CHEMICAL SYNTHESIS AND BIOASSAY OF ANORDRIN AND DINORDRIN I AND II

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SUMMARY

The chemical synthesis of 2α,17α-diethynyl-A-nor-5α-androstane-2β,17β-diol dipropionate (Anordrin) and the corresponding diacetate is reported. Similarly, the preparation of the 2α,17α-diethynyl-A-nor-5α-estrane-2β,17β-diol, its diacetate and dipropionate (Dinordrin I), along with the corresponding 2β-epimer (Dinordrin II) from 17β-hydroxy-A-nor-5α-estran-2-one is described.

In rat uterotrophic activity bioassay, the slope of ethynylestradiol differed significantly from the slopes of the other three compounds, thus vitiating potency estimates with this reference compound. Dinordrin I was 20 times more potent than Anordrin and considerably more potent than Dinordrin II. The single-dose oral antifertility effect in rats generally paralleled uterotrophic activity. Immediate postovulatory contraceptive effectiveness was assessed in adult cycling female baboons given two doses daily for 4 days. Both Anordrin and Dinordrin I showed antifertility activity worthy of further study. Moreover, a definite luteolytic effect, with depression of both plasma estrogen and progesterone levels, was observed with these two steroids.

INTRODUCTION

As early as in 1962, Pincus et al. (1-3) reported the implantation inhibitor properties exhibited by some nor-androstanes. Since that time, other reports have appeared (4-7) on antifertility aspects of several steroids belonging to this class of compounds.

The biological properties associated with these nor-steroids (Figure 1) have seen a revival of interest following recent publications by Chinese investigators (8-9) who reported that a significant antifertility activity is associated with the dipropionate of 2α,17α-diethynyl-A-nor-5α-androstane-2β,17β-diol, existing probably as a mixture of isomers at position 2; i.e., a 95:5 mixture of (1a) and (2) ("Anordrin"). The individual isomers have not been prepared and tested for the possibility of differences in biological potency (4).

Chemical Synthesis

Following the report by the Chinese scientists, the preparation of the pure 2α,17α-diethynyl substance (1a) has been undertaken by a known procedure (10).

The diethynyl derivative (1b) has been obtained in the pure form by treatment of the A-nor-5α-androstane-2,17-dione (10) with an excess of lithium acetylide-ethylenediamine complex in dimethylsulfoxide (DMSO) (11), followed by chromatography and crystallization. Esterification of diol (1b) with propionic anhydride in pyridine solution then afforded the dipropionate (1a). The corresponding diacetate (1c) has also been prepared by esterification of the known diol (1b) (10) with acetic anhydride.

In view of the potent antifertility properties reported for "Anordrin" (8-9), its dinor counterpart (3a) as well as the corresponding diacetate (3b) have also been synthesized.

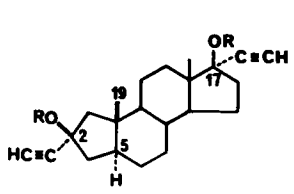
The starting material for the preparation of these dinor-steroids was 19-nor-testosterone, which has been converted to the 2-keto-dinor-steroid (4) by conventional techniques (12). Oxidation of the 17-hydroxyl group in the intermediate (4) provided the corresponding 2,17-diketo-dinor-steroid, which was treated with an excess of lithium acetylide-ethylenediamine complex to afford a 3:2 mixture of the 2α-ethynyl compound (3c) and its 2β-epimer (5a), separated by preparative thin layer chromatography (TLC).

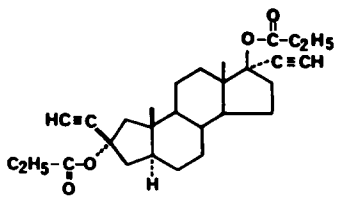
Esterification of the tertiary hydroxyl groups of diols (3c) and (5a) with propionic anhydride provided the dipropionates (3a) ("Dinordrin I") and (5b) ("Dinordrin II"). Similarly, treatment of diols (3c) and (5a) with acetic anhydride furnished the corresponding diacetates (3b) and (5c).

Although there is no detailed mention of the steroids (3a,b,c) and (5a,b,c) in the chemical literature, a report was published on some biological properties associated with the diol (3c) (4,13).

