60–65° for 1 hr, was filtered to remove pyridine hydrochloride. The filtrate was washed with 20 ml of H_2O, dried ($MgSO_4$), concentrated, and distilled giving 4.5 g (69%) of the product, bp 120–122° (0.05 mm), $n^{25}D$ 1.5143. *Anal.* ($C_{11}H_{16}ClNO_2$) C, H, Cl.

8-(3-Chloropropyl)-8-azaspiro[4.5]decane-7,9-dione was prepared similarly in 73% yield, bp 155–162° (0.06 mm), $n^{25}D$ 1.5114. *Anal.* ($C_{12}H_{18}ClNO_2$) C, H, N.

8-[2-(2-Chloroethoxy)ethyl]-8-azaspiro[4.5]decane-7,9-dione was obtained similarly in 50% yield, bp 155–165° (0.25 mm), $n^{25}D$ 1.5069. *Anal.* ($C_{13}H_{20}ClNO_3$) C, H.

8-(2-Propargyl)-8-azaspiro[4.5]decane-7,9-dione.—A solution of 3,3-tetramethyleneglutaric anhydride (15.2 g, 0.09 mole) and propargylamine (5.0 g, 0.09 mole) in 200 ml of pyridine was refluxed for 15 hr. The reaction mixture was concentrated and distilled giving 14.1 g (76%) of product, bp 129–145° (0.15 mm). *Anal.* ($C_{12}H_{15}NO_2$) C, H, N.

N-[ω-(4-Phenyl-1-piperazinyl)alkyl]Cyclic Imides. Method A.—An equimolar mixture of cyclic acid anhydride and 1-(ω-aminoalkyl)-4-phenylpiperazine in dry pyridine (0.1 mole/400 ml) was refluxed for 15 hr. The mixture was concentrated; if the ir spectrum showed typical imide bands (1700 and 1710 cm^{-1}), the residue was purified by either distillation or crystallization. If the spectrum showed amide acid bands (1680, 1760, 330 cm^{-1}) instead, the residue was refluxed with ten times its weight of Ac_2O for 15 hr. The residue obtained by removal of Ac_2O was purified either by distillation or recrystallization.

Method B.—A mixture of 8-(ω-chloroalkyl)-8-azaspiro[4.5]-decane-7,9-dione (0.1 mole), 1-phenylpiperazine (0.1 mole), anhydrous Na_2CO_3 (0.3 mole), and dry C_6H_6 was refluxed for 15 hr. The reaction mixture was filtered. The filtrate was concentrated and distilled to give the product.

Method C. 8-(4-Phenyl-1-piperazinyl)-8-azaspiro[4.5]decane-7,9-dione.—A mixture of 3,3-tetramethyleneglutarimide (3.3 g, 0.02 mole), 37% formalin (1.8 ml, 0.022 mole), 1-phenylpiperazine (3.2 g, 0.02 mole), and 20 ml of EtOH was heated at 100° for 30 min. Dilution of the reaction mixture with 30 ml of H_2O separated 2.0 g of the white crystalline product, mp 135–137°.

8-[4-(4-Phenyl-1-piperazinyl)-2-butynyl]-8-azaspiro[4.5]decane-7,9-dione Dihydrochloride.—A mixture of 8-(2-propargyl)-8-azaspiro[4.5]decane-7,9-dione (6.0 g, 0.03 mole), 37% formalin (2.4 g, 0.03 mole), Cu_2Cl_2 (73 mg), AcOH (1.8 g, 0.03 mole), H_2O (2.9 ml), and 1-phenylpiperazine (4.8 g, 0.03 mole) was heated at 40° under N_2 for 7 hr. The mixture was extracted with three 75-ml portions of $CHCl_3$. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was treated with a calculated amount of EtOH–HCl giving the product in 20% yield as dihydrochloride salt, mp 173–174°.

Acknowledgments.—We are grateful to Dr. A. A. Larsen for his interest and advice and to Dr. D. G. Mikolasek, Messrs. L. E. Allen, W. G. Lobeck, Jr., T. C. Mays, Jr., and J. F. Purcell, Jr., for their technical assistance. We are also indebted to Dr. A. Kandel for preliminary screening data.

