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# Synthesis and Antifertility Activity of Some Oximinoandrostenes

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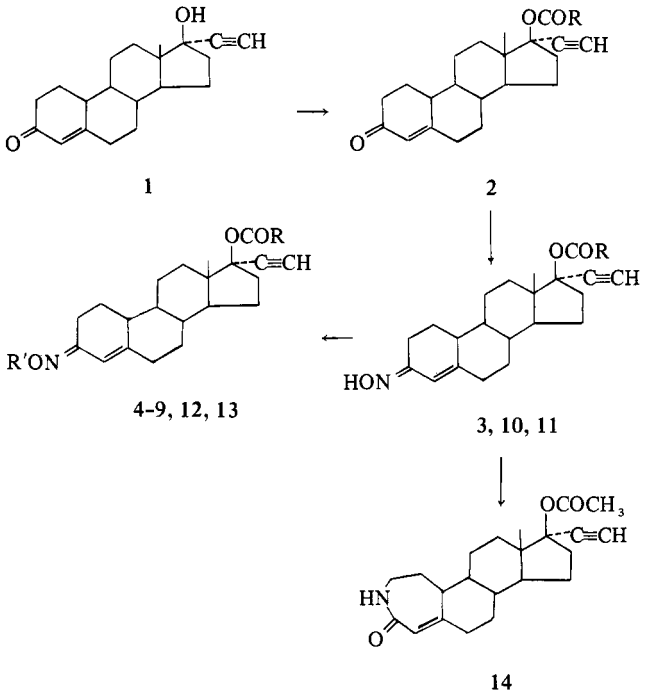
A number of oximino and 3-aza-*A*-homoandrostenes were synthesized from 17α-ethynyl-19-nortestosterone and evaluated for antifertility activity. Based on relative potency and Clauberg responses, 17β-acetoxy-19-norandrost-4-en-3-one oxime was selected for mechanism of action studies and human trials.

As part of a continuing program directed toward the development of new and novel progestational agents, 3-aza-*A*-homo steroids have been the object of considerable interest in our laboratory.[1-4] The rationale for this work and probable mode of action of the specific compounds have been described earlier.[3]

We chose 17α-ethynyl-19-nortestosterone (norethindrone) for our molecular modifications because it had exhibited antifertility activity in both animals and humans. The 17β-hydroxyl group was acylated by the known procedures[5-7] and converted to the oximino compounds (Table I) by the method described in the Experimental Section. Beckmann rearrangement of the free oxime gave the desired 3-aza-17α-ethynyl-17β-acetoxy-19-nor-*A*-homoandrost-4a-en-4-one (Scheme I).

Scheme I

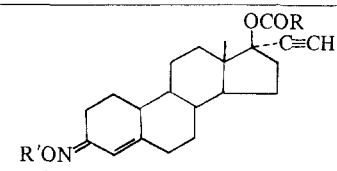



The progestational response of these compounds was determined by the Clauberg test[8] after oral administration and the endometrial response was scored according to the index of McPhail.[9] Table II presents the response obtained with all the compounds. Norethindrone **1** and its acetate **2** are included for comparative purposes. On a milligram basis it appears that **2** is about 2.5 times as potent as the parent compound **1**. However, when **2** is converted to an oxime the activity drops 2.5-fold and is comparable to **1**. Most of the other oximino steroids do not increase progestational potency probably due to the fact that bulky substitutions at C-3 and C-17 prevent adsorption to the receptor. An exception to this is **8**. The THP ether group probably undergoes spontaneous hydrolysis to **3** which, in fact, is responsible for the observed activity.

A strikingly dissimilar activity of a ketone and its oximino derivative was observed when the compounds were tested for their antilittering activity. In this test the compound is administered in the diet or by gavage for 7 days to both male and female rats with sexes segregated. The treatment is continued for 15 days during which time the rats are permitted to cohabit freely. The sexes are once again segregated and are observed for 21 days with no treatment. A control group is similarly treated except that the compound is not administered. The females from both the control and the treated groups are observed for pregnancies and the size of litters. A minimum effective dose (MED) is then computed and is defined as the amount of compound in milligrams per kilogram per day which completely suppresses the production of litters.

