which time 6.4 g. of solid had been deposited. The mother liquors were treated with hydrogen sulfide for an additional 6 hr. to yield an additional 2 g. (36% total) of 1-methyl-4,4-dimercaptopiperidine hydrate (III), m.p. 48–50°.

Anal. Calcd. for $C_6H_{15}NOS_2$: C, 39.74; H, 8.34; S, 35.37. Found: C, 40.30, 40.59; H, 8.43, 8.66; S, 34.48, 34.27.

An isopropyl alcohol solution of 1-methyl-4,4-dimercaptopiperidine hydrate (II) was treated with hydrogen chloride to form the hydrochloride (IV), m.p. 142–144°, resolidified, m.p. 168–171°, identical in infrared spectrum with IV isolated from 1-methyl-4-piperidone hydrochloride hydrate (II).

Polymer of 1-methyl-4-thiopiperidone hydrochloride (V). A solution of 22 g. of 1-methyl-4-piperidone (I) in 180 ml. of isopropyl alcohol was saturated with anhydrous hydrogen chloride, and hydrogen sulfide was then passed into the solution for 5 hr. The addition of anhydrous ether caused the precipitation of an oil which partially crystallized on standing. The solid was removed by filtration and washed with isopropyl alcohol and ether. About 18 g. (55%) of V, m.p. 178–191°, was obtained, but it could not be purified by recrystallization due to decomposition. Fractional precipitation of V from the reaction mixture obtained with pure 1-methyl-4-piperidone (I) gave analytically pure V, m.p. 189–191°.

Anal. Calcd. for $(C_6H_{12}ClNS)_n$: C, 43.49; H, 7.30; S, 19.35; Cl, 21.40. Found: C, 43.40, 43.11; H, 7.32, 7.15; S, 20.15, 20.12; Cl, 21.43.

The reaction of V with nitrous acid gave a green color and V gave an orange precipitate which darkened rapidly on reaction with alcoholic lead acetate.[7] Grote's reagent[8] gave with V a red-purple color which changed to violet and finally blue.

Dispiro-1,2,4-trithiolane hydrochloride (VI). A solution of 1-methyl-4-piperidone hydrochloride hydrate (II) in isopropyl alcohol prepared from 28.3 g. of pure 1-methyl-4-piperidone (I) was saturated with hydrogen sulfide. The 1-methyl-4,4-dimercaptopiperidine hydrochloride (IV) which precipitated was removed by filtration. The filtrate was concentrated and 5.9 g. (13%) of VI, m.p. 225–227°, precipitated. Recrystallization of the solid from 95% ethanol gave VI, m.p. 233° dec.

Anal. Calcd. for $C_{12}H_{24}Cl_2N_2S_3$: C, 39.66; H, 6.66; Cl, 19.51; S, 26.47. Calcd. for $C_{12}H_{24}Cl_2N_2S_3 \cdot H_2O$: C, 37.78; H, 6.87; Cl, 18.59; S, 25.22. Found: C, 38.76, 38.67; H, 6.93, 7.07; Cl, 17.83; S, 27.14.

The base was prepared by neutralization of a solution of VI with potassium carbonate. Recrystallization of the base (VII) from ligroin gave colorless crystals, m.p. 78–80°.

Anal. Calcd. for $C_{12}H_{22}N_2S_3$: C, 49.61; H, 7.63; S, 33.11. Found: C, 49.85; H, 7.87; S, 32.96.

1-Methyl-4-mercaptopiperidine (VIII). To a suspension of 6.4 g. of sodium borohydride in 50 ml. of isopropyl alcohol, 20 g. of 1-methyl-4,4-dimercaptopiperidine hydrate (III) was added in portions. An additional 40 ml. of isopropyl alcohol was added and stirring was continued for 1 hr. The reaction mixture was heated at 58° on a water bath and stirred for 2 hr. Dilute hydrochloric acid was added until all of the solid dissolved, and the acidified solution was heated on the steam bath. The solution was neutralized with 20% potassium hydroxide until the addition of alkali caused no further clouding. The aqueous mixture was extracted several times with ether, and the ether extracts were dried. The ether was removed by distillation, and the residual oil was distilled under reduced pressure to give 10.1 g. (70%) of 1-methyl-4-mercaptopiperidine (VIII), b.p. 62° at 0.8 mm., and 2.5 g. (17%) of the corresponding disulfide (IX), b.p. 180°, at 0.8 mm. The two bases were converted to their hydrochlorides in isopropyl alcohol to give 1-methyl-4-mercaptopiperidine hydrochloride, m.p. 172–173°, and bis(1-methyl-4-piperidyl) disulfide hydrochloride, m.p. 237–238°.