Mammalian Antifertility Agents. VI. A Novel Sequence for the Preparation of 1,2-Disubstituted 3,4-Dihydronaphthalenes[1]

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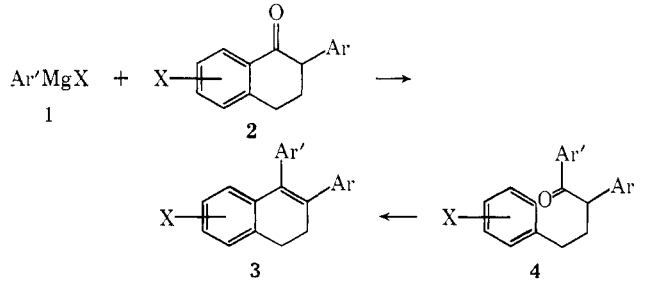
Condensation of the formyl derivatives of substituted acetophenones with the ylide from *m*-methoxybenzyltriphenylphosphonium chloride afforded an intermediate which was elaborated to 1,2-disubstituted dihydronaphthalenes. A series of basic and glyceryl ethers of the *cis*-tetrahydronaphthalenes was prepared. The same intermediate was converted by a different route to the *trans*-tetrahydronaphthalene. Several of the compounds are potent estrogen antagonists.

The 1,2-diaryl-3,4-dihydronaphthalenes constitute a group of compounds with potent antigonadotrophic and uterotrophic activities.[1-3] The nucleus of this system has usually been prepared by condensation of the appropriate 2-aryl-1-tetralone with the Grignard reagent of the aryl group which is to appear at the 1 position. Yields in this reaction have tended to be poor due to extensive enolization of the ketone by the Grignard reagent; large amounts of unreacted ketone are characteristically recovered. Preparation of the nucleus by cyclization of a ketone such as **4** would circumvent the Grignard reaction.



The recently reported condensation of phosphoranes with hydroxymethylene derivatives of ketones at the potential aldehyde[4] promised ready access to the desired intermediates (**11–13**) (Scheme I). The substituted acetophenones were formylated with ethyl formate and NaOEt in EtOH.[5] Reaction of **8** with the preformed ylide from *m*-methoxybenzyltriphenylphosphonium chloride led to a complex mixture. We then found, however, that simply refluxing the sodium enolate of **8** with the phosphonium salt in THF led cleanly to condensation products whose ir absorption (1700, 1660 cm^{-1}) and nmr spectra (integral ratio Ar*H*:O*CH*$_3$, 8:3) suggested a mixture of the α,β and β,γ unsaturated ketones. Catalytic hydrogenation of the total mixture gave the oily **11**. Treatment of this with *p*-toluenesulfonic acid in refluxing C_6H_6 gave the dihydronaphthalene **14** identical in all respects with an authentic sample.[6]

Desoxyanisoin (**6**) and *p*-methoxy-α-cyclopentylacetophenone (**7**) gave the corresponding substituted bu-

(1) Previous paper in this series: D. Lednicer, D. E. Emmert, G. W. Duncan, and S. C. Lyster, *J. Med. Chem.*, **10**, 1051 (1967).

(2) W. L. Bencze, L. I. Barsky, R. W. J. Carney, A. A. Renzi, and G. deStevens, *ibid.*, **10**, 138 (1967).

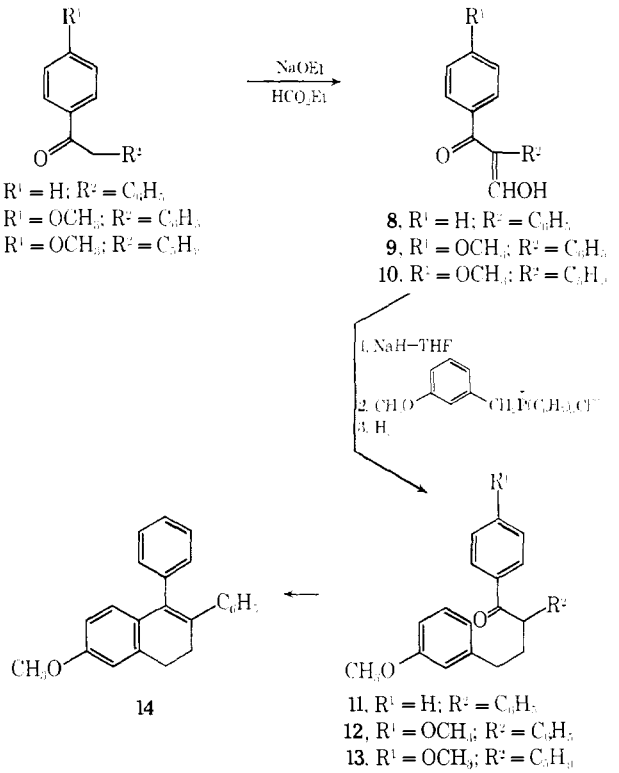
(3) For a recent review see I. Scheer, *Ann. Rept. Med. Chem.*, **3**, 200 (1967).