The data thus obtained on compounds **1-14** are tabulated in Table III. The relative potency of the steroids is expressed in terms of the standard, norethindrone **1**. As observed earlier in the Clauberg test, an introduction of an acetate group at the C-17 position increases the activity by eightfold (compound **2**). However, contrary to the progestational data the conversion of the ketone to an oximino derivative (**3-13**) markedly enhances the antifertility activity. A 137-fold increase over norethindrone suggests that the mechanism of action of these compounds is vastly different. The data in Table III also suggest that there may be a different receptor involved and that the sterochemical requirements of a steroid to bind are different from those required to elicit progestational response. The oximino steroids may be acting postcoitally.

**Table I. 3-Oximinoandrostenes**




| Compd[a] no. | R | R' | Recrystn solvent[b] | Mp, °C | Formula[c] |
|---|---|---|---|---|---|
| 3 | $CH_3$ | H | W-M | 229-230 | $C_{22}H_{29}NO_3$ |
| 4 | $CH_3$ | $COCH_3$ | H | 142-144 | $C_{24}H_{31}NO_4$ |
| 5 | $CH_3$ | $COC_2H_5$ | H | 152-154 | $C_{25}H_{33}NO_4$ |
| 6 | $CH_3$ | CO-*i*-$C_4H_9$ | H | 150-151 | $C_{28}H_{35}NO_4$ |
| 7 | $CH_3$ | $CO(CH_2)_4CH_3$ | H | 102-104 | $C_{28}H_{39}NO_4$ |
| 8 | $CH_3$ | 2'-THP | MCl-H | 172-174 | $C_{27}H_{37}NO_4$ |
| 9 | $CH_3$ | $CH_2COOH$ | H | 236-237 | $C_{24}H_{31}NO_5$ |
| 10 | $C_2H_5$ | H | W-M | 100-101 | $C_{23}H_{31}NO_3$ |
| 11 | $(CH_2)_4CH_3$ | H | W-M | 75-76 | $C_{26}H_{37}NO_3$ |
| 12 | $(CH_2)_4CH_3$ | $COCH_3$ | M | 110-112 | $C_{28}H_{39}NO_4$ |
| 13 | Adamant | H | MCl-M | 191-193 | $C_{31}H_{41}NO_3$ |

[a] All compounds were characterized by their ir and uv spectra. [b] H, hexane; M, methanol; MCl, methylene chloride; W, water. [c] Acceptable C, H, and N values were obtained for all compounds.

**Table II.** Progestational Response in Rabbit Uteri to a Total of 1 mg of Various Steroids

| Compd no. | McPhail index | Compd no. | McPhail index |
|---|---|---|---|
| 1 | 2.1 | 8 | 1.0 |
| 2 | 3.2 | 9 | 2.8 |
| 3 | 2.0 | 10 | 1.7 |
| 4 | 2.0 | 11 | 0.5 |
| 5 | 1.5 | 12 | |
| 6 | 2.2 | 13 | 0 |
| 7 | | 14 | 0.2 |

**Table III.** *Inhibition of Fertility in Rats*

| Compd no. | MED, mg/kg | Rel potency |
|---|---|---|
| 1 | 13.7 | 1 |
| 2 | 1.8 | 8 |
| 3 | 0.1 | 137 |
| 4 | 0.1 | 137 |
| 5 | 0.4 | 34 |
| 6 | 0.4 | 34 |
| 7 | 0.3 | 46 |
| 8 | 0.2 | 68 |
| 9 | 0.7 | 20 |
| 10 | 0.1 | 137 |
| 11 | 0.1 | 137 |
| 12[a] | 0.2 | 68 |
| 13 | 0.2 | 68 |
| 14 | 2.2 | 6 |

[a] IG administration.

Hence, one of the oximino compounds (**3**) was studied for its postcoital activity. Here the female rats of the Wistar strain are given the compound by gavage on specific days of gestation after sperm are observed in the vagina. The rats are sacrificed and the uteri are examined for implantation and resorption sites. In Table IV day 1 is the day on which sperm is observed in vaginal washings.

The data in Table IV suggest that compound **3** was most efficacious at dose levels of 10 and 5 mg/kg on day 2 and 3 of pregnancy. Unpublished data from our laboratories indicate that the postcoital antifertility action of the compound is due to lytic degeneration of zygotes and/or their rapid expulsion from the reproductive tract.

McQuarrie and coworkers[10] performed clinical investigation with compound **3**. In their evaluation of safety and efficacy they report that **3** is well tolerated in humans up to a dose of 100 mg dq. At 1-mg dose they found no pregnancy in 30 treatment cycles of therapy.

