theoretical amount of cream-colored crystals, mp 155.5–157 °C. Anal. ($C_{18}H_{16}NO_4I$) C, H, N.

N-[2-(2,5-Dimethoxy-4-iodophenyl)-1-ethylethyl]-phthalimide (2c). Employing the procedure described for **2d**, 1c was iodinated with 5 mCi of $Na^{131}I$. In the labeled run, as in the unlabeled runs, the product **3c** was obtained only as an oil and was processed directly on to the final amine without characterization or further purification.

2,5-Dimethoxy-4-iodophenyl-α,β-dideuterioisopropylamine Hydrochloride (3d). The crude product **2d** (from the iodination of **1d**) was transferred to a 25-mL round-bottomed flask equipped for refluxing. The transfer was accomplished with 12 mL of 95% ethanol, 0.2 mL of hydrazine hydrate was added, and the mixture was held at reflux for 18 h, during which time solid phthalizide appeared. The reaction mixture was quenched in 200 mL of water, made basic with NaOH to a pH of about 10, and extracted with 3 × 50 mL of methylene chloride. The pooled extracts were washed with a 1% solution of KI and $Na_2S_2O_4$ in water, and the solvent was removed in vacuo. The residual pale amber oil was dissolved in 8 mL of isopropyl alcohol, acidified with concentrated HCl (8 drops), and flooded with anhydrous ether (200 mL). After several minutes, fine crystals began to form. After about 1 h of standing at room temperature, these were removed by filtration and washed with anhydrous ether. The product weighed 0.232 g and assayed at 9.44 mCi/mM, representing an overall chemical yield of 43% and a radioisotope incorporation efficiency of 12%. The physical properties of the product **3b** were determined from unlabeled runs: mp (after recrystallization from ethanol–ether) 200.5–201.5 °C. The melting point was undepressed when admixed with an authentic sample prepared by a different synthesis (lit.[4] mp 199.5–201.0 °C; mmp 199.5–201.0 °C). The possible incorporation of chlorine into the product was assayed by chemical ionization mass spectroscopy (reactant isobutane, at 0.6 Torr and 210 °C), mH^+ = 322 principle peak, with a companion pair (peak height of 4%) at mH^+ = 230 and 232 indicating minor chlorination. Anal. ($C_{11}H_{17}ClINO_2$) C, H, N.

2,5-Dimethoxy-4-iodophenylethylamine Hydrochoride (3a). Employing the procedure described for **3d**, **2a** was converted to **3a**. The product was obtained with a specific activity of 3.16 mCi/mM, in an overall chemical yield of 52% and an overall radioisotope incorporation efficiency of 22%. The physical properties and characterization were achieved on an unlabeled sample. An analytical sample from 2-propanol gave mp 246–247 °C; NMR (D_2O) δ 3.37 (m, 4 H, CH_2), 4.06, 4.08 (2 s, 6 H, OCH_3), 7.17, 7.67 (2 s, 2 H, ArH) (DOH at 4.95). Anal. ($C_{10}H_{15}ClINO_2$) C, H, N.

1-(2,5-Dimethoxy-4-iodophenyl)-2-aminobutane (3c). Employing the procedure described for **3d**, **2c** was converted to **3c**. The product was obtained in a specific activity of 1.7 mCi/mM. The physical properties were determined on a nonradioactive sample: white crystalline solids; mp 214–215 °C. Anal. ($C_{12}H_{19}ClINO_2$) C, H, N.

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Contragestational Agents. 1. Steroidal *O*-Aryloximes

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The preparation of a series of *O*-aryloximes of various steroids by two different routes is described. These compounds were prepared by reacting a keto steroid with a substituted *O*-arylhydroxylamine in the presence of an acid catalyst or, alternatively, by the reaction of a steroidal oxime with a substituted aryl halide in the presence of a suitable base. These compounds were examined for their ability to interrupt postimplantive gestation in female rats. The most significant contragestational activity was seen with compounds in which the basic steroid structure was a 5α-androstane and the 3-oxime was of the *p*-nitrophenyl series. One of the most active compounds in the series (**16**) was shown to have the ability to terminate pregnancy, when orally administered to rats at 2.5 mg/kg on days 9–12 of gestation. This compound was found to be devoid of androgenic activity at this dose level.

Efforts in our laboratory have been directed toward the synthesis of a new generation of antifertility agents having contragestational effects, i.e., the ability to interrupt pregnancy. Reports on the first preparation of *O*-phenylhydroxylamine[1] and the synthesis and reactions of *O*-arylhydroxylamines and *O*-aryloximes[2] led us to prepare a series of steroidal *O*-aryloximes. This paper describes the synthesis and some of the biological properties of this series of compounds, several members of which have contragestational activity while being devoid of androgenic activity at the active dose levels.

