ion interferes with the absorption of the chromophoric group in the 220-240 nm region, the iodides were converted to the quaternary perchlorates 1b, 2b, 3b and 4b[1] respectively by treatment with 70% perchloric acid. The perchlorate ion is transparent in the spectral range of interest.

The carbocyclic analogs (see scheme II) possess nearly the same conformational and other steric features present in the hetero substituted compounds, thus making a comparison of ultraviolet displacements more meaningful.

Scheme II



9(a, b)

a, R = OH

b, R = HCOO

$2c \longrightarrow 3c$

The D-homo steroid 9a was synthesized from D-homo-3β-hydroxy-5-androsten-17-one by Wolff-Kishner reduction (7). The formyl derivative 9b was oxidized to α, β-unsaturated ketone 1c. Bromination and dehydrobromination of D-homo-5-androsten-3β-formate gave the diene 10 in 40% yield. Oxidation of the diene 10 afforded the monoconjugated dienone 2c, a part of which was isomerized to the conjugated dienone 3c. The conjugated ketone 4c[1] was obtained in excellent yield from 3β-hydroxy-5-androsten-17-one by Wolff-Kishner reduction followed by Oppenauer oxidation.

TABLE I

The wavelength of maximum ultraviolet absorption ($\lambda_{\text{ethanol}}^{\text{max}}$ nm) for each compound and the displacement in absorption ($\Delta\lambda_{\text{ethanol}}^{\text{max}}$ nm) of the reference carbocyclic compound produced by the hetero substitution.

Compounds	$\lambda_{\text{ethanol}}^{\text{max}}$ [a]	$\Delta\lambda_{\text{ethanol}}^{\text{max}}$ nm
1c	242.0	
1a	241.0	1a-1c = -1.0
1b	238.0	1b-1c = -4.0
2c	239.0	
2a	238.0	2a-2c = -1.0
2b	235.5	2b-2c = -3.5
3c	284.5	
3a	283.5	3a-3c = -1.0
3b	280.0	3b-3c = -4.5
4c	241.5	
4a	240.5	4a-4c - -1.0
4b	239.0	4b-4c = -2.5

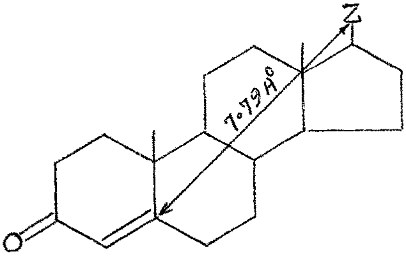
[a] The spectra were taken consecutively in 95% ethanol on a Perkin-Elmer spectrophotometer, Model 450. $\lambda_{\text{ethanol}}^{\text{max}}$ for each compound is the result of three independent determinations.

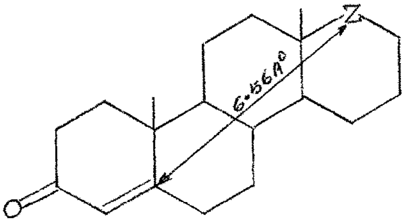
The dependence of the perturbation by center Z upon the polarisable function $(en)_n$ one on the distance of separation <u>r</u> in the usual electrostatic manner involving some inverse power of <u>r</u> is well borne out experimentally by the displacement recorded in Table 1. Correlation was made with interatomic distances measured from crystallographic data on model structures, testosterone (8) and potassium canrenoate (9).

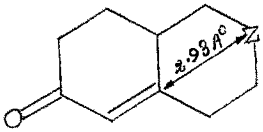
Testosterone:	C(5) - C(8)	2.93A°
	C(5) - C(17)	6.56 A°
	C(5) - O(17)	7.79 A°

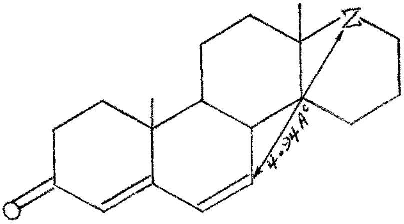
Potassium Canrenoate: C(7) - C(17) 4.94 A°

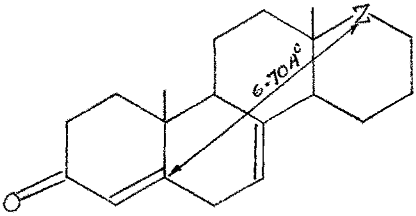
Although no 4,7-diene-3-one steroid has been studied crystallographically, the C(5) -Z(17) distance may be assumed to be slightly greater than 6.56 A° due to flattening of the B-ring introduced by the 7-8 double bond. This is also apparent from examination of Dreiding Stereo Models, which in all cases showed interatomic distances that agreed to within 0.2 A° with the crystallographic observation. The diagrams below set forth the distance r for the cases of interest.











