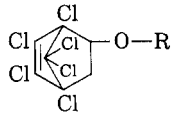
TABLE I

ADDUCTS OF THE TYPE 

R	Yield, %	B.P.	Mm.	n_D^{25}	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
Acetyl	97	110–113	0.5	[a]	30.09	29.92	1.69	1.78	60.63	60.01
Butyryl	75	126–127	0.3	1.5224	34.14	34.06	2.61	2.56	54.96	54.88
2-Ethylhexanoyl	88	145–147	0.3	1.5084	40.66	40.39	4.10	4.02	48.01	48.17
Nonanoyl	88	176–178	1.0	1.5083	42.05	41.94	4.41	4.46	46.42	45.91
Benzoyl	71	160–163	0.2	[b]	39.96	39.85	1.92	1.96	50.52	50.32

[a] M.p. 44° (from hexane). [b] M.p. 91° (from hexane).

1.5692] which was a reddish oil and dichlorinated II [b.p. 148–152° (1.7 mm.) n_D^{25} 1.5775] which was a yellow oil were also obtained. The infrared spectra of the latter two materials are consistent with the proposed structures.

1,2,3,4,7,7-Hexachloro-5-methylene-2-norbornene (IV). A mixture of 1,2,3,4,7,7-hexachloro-5-(chloromethyl)-2-norbornene[9] (60.0 g., 0.172 mole), potassium hydroxide (9.6 g., 0.172 mole) and 500 ml. of absolute ethanol was refluxed for 9 hr. The solvent was removed by distillation at reduced pressure and the pentane soluble portion of the residue distilled. The methylene compound distilled at 104° (2 mm.) as a colorless oil n_D^{25} 1.5560 and was obtained in a yield of 95% (51.1 g.). Infrared maxima: 5.97, 6.23, 6.98, 7.07, 7.99, 8.37, 8.72, 9.22, 9.53, 9.67, 10.07, 10.36, 10.92, 11.32, 11.45, 11.79, 13.53, and 13.82 μ.

Anal. Calcd. for $C_8H_4Cl_6$: C, 30.71; H, 1.29; Cl, 68.00. Found: C, 30.97; H, 1.44; Cl, 67.65.

The olefin IV (3.2 g., 10.3 mmoles) in 90 ml. of ethyl acetate was ozonized to confirm that the double bond was exocyclic. The theoretical amount of ozone was consumed, and the ozonide was hydrogenated over a palladium on strontium carbonate catalyst[10] first at atmospheric pressure and finally in a Parr hydrogenator at 50 p.s.i.g. for 20 min. (a sample gave negative peroxide test with KI). The catalyst was separated by filtration and the ethyl acetate solution shaken out with water. The water extracts furnished a 43% yield of formaldehyde as the dimedone derivative,[11] and evaporation of the ethyl acetate yielded 2.9 g. of the ketone II (90%) whose infrared spectrum was identical with that obtained by the methods reported above.

1,2,3,4,5,7,7-Heptachloro-5-(chloromethyl)-2-norbornene. (V). A solution of IV (13.5 g., 0.0432 mole) in 30 ml. of methylene chloride was treated with chlorine in ultraviolet light until a yellow color persisted. Evaporation of the solvent left behind a colorless oil (16.2 g., 98% yield) which had n_D^{25} 1.5692. Infrared maxima: 6.21, 6.94, 7.83, 8.15, 8.21, 8.49, 8.80, 8.93, 9.24, 9.37, 9.80, 10.31, 10.82, 11.27, 11.62, 11.96, 12.45, 12.79, 13.28, 13.38, 14.12, 14.60, and 15.16 μ.

Anal. Calcd. for $C_8H_4Cl_8$: C, 25.04; H, 1.05; Cl, 73.91. Found: C, 24.80; H, 1.04; Cl, 73.16.

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Steroids. VII. Synthesis of Some 4-Azaandrostanes[1-3]

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The synthesis of a series of 4-azacholestanes was recently described.[6] This paper reports the synthesis of a related group of 4-azaandrostanes with preliminary biological data.

17α-Methyl-4-azaandrost-5-en-17β-ol-3-one (II) was prepared (a) by refluxing the ammonium salt of 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid (I)[7] in *n*-amyl alcohol for eight hours and (b) by heating a solution of the ammonium salt of the oxo acid (I) in concentrated ammonium hydroxide in a sealed reaction vessel at 180° for six hours. The low yield by method (*a*) was shown to be due largely to the decomposition of the ammonia salt to ammonia and acid (I). 4,17α-Dimethyl-4-azaandrost-5-en-17β-ol-3-one (III) was obtained in good yield (a) by refluxing the methylammonium salt of the acid (I) in xylene and (b) by heating a solution of the acid (I) in ethanolic methylamine in a sealed reaction vessel at 140°. 4-(β-Hydroxyethyl)-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (IV) and 4-benzyl-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (V) were

(1) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960.