(4) P. F. Beal III, J. C. Babcock, and F. H. Lincoln, *J. Am. Chem. Soc.*, **88**, 3131 (1966).

(5) W. Wislicenus and A. Ruthing, *Ann.*, **379**, 229 (1911); attempts to carry out this reaction under the more usual conditions (Et_2O and EtOH-free NaOEt) gave only traces of product.

(6) D. Lednicer, S. C. Lyster, B. D. Aspergren, and G. W. Duncan, *J. Med. Chem.*, **9**, 172 (1966).

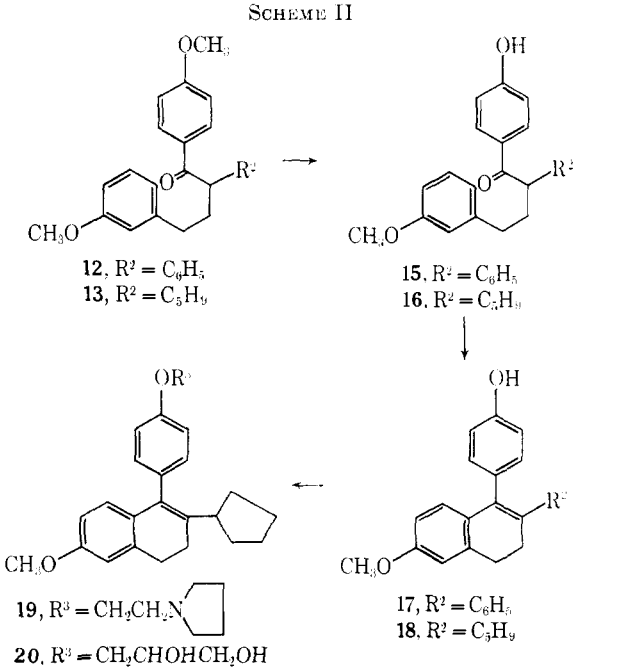
SCHEME I



tyrophenones **12** and **13** when subjected to the same reaction scheme.

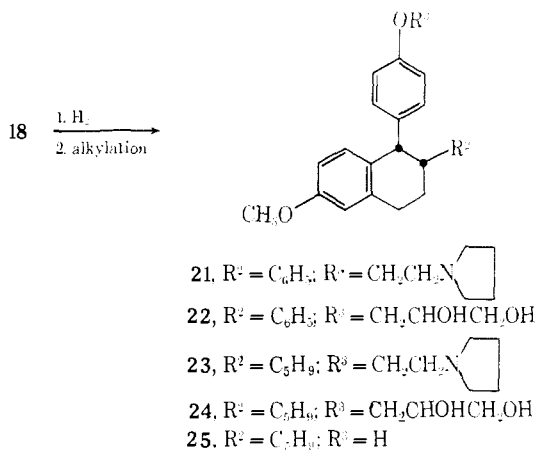
Exposure of the dianisylbutyrophenones **12** and **13** to 3 moles of $AlCl_3$ in refluxing benzene led to the selective removal of the methyl group of the ether *para* to the carbonyl group (Scheme II). Cyclization as above gave

SCHEME II



the desired bicyclic compounds; the product from **15** proved identical with a sample prepared by the Grignard method.[6] Alkylation of the phenol **18** proceeded uneventfully to afford ethers **19** and **20**; corresponding derivatives of **17** have been reported earlier.[1]

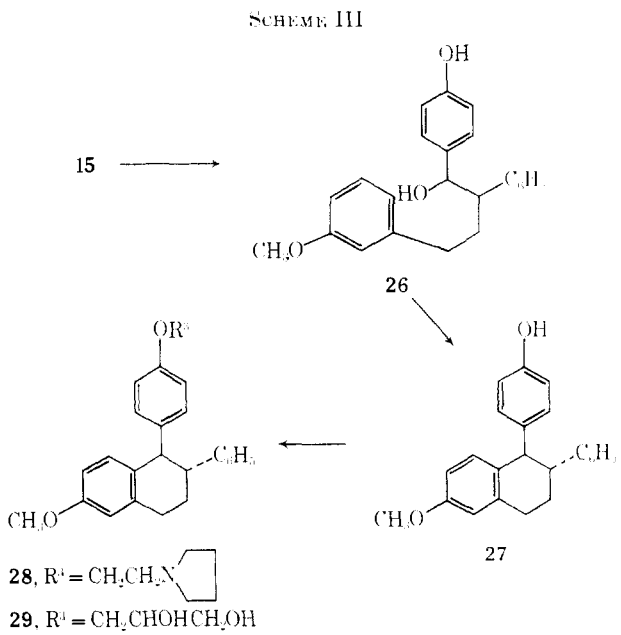
Tetrahydronaphthalenes.—Catalytic reduction of the dihydronaphthalene **18** proceeds as expected to afford the *cis*-tetrahydro compound (Table I); confirmation for this assignment came from the presence of a broad unresolved band (5 cps half-width) for the proton on C-1 in the nmr spectrum.[7] Both di- and tetrahydrophenols were alkylated to afford the basic and glyceryl ethers.