Anal. Calcd. for $C_6H_{14}ClNS$: C, 42.97; H, 8.41; S, 19.12. Found: C, 43.21; H, 8.54; S, 18.20.

Anal. Calcd. for $C_{12}H_{26}Cl_2N_2S_2$: C, 43.23; H, 7.86; S, 19.24. Found: C, 43.17; H, 8.04; S, 18.17.

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Azasteroids. III[1,2]

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Received June 29, 1961

The preparation of 17β-acetoxy-19-nor-4-aza-androst-5-en-3-one (II) and its dehydrogenation to 4-azaestradiol 17β-acetate (V) has already been mentioned in a preliminary communication.[4] Further experiments have now demonstrated that II can be prepared in superior yields from 17β-acetoxy-19-nor-4-oxa-androst-5-en-3-one (I) by treatment of its benzene solution with ammonia, whereby II precipitates from the reaction mixture. Alkaline hydrolysis of II gives 17β-hydroxy-19-nor-4-aza-androst-5-en-3-one (III), which is oxidized to 19-nor-4-aza-androst-5-en-3,17-dione (IV) with chromic acid.

All the 3-keto-4-aza Δ^5-steroids have a strong ultraviolet absorption with an absorption maximum in the region of 230–235 mμ in neutral solution.

TABLE I

	λ_{max}	ϵ
4-Azacholest-5-en-3-one[4]	233	13,500
4-Azapregn-5-en-3,20-dione[4]	233	13,430
17β-Hydroxy-4-azaandrost-5-en-3-one[4]	233	13,790
17β-Acetoxy-4-azaandrost-5-en-3-one[4]	233	13,630
17β-Acetoxy-4-aza-19-norandrost-5-en-3-one[4]	234	9,630
4-Aza-4-methyl-5-cholesten-3-one	234	13,490[5]
4-Aza-4-methyl-5-pregnene-3,20-dione	234	13,180[5]
4-Aza-4-methyl-5-pregnen-20β-ol-3-one	234	13,490[5]
4-Aza-4,17α-dimethyl-5-androsten-17β-ol-3-one	234	13,490[5]

With increasing hydrochloric acid addition to the methanolic solution the maximum gradually disappears. This can be explained by the fact that the absorption is due to the form IX[6] and its disappearance to the formation of the protonated X.

Upon repeating[4] the oxidation of II with selenium dioxide in *tert*-butyl alcohol solution with a catalytic amount of either acetic acid or pyridine,

(1) Azasteroids. II, M. Gut and M. Uskoković, *J. Org. Chem.*, 26, 1943 (1961).

(2) This study was supported by National Institute of Health Grant H-5266.

(3) Hoffmann-LaRoche, Inc., Nutley 10, N. J.

(4) M. Uskoković and M. Gut, *Helv. Chim. Acta*, 42, 2258 (1959).

(5) Dr. N. J. Doorenbos, private communication.

(6) NMR gives peaks for 1 H each, attached to N and C_6.