(2) For paper VI see N. J. Doorenbos and C. P. Dorn, Jr., *J. Pharm. Sci.*, **50**, 271 (1961).

(3) Abstracted from a thesis submitted by Chien Li Huang to the graduate faculty of the University of Maryland in partial fulfillment of the requirements for the Ph.D. in Pharmaceutical Chemistry, February 1960.

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(5) Present address: Research Laboratories, Spring Grove State Hospital, Baltimore 28, Md.

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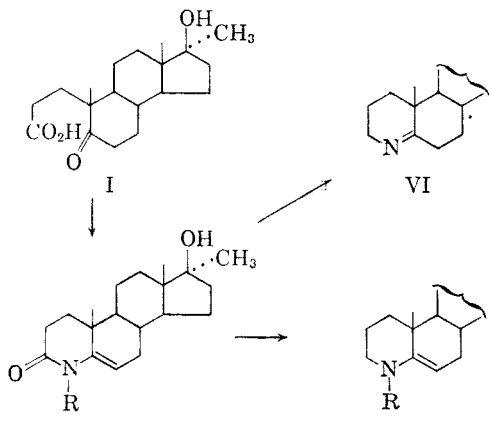
synthesized by refluxing a solution of the acid (I) in excess ethanolamine and benzylamine, respectively.

The lithium aluminum hydride reduction of II, III, IV, and V yielded 17α-methyl-4-azaandrost-4-en-17β-ol (VI), 4,17α-dimethyl-4-azaandrost-5-en-17β-ol (VII), 4-(β-hydroxyethyl)-17β-methyl-4-azaandrost-5-en-17β-ol (VIII), and 4-benzyl-17α-methyl-4-azaandrost-5-en-17β-ol (IX) in high yield.



II. R = H—
III. R = CH_3—
IV. R = $HOCH_2CH_2$—
V. R = $C_6H_5CH_2$—

VII. R = CH_3—
VIII. R = $HOCH_2CH_2$—
IX. R = $C_6H_5CH_2$—

The weak absorption of VII, VIII, and IX at 6.08 μ has been assigned to C=C stretching of the 5,6- double bond. Each of these enamines was shown to be an α,β-unsaturated amine by a comparison of the infrared spectra of the bases and their hydrogen sulfate salts. The absorption of the double bond of the salts had shifted from 6.08 to 6.02 μ and increased in intensity.[6,8] The 6.03-μ band of VI did not shift or change in intensity when the salt was made. The fact that the absorption peak of the three enamines is below 220 mμ indicates that there is poor conjugation between nitrogen and the double bond.[6]

The double bond of VI was assigned to the 4,5-position for the following reasons: (1) VI does not exhibit N—H stretching in the infrared. (2) VI has a moderately strong sharp peak at 6.03 μ which is not reduced in intensity by further treatment with lithium aluminum hydride. Similar peaks have been reported for 6-azacholest-5-ene[9] and 4-azacholest-4-ene.[6] (3) The M_D value changed +518° upon reduction of II with lithium aluminum hydride while the M_D values of the other lactams became more negative. The shift of a double bond from the 5,6-position to a 4,5-position in natural steroids results in a change in M_D of about +500°.[10] Jacobs shifted the double bond in the other direction when he reduced 6-azacholest-4-en-7-one to 6-azacholest-5-ene with lithium aluminum hydride. He reported a change in M_D of −606°.[9]

Biological data provided by the Cancer Chemotherapy National Service Center indicates that lactam IV has antiestrogenic activity, weak androgenic activity, and the ability to potentiate the action of testosterone. Lactam III has weak androgenic activity.

EXPERIMENTAL[11]

17α-Methyl-4-azaandrost-5-en-17β-ol-3-one (II) (Method A). A solution of 15.0 g. of 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid[7] (I), which had been prepared by the ozonolysis of 17α-methyltestosterone, in 200 ml. of *n*-amyl alcohol was saturated with ammonia. The mixture was refluxed (140°) for 8 hr. Ammonia was introduced slowly during the first 30 min. of reflux. Upon cooling, the solution was washed with 2% sodium hydroxide and water, and then dried over sodium sulfate. The residue obtained by distilling the solvent was crystallized from acetone to obtain 2.35 g. (17%) of 17α-methyl-4-azaandrost-5-en-17β-ol-3-one (II) as white needles; m.p. 256–258°; $[\alpha]_D$ −120.2°; λ_{max} 233 mμ (log ϵ 4.14), 2.95 μ, 3.14 μ, and 6.04 μ with an inflection at 5.96 μ.