**Table IV.** Postcoital Activity of Compound 3

| Dose, mg/kg | Day of administrations | Pregnant/ total | Implantations | |
|---|---|---|---|---|
| | | | Normal | Resorbed |
| 10 | 1 | 6/10 | 25 | 3 |
| 10 | 2 | 0/5 | 0 | 0 |
| 10 | 3 | 0/5 | 0 | 0 |
| 10 | 4 | 1/5 | 7 | 2 |
| 10 | 5 | 1/5 | 0 | 11 |
| 5 | 2 | 1/5 | 0 | 2 |
| 5 | 3 | 0/10 | 0 | 0 |
| 1 | 2 | 4/5 | 30 | 3 |
| 2 | 3 | 4/5 | 12 | 2 |
| 20 | 1 | 2/5 | 0 | 12 |
| 40 | 1 | 1/5 | 0 | 1 |

## Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The uv and ir data were obtained on Cary Model II and Beckmann IR-5 spectrophotometers, respectively. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements (Table I), analytical results obtained for these elements were within ±0.4% of the theoretical value.

**General Method Oximes. 17α-Ethynyl-17β-acetoxy-19-norandrost-4-en-3-one Oxime (3).** A solution of 2.0 g of 17α-ethynyl-17β-acetoxy-19-norandrost-4-en-3-one, 10 ml of pyridine, and 1.0 g of hydroxylamine hydrochloride was heated on a steam bath for 0.5 hr. The mixture was poured into a large amount of ice and water and the solid thus separated was collected by filtration. It was recrystallized from methanol–water to give 1.6 g (78%) of 17α-ethynyl-17β-acetoxy-19-norandrost-4-en-3-one oxime, mp 229–230°.

**3-Aza-17α-ethynyl-17β-acetoxy-19-nor-*A*-homoandrost-4a-en-4-one (14).** To a solution of 19.5 g of 17α-ethynyl-17β-acetoxy-19-norandrost-4-en-3-one oxime in 600 ml of purified dioxane there was added 10 ml of thionyl chloride. The mixture was stirred at room temperature for 1.5 hr and poured into a large amount of ice and water. The excess acid was neutralized with sodium bicarbonate and the solution was extracted with a total of 1000 ml of methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and filtered. The filtrate was stirred for 3 hr with 100 g of IR-45 amberlite and refiltered. The filtrate was evaporated to give an oil which could be recrystallized from hexane–benzene (3:1). Final recrystallization from ethyl acetate gave 4.1 g (22%) of 3-aza-17α-ethynyl-17β-acetoxy-19-nor-*A*-homoandrost-4a-en-4-one: mp 221–223°; $\lambda_{max}^{EtOH}$ 220 nm; $\lambda_{max}^{KBr}$ 2.90, 3.01, 5.75, and 6.04 μ. *Anal.* ($C_{22}H_{29}NO_3$), C, H, N.

**General Method Oximino Esters. *N*,17β-Diacetoxy-17α-ethynyl-19-norandrost-4-en-3-one Oxime (4).** A solution containing 3.0 g of 17α-ethynyl-17β-acetoxy-19-norandrost-4-en-3-one oxime in 5.0 ml of pyridine was treated with 9.0 ml of acetic anhydride and stirred at room temperature for 15 min. The mixture was poured

into a large amount of ice and water and neutralized with ammonium hydroxide. The solid thus separated was collected by filtration. It was dried and recrystallized from hexane to give *N*,17β-diacetoxy-17α-ethynyl-19-norandrost-4-en-3-one oxime: mp 142–144°; $\lambda_{max}^{EtOH}$ 244 nm; $\lambda_{max}^{KBr}$ 3.09, 4.17, 5.68, and 5.72 μ. *Anal.* ($C_{24}H_{31}NO_4$) C, H, N.

**3-(*O*-Carboxymethyl)-17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one Oxime (9).** 17α-Ethynyl-17β-acetoxy-19-norandrost-4-en-3-one oxime (2.0 g) was dissolved in 10 ml of pyridine and treated with 1.0 g of carboxymethoxylamine hemihydrochloride. The mixture was heated on a steam bath for 0.5 hr and poured into a large amount of ice and water. The solid material was collected by filtration and recrystallized from methanol–water to give 3-(*O*-carboxymethyl)-17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one oxime: mp 236–237°; $\lambda_{max}^{EtOH}$ 248 mμ; $\lambda_{max}^{KBr}$ 3.08, 4.71, 5.65, and 5.89 μ. *Anal.* ($C_{24}H_{31}NO_5$) C, H, N.