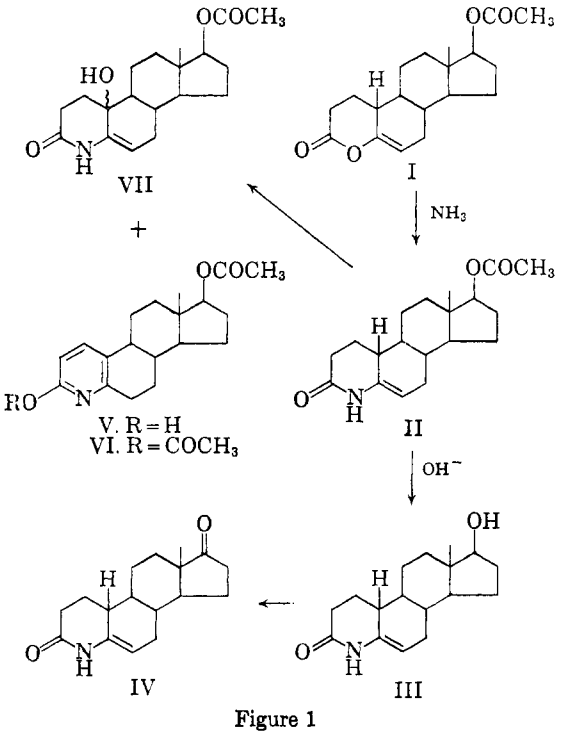
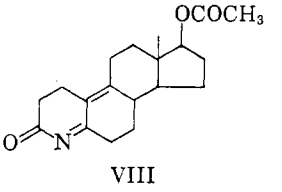


Figure 1

we found 4-azaestradiol 17β-acetate (V) to be a minor product (10%). Careful rechromatography of the fractions containing V allowed the separation of a less polar product, identified as 4-azaestradiol 3,17β-diacetate (VI). The major product was polar and is formulated as 10ξ,17β-dihydroxy-19-nor-4-azaandrost-5-en-3-one 17β-monoacetate (VII) on the basis of its properties and the reactions it undergoes. The elemental analysis indicates $C_{19}H_{27}O_4N$; infrared analysis shows the presence of a tertiary hydroxyl group (3520, 1200, and 1055 cm.$^{-1}$). The hydroxyl resisted acetylation with acetic anhydride–pyridine and could not be oxidized with chromic acid. A solution of VII in acetic acid was saturated with hydrogen chloride at 10° without undergoing aromatization, indicating that formation of a carbonium ion, followed by trans axial elimination does not occur as readily[7] with unsaturated lactams as with the conjugated ketone analog. A hypsochromic shift in the ultraviolet absorption, compared to II, from 234 mμ to 230 mμ is paralleled by the shift in the absorption[8] of 19-nor-10β-hydroxytestosterone compared to 19-nortestosterone. The near infrared reveals the presence of a hydroxyl (1.417 μ) and of an NH-group (1.505 μ). No color is produced with ferric chloride, thereby excluding a hydroxamic acid. A solution of VII in glacial acetic acid was boiled for 1$^1/_2$ hr., then evaporated, and the residue recrystallized from methanol. The product underwent a transformation at 310–315° and did not melt under 330°. Lack of material allowed only a qualitative determination of the ultraviolet spectrum, which showed λ_{max} at 232 mμ and 310–317 mμ, which might be suggestive to formulation VIII.[9]



VIII

The rotatory dispersion curve of ring A unsaturated amides lacks[10] the fine structure typical of Δ^4-3-keto steroids.

The completely aromatic character[11] of 4-azaestradiol 3,17β-diacetate is demonstrated by the fact that its ultraviolet absorption maximum is not shifted by addition of acid or base. A shift of the absorption was, however, observed by subjecting the methanolic solution of either 4-azaestradiol or 4-azaestradiol 17β-acetate to *p*H changes.

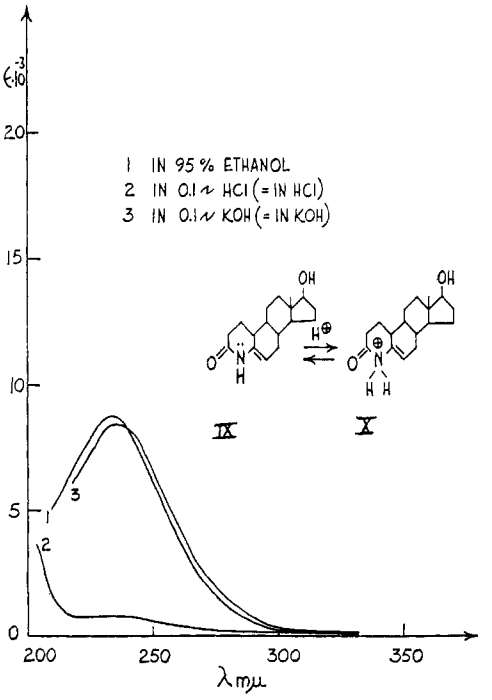


Figure 2

EXPERIMENTAL

17β-Acetoxy-19-nor-4-azaandrost-5-en-3-one (II) *from* I. To the solution of 100 g. of 17β-acetoxy-19-nor-4-oxa-

