can be explained by assuming β-elimination of the oxime from VI leaving an α-aminoacrylic ester which polymerized.

$$R'CH{=}NOCH_2\underset{\displaystyle NH_2}{\overset{|}{C}}HCOOR \qquad VI$$

We conclude from these results that D-cycloserine forms a Schiff base quite readily and that dimerization is *not* prerequisite to its reaction with aldehydes. Thus, Schiff base formation may well be the predominant means by which the antibiotic removes pyridoxal from enzyme systems. We have shown also that the dimer derivatives obtained in boiling ethanol are most likely due to dimerization of D-cycloserine *prior* to its reaction with the aldehyde. Pathways including Schiff base rearrangement or reaction at the isoxazolidone ring nitrogen atom are contraindicated. We are presently investigating the reaction between D-cycloserine and pyridoxal itself[10].

Zusammenfassung. Von D-Cycloserin ist die erste Schiffsche Base isoliert und charakterisiert worden. Bei Erhitzen in Äthylalkohol unterbleibt die Umlagerung in einen Cycloserindimerenabkömmling und ergibt Racemisierung. Es wird gefolgert, dass Aldehyde nicht auf das Stickstoffatom des Isoxazolidons reagieren und dass Dimerisation von Cycloserin *nicht* für die Reaktion mit Aldehyden erforderlich ist.

CH. H. STAMMER

Department of Chemistry, University of Georgia, Athens (USA), February 7, 1964.

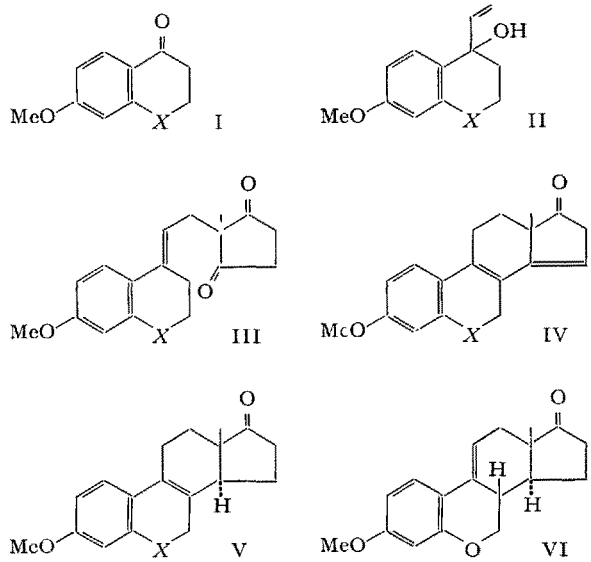
[10] *Acknowledgment.* We gratefully acknowledge the financial support of the National Institutes of Health, Grant number AI 05539-01. We thank Dr. W. F. RUNGE for a generous sample of D-cycloserine.

Total Synthesis of Derivatives of (±)-6-Oxa and Aza-Estrone

We wish to report extensions of our total syntheses of estrone, equilenin, and related compounds[1,2] to several corresponding 6-oxa- and -aza-analogs, and the conversion of (±)-17β-hydroxy-3-methoxy-6-oxa-estra-1,3,5-(10)-triene to compounds of the (±)-19-nor-6-oxa-testosterone series.

The ketones (I; $X=O$ and $C_6H_5SO_2N$)[3,4], made by cyclodehydration of the corresponding 3-substituted propionic acids, were used as starting materials. Their structures were confirmed by examining the aromatic proton signals in the proton nuclear magnetic resonance spectra of the first substance and the quinolone (I; $X=NH$) formed by acid hydrolysis of the second. The spectrum of the chromanone shows a doublet centered at 2.17 τ[5] (J 8.5 c/sec) assigned to the C_5-proton resonance split by coupling with the C_6-proton, a doublet at 3.59 τ (J 2.5 c/sec) assigned to the C_8-proton resonance split by coupling with the C_6-proton, and a pair of doublets centered at 3.43 τ assigned to the C_6-proton resonance split by coupling with both the C_5 and C_8-protons ($J_{6,5}$ and $J_{6,8}$ 9 and 2 c/sec, respectively). The spectrum of the quinolone (I; $X=NH$) is broadly similar with doublets centered at 2.18 and 3.84 τ (J 8.9 and 2.5 c/sec, respectively), and a pair of doublets at 3.67 τ ($J_{6,5}$ and $J_{6,8}$ 9 and 2.2 c/sec, respectively). These patterns are related to that found in the spectrum of the tetralone (I; $X=CH_2$) as two doublets centered at 2.01 and 3.31 τ (J 8.4 and 2.4 c/sec, respectively) and a pair of doublets at 3.18 τ (J 8.8 and 2.5 c/sec).