Naqvi and Warren[3] reported that oxymetholone (17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one) and nandrolone phenpropionate (17β-hydroxyestr-4-en-3-one 17-phenylpropionate) had the ability to interrupt pregnancy in the rat when adminstered daily subcutaneously for 6 days, starting on the seventh day of pregnancy at doses of 5.0 and 2.0 mg per animal, respectively. Marois[4] reported that a single subcutaneous dose of 3 mg of testosterone propionate to rats on either days 7, 8, 9, 10, or 11 postcoitally is effective in interrupting pregnancy. Likewise, Dreisbach[5] found that a single 4 mg/kg dose of testosterone given to rats produced fetal loss when subcutaneously injected on days 9–11.

The steroidal *O*-aryloximes reported herein also exert their effects postimplantively but unlike oxymetholone, nandrolone phenpropionate, testosterone, or testosterone propionate they are effective orally and have no androgenic

Table I. Antifertility Effect of Compound 1 as Compared to Its Parent Ketone or Oxime[a]

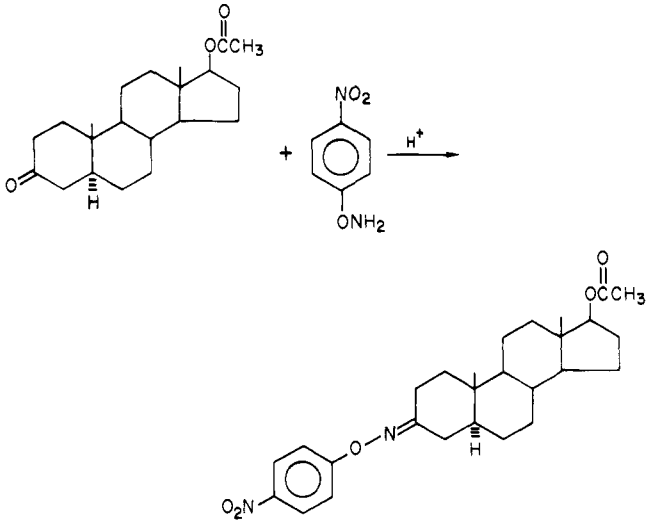
	Dosage level, mg/kg	% resorption
Compound 1	2.5	96.6
5α-Dihydrotestosterone acetate	40	5.0
5α-Dihydrotestosterone acetate oxime	20	2.5

[a] See Experimental Section for a description of the contragestational screen.

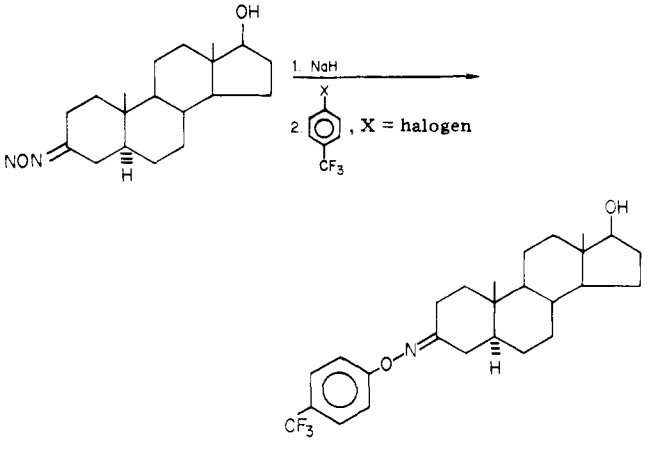
or anabolic hormonal properties at dose levels which cause resorptions. Their mechanism of action remains to be defined.

Chemistry. The compounds were prepared by reacting a keto steroid with a substituted *O*-arylhydroxylamine in the presence of an acid catalyst (method A) or, alternatively, by reacting a steroidal oxime with a substituted aryl halide in the presence of a suitable base (method B).

method A



method B



Biological Results and Discussion. If a comparison is made between norethindrone, norethindrone acetate, and norethindrone acetate oxime in their ability to inhibit preimplantive gestation in the rat, the relative potencies are 1, 8, and 137, respectively.[6] This apparent enhancement of antifertility activity by the introduction of an oxime group as compared to its parent ketone is reversed when comparing the progestational response of the two compounds. When a comparison of the postimplantive antifertility activity of a steroidal *O*-aryloxime and its parent ketone or oxime is made (Table I), both of the latter compounds are essentially inactive at the doses tested whereas the *O*-aryloxime is active.