Experimental

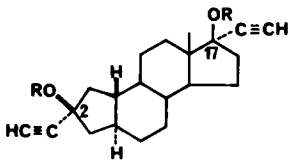
Microanalyses were performed by the CNRS, Lyon. Melting points were determined with a Büchi apparatus. Infrared (IR) spectra were determined in chloroform solution on a Beckman Acculab 4 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Jeol PMX-60 spectrometer in deuteriochloroform solution, using tetramethylsilane (TMS) as an internal reference (s, singlet; d, doublet; t, triplet). Coupling constants J are accurate to ± 1 Hz. Mass spectra (MS) were recorded on an MS-30 AEI mass spectrometer at 70 ev using a direct insertion probe. Unless stated otherwise, optical rotations were determined on a Perkin-Elmer 141 polarimeter, in

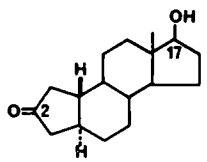




1 a, R=C(=O)-C_2H_5
b, R=H
c, R=C(=O)-CH_3

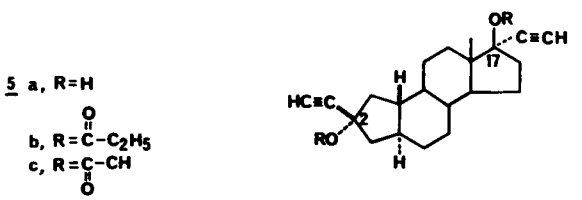
2





3 a, R=C(=O)-C_2H_5
b, R=C(=O)-CH_3
c, R=H

4



5 a, R=H
b, R=C(=O)-C_2H_5
c, R=C(=O)-CH

ethanol solution (concentration c = 1). Thin layer chromatography (TLC) was carried out using Merck $60F_{254}$ (0.25 mm) sheets. For column chromatography, Merck 230-400 mesh silica gel 60 and Mallinckrodt silicic acid silicar CC-4 and CC-7 were used.

2α,17α-Diethynyl-A-nor-5α-androstane-2β,17β-diol (1b)

Lithium acetylide-ethylene-diamine complex (2.3 g) was dissolved in 4 ml anhydrous DMSO (11). A stream of dry acetylene was passed through this solution for 20 min, with stirring. The reaction mixture was cooled to 0-5° and 860 mg of A-nor-5α-androstane-2,17-dione (10) in 25 ml anhydrous DMSO was then added. A stream of acetylene was passed through this solution for an additional 30 min. After addition of aqueous ammonium chloride, followed by extraction with methylene chloride, the organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness *in vacuo*.

The crude material was chromatographed over silicic acid to afford 855 mg of pure 2β,17β-diol (1b), which was recrystallized from methylene chloride-pentane: m.p. 169-170°; $[\alpha]_D$ -23° ($CHCl_3$) (in agreement with published data, ref. 10); IR: 3600 (OH), 3310 cm^{-1} (C≡CH); NMR: δ 2.53 and 2.46 (2s, C≡CH), 0.92 (19-Me), 0.83 ppm (18-Me).

2α,17α-Diethynyl-A-nor-5α-androstane-2β,17β-diol diacetate (1c)

A solution containing 700 mg of diol (1b) in 3 ml anhydrous pyridine and 7 ml redistilled acetic anhydride was heated at 110-115° for 15 hr. The reaction mixture was then cooled to room temperature and methanol was carefully added to decompose the excess of anhydride. Ice-water was then added and the diacetate which precipitated was filtered. The diester (1c) was recrystallized from methanol to provide the analytical sample (642 mg): m.p. 190-191°; $[\alpha]_D$ -39° ($CHCl_3$); IR: 3310 (C≡CH), 1735 cm^{-1} (ester); NMR: δ 2.56 and 2.53 (2s, C≡CH), 2.03 (s, 2 x Ac), 0.83 ppm (18-Me + 19-Me).

Anal. Calcd. for $C_{26}H_{34}O_4$: C, 76.06; H, 8.34. Found: C, 76.16; H, 8.39.