The chromanone (I; $X=O$) was converted by vinylmagnesium chloride in tetrahydrofuran, into the alcohol (II; $X=O$) (not obtained pure), and thence, by potassium hydrogen carbonate catalysed condensation with 2-methylcyclopentane-1,3-dione in methanol, into the seco-oxasteroid (III; $X=O$)[6], m.p. 107–111°, λ_{max} 264.5 and 309 mμ (ε 15 500 and 9400). Cyclodehydration of the last compound in ethanolic hydrochloric acid afforded the oxa-estrapentaene (IV; $X=O$)[7], m.p. 148–152°, λ_{max} 245 and 331 mμ (ε 16 700 and 21 700), which was selectively hydrogenated in benzene over 2% palladized calcium carbonate to the oxa-estratetraene (V; $X=O$), m.p. 146–151°, λ_{max} 286.5 and 307 mμ (ε 9000 and 10,500). Boiling ethanolic hydrochloric acid transformed the oxa-estratetraene into the $\Delta^{9(11)}$-isomer (VI), m.p. 175–179°, λ_{max}



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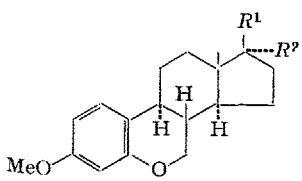
[6] Satisfactory analytical figures have been obtained for this and the other new compounds reported here.
[7] This and other racemic compounds described in the sequel are depicted by the enantiomorph having the 13-methyl group in the β-configuration.

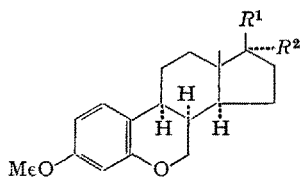
260, 267, and 307 mμ (ε 14 300, 13 200 and 8 400), and subsequent catalytic hydrogenation over 10% palladized charcoal in ethyl acetate-acetic acid gave (±)-6-oxa-estrone methyl ether (VII), m.p. 151–154°, λ_{max} 282 and 287 mμ (ε 3200 and 3000), converted by sodium borohydride in methanol to the alcohol (VIII), m.p. 138–140°; λ_{max} 282 and 289 mμ (ε 3400 and 3400). Exhaustive hydrogenation of the ketone (IV; $X=O$) in benzene over 2% palladized calcium carbonate gave (±)-6-oxa-8α-estrone methyl ether (IX), m.p. 146–148°, λ_{max} 281 and 287 mμ (ε 3600 and 3600), converted by sodium borohydride in methanol-tetrahydrofuran into the alcohol (X), m.p. 130–132°, λ_{max} 282 and 288 mμ (ε 3500 and 3100). The same compound is made from the ketone (IV) by sodium borohydride reduction in ethanol followed by hydrogenation in ethanol over 10% palladized charcoal. We have no chemical proof for the structures (V; $X=O$) and (VI-X) which are assigned by analogy with the stereochemical course of reactions, precisely similar to those described here, used to convert 6-methoxy 1-tetralone (I; $X=CH_2$) into (±)-estrone methyl ether and its 8α-isomer[1,2] and the last two compounds into the corresponding 17β-ols[2,8]. Appropriate members of the series are currently being examined by X-ray crystallography[9].

Reduction of the alcohol (VIII) with lithium and ethanol in liquid ammonia, gave (±)-3-methoxy-6-oxa-estra-2,5(10)-dien-17β-ol, m.p. 166–171°, ν_{max} 3484, 1701 and 1672 cm^{-1}, which was converted by methanolic hydrochloric acid into (±)-19-nor-6-oxatestosterone (XI; $R=H$), m.p. 199–201°, λ_{max} 259 mμ (ε 21,800), ν_{max} 3448, 1639 and 1600 cm^{-1}. Oppenauer oxidation of the former alcohol afforded (±)-3-methoxy-6-oxaestra-2,5(10)-dien-17-one, m.p. 141–149°, ν_{max} 1754, 1695 and 1667 cm^{-1}, which, after treatment with the lithium acetylide-ethylenediamine complex in dimethyl-acetamide[10] and acid hydrolysis, yielded the (±)-6-oxa-estrenone (XI; $R=C:CH$), m.p. 229–232°, λ_{max} 259 mμ (ε 22 100), ν_{max} 3390, 3205, 1639 and 1592 cm^{-1}.