(7) Compare the aromatization[8] of the 17-acetate of 10β-hydroxy-19-nortestosterone to estradiol 17-monoacetate under identical conditions.

(8) J. P. Ruelas, J. Iriarte, F. Kincl, and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(9) Compare M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960).

(10) Proof of configuration for the 10-hydroxyl of VII can therefore not be obtained from rotatory dispersion measurements.

(11) For 2-hydroxypyridine-pyridine equilibria compare S. F. Mason, *J. Chem. Soc.*, 5010 (1947).

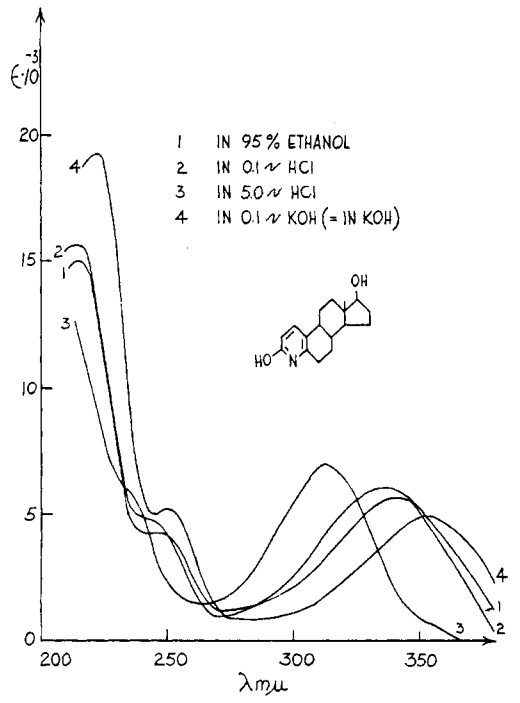


Figure 3

androst-5-en-3-one (I)[12] in 1000 ml. of dry benzene was introduced a stream of gaseous ammonia at room temperature, whereby a copious precipitate deposited. The crystals were filtered off and recrystallized from methanol. The 55 g. of colorless prisms had a m.p. 301–310°, dec. and the infrared and ultraviolet spectra were identical with those of a specimen obtained previously.[4]

17β-Hydroxy-19-nor-4-azaandrost-5-en-3-one (III) *from* II. The solution of 15 g. of II in 150 ml. of 2% sodium hydroxide in methanol was left overnight at room temperature, then a large amount of water was added, and the resulting suspension extracted with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from methanol to give 10.5 g. of III, m.p. 248–258° (transformations at 160–180° and 244–248°). $[\alpha]_D^{20}$ −5° (*c*, 0.5 in $CHCl_3$); λ_{max} 234 mμ (ε 8800); infrared absorption ν_{max} 3600 and 1020 (hydroxyl), 3200 (NH-group) and 1660 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_{17}H_{25}O_2N$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.24; H, 9.28; N, 5.32.

Selenium dioxide oxidation of 17β-acetoxy-19-nor-4-azaandrost-5-en-3-one (II). To the solution of 5 g. of II in 900 ml. *tert*-butyl alcohol were added 9 ml. of acetic acid and 5.4 g. of selenium dioxide and the reaction mixture refluxed for 24 hr. After cooling, the liquid was decanted, the residue washed with ethyl acetate, and the combined solutions evaporated and chromatographed on silica gel. The fractions eluted with 25% ethyl acetate in benzene were pooled and rechromatographed (see below). The fractions eluted with 50% ethyl acetate–benzene gave, after recrystallization from ether, 650 mg. VII, m.p. >286°, dec.; $[\alpha]_D^{22}$ −174° (*c*, 0.8 in chloroform), infrared absorption maxima ν_{max} 3520, 1200, and 1055 (tert. OH-group); 3180 and 3060 (NH-group); 1710 and 1250 (acetoxy group); 1664 cm.$^{-1}$ (amide carbonyl); ultraviolet absorption maximum λ_{max} 230 mμ (ε 16,000).