Table II. Comparison of the Contragestational and Androgenic Activities of O-Aryloximes

	Compd 51	Compd 1	Compd 16
Contragestational Activity[a]			
Dose, mg/kg	10	2.5	2.5
% resorptions	80.8	96.6	100
Androgenicity[b]			
Rel potency compared to 17-methyltestosterone, %	~80	~2.5	
MED, mg/kg[c]	1.5	30	>90

[a] See Experimental Section for a description of the contragestational screen. [b] The compounds were orally administered in sesame oil (0.2 mL of sesame oil per dose) to castrate immature rats, once a day for 7 days. See ref 7. [c] Smallest tested dose to produce a significant increase in ventral prostate weight.

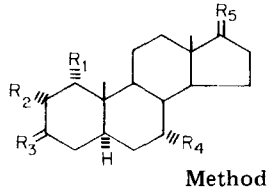
Compound **51** was the first active member of the series which had the desired contragestational activity but was also androgenic (Table II). Because of this dual activity, efforts were directed toward the synthesis of compounds which were effective contragestational agents but were devoid of hormonal activity. These properties were found in **1** (Table II) which was a more potent contragestational agent than **51** while having very weak androgenic properties. A further separation of contragestational vs. androgenic activity is seen in compound **16** (Table II).

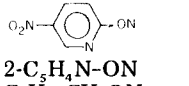
Compound **16** (Table III), one of the most effective members of the series, is completely effective in interrupting pregnancy in female rats at 2.5 mg/kg administered orally on days 9–12 postcoitally. Likewise it is active when given as a single dose of 2.5 mg/kg on day 11 of pregnancy. It can also be administered orally on days 1–6 at 5 mg/kg and still exert a postimplantive antifertility effect. Standard endocrine bioassays in rats and rabbits revealed that the compound is not estrogenic, androgenic, progestational, antiestrogenic, antiandrogenic, or antiprogestational at dose levels of 10–100 mg/kg. At these dose levels, no adverse effects on health were noted.

Structure–Activity Relationships. The most significant contragestational activity was seen with compounds in which the basic steroid structure was a 5α-androstane and the oxime was of the *p*-nitrophenyl series (Table III). Agents which produced at least a 25% resorption rate were considered active. Substitution of a trifluoromethyl group (**20**) for a nitro group resulted in a loss of contragestational activity even though the two groups appear in the same quadrant of a Hammet σ vs. Hansch π scatter diagram.[8] Similarly, activity was lost with any other alteration of the *p*-nitrophenyloxime moiety in this series. It was found that an oxygen atom at C-17 was necessary for effectiveness. This oxygen could be in the form of an alcohol, ester, or ketone. The only exception appeared to be tertiary alcohols which contained a 17β-alkyl group (**9**) which showed a dramatic reduction in potency. Activity was retained by halogen substitution at C-2 (**13–18**). However, no activity was found for the C-1 methyl analogue **19**.

The results in Table IV clearly demonstrate that the trans AB ring juncture is necessary for contragestational activity in the androstane series. However, in the case of the corresponding 19-nor-5α-androstanes **41–43**, little or no contragestational activity is evident (Table V).

Table III. Contragestational Activity of 5α-Androstane *O*-Aryloximes and Analogues