2α,17α-Diethynyl-A-nor-5α-androstane-2β,17β-diol dipropionate (1a)

A solution containing 350 mg of diol (1b) in 1.5 ml anhydrous pyridine and 4 ml propionic anhydride was heated for 15 hr at 112-115°. The mixture was then cooled to room temperature and methanol was carefully added to decompose the excess of acetic anhydride. Ice-water was then added and the solution was extracted with methylene chloride. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude material which was obtained was recrystallized from methanol to afford 341 mg of pure dipropionate (1a): m.p. 152.5-153°; $[\alpha]_D$ -32° ($CHCl_3$); IR: 3310 (C≡CH), 1740 cm^{-1} (ester); NMR: δ 2.56 and 2.53 (2s, C≡CH), 1.13 (t, 2 x CH_2CH_3 = 8 Hz), 0.86 (19-Me), 0.83 ppm (18-Me); MS: m/e 438 (M^+).

Anal. Calcd. for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.68; H, 8.61.

2α,17α-Diethynyl-A-nor-5α-estrane-2β,17β-diol (3c)

Addition of n-butyllithium (3.2 ml) to tetrahydrofuran (THF) (20 ml), distilled over lithium aluminum hydride, was performed at -78°, under nitrogen atmosphere. A stream of dry acetylene was then bubbled through the solution, kept at -78° for 30 min. A solution of 211 mg of A-nor-estrane-2,17-dione, obtained by oxidation of (4), in 3.2 ml anhydrous THF was then added to the above prepared solution of lithium acetylide and the reaction mixture was kept for 1 hr at -78°. The temperature was raised to 20°, then water (10 ml) and potassium carbonate were added to saturation. After extraction with methylene chloride, the organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness under vacuum. The crude diethynyl mixture was chromatographed on silicic acid, followed by crystallization from ethanol-hexane to give 2α,17α-diethynyl-A-nor-5α-estrane-2β,17β-diol (3c) (57%), exhibiting: m.p. 145°; $[\alpha]_D$ -6°, -10° (Dioxane); IR: 3590 (OH), 3300 cm^{-1} (C≡CH); NMR: δ 2.43 (2s, C≡CH), 0.84 ppm (s, 18-Me); MS: m/e 312 (M^+), 294 (M^+-H_2O).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.55; H, 8.96.

2β,17α-Diethynyl-A-nor-5α-estrane-2α,17β-diol (5a)

After chromatographic purification (preparative TLC) and crystallization from hexane the pure 2α,17β-diol (5a) was obtained (43%): m.p. 60° (half-solid); $[\alpha]_D$ -46°; -49° (Dioxane); -51° ($CHCl_3$); IR: 3580 (OH), 3300 cm^{-1} (C≡CH); NMR: δ 2.52 and 2.45 (2s, C≡CH), 0.83 ppm (s, 18-Me); MS: m/e 312 (M^+); 297 (M^+-CH_3), 294 (M^+H_2O).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.60; H, 9.13.

2α,17α-Diethynyl-A-nor-5α-estrane-2β,17β-diol diacetate (3b)

A solution containing 100 mg of diol (3c) in 1 ml anhydrous pyridine and 1 ml acetic anhydride was heated at 80° for 40 hr. The esterification was followed by TLC. The reaction mixture was cooled to 20° and then the excess of acetic anhydride was carefully destroyed by addition of methanol. A saturated sodium chloride-water solution was added and the compound extracted with methylene chloride. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo*. The product was chromatographed over silicic acid to afford 112 mg of the diacetate (3b): m.p. 60-65° (half-solid); $[\alpha]_D$ -20°; IR: 3310 (C≡CH), 1740 cm^{-1} (ester); NMR: δ 2.40 and 2.33 (2s, C≡CH), 1.93 (s, 6H, 2,17-Ac), 0.82 ppm (s, 18-Me); MS: m/e 396 (M^+); 381 (M^+-CH_3).

Anal. Calcd. for $C_{25}H_{32}O_4$: C, 75.72; H, 8.13. Found: C, 75.65; H, 8.23.

2β,17α-Diethynyl-A-nor-5α-estrane-2α,17β-diol diacetate (5c)

The esterification of diol (5a) (100 mg) under the same conditions as described above afforded the diacetate (5c) (122 mg), which was recrystallized from hexane: m.p. 178° $[\alpha]_D$ -54°; IR: 3310 (C≡CH), 1740 cm^{-1} (ester); NMR: δ 2.40 and 2.37 (2s, C≡CH), 1.93 (s, 6H, 2,17-Ac), 0.83 ppm (s, 18-Me); MS: m/e 396 (M^+); 381 (M^+-CH_3).