Anal. Calcd. for $C_{19}H_{29}O_2N$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.17; H, 9.35; N, 4.69.

17α-Methyl-4-azaandrost-5-en-17β-ol-3-one (II) (Method B). A solution of 3.2 g. of 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid[7] (I) in 200 ml. of concd. aqueous ammonium hydroxide was heated in a pressure vessel under a nitrogen atmosphere at 180° for 6 hr. The mixture was cooled, filtered, and dried. The precipitate was crystallized from acetone to yield 2.42 g. (80%) of 17α-methyl-4-azaandrost-5-en-17β-ol-3-one (II), m.p. 256–259°. This product was shown to be identical with that obtained by method A by a mixed melting point and a comparison of infrared spectra and specific rotation values.

4,17α-Dimethyl-4-azaandrost-5-en-17β-ol-3-one (III) (Method A). 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid[7] (I) (15.0 g.) was dissolved in 150 ml. of xylene with the aid of 10 ml. of ethanol. The solution was saturated with methylamine and refluxed for 8 hr. After cooling, the solution was washed with sodium carbonate solution and then water. After drying over sodium sulfate, the solvent was removed. The residue, after crystallization from ethanol, yielded 9.4 g. (63%) of 4,17α-dimethyl-4-azaandrost-5-en-17β-ol-3-one (III) as white needles; m.p. 173–175°; $[\alpha]_D$ −188°; λ_{max} 234 mμ (log ϵ 4.13), and 6.14 μ with an inflection at 6.00 μ.

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(11) Melting points were taken on a Fisher-Johns block and are uncorrected. Steroid intermediates, analyses, and specific rotations were furnished by Sterling-Winthrop Research Institute. Specific rotations were taken on 1.00% solutions in chloroform at 25°. Ultraviolet spectra were obtained on ethanol solutions with a Beckmann DU spectrophotometer. Infrared spectra were obtained on chloroform solutions with a Perkin-Elmer Infracord spectrophotometer.

Anal. Calcd. for $C_{20}H_{31}O_2N$: C, 75.67; H, 9.84; N, 4.41. Found: C, 76.01; H, 10.05; N, 4.61.

4,17α-Dimethyl-4-azaandrost-5-en-17β-ol-3-one (III) (Method B). A solution of 3.2 g. of 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid[7] (I) in 200 ml. of ethanol was saturated with methylamine. The solution was heated in a sealed tube for 8 hr. at 140°. The solvent was distilled and the residue crystallized from ethanol to yield 2.54 g. (80%) of III as white needles, m.p. 172–174°. This product was shown to be identical with that obtained by method A by a mixed melting point and a comparison of infrared spectra and specific rotation values.

4-(β-Hydroxyethyl)-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (IV). A mixture of 15.0 g. of 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid[7] (I) and 60 ml. of ethanolamine was refluxed for 4 hr. After cooling, water was added and the mixture was extracted with benzene. The benzene extracts were washed with dilute hydrochloric acid and water, and then dried over sodium sulfate. The residue obtained, after evaporating the solvent, was crystallized from acetone to yield 4.8 g. (31%) of 4-(β-hydroxyethyl)-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (IV) as white needles; m.p. 172–175°; $[\alpha]_D$ −137.4°; λ_{max} 235 mμ (log ε 4.06), and 6.14 μ with an inflection at 6.00 μ.

Anal. Calcd. for $C_{21}H_{33}O_3N$: C, 72.59; H, 8.46; N, 4.03. Found: C, 72.40; H, 9.26; N, 3.71.

4-Benzyl-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (V). Lactam V was prepared from a mixture of 15.0 g. of the acid (I) and 60 ml. of benzylamine by a procedure similar to that used for IV. Crystallization of the product from ether yielded 13.0 g. (71%) of the lactam (V) as white needles; m.p. 104–106°; $[\alpha]_D$ −138°; λ_{max} 235 mμ (log ε 4.04), and 6.13 μ with an inflection at 6.00 μ.

Anal. Calcd. for $C_{26}H_{35}O_2N$: C, 79.33; H, 8.96; N, 3.56. Found: C, 79.53; H, 9.00; N, 3.53.