No.	R_1	R_2	R_3	R_4	R_5	Mp, °C	Method of prepn (% yield)	Recrystn solvent	Formula	Analyses	Dose, mg/kg	% resorptions
1	H	H	4-NO_2-C_6H_4-ON	H	α-H,β-OAc	173–175	A (64)	EtOH	$C_{27}H_{36}N_2O_5$	C, H, N	2.5	96.6
2	H	H	4-NO_2-C_6H_4-ON	H	α-H,β-OC(=O)-$(CH_2)_5CH_3$	110–114	A (76)	EtOH	$C_{32}H_{46}N_2O_5$	C, H, N	5.0	100
3	H	H	4-NO_2-C_6H_4-ON	H	α-H,β-ONO_2	177–178	A[a] (36)	C_6H_6-hexane	$C_{25}H_{33}N_3O_6$	C, H, N	40	30.8
4	H	H	4-NO_2-C_6H_4-ON	H	α-H,β-OH	170–173	A (38)	EtOH	$C_{25}H_{34}N_2O_4$	C, H, N	2.5	100
5	H	H	4-NO_2-C_6H_4-ON	H	O	170–172	*b* (88)	C_6H_6-hexane	$C_{25}H_{32}N_2O_4$	C, H, N	5.0	100
6	H	H	4-NO_2-C_6H_4-ON	H	H_2	181–183.5	A (51)	CH_2Cl_2-EtOH	$C_{25}H_{34}N_2O_3$	C, H, N	40	0
7	H	H	4-NO_2-C_6H_4-ON	H		199.5–201	*c* (80)	EtOH	$C_{27}H_{36}N_2O_3S_2$	C, H, N, S	40	4
8	H	H	4-NO_2-C_6H_4-ON	H	NOH	179–180	*d* (29)	EtOH	$C_{25}H_{34}N_3O_4$	C, H, N	36	0
9	H	H	4-NO_2-C_6H_4-ON	H	α-CH_3,β-OH	182–184	A (77)	EtOH	$C_{26}H_{36}N_2O_4$	C, H, N	40	14.7
10	H	H	4-NO_2-C_6H_4-ON	H	α-C≡CH,β-OH	180–182.5	A (50)	EtOH-H_2O	$C_{27}H_{34}N_2O_4$	C, H, N	40	76.9
11	H	H	4-NO_2-C_6H_4ON	H	α-H,β-NH_2	150–155	A[e] (62)	EtOH	$C_{25}H_{35}N_3O_3$	C, H, N	40	**2**
12	H	H	4-NO_2-C_6H_4-ON	H	α-H,β-C(=O)CH_3	184–185	A[f] (29)	C_6H_6-hexane	$C_{27}H_{36}N_2O_4$	C, H, N	40	4
13	H	Br	4-NO_2-C_6H_4-ON	H	α-H,β-OAc	180–183	A (84)	EtOH	$C_{27}H_{35}BrN_2$	C, H, Br, N	2.5	100
14	H	Br	4-NO_2-C_6H_4-ON	H	O	184.5–185	*g* (74)	EtOH	$C_{25}H_{35}BrN_2O_4$	C, H, Br, N	2.5	100
15	H	Br	4-NO_2-C_6H_4-ON	H	α-H,β-OH	165.5–166	A (83)	EtOH	$C_{25}H_{33}BrN_2O_4$	C, H, Br, N	2.5	100
16	H	Cl	4-NO_2-C_6H_4-ON	H	α-H,β-OAc	170–172	A (77)	EtOH	$C_{27}H_{35}ClN_2O_5$	C, H, Cl, N	2.5	100
17	H	Cl	4-NO_2-C_6H_4-ON	H	α-H,β-OH	181–181.5	A (42)	EtOH	$C_{25}H_{33}ClN_2O_4$	C, H, Cl, N	5.0	100
18	H	Cl	4-NO_2-C_6H_4-ON	H	O	202–203	*h* (56)	EtOH	$C_{25}H_{31}ClN_2O_4$	C, H, Cl, N	2.5	100
19	CH_3	H	4-NO_2-C_6H_4-ON	H	α-H,β-OAc	149–154	A (72)	EtOH	$C_{28}H_{36}N_2O_5$	C, H, N	40	5.8
20	H	H	4-CF_3-C_6H_4-ON	H	α-H,β-OH	168–170	B (24)	EtOH	$C_{26}H_{34}NO_2F_3$	C, H, F, N	40	4.8
21	H	H	4-N≡C-C_6H_4-ON	H	α-H,β-OH	185–187.5	B[i] (26)	EtOH	$C_{25}H_{34}N_2O_2$	C, H, N	40	12.9
22	H	H	2,4-NO_2-C_6H_3-ON	H	α-H,β-OH	168–171	B[j] (34)	EtOH	$C_{25}H_{33}N_3O_6$	C, H, N	40	8.2
23	H	H	2-CF_3,4-NO_2-C_6H_3-ON	H	α-H,β-OH	164–171	B[j] (62)	C_6H_6-hexane	$C_{26}H_{33}F_3N_2O_4$	C, H, F, N	50	0
24	H	H	2-Cl,4-NO_2-C_6H_3-ON	H	α-H,β-OH	161–164	B[j] (76)	C_6H_6-hexane	$C_{25}H_{33}ClN_2O_4$	C, H, Cl, N	40	5.8
25	H	H	2-CH_3,4-NO_2-C_6H_3-ON	H	α-H,β-OH	148–150	B (44)	EtOH	$C_{26}H_{36}N_2O_4$	C, H, N	40	5.7
26	H	H	3-CH_3,4-NO_2-C_6H_3-ON	H	α-H,β-OH	173–174.5	B (28)	EtOH	$C_{26}H_{36}N_2O_4$	C, H, N	40	13.1
27	H	H	C_6H_5-ON	H	α-H,β-OH	151–152	*k* (66)	EtOH	$C_{25}H_{35}NO_2$	C, H, N	40	1.9
28	H	H		H	α-H,β-OH	190–194	B[i] (65)	C_6H_6-hexane	$C_{24}H_{33}N_3O_4$	C, H, N	40	6
29	H	H	2-C_5H_4N-ON	H	α-H,β-OH	194–195	B (9)	EtOH	$C_{24}H_{35}N_2O_3$	C, H, N	40	0
30	H	H	C_6H_5-CH_2ON	H	α-H,β-OH	174–177	A (73)	EtOH	$C_{26}H_{37}NO_2$	C, H, N	40	13.3