Anal. Calcd. for $C_{25}H_{32}O_4$: C, 75.72; H, 8.13. Found: C, 75.67; H, 8.24.

2α,17α-Diethynyl-A-nor-5α-estrane-2β,17β-diol dipropionate (3a)

A solution containing 80 mg of diol (3c) in 0.8 ml anhydrous pyridine and 0.8 ml redistilled propionic anhydride was gently heated at reflux temperature for 20 hr. The esterification was followed by TLC. The mixture was then cooled to 20° and a saturated sodium chloride water solution was then added. After extraction with methylene chloride, the organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo*. The crude dipropionate (3a) was purified by chromatography on silicic acid to afford the amorphous ester (90 mg): $[\alpha]_D$ -19°; IR:

3300 (C≡CH), 1735 cm^{-1} (ester); NMR: δ 2.53 and 2.50 (2s, C≡CH), 1.10 (t, 2 x CH_2CH_3, J = 7 Hz), 0.87 ppm (s, 18-Me); MS: m/e 424 (M^+); 350 (M^+-$C_2H_5CO_2$).

Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.37; H, 8.73.

2β,17α-Diethynyl-A-nor-5α-estrane-2α,17β-diol dipropionate (5b)

A solution of 100 mg of diol (5a) in 1 ml anhydrous pyridine and 1 ml propionic anhydride was heated at 80° for 100 hr, the esterification being followed by TLC. The reaction mixture was cooled to 20° and the anhydride in excess was decomposed by slow addition of methanol. A saturated solution of sodium chloride was then added and the extraction was performed with methylene chloride. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure.

The crude dipropionate (5b) (126 mg) was purified by column chromatography on silicic acid, followed by recrystallization from pentane: m.p. 106°; $[\alpha]_D$ -48°; IR: 3300 (C≡CH), 1735 cm^{-1} (ester); NMR: δ 2.42 and 2.38 (2s, C≡CH), 1.08 (t, 2 x CH_2CH_3, J = 7 Hz), 0.83 ppm (s, 18-Me); MS: m/e 424 (M^+); 409 (M^+-CH_3).

Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.60; H, 8.48.

BIOLOGICAL ACTIVITY IN RODENTS

Uterotrophic activity

This was assayed in 21-day-old rats (groups of six) given 0.4 ml of the test substance orally once daily for 3 days in a total of 1.2 ml of arachis oil. The animals were sacrificed 24 hours after the administration of the last dose. Mean uterine weights ± S.D. are shown in Figure 2.

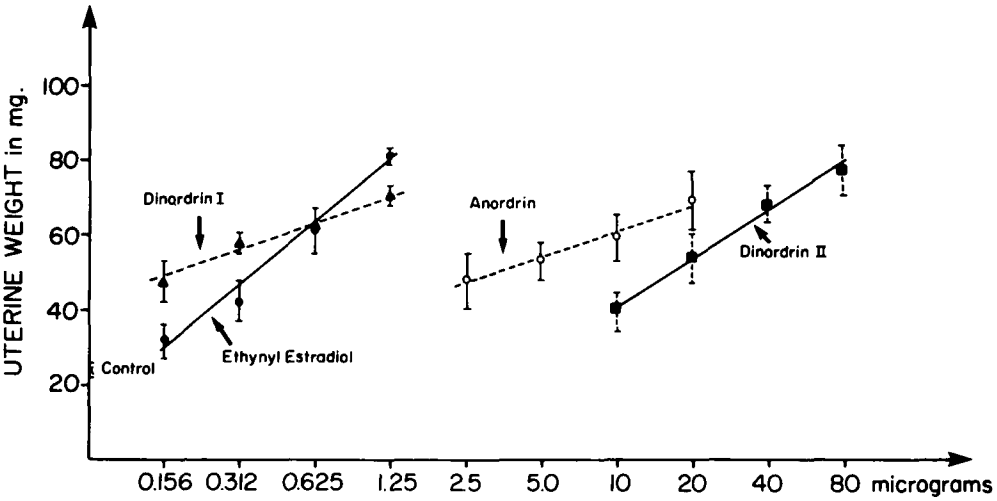
The slopes (b ± S_b) of the dose-effect curves are as follows:

ethynylestradiol:	55.29 ± 3.20
Dinordrin I:	23.93 ± 2.87
Dinordrin II:	41.61 ± 3.69
Anordrin:	23.08 ± 4.05