We next wished to examine the effect of stereochemistry on biological activity. Birch reduction of **17** was found earlier[1] to afford the *cis* compound.[7] It was thus clear that an alternate route was needed in order to obtain the *trans* compound.

Reduction of the ketone **15** with LAH led in good yield to the corresponding alcohol, apparently as a single isomer (Scheme III). Cyclization of this with *p*-tol-

SCHEME III

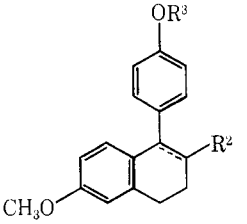


uenesulfonic acid in refluxing C_6H_6 led in good yield to a phenol isomeric with that reported previously.[1] The presence of the proton at C-1 as a 10-cps doublet in the nmr spectrum of **27** confirmed the *trans* assignment. It is of interest that the crude reaction product fails to show any of the 5-cps doublet characteristic of the *cis*

(7) This may actually be a reflection of kinetically controlled protonation rather than thermodynamic stability.

TABLE I

DIHYDRO- AND TETRAHYDRONAPHTHALENES



No.	Reduction stage	R^3	R^2	Mp, °C	Recrystn solvent	% yield	Formula	Analyses
18	Dihydro	H	C_5H_9	88–92	S[a]	33	$C_{22}H_{24}O_2$	C, H
19	Dihydro	CH_2CH_2N⟨ ⟩	C_5H_9	206.5–208	EtOAc–Me_2CO	64	$C_{28}H_{36}ClNO_2$	C, H, Cl
20	Dihydro	$CH_2CHOHCH_2OH$	C_5H_9	Amorphous		50	$C_{25}H_{30}O_4$	...[b]
21	*cis*-Tetrahydro	CH_2CH_2N⟨ ⟩	C_6H_5	211–213	CH_2Cl_2–EtOAc	80	$C_{29}H_{34}ClNO_2$	C, H, Cl
22	*cis*-Tetrahydro	$CH_2CHOHCH_2OH$	C_6H_5	135–136.5	Et_2O	29	$C_{26}H_{28}O_4$	C, H
25	*cis*-Tetrahydro	H	C_6H_9	135–143	S	83	$C_{22}H_{26}O_2$	C, H
23	*cis*-Tetrahydro	CH_2CH_2N⟨ ⟩	C_5H_9	237–240	CH_3CN	64	$C_{28}H_{38}ClNO_2$	C, H, Cl
24	*cis*-Tetrahydro	$CH_2CHOHCH_2OH$	C_5H_9	103–105.5	C_6H_{12}	42	$C_{25}H_{32}O_4$	C, H
27	*trans*-Tetrahydro	H	C_6H_5	55–57.5	Et_2O	56	$C_{28}H_{22}O_2$[c]	C, H
28	*trans*-Tetrahydro	CH_2CH_2N⟨ ⟩	C_6H_5	168–170.5	EtOAc	58	$C_{29}H_{34}ClNO_2$	C, H, Cl
29	*trans*-Tetrahydro	$CH_2CHOHCH_2OH$	C_6H_5	Amorphous		40	$C_{26}H_{28}O_4$	...[b]

[a] Skellysolve B (see ref 8). [b] Material showed a single spot on tlc; satisfactory analysis could not be obtained. [c] Obtained as the ether solvate.