31	H	H	CH_3ON	H	α-H,β-OH	145–149	*l* (70)	EtOH	$C_{22}H_{35}NO_2$	C, H, N	40	10.9
32	H	H	C_6H_5–C(=O)–C_6H_4–ON	H	α-H,β-OH	126–128	B[f] (25)	EtOH	$C_{33}H_{39}NO_3$	C, H, N	35.8	0
33	H	H	3-OH,4-Br–C_6H_3–CH_2ON	H	α-H,β-OH	101–106	A (42)	EtOH	$C_{26}H_{36}BrNO_3$	H, Br, N; C[m]	40	8.8
34	H	H	C_6H_5–SO_2–C_6H_4–ON	H	α-H,β-OH	176.5–178	B[f] (11)	EtOH	$C_{31}H_{39}NO_4S$	H, N, S; C[n]	33.7	9.1
35	H	H	2-NO_2–C_6H_4–ON	H	α-H,β-OAc	94–98	A (57)	EtOH	$C_{27}H_{36}N_2O_5$	C, H, N	40	4.0
36	H	H	4-NO_2–C_6H_4–NHN	H	α-H,β-OAc	244–249	*o* (89)	EtOH	$C_{27}H_{37}N_3O_4$	C, H, N	40	7.7
37	H	H	4-NO_2–C_6H_4–SN	H	α-H,β-OAc	199–200.5	*p* (60)	EtOH	$C_{27}H_{36}N_2O_4S$	H, N, S; C[q]	40	7.5

[a] Benzene and *p*-TSA were substituted for EtOH and HCl. [b] Prepared from 4 by reacting with Jones reagent. [c] Prepared from 5 by reacting with ethanedithiol and boron trifluoride etherate in AcOH for 30 min at room temperature. [d] Prepared from 5 by refluxing with NH_2OH·HCl and NaOAc in an aqueous CH_3OH solution for 5 h. [e] Prepared from 17β-amino-5α-androstan-3-one acetic acid salt (60). The free amine was obtained by neutralization with 1 N NaOH. [f] Required column chromatography on silica gel (5% EtOAc–benzene) for purification. [g] Prepared from 15 by reacting with Jones reagent. [h] Prepared from 17 by reacting with Jones reagent. [i] Required column chromatography on silica gel (5% acetone–$CHCl_3$) for purification. [j] Required column chromatography on silica gel (10% acetone–$CHCl_3$) for purification. [k] Prepared by reacting 5α-dihydrotestosterone acetate with *O*-phenylhydroxylamine hydrochloride and NaOAc in an aqueous EtOH solution at room temperature for 3 min. [l] Prepared by refluxing 5α-dihydrotestosterone acetate, *O*-methylhydroxylamine hydrochloride, and NaOAc in an aqueous EtOH solution for 12 h. [m] C: calcd, 63.66; found, 62.79. [n] C: calcd, 71.36; found, 70.93. [o] Prepared by reacting 5α-dihydrotestosterone acetate with 2,4-dinitrophenylhydrazine and a catalytic amount of HCl in EtOH at room temperature for 12 h. [p] Prepared by refluxing 5α-dihydrotestosterone, *p*-nitrobenzenesulfenamide,[9] and *p*-TSA in benzene for 8 h. [q] C: calcd, 66.91; found, 66.25.

A close correlation of structure–function relationship exists if one compares the 19-nor-Δ^4-androstene series **44–49** to the Δ^4-androstene series (Table VI). In both cases activity is achieved with either the *p*-nitrophenyloxime or the *o*,*p*-dinitrophenyloxime. In addition, it is not necessary to have a nitroaryloxime in these series as the *O*-phenyloxime **49** in the 19-nor-Δ^4-androstene series and the 2-pyridyloxime in both unsaturated series (**48** and **54**) have contragestational activity (Table VI).

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-melt apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within ±0.4% of the theoretical value. NMR spectra were recorded on a Varian Associates A-60 instrument in $CDCl_3$ with Me_4Si as an internal standard. IR spectra were measured as KBr disks on a Beckman IR-8 infrared spectrophotometer. All spectra were consistent with the assigned structures. All steroids employed were either readily available or their preparation has been reported in the literature. The aromatic halides used in method B below are readily available compounds. The preparation of *O*-(2,4-dinitrophenoxy)hydroxylamine[2f,10] and *O*-(4-nitrophenoxy)hydroxylamine[11] has been reported.

Though no overall attempt was made to separate or characterize each compound as its syn or anti isomer, it was evident from spectroscopic and chromatographic means that mixtures of these isomers had been formed, especially in the case of the α,β-unsaturated steroids.