Anal. Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16; N, 3.20. Found: C, 68.17; H, 8.08; N, 4.05.

The mixture which was eluted with 25% ethyl acetate–benzene (see above) was rechromatographed on silica gel, whereby the fractions with 15% ethyl acetate in benzene gave, after crystallization from methanol, 150 mg. VI, m.p. >320°, dec.; $[\alpha]_D^{21}$ −3° (*c*, 0.25 in chloroform); λ_{max} 212 mμ (ε 23,000), 254 mμ (ε 16000); λ_{min} 220 mμ (ε 7600); unchanged in 0.1*N* HCl or 0.1*N* KOH.

Anal. Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.60; H, 7.24; N, 4.10.

The fractions eluted with 25% ethyl acetate–benzene gave 300 mg. V, $[\alpha]_D^{21}$ +31° (*c*, 0.4 in chloroform); λ_{max} 220 mμ (ε 7800)[13] and 288 mμ (ε 6600); λ_{min} 259 mμ (ε 3500), m.p. and infrared absorption as published previously; unchanged in 0.1 *N* HCl; 0.1 *N* KOH: λ_{max} 221 mμ (ε 16,100), 250 mμ (ε 6000) (shoulder), and 334 mμ (ε 5500); λ_{min} 281 mμ (ε 1200).

19-Nor-4-azaandrost-5-en-3,17-dione (IV) *from* III. To the solution of 3 g. of III in 200 ml. methylene chloride was added 40 ml. of 2% chromic oxide solution in 80% acetic acid and shaken overnight at room temperature. The methylene chloride layer was separated, washed with dilute sodium hydrogen sulfite solution, then with 2*N* sodium hydroxide solution and water, dried over anhydrous sodium sulfate, and evaporated. The crystalline residue was recrystallized from acetone to yield 2.6 g. of IV, m.p. 280–300°, dec.; $[\alpha]_D^{22}$ +18° (*c*, 0.7 in $CHCl_3$): ultraviolet absorption λ_{max} 233 mμ (ε 9500) and 300–310 mμ (ε 800); infrared absorption ν_{max} 3200 (—HN), 1660 (amide carbonyl), 1740 cm.$^{-1}$ (>CO).

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 7 .69; H, 8.48; N, 5.12. Found: C, 74.59; H, 8.77; N, 4.92.

Attempted dehydration of VII. A solution of 20 mg. of VII in 8 ml. of acetic acid at 10° was saturated with hydrogen chloride and left for 2 hours at 5°. The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel. The fractions eluted with 25% ethyl acetate in methylene chloride gave, after recrystallization from ether, 18 mg. prisms, m.p. >310°; λ_{max} 238 mμ (ε 630).

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(12) I. A. Hartman, A. J. Tomasewski, and A. S. Dreiding, *J. Am. Chem. Soc.*, **78**, 5662 (1956).

(13) Previously reported erroneously as λ_{max} 226 mμ (ε 6460).

Spectral Properties of Some Aromatic Thiols[1]

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Received June 29, 1961

As part of our broad concern with structure-reactivity correlations, we reported on the kinetics of addition of arylthiols (nucleophiles) to a series of ethyl phenylpropiolates (electrophiles).[2] Here we inquire whether there are independent measures of reactivity. Specifically, what relation, if any exists between the spectral properties of thiols and their nucleophilicity?

There are a few reports on ultraviolet spectral

(1) (a) Supported by the Office of Ordnance Research, U. S. Army. (b) Abstracted in part from the Ph.D. thesis of G. S. Krishnamurthy, Illinois Institute of Technology, June 1960.

(2) G. S. Krishnamurthy and S. I. Miller, *J. Am. Chem. Soc.*, **83**, 3961 (1961).