The slope of ethynylestradiol differs significantly from those of the three test substances and therefore no valid potency estimates can be given in terms of ethynylestradiol. It would appear, however, that the uterotrophic activity of Dinordrin I is considerably greater than that of Anordrin or Dinordrin II. The only exact potency estimate that can be made is a comparison of Dinordrin I and Anordrin: the former is 20 times more active in this test than the latter.

Figure 2

UTEROTROPHIC ACTIVITY IN 21 DAY– OLD RATS. MEAN ±SD.



Single-dose oral antifertility effect

This was assayed in Sprague-Dawley rats of approximately 250 g weight (3-4 months of age). A single dose in 1.0 ml oil was administered on day 0 (i.e., the day when sperm were found in the vaginal smears), and the animals were sacrificed 14 days later. The number of implantation sites and corpora lutea were counted. The results are indicated in Table 1.

The potency of these compounds, as judged by the number of implantation sites, generally paralleled the uterotrophic activity; Dinordrin I being the most potent and Dinordrin II exhibiting the lowest activity. The ED_{50} for Dinordrin I (whether administered as the dipropionate, the diacetate, or the free alcohol) was between 12.5 and 50 μg/kg; for Anordrin it was between 250 and 500 μg/kg; and for Dinordrin II it was between 1,800 and 2,700 μg/kg.

BIOLOGICAL ACTIVITY IN NONHUMAN PRIMATES

Estrogenic activity

In five oophorectomized baboons, an oral dose of 1.3 μg/kg/day ethynylestradiol for 10 days produced maximum sex skin turgescence. Two other animals were given

Table 1.—Single Dose Antifertility Effect

Compound	Derivative	Dose (μg/kg)	No. of Rats	Mean No. of Implantation Sites/Rat
Anordrin	Dipropionate	0	27	13.7
		125	5	11.6
		250	8	11.25
		500	9	4.4
		1000	10	0.8
		4000	10	0
Dinordrin I	Dipropionate	0	5	13.7
		6.25	9	10.1
		25	8	9.5
		50	11	4.5
		100	10	1.1
		200	10	0.7
Dinordrin I	Diacetate	0	8	13.8
		12.5	5	11.2
		50	8	5.5
		200	8	1.4
		800	6	0
Dinordrin I	Free alcohol	0	8	13.8
		12.5	5	13.6
		50	8	3.4
		200	8	0.6
		800	6	0
Dinordrin II	Dipropionate	0	33	13.8
		800	7	12.0
		1200	8	12.1
		1800	8	9.9
		2700	8	2.8
		4050	8	4.5

100 μg/kg/day Dinordrin I twice daily for 4 days, and this produced roughly comparable effects in terms of the rate of development and degree of turgescence. On this preliminary basis, one would estimate the estrogenic effect of Dinordrin I to be about 1/150 that of ethynylestradiol based on the nonhuman primate sex skin assay.

Antifertility effects

The time-consuming and expensive nature of primate investigation precludes the use of classical experimental designs. We have demonstrated (14) that a two-stage sequential design is more efficient for investigations such as the present one. For screening purposes, it can be demonstrated statistically that a compound is unlikely to have significant antifertility properties at the given dose if more than two pregnancies occur in the first 10 test animals in comparison to our usual pregnancy rate in similarly maintained control

animals. If two pregnancies or fewer occur in this first stage, an additional 10 animals are tested. If there are three pregnancies or fewer in the total of 20 animals, this is an indication by the screen that the compound has significant potential as an antifertility agent and warrants further investigation.

Careful observation of the baboon sex skin allows a reasonably accurate prediction of the time of ovulation, which occurs about 1 to 3 days before deturgescence. Two days before the first sign of deturgescence is assumed to be the day of ovulation, or the day of conception in the case of successful matings.

Adult, regularly cycling female baboons were used to assess postovulatory contraceptive effectiveness. Animals were mated during the period of maximal sex skin turgescence on the basis of previous cycle records and of direct observation of subtle changes in the appearance of the sex skin. Daily vaginal smears were taken following introduction of the male into the female's cage until a smear positive for sperm was recorded. Animals showing only negative smears were excluded from the data.