17α-Methyl-4-azaandrost-4-en-17β-ol (VI). Lactam II (6.07 g.) was reduced by lithium aluminum hydride in tetrahydrofuran following standard procedures.[6] The crude product, after two recrystallizations from methanol, yielded 3.6 g. (62%) of VI as white needles; m.p. 183–185°; $[\alpha]_D$ +53.2°; λ_{max} 6.03 μ (a sharp peak of moderately high intensity).

Anal. Calcd. for $C_{19}H_{31}ON$: C, 78.84; H, 10.80; N, 4.84. Found: C, 79.10; H, 10.70; N, 4.87.

4,17α-Dimethyl-4-azaandrost-5-en-17β-ol (VII). Lactam III (8.82 g.) was added to a slurry of lithium aluminum hydride in ether, by means of a Soxhlet extractor, and refluxed for 12 hr. After working up,[6] the product was crystallized from ether to obtain 8.14 g. (97%) of VII as white needles; m.p. 148–152°; λ_{max} 6.08 μ (weak absorption).

Anal. Calcd. for $C_{20}H_{33}ON$: C, 79.16; H, 10.96; N, 4.62. Found: C, 79.03; H, 10.70; N, 4.34.

4-(β-Hydroxyethyl)-17α-methyl-4-azaandrost-5-en-17β-ol (VIII). Lactam IV (3.48 g.) was reduced with lithium aluminum hydride in tetrahydrofuran. The crude product was crystallized from methanol to obtain 3.10 g. (93%) of VIII as white needles; m.p. 175–176°; $[\alpha]_D$ −152°; λ_{max} 6.08 μ (weak absorption).

Anal. Calcd. for $C_{21}H_{35}O_2N$: C, 75.65; H, 10.58; N, 4.20. Found: C, 75.90; H, 10.69; N, 4.23.

4-Benzyl-17α-methyl-4-azaandrost-5-en-17β-ol (IX). Lactam V (3.30 g.) was reduced in the same manner as lactam III above. The product was crystallized from acetone to yield 3.09 g. (97%) of IX as white needles; m.p. 122–126°; $[\alpha]_D$ −175°; λ_{max} 6.08 μ (weak).

Anal. Calcd. for $C_{26}H_{37}ON$: C, 82.27; H, 9.83; N, 3.69. Found: C, 82.30; H, 10.02; N, 3.80.

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The Vapor Phase Pyrolysis of Several Substituted Azidobenzenes

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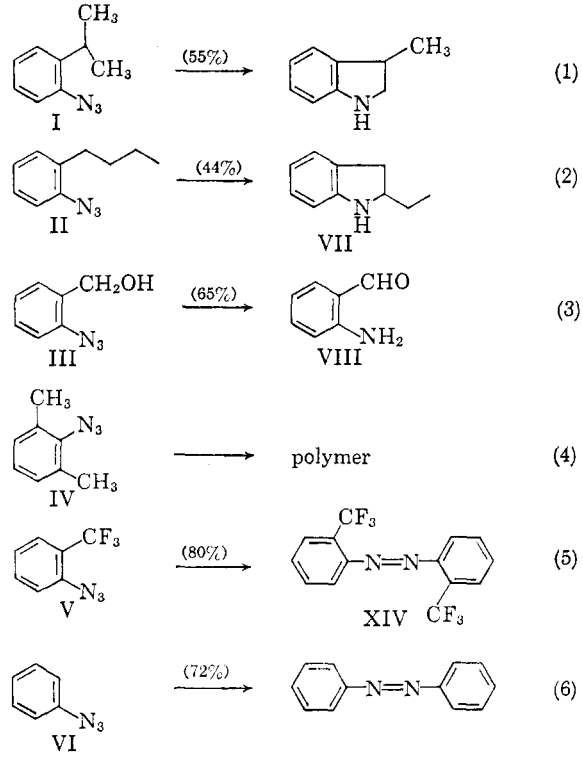
In two previous papers in this series[1] it was reported that pyrolysis of properly constituted aromatic azides resulted in attack of the azene intermediate upon the C–H bond of a saturated carbon atom with insertion of the nitrogen atom into the bond. Moreover, evidence was presented[1b] which indicated that the azene was most likely an imino radical (—$\dot{N}$:). These earlier pyrolyses were accomplished in solution and suffered from the disadvantage of affording the azene an opportunity of reacting with the solvent. Thus, it was decided to study the decompositions of several azides in the vapor phase, as in this way one would preclude reaction with solvent and would provide the maximum opportunity for intramolecular reaction of the azene.

The products obtained from the decomposition of 2-isopropylazidobenzene (I), 2-butylazidobenzene (II), and *o*-azidobenzyl alcohol (III) are consistent with the view that the azene intermediate reacts as a radical[1] (Equations 1, 2, and 3). The fact



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