# Steroids XXIII. Synthesis of Some Ring A-Fused Heterocyclic Steroids

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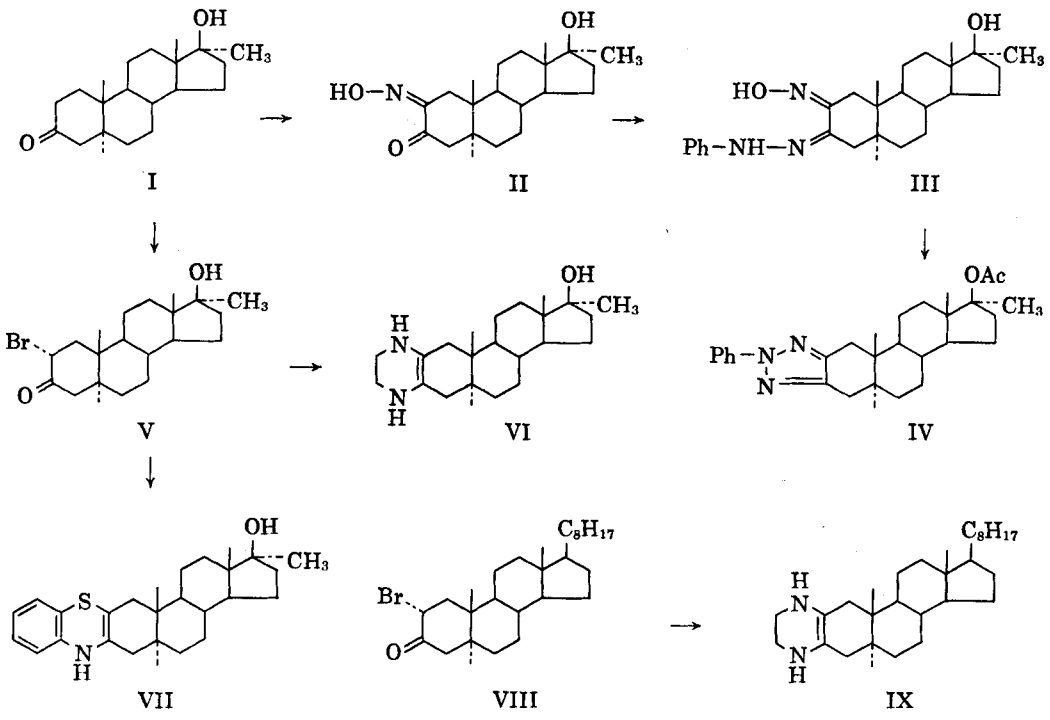
**Several ring A-fused heterocyclic steroids, which were prepared as potential anabolic agents, are described. These include steroids with triazole, tetrahydropyrazine, and benzothiazine rings fused onto positions 2,3 of a derivative of methyltestosterone.**

THE DISCOVERY by Clinton and his co-workers (1), that pyrazolo[*c*-3,2]-17α-methyl-5α-androstan-17β-ol has pronounced anabolic but only weak androgenic activity has led to the synthesis of many compounds having a heterocyclic ring fused to carbons 2 and 3 of the steroid nucleus. Ring A-fused heterocyclic compounds prepared as potential anabolic agents include various isoxazole (2, 3), pyrimidine (2, 4, 5), thiazole (2, 6), triazole (7), imidazole (5), oxazole (5), and pyrazole (8) derivatives.

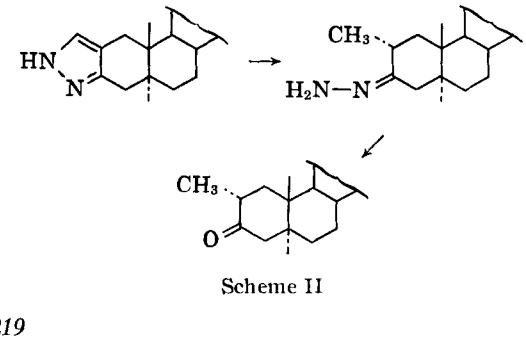
The following ring A-fused heterocyclic compounds were prepared in the hope that they would possess anabolic activity: 2′-phenyl-v-triazolo[*d*-2,3]-17β-acetoxy-17α-methyl-5α-androstane (IV), 1′,2′,3′,4′-tetrahydropyrazino-[*e*-2,3]-17α-methyl-5α-androst-2-en-17β-ol (VI), and 4H-1,4-benzothiazino[*b*-2,3]-17α-methyl-5α-androst-2-en-17β-ol (VII). (Scheme I.)