TABLE II

ANTIFERTILITY (AF) AND UTEROTROPIC ACTIVITIES OF DI- AND TETRAHYDRONAPHTHALENES

		Uterotropic act.[b]			
		Without concomitant estradiol		With concomitant estradiol (0.04 μg sc)	
Compd	AF MED_{100},[a] mg	Daily dose/rat, μg	Av uterine wt, mg	Daily dose/rat, μg	Av uterine wt, mg
18	<2.5 sc[d]	100 sc	145 ± 6.4[f]	100 sc	156 ± 0.4 (108 ± 4.4)[c]
19	0.20 sc	200 sc	66 ± 8.0[f]	200 sc	90 ± 12 (108 ± 4.4)
20	0.20 sc	200 sc	32 ± 2.5	200 sc	101 ± 5.2 (108 ± 4.4)
21	0.010 oral[e]				
22	0.025 oral	12.5 oral	62 ± 3.7[f]	12.5 oral	73 ± 3.1[f] (125 ± 7.0)
		50.0 oral	72 ± 4.0[f]	50.0 oral	73 ± 3.1[f] (125 ± 7.0)
		200 oral	89 ± 8.3[f]	200 oral	77 ± 6.1[f] (125 ± 7.0)
		400 oral	89 ± 5.8[f]	400 oral	86 ± 4.0[f] (125 ± 7.0)
25		200 sc	83 ± 5.4[f]	200 sc	120 ± 5.8 (108 ± 4.4)
23	0.010 sc	200 sc	54 ± 3.5[f]	200 sc	60 ± 2.6[f] (108 ± 4.4)
24	0.40 sc	200 sc	67 ± 2.0[f]	200 sc	68 ± 3.0[f] (108 ± 4.4)
28	0.010 oral				
29	0.20 oral				
Estradiol		0.00 sc	25 ± 0.80		
		0.01 sc	39 ± 1.7		
		0.02 sc	58 ± 1.9[f]		
		0.06 sc	121 ± 5.4[f]		

[a] Minimal daily dose at which none of the rats contained implants. [b] Five ovariectomized immature rats per dose, except for estradiol standard where ten were used. [c] Uterine weight induced by 0.04 μg of estradiol. [d] Subcutaneous administration. [e] Oral administration. [f] Significantly different from control (p = <0.01).

isomer. Alkylation of the phenol gave the basic and glyceryl ethers.

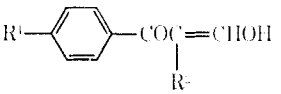
Biological Activities.—Compounds were assayed for antifertility, uterotropic, and estrogen antagonistic properties in the manner described previously.[6] The results of these assays are summarized in Table II.

It is of note that in the basic ether series three of the compounds (**21**, **23**, and **28**) are effective as antifertility agents at a dose of 10 μg/day/rat. In this series neither the nature of the substituent at the 2 position or the stereochemistry seem to have a major influence on potency (with the exception of **19**). The glyceryl ethers (**20**, **22**, **24**, and **29**) are as a rule less potent agents; though one might intuitively expect the more planar *trans*-tetrahydro compound to show the best potency, in fact the *cis* compound **22** is by far the most active compound in this series.

In line with our previous findings, the free phenols (**18**, **25**) augment the uterotropic response of concomitantly administered estrogen. With the notable excep-

TABLE III

α-SUBSTITUTED β-HYDROXYACRYLOPHENONES



No.	R¹	R²	Mp, °C	Recrystn solvent	% yield[a]	Formula	Analyses
8	H	C_6H_5	110–114[b]		90		
9	OCH_3	C_6H_5	83.5–86.5	S[c]	95	$C_{16}H_{14}O_3$	*d*
10	OCH_3	C_5H_9	109–112	Et_2O–S	55	$C_{15}H_{18}O_3$	C, H

[a] Based on ketone consumed. [b] Lit.[5] mp 110°. [c] Skellysolve B. [d] *Anal.* Calcd: C, 75.57; H, 5.55. Found: C, 74.95, 75.09; H, 5.33, 4.98.

tion of **20** each of the ethers induced significant increases in uterine weight at doses equivalent to the antifertility MED_{100}, and antagonized the uterotropic response to concomitantly administered estradiol.

Experimental Section[8,9]

α-Substituted β-Hydroxyacrylophenones (Table III).—Na (6 g) was dissolved in 75 ml of absolute EtOH (heating). The solution was cooled in ice–MeOH and treated with 21.5 ml of ethyl formate. Following 2.5 hr of standing in the cold, 50 g of finely powdered ketone was added with vigorous agitation. The ice was allowed to melt and the pasty mixture was stirred for 16 hr at room temperature. The mixture was then diluted with ice–H_2O to 800 ml and the precipitated solid collected on a filter. There was thus obtained 12.81 g of recovered ketone. The filtrate was again cooled and cautiously acidified with concentrated HCl. The precipitated solid was collected on a filter and dried *in vacuo*.

***m*-Methoxybenzyltriphenylphosphonium Chloride.**—A mixture 44.16 g of *m*-methoxybenzyl chloride and 74.0 g of triphenylphosphine was heated in an oil bath at 100° for 1 hr. The resulting solid cake was broken up and recrystallized from CH_2Cl_2–CH_3CN. There was obtained 86.1 g of salt, mp 271–272°. The mother liquors were concentrated and allowed to cool. An additional 21.6 g of product, mp 271–272°, was obtained (total yield = 91%). *Anal.* ($C_{26}H_{24}OPCl$) C, H, Cl.