Comparison of the values of λ^{max}, as listed in Table I with structures and dimensions of the apposite molecules as diagrammed in the schedule above permits the overall conclusion that at distances of the order 4.94 - 7.79 A° there are demonstrable hypsochromic displacements of 2.5 - 4.5 nm generated by the most powerful electronegative centers. The smallest displacement correlates with the longest reach and as expected, the more pronounced displacement (4.5 nm) occurs with the shortest separation (4.94 A°) of charges. The more striking displacement reported previously in the bicyclic cases correlates well with the much shorter distances (2.93 A°) of transannular separation of charges.

EXPERIMENTAL SECTION

Microanalyses were performed in Microchemical Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts. Melting points (m.p.) were not corrected. Infrared spectra were obtained with a Beckman IR-5 spectrometer in Nujol mull.

17a-N-Methylamino-D-homo-5-androsten-3β-ol (5). A mixture of 17a -Aza-D-homo-5-androsten-3β-ol (10 g, 35 mmol), formic acid (9 g, 99%) and formaldehyde (7 g, 40%) was heated on a steam bath for three hours. The brown colored oil was taken up in methanol (75 ml) and water (10 ml). Solid potassium hydroxide was added until the medium was alkaline and the whole was heated on the steam bath for 10-15 min. After removal of methanol the brown colored solid residue was filtered and recrystallized from methanol to give 7.8 g (74%) white crystal, m.p. 173-174°. Anal. Calcd for $C_{20}H_{33}NO$: C, 79.15; H, 10.96. Found: C, 79.20; H, 11.06.

17a-N-Methylamino-D-homo-4-androsten-3-one (Ia). 5b (3 g, 9.9 mmol) was converted to 2.3 g (77%) Ia, m.p. 171-172° under the condition of Oppenauer oxidation (5).Ir (nujol) 5.98 μ and 6.15 μ. Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36. Found: C, 79.83; H, 10.49.

17a-N-Methylamino-D-homo-4,6-androstadiene-3-one (3a). 2a (250 mg, 0.83 mmol) in 3% methanolic hydrochloric acid (75 ml) was heated to reflux for an hour. After removal of methanol under reduced pressure the oily residue was treated with water, neutralized with 3% caustic soda solution and extracted with methylene chloride. The organic layer after washing with water was dried and evaporated in a rotary evaporator. The crude product was recrystallised from a mixture of acetone and hexane. Yield 225 mg (80%); m.p. 141-142°; ir (nujol) had bands at 5.98, 6.15 and 6.26 μ. Anal. Calcd. for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.28; H, 10.00; N, 4.55.

3β-Acetoxy-13α-amino-5,7-androstadien-13,17-seco-17-oic-13,17-lactam (7). A mixture of the lactam 6 (3.4 g, 10 mmol) and N-bromosuccinimide (2.2 g) in dry chloroform (125 ml) was refluxed under the heat and light of a General Electric Photospot lamp for 5-10 min. The mixture was then cooled immediately with cold water. The clear solution was washed repeatedly with water, followed by sodium bicarbonate solution and water again. After drying the chloroform was removed in a rotary evaporator. The crude product (5 g) was dissolved in xylene (180 ml) and trimethylphosphite (20 ml) was added. The reaction mixture was refluxed at 130° for $1\frac{1}{4}$ hrs. After removal of solvent under reduced pressure, the residue was a crystalline solid product. Yield 2 g (50%); m.p. 270-272° (decom); ir (nujol) 3.0, 5.7, 6.0, 6.2 and 8.0 μ; λ_{etoh}^{max} 288 nm (ϵ = 5,500), 278 nm (ϵ = 9,800), 268 nm (ϵ = 9,800) and 258 nm (ϵ = 7,200), characteristic of homoannular diene. Anal. Calcd. for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.25; H, 8.42; N, 4.03.

Lithium aluminum hydride reduction of 7 gave 8a in 70% yield; m.p. 225-227°; ir (nujol) 2.8, 3.0, 6.0 and 6.2 μ; λ_{etoh}^{max} 288 nm (ϵ = 5,000), 278 nm (ϵ = 9,000), 268 (ϵ = 9,000) and 258 (ϵ = 7,000). Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.27; H, 10.11; N, 5.09.