In addition, one of the intermediates used in the synthesis of IV—namely, 17α-methyl-2-oximino-5α-androstan-17β-ol-3-one (II)—is of interest as a potential anabolic agent since it is an isostere of 2-hydroxymethylene-17α-methyl-5α-androstan-17β-ol-3-one, a compound known to have a favorable anabolic–androgenic ratio (9).

The observation by de Ruggieri and his group




Scheme I




Scheme II

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(10) that 2α,17α-dimethyl-5α-androstan-17β-ol-3-one is recovered from the urine following the administration of pyrazolo[*c*-3,2]-17α-methyl-5α-androstan-17β-ol[1] has led these workers to postulate the metabolic sequence shown in Scheme II.

On the assumption that the anabolic activity of the pyrazolo compound might be due to the 2α-methyl-3-hydrazone metabolite, de Ruggieri and his co-workers prepared a series of $C_3$ hydrazino steroids. These compounds showed remarkable anabolic activity and had only limited androgenic activity. One such compound, 2α,17α-dimethyl-5α-androstan-17β-ol-3,3′-azine,[2] is in clinical use in Europe. In the light of these findings, an intermediate synthesized in the preparation of IV—namely, 17α-methyl-2-oximino-3-phenylhydrazono-5α-androstan-17β-ol (III)—may possess anabolic activity.

The starting material for the preparation of the ring A-fused steroids was 17α-methyl-5α-androstan-17β-ol-3-one (1). Treatment of this ketone with potassium *tert*-butoxide and one equivalent of freshly distilled *n*-butyl nitrite gave 17α-methyl-2-oximino-5α-androstan-17β-ol-3-one (II) in a 32% yield. Treatment of II with phenylhydrazine gave 17α-methyl-2-oximino-3-phenylhydrazono-5α-androstan-17β-ol (III) in a 71% yield. Cyclization of III, using acetic anhydride as the acid catalyst, gave 2′-phenyl-v-triazolo[*d*-2,3]-17β-acetoxy-17α-methyl-5α-androstane (IV) in a 69% yield.

Bromination of I with pyridine hydrobromide perbromide gave 2α-bromo-17α-methyl-5α-androstan-17β-ol-3-one (V) in a 41% yield. Treatment of V with ethylenediamine at room temperature resulted in the formation of 1′,2′,3′,4′-tetrahydropyrazino[*e*-2,3]-17α-methyl-5α-androst-2-en-17β-ol (VI) in 45% yield. A related structure, 1′,2′,3′,4′-tetrahydropyrazino[*e*-2,3]-5α-cholest-2-ene (IX), was prepared in a similar manner from 2α-bromo-5α-cholestan-3-one, in 82% yield. Infrared spectra of these compounds indicated that the double bond was between positions 2 and 3 and not exocyclic to position 3. In this position, the double bond is endocyclic to two six-membered rings, while in the alternate structure it would be exocyclic to ring A. The former situation is more favorable thermodynamically. Attempted reduction of VI with lithium aluminum hydride gave only starting material, providing chemical support for the assigned structure. The enamine structure would be resistant to hydride reduction whereas a C=N double bond would have been reduced.

It is known that α-halo ketones, such as bromoacetophenone, react with *o*-aminobenzenethiol to yield benzothiazines (11). Treatment of 2α-bromo-17α-methyl-5α-androstan-17β-ol-3-one (V) with *o*-aminobenzenethiol gave 4H-1,4-benzothiazino[*b*-2,3]-17α-methyl-5α-androst-2-en-17β-ol (VII) in 42% yield.

Structural assignments were made on the basis of analyses, spectra, and methods of synthesis.

Samples have been submitted to several laboratories for biological study. III, VI, and IX have been examined for antimicrobial properties in the authors' laboratory and were found inactive.

[1] Marketed as Winstrol.
[2] Marketed as Roxilon by Ormonoterapia Richter s.P.a., Milan, Italy.