Substituted Butyrophenones. (a) 4-(*m*-Methoxyphenyl)-1-(*p*-methoxyphenyl)-2-phenyl-1-butanone.—To a well-stirred, ice-cooled solution of 10.32 g of *p*-methoxy-β-hydroxy-α-phenylacrylophenone in 430 ml of THF there was added 1.84 g of NaH (56% in mineral oil). Following 40 min of stirring, 17.9 g of finely powdered (*m*-methoxybenzyl)triphenylphosphonium chloride was added. Following 18 hr of heating at reflux, the bulk of the solvent was removed *in vacuo*. The residue was worked up in the usual way and chromatographed on Florisil. The mineral oil was washed off with Skellysolve B. Elution with 10% Me_2CO afforded 13.76 g of the isomeric ketones as a series of gums (yield, 84%).

The solution of the crude product obtained from the previous reaction (13.76 g) in 200 ml of EtOH was shaken under H_2 with 1.40 g of 10% Pd–C (starting at 3.5 kg/cm²). When 1 molar equiv of H_2 (10 min) was taken up, the rate of gas uptake slowed considerably. The reaction was stopped and the catalyst was removed by filtration. The slightly oily solid which remained when the filtrate was taken to dryness was recrystallized from MeOH. There was obtained 10.78 g (79%) of ketone, mp 79–85°. *Anal.* ($C_{24}H_{24}O_3$) C, H.

(8) All melting points are uncorrected and recorded as obtained on a Thomas–Hoover melting point apparatus; nmr spectra were obtained in $CDCl_3$ on a Varian A-60A nmr spectrometer. The authors are indebted to the Department of Physical and Analytical Chemistry for elemental analysis and spectral determinations. Those analyses whose results are within ±0.4% of the calculated values are denoted by the symbols for those elements. Chromatography was carried out on Florisil (a synthetic magnesia–silica gel absorbent manufactured by the Floridin Co., Warren, Pa.) with Me_2CO–Skellysolve B as the eluent (Skellysolve B is a saturated hydrocarbon fraction, bp 60–70°, available from Skelly Oil Co., Kansas City, Mo.). Only the percentage Me_2CO is given in the text.

(9) The phrase "worked up in the usual manner" denotes: The residue or mixture was taken up in Et_2O and H_2O, and the organic layer was washed with H_2O and brine and taken to dryness. Acid or basic washes are indicated in parentheses after the phrase.

(b) Proceeding as above, 3.06 g of α-phenyl-β-hydroxyacrylophenone was taken on to 3.76 g of 1,2-diphenyl-4-(*m*-methoxyphenyl)-1-butanone (79% yield). The product was obtained as an oil, ν_{max} 1700 cm⁻¹; single spot on tlc.

(c) Again as above, 4.93 g of α-cyclopentyl-*p*-methoxyacrylophenone was taken on to 3.75 g (53% yield) of **13**. The product was a gum, largely single spot on tlc; nmr: OCH_3 (δ 3.85), OCH_3 (δ 3.70), ratio of Ar*H* to aliphatic 1:2.6.

1,2-Diphenyl-6-methoxy-3,4-dihydronaphthalene (14).—A solution of 3.76 g of crude 1,2-diphenyl-4-(*m*-methoxyphenyl)-1-butanone (used as obtained from the previous step) and 0.75 g of *p*-TsOH in 60 ml of C_6H_6 was heated at reflux under a Dean–Stark trap for 2.5 hr. The solution was worked up in the usual way and the residue was chromatographed on 400 g of Florisil (elution with 0.75% Me_2CO). The crystalline fractions were combined and recrystallized from Skellysolve B. There was obtained 1.57 g of product, mp 98–101° (45% yield). The mixture melting point of this with authentic material was 99–101°.

1-(*p*-Hydroxyphenyl)-4-(*m*-methoxyphenyl)-2-phenyl-1-butanone (15).—A mixture of 11.65 g of 4-(*m*-methoxyphenyl)-1-(*p*-methoxyphenyl)-1-butanone and 13.6 g of $AlCl_3$ in 270 ml of C_6H_6 was heated at reflux for 3.5 hr. The solution was allowed to cool and washed in turn with 2.5 *N* HCl, H_2O, and brine. The organic layer was then extracted with five portions of 110 ml each of 1 *N* NaOH. Acidification of this last extract gave 11.04 g of the crude phenol. A single recrystallization from MeOH–H_2O afforded 8.42 g of product, mp 125–129° (yield 75%). *Anal.* ($C_{23}H_{22}O_3$) C, H.