***O*-(2-Nitrophenyl)hydroxylamine (58).** To a solution of 1.3 g (0.01 mol) of *tert*-butyl *N*-hydroxycarbamate[12] and 0.66 g of 85% KOH in 20 mL of EtOH was added dropwise a solution of 1.4 g (0.01 mol) of *o*-fluoronitrobenzene in 20 mL of EtOH. The solution was stirred for 18 h, poured into ice water, neutralized with AcOH, and filtered. Crystallization from EtOH–H_2O afforded 1.8 g (71% yield) of *tert*-butyl *N*-(2-nitrophenoxy)carbamate (**59**): mp 87.5–89 °C. Anal. ($C_{11}H_{14}N_2O_5$) C, H, N.

A solution of 25.8 g (0.1 mol) of **59** in 100 mL of trifluoroacetic acid was stirred at room temperature for 45 min. It was then poured into ice water and neutralized with K_2CO_3, and the precipitate was filtered. Crystallization of the solid from benzene–hexane afforded 11.2 g (72%) of **58**: mp 89–90 °C. Anal. ($C_6H_6N_2O_3$) C, H, N.

17β-Amino-5α-androstan-3-one Acetic Acid Salt (60). A mixture of 8.6 g (0.03 mol) of 17β-amino-5α-androstan-3β-ol[13] and 9.4 g (0.09 mol) of benzaldehyde in 1 L of benzene was refluxed in a Dean-Stark apparatus for 72 h. After concentrating in vacuo the residue was crystallized from benzene–hexane affording 6.9 g (55%) of 17β-benzylideneamino-5α-androstan-3β-ol (**61**): mp 207.5–211 °C. Anal. ($C_{26}H_{37}NO$) H, N; C: calcd, 82.77; found, 81.82.

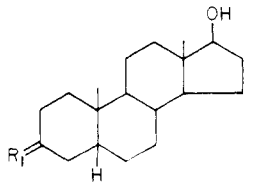
To a mixture of 5.9 g (0.016 mol) of **61** and 17.7 mL of cyclohexanone was added a solution of 5.9 g of aluminum isopropoxide in 190 mL of toluene. After refluxing for 3 h the mixture was diluted with ether and 15% NaOH. The aqueous solution was extracted several times with ether and the ether extracts were dried ($MgSO_4$) and concentrated in vacuo until the product solidified. Crystallization of the residue from EtOH afforded 3.6 g (61%) of 17β-benzylideneamino-5α-androstan-3-one (**62**): mp 200–203 °C. Anal. ($C_{26}H_{35}NO$) C, H, N.

A mixture of 21 g (0.056 mol) of **62** and 300 mL of 50% AcOH–H_2O was steam distilled until the benzaldehyde odor was no longer present in the distillate. The mixture was extracted with benzene and the aqueous solution was concentrated in vacuo. The residue was crystallized from H_2O affording 13.6 g (69%) of **60**. Anal. ($C_{21}H_{35}NO_3$) C, H, N.

General Synthesis of *O*-Aryloximes. Method A. A solution of a steroid, and *O*-arylhydroxylamine (equimolar), and 2 drops of concentrated HCl in EtOH was stirred overnight in the dark. The solvent was removed in vacuo and the resulting solid was crystallized to afford the desired product.

Method B. To a solution of a steroid in anhydrous THF was added an equimolar quantity of NaH. The suspension was stirred in the dark under a nitrogen atmosphere until the evolution of

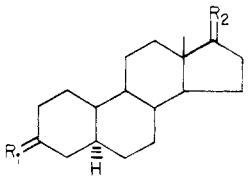
Table IV. Contragestational Activity of 5β-Androstane O-Aryloximes



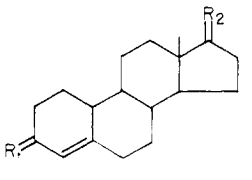
No.	R_1	Mp, °C	Method of prepn (% yield)	Recrystn solvent	Formula	Analyses	Dose, mg/kg	% resorptions
38	4-NO_2-C_6H_4-ON	141-143	A (76)	C_6H_6-hexane	$C_{25}H_{34}N_2O_4$	C, H, N	40	10.9
39	2,4-NO_2-C_6H_3-ON	184-186	A (22)	C_6H_6-hexane	$C_{25}H_{33}N_3O_6$	C, H, N	40	5.4
40	C_6H_5-ON	124-126	*a* (85)	EtOH-H_2O	$C_{25}H_{35}NO_2$	C, H, N	40	11.9

[a] Prepared by reacting 5β-dihydrotestosterone with O-phenylhydroxylamine hydrochloride and NaOAc in an aqueous EtOH solution at room temperature for 45 min.