## EXPERIMENTAL[3]

**17α-Methyl-2-oximino-5α-androstan-17β-ol-3-one (II).**—To a solution of 2.3 Gm. (0.06 *M*) of potassium metal in 150 ml. of *tert*-butyl alcohol, there was added 9.1 Gm. (0.03 *M*) of 17α-methyl-5α-androstan-17β-ol-3-one (I) (6). The solution was stirred under a nitrogen atmosphere at room temperature for 1 hr. After the dropwise addition of 4.0 ml. (0.035 *M*) of freshly distilled *n*-butyl nitrite, the reaction mixture was stirred 2 additional hr. and allowed to stand overnight at room temperature. There was then added 300 ml. of ether and the resulting precipitate collected by filtration. The filtrate was extracted two times with 100-ml. portions of water. The aqueous extracts were added to a solution of the above precipitate in 300 ml. of water. The combined aqueous extracts were washed twice with 100-ml. portions of methylene chloride. There was then added to the aqueous solution 20 ml. of acetic acid in 30 ml. of water. The resulting precipitate was collected by filtration and recrystallized from methanol to yield 3.2 Gm. (32%) of II as fine pale-yellow crystals, m.p. 263–265°. $[\alpha]_D^{25}$ +49.8° (c, 0.53 $CHCl_3$); $\lambda_{max.}^{KBr}$ 2.72, 5.81, and 6.18 μ.

*Anal.*—Calcd. for $C_{20}H_{31}NO_3$: C, 72.03; H, 9.37; N, 4.20. Found: C, 71.65; H, 9.53; N, 4.29.

**17α-Methyl-2-oximino-3-phenylhydrazono-5α-androstan-17β-ol (III).**—To a solution of 1.0 Gm. (0.003 *M*) of II in 25 ml. of ethanol were added 5 drops of acetic acid and 1.0 ml. of phenylhydrazine. After the solution had been refluxed for 1 hr., water was added until a precipitate began to appear. The reaction vessel was cooled, and the crude product was collected by filtration and recrystallized from methanol to obtain 0.90 Gm. (71%) of III as yellow-green needles, m.p. 261–262°; $\lambda_{max.}^{KBr}$ 2.72, 6.0–6.1, 6.21, and 6.55 μ.

*Anal.*—Calcd. for $C_{26}H_{37}N_3O_2$: C, 73.72; H 8.80; N, 9.92. Found: C, 73.70; H, 8.70; N 9.73.

**2′-Phenyl-v-triazolo[d-2,3]-17β-acetoxy-17α-methyl-5α-androstane (IV).**—III (0.75 Gm.) was refluxed 1 hr. in 20 ml. of acetic anhydride. The reaction mixture was poured into 150 ml. of water, and 50 ml. of 10% potassium hydroxide was added. A brown oil appeared which gradually solidified as the solution cooled. The solid was filtered and recrystallized from acetone–water to yield 0.55 Gm. (69%) of IV as tan platelets, m.p. 203.5–204.5°. $[\alpha]_D^{25}$ +51.7° (c, 1.1 $CHCl_3$); $\lambda_{max.}^{EtOH}$ 293 mμ (log ε 4.29); $\lambda_{max.}^{CHCl_3}$ 5.78, 6.21, and 6.68 μ.

*Anal.*—Calcd. for $C_{28}H_{37}N_3O_2$: C, 75.13; H, 8.33; N, 9.39. Found: C, 74.54; H, 8.38; N, 9.66.

**1′,2′,3′,4′-Tetrahydropyrazino[e-2,3]-17α-methyl-5α-androst-2-en-17β-ol (VI).**—2α-Bromo-17α-methyl-5α-androstan-17β-ol-3-one (V) (6) (2.0 Gm., 0.005 *M*) and 2.0 ml. of ethylenediamine were dissolved in 100 ml. of 1:1 chloroform–ethanol and kept at room temperature for 5 days. The residue obtained by evaporating the solvent was suspended in 80% ethanol and filtered. Thus, 0.8 Gm. (45%) of VI was obtained as a light tan powder, m.p. 209.5–

[3] All melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus. Infrared spectra were prepared on a Perkin-Elmer Infracord recording spectrophotometer. Analyses were obtained from Weiler and Strauss, Oxford, England.

210°. $[\alpha]_D^{25}$ +152° (c, 1.1 $CHCl_3$); $\lambda_{max.}^{CHCl_3}$ 2.72 and 6.21 $\mu$.