1-(*p*-Hydroxyphenyl)-2-cyclopentyl-4-(*m*-methoxyphenyl)-1-butanone (16).—A mixture of 3.75 g of the ketone and 4.25 g of $AlCl_3$ in 100 ml of C_6H_6 was heated at reflux for 4 hr. The mixture was allowed to cool, and 50 ml of 2.5 *N* HCl was added. The organic layer was separated, washed once with H_2O, and extracted with six portions of 50 ml each of 1 *N* NaOH. The gum which precipitated when the alkaline extracts were acidified was taken up in ether. This last solution was taken to dryness and the residue was chromatographed on Florisil. The gummy fractions were combined on the basis of tlc to give 2.53 g; nmr: 1 exchangeable proton, 1 OCH_3 (71% yield).

1-(*p*-Hydroxyphenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene (17).—A solution of 5.70 g of 1-(*p*-hydroxyphenyl)-4-(*m*-methoxyphenyl)-1-butanone and 5.70 g of *p*-TsOH in 250 ml of C_6H_6 was heated under a Dean–Stark trap until the evolution of H_2O ceased (2.5 hr). The mixture was allowed to cool and worked up in the usual way ($NaHCO_3$). The residue was recrystallized from Me_2CO–C_6H_{12} to give 4.37 g (82%) of the phenol, mp 158–162°. A small sample was recrystallized to mp 160–162°. The mixture melting point of this with phenol prepared *via* 2-phenyl-6-methoxytetralone (mp 163–165°) was 160–163°.

1-(*p*-Hydroxyphenyl)-2-cyclopentyl-6-methoxy-3,4-dihydronaphthalene (18).—A solution of 2.53 g of the ketone and 2.50 g of *p*-TsOH in 100 ml of C_6H_6 was heated at reflux for 4 hr. The solution was allowed to cool and worked up in the usual way ($NaHCO_3$). The residue was chromatographed on 250 ml of silica gel (elution with CH_2Cl_2). The crystalline fractions were combined and recrystallized twice.

***cis*-1-(*p*-Hydroxyphenyl)-2-cyclopentyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (25).**—A mixture of 4.65 g of the phenol and 0.46 g of 10% Pd–C in 200 ml of EtOAc was shaken under H_2 until 1 equiv was taken up (1 hr). The catalyst was collected on a filter and the filtrate was taken to dryness. The residue was recrystallized to give 4.00 g of tetrahydro compound.

1-(*p*-Hydroxyphenyl)-2-phenyl-4-(*m*-methoxyphenyl)-1-butanol (26).—A solution of 2.0 g of 1-(*p*-hydroxyphenyl)-2-phenyl-4-(*m*-methoxyphenyl)-1-butanone in 50 ml of THF was added to 1.0 g of LAH in 10 ml of THF over 10 min. Following 2 hr of stirring at room temperature the mixture was cooled in ice and 50 ml each of saturated NH_4Cl and H_2O were added. The inorganic gel was removed by filtration through Supercel. The organic layer was diluted with Et_2O, washed with H_2O and brine, and taken to dryness. The residual solid was recrystallized twice from C_6H_6 to give 1.01 g of the carbinol, mp 100–103° (50% yield). *Anal.* ($C_{23}H_{24}O_3$) C, H.

***trans*-1-(*p*-Hydroxyphenyl)-2-phenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene.**—A solution of 6.35 g of the carbinol and 3.80 g of *p*-TsOH in 250 ml of C_6H_6 was heated for 2 hr under a Dean–Stark trap. It was then allowed to cool and worked up in the usual way ($NaHCO_3$). The residue was chromatographed over silica gel (elution with CH_2Cl_2). Those fractions which were similar to tlc were combined and chromatographed over Florisil (elution with 5% Me_2CO). Those fractions which crystallized on trituration with Et_2O were combined and recrystallized. There was obtained 3.32 g of the tetralin as its Et_2O solvate; nmr: doublet (1 H) δ 4.05 (J = 10 cps).

2,N-Pyrrolidinoethoxy Ethers.—To a solution of 1.46 g of the phenol in 9 ml of DMF and 50 ml of C_6H_6 there was added 0.19 g of 56% NaH in mineral oil and, after effervescence had ceased (20 min), 1.19 g of a 1:1 mixture of PhMe and N-(β-chloroethyl)-pyrrolidine. The mixture was heated at reflux overnight, allowed to cool, and diluted with an equal volume of Et_2O. The organic solution was washed with H_2O and brine and taken to dryness. The residual gum was dissolved in Et_2O, and extracted with 2.5 *N* HCl. These aqueous extracts were combined and extracted in turn with CH_2Cl_2. The solid which remained when this last solution was taken to dryness was recrystallized.