In the first series of studies, a single oral dose of Anordrin (0.2 mg/kg), Dinordrin I (0.1 mg/kg) or Dinordrin II (0.1 mg/kg) incorporated into a fig bar was administered at the first sign of sex skin deturgescence, at which time the male was removed from the cage. Control animals received a plain fig bar according to the same schedule. In the few instances where animals would not eat the fig bar, the drug was incorporated into a gelatin capsule and force-fed. In the second series of experiments, the drugs were administered twice daily (morning and late afternoon) for 4 consecutive days, again commencing at the first sign of sex skin deturgescence. Blood samples for the determination of estrogen and progesterone were obtained on day 8 and day 18 after ovulation. We have demonstrated that these testing procedures provide a rapid confirmation of ovulation in the day 8 sample and of pregnancy in the day 18 sample (15).

The studies with a single dose given 2 days after ovulation showed inadequate contraceptive effectiveness with all three compounds (Table 2): there were three pregnancies in 10 matings with Anordrin, and three pregnancies within six matings for both Dinordrins. In the second series of experiments, using the same daily dose of steroid but administered twice daily for 4 consecutive days, both Anordrin and Dinordrin I fell within the acceptable limits of the screen, indicating antifertility potency worthy of further investigation. The pregnancy rate in the controls for these studies was 29%.

Effects on corpus luteum function

In control baboons, only one of the 31 cycles examined yielded a plasma progesterone value of less than 1 ng/ml on day 8 postovulation; thus, at least 30 of these cycles were ovulatory.

Table 2

Drug and Dose	No. Pregnancies/ No. Cycles Exposure	No. Cycles With Plasma Progesterone <1 ng/ml 8 Days Post Ovulation	Hormone Levels 8 Days Post Ovulation (Mean ± SE[n])	
			Estradiol + Estrone, pg/ml	Progesterone, ng/ml
Control	9/31	1/31	98.8 ± 4.9 [31]	3.7 ± 0.3
A 0.2 mg/kg x 1	3/10			
0.2 mg/kg x 8	2/20	11/19	59.1 ± 4.6 [19]	1.4 ± 0.4
Di I 0.1 mg/kg x 1	3/6			
0.1 mg/kg x 8	1/20	10/20	68.4 ± 7.7 [20]	1.4 ± 0.3
Di II 0.1 mg/kg x 1	3/6			
0.1 mg/kg x 8	4/20	1/20	74.1 ± 2.2 [20]	3.8 ± 0.5

In the 4-day treatment with Anordrin, 11 of 19 animals had a plasma progesterone level less than 1 ng/ml on day 8 postovulation, and both estrogen and progesterone levels were lower than those of the controls (Table 2), suggesting a luteolytic action. Dinordrin I yielded similar results, with only one pregnancy in 20 matings. Progesterone levels of less than 1 ng/ml on day 8 postovulation were seen in 10 of the 20 baboons and a reduction in the mean estrogen and progesterone levels below that of the controls was observed. Despite this effect on steroid levels, cycle length in baboons treated with Anordrin or Dinordrin I remained of normal length. Dinordrin II yielded four pregnancies in 20 matings, which falls below the acceptable level of effectiveness. In keeping with this observation, only one of 20 progesterone determinations on day 8 postovulation was below 1 ng/ml. The estrogen levels were significantly ($p < .001$) lower than the controls, but the progesterone level was unaffected.

DISCUSSION

Brief clinical reports have described the use of Anordrin administered postcoitally, and also as an agent to be initiated shortly before anticipated sexual exposure and continued for the duration of the exposure ("vacation pill"). Effectiveness under these conditions is clearly unrelated to pituitary inhibition, and is also not comparable to very high dose estrogen administration for immediate postexposure use ("interception"). The mechanism(s) of contraceptive efficacy therefore remain to be clarified, and are of considerable interest in view of the high rate of protection that has been reported. There are, however, no published clinical dose-effectiveness data, and since side effects are also

dose-related, it is not possible to evaluate the incidence, severity or acceptability of adverse reactions. In this light, the preparation and testing of synthetic analogues was especially pertinent.