Table V. Contragestational Activity of 19-Norandrostane and 19-Norandrostene O-Aryloximes



41-43

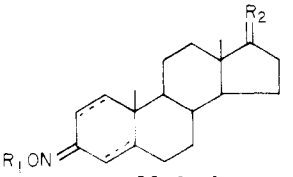


44-49

No.	R_1	R_2	Mp, °C	Method of prepn (% yield)	Recrystn solvent	Formula	Analyses	Dose, mg/kg	% resorptions
41	4-NO_2-C_6H_4-ON	α-H,β-OH	187.5-188.5	A (62)	EtOAc	$C_{24}H_{32}N_2O_4$	C, H, N	40	9.8
42	2,4-NO_2-C_6H_3-ON	α-CH_3,β-OH	175-178	A (41)	EtOH	$C_{25}H_{35}N_3O_6$	C, H, N	40	9.5
43	2,4-NO_2-C_6H_3-ON	α-H,β-OH	150-154	A (59)	EtOH	$C_{24}H_{31}N_3O_6$	C, H, N	40	16.4
44	4-NO_2-C_6H_4-ON	α-H,β-OH	174-184	A (42)	EtOH	$C_{24}H_{30}N_2O_4$	C, H, N	20	63.9
45	2,4-NO_2-C_6H_3-ON	α-H,β-OH	107-147	A (73)	EtOH	$C_{24}H_{29}N_3O_6$	C, H, N	20	100
46	2-NO_2-C_6H_4-ON	α-H,β-OH	85-128	A (64)	EtOH	$C_{24}H_{30}N_2O_4$	C, H, N	40	11.9
47	4-NO_2-C_6H_4-ON	α-C≡CH,β-OH	170-172	A (47)	C_6H_6-hexane	$C_{26}H_{30}N_2O_4$	C, H, N	40	25
48	2-C_5H_4N-ON	α-H,β-OH	128.5-131	B[a] (15)	EtOEt	$C_{23}H_{30}N_2O_2$	C, H, N	20	100
49	C_6H_5-ON	α-H,β-OH	155-157	*b* (29)	EtOH	$C_{24}H_{31}NO_2$	C, H, N	40	100

[a] Required column chromatography on silica gel (10% acetone-$CHCl_3$) for purification. [b] Prepared by reacting 19-nortestosterone with O-phenylhydroxylamine hydrochloride and NaOAc in aqueous EtOH at room temperature for 5 min.

Table VI. Contragestational Activity of Androstene O-Aryloximes



No.	R_1	R_2	Unsaturation	Mp, °C	Method of prepn (% yield)	Recrystn solvent	Formula	Analyses	Dose, mg/kg	% resorptions
50	4-NO_2-C_6H_4-	α-H,β-OH	Δ^4	133.5-188	A (74)	EtOH	$C_{25}H_{32}N_2O_4$	C, H, N	40	93.8
51	2,4-NO_2-C_6H_3-	α-H,β-OH	Δ^4	170.5-174	A (83)	EtOH	$C_{25}H_{31}N_3O_6$	C, H, N	10	80.8
52	2,4-NO_2-C_6H_3-	α-CH_3,β-OH	Δ^4	180-183	A (75)	EtOH	$C_{26}H_{33}N_3O_6$	C, H, N	20	2.2
53	4-CF_3-C_6H_4-	α-H,β-OH	Δ^4	136-139	B[a] (19)	Hexane	$C_{26}H_{32}F_3NO_2$	C, H, N, F	40	11.8
54	2-C_5H_4N-	α-H,β-OH	Δ^4	89-91	B[b] (20)	Hexane	$C_{24}H_{33}N_2O_2$	C, H, N	40	75.9
55	4-NO_2-C_6H_4-	α-H,β-OAc	Δ^1	171-190	A (63)	EtOH	$C_{27}H_{34}N_2O_5$	C, H, N	40	2.0
56	4-NO_2-C_6H_4-	α-H,β-OH	$\Delta^{1,4}$	104-135	A (61)	EtOH	$C_{25}H_{30}N_2O_4$	C, H, N	20	6.0
57	2,4-NO_2-C_6H_3-	α-H,β-OH	$\Delta^{1,4}$	154-157	A (66)	EtOH	$C_{25}H_{29}N_3O_6$	C, H, N	20	92.6

[a] Required column chromatography on silica gel (10% acetone-$CHCl_3$) for purification. [b] Required column chromatography on silica gel ($CHCl_3$) for purification.

gas ceased. Then an equimolar quantity of an aromatic halide (the fluoride was used in all cases except for the use of the chloride for compound **28**) in anhydrous Me_2SO was added and the solution was stirred overnight. The mixture was poured into ice water and filtered, and the solid was purified by either crystallization or chromatography followed by crystallization.