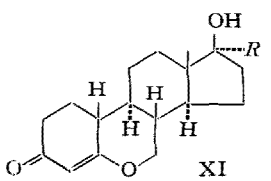
Analogously, the quinolone (I; $X=C_6H_5SO_2N$) was converted by way of the alcohol (II; $X=C_6H_5SO_2N$), m.p. 90–94°, ν_{max} 3509, 1351, 1330, 1176, 1163 and 1147 cm^{-1}, and the dione (III; $X=C_6H_5SO_2N$), m.p. 112–116°, λ_{max} 240–270 mμ (plateau) (ε 17 000), ν_{max} 1767, 1724, 1337, 1316 and 1156 cm^{-1}, to the aza-estrapentaene (IV; $X=C_6H_5SO_2N$)[11], m.p. 169–173°, λ_{max} 255 and 319 mμ (ε 17,500 and 21,700), ν_{max} 1745 1348, and 1171 cm^{-1}. Hydrogenation of the pentaene in benzene over palladized strontium carbonate gave the tetraene (V; $C_6H_5SO_2N$), m.p. 171–176°, λ_{max} 242 and 279 mμ (ε 21 200 and 17 200),



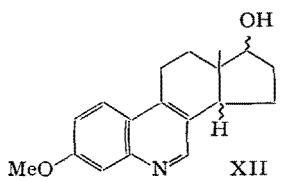
(VII; $R^1+R^2=O$)
(VIII; $R^1=OH$; $R^2=H$)



(XI; $R^1+R^2=O$)
(X; $R^1=OH$; $R^2=H$)



XI



XII

which, with sodium borohydride in methanol-tetrahydrofuran, gave the corresponding 17-ol, but both compounds have resisted conversion into the corresponding (±)-6-aza-estra-1,3,5(10)-trienes. The ketone failed to rearrange to the $\Delta^{9(11)}$-isomer in refluxing ethanolic hydrochloric acid, and the alcohol, with lithium in liquid ammonia in the presence or absence of ethanol, gave an alcohol formulated as the (±)-6-aza-dihydroequilenin (XII), m.p. 188–193°, λ_{max} 234, 329 and 341 mμ (ε 52 500, 4850 and 5100). Formally similar fission-aromatization reactions are induced by refluxing the ketone (V; $X=C_6H_5SO_2N$) in mixtures of hydrochloric and acetic acid, red phosphorus and hydriodic acid, and lithium aluminium hydride and tetrahydrofuran. BURCKHALTER and WATANABE[12] have disclosed alternative total syntheses of (±)-6-aza-equilenin derivatives.

Biological activities. The alcohol (X) has 66% of the activity of estradiol in a 3-day rat blood-lipid depressing test[13] but has only 0.01% of the activity of estrone in a mouse uterine growth test[14]. The alcohol (XI; $R=C:CH$) has 3% of the activity of progesterone in the Clauberg test[15] as compared to 10% for 17α-ethynyl-17β-hydroxy-estr-4-en-3-one[16]. This work will be reported in full elsewhere[17].

Zusammenfassung. Es wird über die Totalsynthese von verschiedenen Derivaten des (±)-6-Oxa- und Aza-Östrons und die Umwandlung von (±)-17β-Oxy-3-methoxy-6-oxa-östratrien-1,3,5[10] zu Verbindungen der (±)-19-Nor-6-oxa-testosteron-Klasse berichtet. Die biologische Wirksamkeit der Glieder in der 6-Oxa-Reihe wird beschrieben.

H. SMITH, G. H. DOUGLAS, and C. R. WALK

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[9] In collaboration with Professor T. H. DOYNE, Villanova (Pennsylvania).

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[17] *Acknowledgments.* We thank Dr. G. A. HUGHES and Dr. G. R. WENDT for discussions, Drs. F. BERNHART, R. A. EDGREN, and R. TOMARELLI, and their staff (Nutrition and Endocrinological Department, Wyeth Laboratories Inc.) for the biological data, and Dr. D. HARTLEY for advice on interpreting the proton nuclear magnetic resonance spectra.