In clinical studies hyperestrogenic side effects have been reported; in the rodent, Anordrin is uterotrophic, although significantly less so than ethynylestradiol. Dinordrin I was approximately of the same uterotrophic potency as ethynylestradiol. On the other hand, in the castrate female baboon, judging by sex skin turgescence, Dinordrin I was about 1/150th the potency of ethynylestradiol. Such differences in potency between species and between end-points are well known, but often neglected in discussions of "estrogenicity," with the result that the use of this term, unless carefully defined, has led to a great deal of confusion.

Although they behaved more or less like impeded estrogens, the single-dose anti-implantation effect in rats of the compounds studied roughly paralleled their uterotrophic activity. In both assay systems Dinordrin I was by far the most active compound. It seems possible, however, that considerable strain differences exist; in the present study the ED_{50} of Anordrin was between 250 and 500 μg/kg whereas in another study conducted in Shanghai, it was between 5.0 and 7.5 mg/kg (8). The relationship between anti-implantation effect and uterotrophic activity could not be evaluated in primates because of the limited dose range employed and the nature of the experimental design. Nor is it apparent whether the same mechanisms are responsible for the antifertility effect in the two species.

In baboons, a definite luteolytic effect was observed in the estrogen and progesterone levels obtained after administration of Anordrin and Dinordrin I. Progesterone production was substantially depressed by the 4-day regimen with both compounds, and estrogen levels were reduced by 30-40% as well. The relationship of these events to the antifertility effect will have to be evaluated by administration of these compounds at various intervals and for various lengths of time after fertilization or implantation.

ACKNOWLEDGEMENT

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REFERENCES

1. Banik, U. K. and G. Pincus: PROC. SOC. EXP. BIOL. MED. 111, 595 (1962).

2. Pincus, G.: CIBA FOUNDATION SYMPOSIUM ON PREIMPLANTATION STAGES OF PREGNANCY, G.E.W. Wolstenholme and M. O'Connor, eds., Little, Brown and Company, Boston, p. 378 (1965).

3. Pincus, G. and H. L. Gordon: STEROIDS 5 (Suppl. I), 193 (1965).

4. Steelman, S. L. and D. J. Patanelli: INTERNATIONAL CONGRESS ON HORMONAL STEROIDS, SECOND, N. Martini, F. Franchini, and M. Motla, eds., Excerpta Medica, Amsterdam, p. 559 (1966).

5. Chang, M. C. and R. Yanagimachi: FERTIL. STERIL. 16, 281 (1965).

6. Pincus, G., U. K. Banik, and J. Jacques: STEROIDS 4, 657 (1964).

7. Jacques, J. and G. Pincus: PROCEEDINGS, INTERNATIONAL CONGRESS ON HORMONAL STEROIDS, FIRST, VOL. I, N. Martini and A. Pecile, eds., Academic Press, New York, p. 3 (1964).

8. Chih-ping, K., C. Ming-kang, C. Hsui-chuan, C. Shih-hsing, P. Ta-wei, and T. Kang: SCI. SIN. 18, 262 (1975).

9. Pi-lien, H.: REGIONAL SEMINAR ON NEW DEVELOPMENTS IN FERTILITY REGULATION, MANILA, PHILIPPINES, 1977 FINAL REPORT, World Health Organization, Manila, Philippines, p. 57 (1978).

10. Minssen, M. and J. Jacques: BULL. SOC. CHIM. FR. 71 (1965).

11. Huffman, J. W. and P. G. Arapakos: J. ORG. CHEM. 30, 1604 (1965).

12. Biellmann, J.-F. and M. Rajic: BULL. SOC. CHEM. FR. 441 (1962).

13. After completion of this work, there appeared a report on the preparation of diols (3c) and (5a): Canceill, J., G. Azadian-Boulanger, D. Philibert, J. P. Raynaud, and J. Jacques: C. R. ACAD. SCI., SER. C 285, 37 (1977).

14. Shaikh, A. A., J. W. Goldzieher, D. C. Kraemer, and T. Dozier: RECENT ADV. PRIMATOL. 4, 127 (1978).

15. Shaikh, A. A., C. Allen-Rowlands, T. Dozier, D. C. Kraemer, and J. W. Goldzieher: CONTRACEPTION 14, 391 (1976).