*Anal.*—Calcd. for $C_{22}H_{36}N_2O$: C, 76.69; H, 10.53; N, 8.13. Found: C, 76.98; H, 10.15; N, 8.31.

**4H-1,4-Benzothiazino[b-2,3]-17α-methyl-5α-androst-2-en-17β-ol (VII).**—2α-Bromo-17α-methyl-5α-androstan-17β-ol-3-one (V) (6) (2.0 Gm., 0.005 *M*) was dissolved in 200 ml. of refluxing ethanol through which a stream of nitrogen was passed. After the addition of 2.0 ml. of freshly distilled *o*-aminobenzenethiol, the solution was refluxed 1 hr. and allowed to stand overnight at room temperature. The reaction mixture was concentrated by distillation under nitrogen, cooled, and the resulting yellow-white precipitate collected by filtration. The product was crystallized from methanol to yield 0.9 Gm. (42%) of VII as pale yellow crystals, m.p. 215–219.5°. $[\alpha]_D^{25}$ −7.9° (c, 1.0 $CHCl_3$); $\lambda_{max.}^{CHCl_3}$ 2.72, 2.90, 6.30, and 6.81 $\mu$.

*Anal.*—Calcd. for $C_{26}H_{35}NOS$: C, 76.24; H, 8.61; N, 3.42; S, 7.83. Found: C, 76.22; H, 8.78; N, 3.48; S, 7.85.

**1′,2′,3′,4′-Tetrahydropyrazino[e-2,3-]5α-cholest-2-ene (IX).**—2α-Bromo-5α-cholestan-3-one (VIII) (6) (7.0 Gm., 0.015 *M*) and 7.0 ml. of ethylenediamine were dissolved in 200 ml. of 1:1 chloroform–ethanol and kept at room temperature for 7 days. The reaction mixture was evaporated to dryness and the solid residue was suspended in 50 ml. of methanol and filtered to obtain 5.3 Gm. (82%) of IX as pale yellow crystals, m.p. 157–159°. $[\alpha]_D^{25}$ +142° (c, 1.1 $CHCl_3$); $\lambda_{max.}^{CHCl_3}$ 3.00–3.10 and 6.21 $\mu$.

*Anal.*—Calcd. for $C_{29}H_{50}N_2$: C, 81.62; H, 11.81; N, 6.57. Found: C, 82.13; H, 11.80; N, 6.89.

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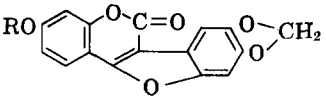
# Synthesis of 7-Hydroxy-5′,6′-methylenedioxy-benzofurano (3′,2′:3,4) Coumarin (Medicagol)

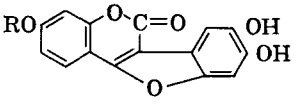
By LEONARD JURD

**Medicagol (I*a*) has been synthesized by hydrogen peroxide oxidation of 3-methoxy-6,7-methylenedioxy-2′,4′-dihydroxyflavylium chloride (V*b*).**

MEDICAGOL, 7-hydroxy-5′,6′-methylenedioxybenzofurano (3′,2′:3,4) coumarin (I*a*), co-occurs with the estrogenic benzofuranocoumarin, coumestrol (1), in alfalfa (2). A synthesis of medicagol methyl ether (I*b*) has now been reported by Fukui *et al.* (3). Modifying Wanzlick's elegant wedelolactone synthesis (4), these authors oxidized a mixture of 4-hydroxy-7-methoxycoumarin and catechol with potassium ferricyanide to give II*a*. This was methylenated to yield I*b*. The Japanese authors reported that attempts to methylenate selectively the trihydroxy compound II*b* to give I*a* were abortive. In their synthetic approach, Livingston *et al.* (2) also synthesized II*b* by Wanzlick's method. They found that methylenation of II*b* gave a mixture of products from which, by countercurrent separation and sublimation, a small quantity of medicagol was isolated (in approximately 5% yield). The recent publication of the Japanese work prompts the report of synthesis of medicagol (and its methyl ether) which is less equivocal than the above. The details of this synthesis, furthermore, may be of some use in devising possible approaches to erosnin III, a constituent of the seeds of yam beans (*Pachyrhizus erosus*) (5), and to pisatin (IV), an antifungal substance in garden peas (*Pisum sativm*) (6).




I*a*, R = H
I*b*, R = Me




II*a*, R = Me
II*b*, R = H

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