Pharmacology. Contragestational Screen. The compounds were administered orally in sesame oil (0.5 mL of sesame oil/200 g of animal body weight) to five female Wistar-derived rats on days 9-12 of pregnancy. Sperm in vaginal washings constituted day 1 of pregnancy. The animals were sacrificed on day 21 and the activity was recorded as the percent of resorptions obtained (percent resorption equals the total number of implantation sites less the number of live fetuses divided by the total number of implantation sites times 100). The dose given in the tables is the lowest dose to cause resorption. In those cases where no activity

is observed, the dose is the highest dose tested.

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Prostaglandins and Congeners. 15.[1] Synthesis and Bronchodilator Activity of *dl*-11-Deoxy-15- or 16-alkylprostaglandins

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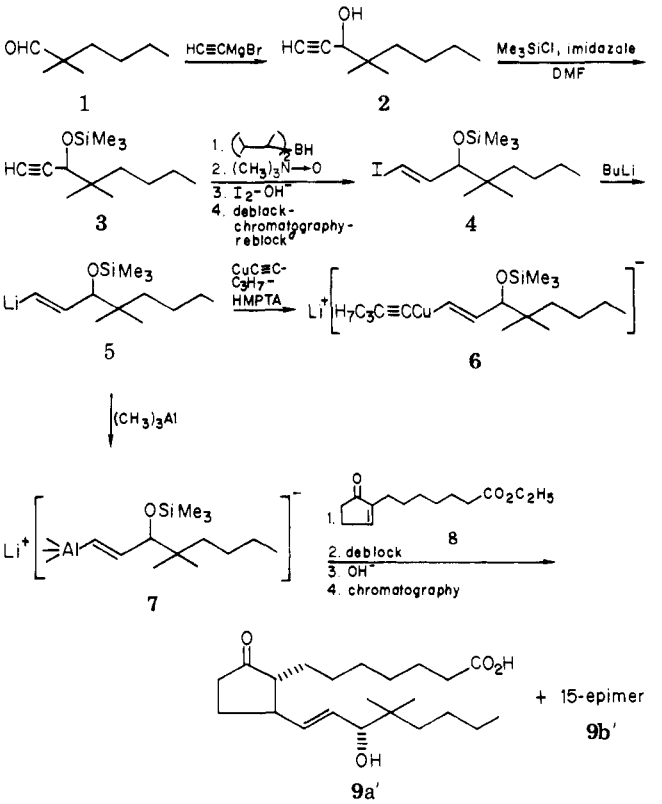
The synthesis of *dl*-11-deoxy-15- or 16-alkylprostaglandins by the conjugate addition of appropriately substituted lithium alanate or lithium cuprate reagents to several cyclopentenones is described as is the preparation of the requisite intermediate (*E*)-1-iodo-1-alkenyl compounds **4**, **22**, **23**, and **31**. The bronchodilator activity of these prostaglandin congeners is presented.

The introduction of alkyl groups at C_{15} or C_{16} in the prostaglandin molecule has provided compounds that are resistant to metabolic inactivation by 15-hydroxyprostaglandin dehydrogenase[2] with resulting enhancement of potency, oral activity at least as inhibitors of gastric acid secretion, and prolongation of effect.[3] Accordingly we were interested in the preparation and biological evaluation of related compounds in the 11-deoxy series, which afford advantages with respect to stability and perhaps also to selectivity of biological effect, a most important consideration. It also was of obvious interest to prepare such compounds in which the α chain (C_1–C_7) would be expected to be resistant to fatty acid β-oxidation,[4] the second major course of prostaglandin metabolic inactivation.[5]

Chemistry. Our synthetic approach utilizes as its key step the facile conjugate addition of an appropriately blocked 3-oxy-3- or 4-substituted (C_{15} or C_{16} in the ultimate prostaglandin) (*E*)-1-alkenyllithium cuprate[1,6] or -lithium alanate[4a] to cyclopentenones. Critical to this approach is the synthesis of the requisite (*E*)-1-alkenyl 1-iodides for the preparation of the organometallic reagent.

For the 16,16-dimethyl series, the required vinyl iodide **4**[7] was prepared as illustrated in Scheme I. Condensation[8] of aldehyde **1**[9] with acetylenemagnesium bromide afforded alcohol **2**, which was converted to the trimethylsilyl ether **3**. The choice of blocking group is important since hindrance by the adjacent *gem*-dimethyl group increases the stability of the blocked ether. Thus, conditions required for effective deblocking of the more bulky trityl or dimethyl *tert*-butylsilyl ethers were now too vigorous and resulted in at least partial disruption of the allylic 15-hydroxy function and, in the 11-hydroxy series, of the β-ketol function. On the other hand, the usually highly labile trimethylsilyl ether was now sufficiently stable to survive the conditions of conjugate addition. Hydroboration–oxidation–iodination of the acetylene function

Scheme I



[a] See ref 11.