17a-N-Methylamino-D-homo-5,7-androstadiene-3β-ol (8b). 8a was methylated with a mixture of formic acid and formaldehyde as in 5 in 78% yield; m.p. 173-174°; ir (nujol) 2.8, 6.0 and 6.2 μ; λ_{etoh}^{max} 288 nm (ϵ = 5,000), 278 nm (ϵ = 9,000), 268 nm (ϵ = 9,000) and 258 nm (ϵ = 6,500). Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65 Found: C, 79.84; H, 10.52; N, 4.63.

17a-N-Methylamino-D-homo-4,7-androstadiene-3-one (2a). 8b was oxidized to 2a under Oppenauer condition as a thick oil which was crystallized from acetone in 33% yield; m.p. 124-125°. Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.15; H, 9.47; N, 4.71.

D-Homo-5-androsten-3β-ol (9a). A mixture of D-homo-5-androsten-3β-ol-17α-one (4.4 g, 14.5 mmol), potassium hydroxide (8 g), hydrazine hydrate (15 ml) and diethylene glycol (140 ml) was heated at 225-30° for three hrs. The mixture was then poured into ice cold water; solid speарated immediately which was filtered. The residue was recrystallized from a mixture of acetone and hexane to give 3.9 g (94%); m.p. 144-145°; ir (nujol) had no carbonyl absorption. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.46; H, 11.15.

D-Homo-5-androsten-3β-ol formate (9b). 9a (3 g, 10.4 mmol) was treated with formic acid (20 ml 99%). The mixture was heated on a steam bath with occassional shaking for 10 min. On cooling crystals separated with water, dried and recrystallized from acetone. Yield 2.8 g (85%); m.p. 119-120°; ir (nujol) 5.8 and 8.5 μ. Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.82; H, 10.07.

Oppenauer oxidation of 9b gave 1c in 85% yield, m.p. 138-139°, ir (nujol) 5.98 and 6.15 μ. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.87, H, 10.63.

D-Homo~~-5,7-~~androstadiene-3β-ol formate (10). Bromination and dehydrobromination of 9b as in 7 gave 10 in 45% yield; m.p. 126-127°. λ^{max}_{etoh} 290 nm (ϵ = 7,000), 280 nm (ϵ = 11,600), 270 nm (ϵ = 11,000). Anal Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.45; H, 9.80.

D-Homo-4,7-androstadiene-3-one (2c). Oppenauer oxidation of 10 gave 2c in 65% yield, m.p. 134-135°; ir (nujol) 6.0 and 6.2 μ. Anal Calcd for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.47; H, 9.95.

D-Homo-4,6-androstadiene-3-one (3c). was prepared from 2c by isomerization with 3% methanolic hydrochloric acid. Yield 50%; m.p. 125-126°; ir (nujol) 5.98, 6.15 and 6.26 μ. Anal. Calcd for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.64; H, 10.04.

ACKNOWLEDGEMENTS

The interest and encouragement of Dr. W. R. Slaunwhite, Jr., Professor of Biochemistry, SUNY/Buffalo, in preparing the manuscript are deeply appreciated.

The crystallographic measurement of interatomic distances by Dr. W. L. Duax, Medical Foundation of Buffalo, is gratefully acknowledged.

REFERENCES

1. Abstracted from Master Thesis, M. Sharma, Department of Chemistry, Tufts University, Medford, Massachusetts, Present address, Department of Biochemistry, SUNY/Buffalo, P.O. Box U, Station B, Buffalo, New York 14207.

2a. V. Georgian, Chem. and Ind., 930 (1954); 1480 (1957).

2b. A. Marchant and A. R. Pinder, J. Chem. Soc., 327 (1956).

2c. E. M. Kosower and D. C. Remy, Tetrahedron, 5:281 (1959).

3. B. M. Regan and F. Hayes, J. Amer. Chem. Soc., 78:639 (1956)

4. D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, Jr., J. E. Stafford, R. L. Pederson and A. C. Ott, J. Amer. Chem. Soc., 77, 1212 (1955).

5. F. Hunziker and F. X. Mullner, Helv. Chim. Acta. 41:70 (1958).

6. P. L. Julian, U. S. Pat. 2:705, 238.

7. H. Minlon, J. Amer. Chem. Soc., 71:3301 (1949).

8. B. Busetta, C. Courseille, F. Leroy, M. Hospital Acta. Cryst. B28, 3293-3299 (1972).

9. D. C. Rohrer, C. M. Weeks and W. L. Duax, private communication to the authors.