***N*-(2′-Tetrahydropyranyloxy)-17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one Oxime.** 17β-Acetoxy-17α-ethynyl-19-norandrost-4-en-3-one oxime (0.5 g) was treated with 20.0 ml of dry benzene, 0.2 g of *p*-toluenesulfonic acid, and 10 ml of dihydropyran and was stirred at room temperature for 0.5 hr. The mixture was treated with a large amount of ice and water followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated. Repeated crystallization from methylene chloride–hexane gave *N*-(2′-tetrahydropyranyloxy)-17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one oxime: mp 172–174°; $\lambda_{max}^{EtOH}$ 244 nm; $\lambda_{max}^{KBr}$ 3.10, 4.75, and 5.75 μ. *Anal.* ($C_{27}H_{37}NO_4$) C, H, N.

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# Antimetabolites of Coenzyme Q. 16. New Alkylmercaptoquinones Having Antimalarial Curative Activity†

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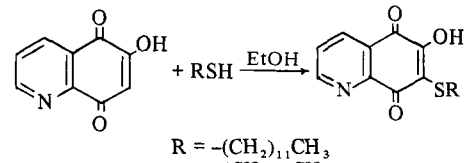
Coenzyme $Q_8$ is apparently indispensable in the metabolism of *Plasmodium*. Based on this knowledge, a new class of lipoidal 5,8-quinolinequinones and a new 1,4-naphthoquinone have been synthesized as potential inhibitors of the biosynthesis and/or function of coenzyme $Q_8$ in the metabolism of *Plasmodium* and as potential antimalarials. Four new 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones and the new 3-alkylmercapto-2-hydroxy-1,4-naphthoquinone have been synthesized and tested for antimalarial activity against *Plasmodium berghei* in the mouse. Each of the new 5,8-quinolinequinones showed marked *in vivo* antimalarial activity without acute toxicity; two of these compounds were curative, and one of these two was completely curative. The 1,4-naphthoquinone derivative exhibited only marginal antimalarial activity in the murine assay. Three alkylmercapto-5,8-quinolinequinones and the alkylmercapto-1,4-naphthoquinone were also tested for antimalarial activity against *Plasmodium gallinaceum* in the chick. One quinolinequinone was somewhat curative, but the 1,4-maphthoquinone exhibited no activity in this avian test. The alkylmercapto-5,8-quinolinequinones, represented by three of the four compounds, and the alkylmercapto-1,4-naphthoquinone showed marked inhibition of both NADH- and succinoxidase mitochondrial CoQ-enzyme systems.

The background research for this work has recently been described.[1] In previous papers[1-3,‡] new 5,8-quinolinequinones and 1,4-naphthoquinones have been synthesized and tested for antimalarial activity against *Plasmodium berghei* in the mouse and for inhibition of mitochondrial NADH- and succinoxidase systems. This paper describes the syntheses and biological activities of four new 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones and one new 3-alkylmercapto-2-hydroxy-1,4-naphthoquinone. In view of the promising antimalarial activity of some of our recently synthesized 5,8-quinolinequinone derivatives,[1,2] it was of interest to synthesize 5,8-quinolinequinones and a 1,4-naphthoquinone with sulfur-containing side chains. The side chains were made long enough to impart lipoidal character to the molecule and in an attempt to design molecules which could function as antimetabolites of the highly lipoidal coenzyme Q. 7-*n*-Octadecylmercapto-6-hydroxy-5,8-quinolinequinone, the most active *in vivo* derivative, was totally curative in the mouse assay (5/5 cures at both 320 and 640 mg/kg) without toxicity.

**Organic Syntheses.** The synthesis of the 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones was accomplished by treating 6-hydroxy-5,8-quinolinequinone[4,5] in ethanol with the appropriate alkyl mercaptan as depicted in Scheme I.

**Scheme I**




R = $-(CH_2)_{11}CH_3$
$-(CH_2)_{13}CH_3$
$-(CH_2)_{15}CH_3$
$-(CH_2)_{17}CH_3$

Dodecyl, tetradecyl, hexadecyl, and octadecyl mercaptans were chosen because of their ready availability and because they provided side-chain lengths near the optimal length

†Coenzyme Q. 153.

‡C. M. Bowman, F. S. Skelton, T. H. Porter, and K. Folkers, unpublished results.