Glyceryl Ethers. To a solution of 2.0 g of the phenol in 40 ml of MeOH was added 1.5 ml of 4.65 *N* NaOMe in MeOH followed after 10 min by 0.73 g of 1-chloro-2,3-propanediol. Following 18 hr of heating under reflux the mixture was taken to dryness. The residue was worked up in the usual way and chromatographed on Florisil. Elution with 10% Me_2CO gave recovered phenol. The product was obtained on elution with 50% Me_2CO.

3-Deoxy-16-haloestra-1,3,5(10)-trienes

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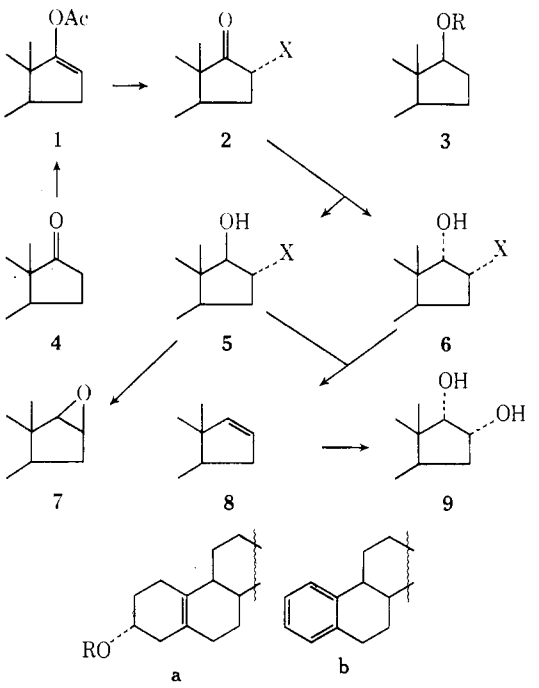
Formation of 3-deoxyestratriene derivative **2b** occurs as a side product in the preparation of 16-halo-19-norandrostanes **2a**. An efficient alternate route to these materials proceeds through halogenation of the enol acetate **1b**. Both the halo ketones **2b** and their derivative alcohols exhibit interesting lipodiatic properties.

The potentially valuable lipodiatic[1] (lipid-shifting) properties of the 16-haloestrone derivatives[2] in prevention of atherosclerosis gave impetus to a program of synthesizing both androstane[3] and 19-norandrostane analogs. Although the biological activities of the target compounds were not outstanding, a pharmacologically potent by-product arose in the synthesis of the norandrostanes. The identification of this compound and the preparation of related compounds form the subject of the present communication.

Synthesis of the 16-halo-19-norandrostanes was initiated by treatment of the 3α-hydroxy ketone **4a**[4] with isopropenyl acetate. The resultant enol diacetate **1a** was chlorinated under neutral conditions to provide chiefly the 16-chloro ketone **2a** (see Scheme I). A similar reaction of enol diacetate **1a** with Br_2 provided the analogous bromo ketone **2a**. The α configuration of the halogen atoms in these compounds is postulated on the basis of the α-face attack demonstrated in other steroidal C-17 enol acetates.[2] Treatment of the chloro ketone **2a** with LAH produced a mixture of the epimeric 17-alcohols (**5a**, **6a**). The first of the pair eluted from a chromatographic column is assigned the 17α-(pseudo axial) configuration **5a**[5] (see also the proof below for **5b**).

Acid-catalyzed hydrolysis of the 3-acetate group of **2a** (X = Br, Cl) proceeded efficiently without causing the halogen loss seen with use of base.[2b] When the

SCHEME I



R = H, $COCH_3$; X = Cl, Br, I

total chlorination product of enol diacetate **1a** was subjected to acid hydrolysis, a monooxygenated material was isolated in *ca.* 10% yield. Low-intensity uv maxima at 266 and 273 mμ, a strong ir band at 13.4 μ (characteristic of four adjacent aromatic protons),[6] and

(1) A. H. Goldkamp, W. H. Hoehn, R. A. Mikulec, E. F. Nutting, and D. L. Cook, *J. Med. Chem.*, **8**, 409 (1965).

(2) (a) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958); (b) G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961).

(3) W. F. Johns, U. S. Patent 2,911,418 (1959).

(4) W. F. Johns, *J. Org. Chem.*, **29**, 1490 (1964).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 14.

(6) A. S. Dreiding, W. J. Pummer, and A. J. Tomasewski, *J. Am. Chem. Soc.*, **75**, 3159 (1953).