Ring-D-Bridged Steroid Analogs. V.[1] 14α,17α-Etheno-15,16-di(trifluoromethyl)pregna-4,15-diene-3,20-dione and 14α,17α-Ethano-15β,16β-di(trifluoromethyl)pregn-4-ene-3,20-dione[2]

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Diels–Alder addition of hexafluoro-2-butyne to 3β-acetoxy-20-keto-5,14,16-pregnatriene (I) afforded 14α,17α-etheno-15,16-di(trifluoromethyl)pregna-5,15-dien-3β-ol-20-one acetate (IIa). Hydrolysis of the acetate, followed by Oppenauer oxidation resulted in the formation of 14α,17α-etheno-15,16-di(trifluoromethyl)pregna-4,15-diene-3,20-dione (III). Selective catalytic reduction of IIa gave 14α,17α-ethano-15β,16β-di(trifluoromethyl)-pregn-5-en-3β-ol-20-one acetate (IVa) which was converted to 14α,17α-ethano-15β,16β-di(trifluoromethyl)-pregn-4-ene-3,20-dione (V). Compounds III and V were found to be weakly active when administered by subcutaneous injection in the Clauberg assay. In a more definitive assay than that previously reported, 14α,17α-ethenopregn-4-ene-3,20-dione was found to have only about 54% the activity of progesterone in the Clauberg assay.

The Clauberg activity found in the preliminary assays of 14α,17α-ethenopregn-4-ene-3,20-dione[1] encouraged us to attempt to synthesize other progestationally active 14α,17α-bridged steroids. Since we have formed the bridged D ring of such compounds by Diels–Alder addition to the β face of 3β-acetoxy-20-keto-5,14,16-pregnatriene,[1,4,5] in principle, a variety of substituents could be introduced at the 15 and 16 positions by suitable choice of dienophile.

The presence of a 16α-methyl or a 16-methylene group appears to be consistent with high progestational activity,[6-8] but such groups would be among the most difficult to introduce by the desired path. Conversely, while carboxy, carboalkoxy, and cyano groups would be expected to be easily introduced at the 16 position by our synthesis, the resulting compounds would not be expected to be active since, while the corresponding 16α-substituted progesterones are well-known compounds, high progestational activity has never been claimed for them.[9,10] In fact, we have previously synthesized 14α,17α-etheno-16α-carbomethoxypregn-4-ene-3,20-dione and found it to be essentially inactive as a gestagen.[5]

Hexafluoro-2-butyne has been reported to be highly reactive as a dienophile.[11,12] As the effect on Clauberg activity of a trifluoromethyl group at the 15 or 16 position of progesterone analogs has not been reported[13,14] and as the trifluoromethyl group appears to be intermediate between methyl and carboalkoxy in its effects on physical properties, it seemed of interest to use hexafluoro-2-butyne in an attempt to synthesize 15,16-di(trifluoromethyl) ring-D-bridged progesterone analogs.

Heating 3β-acetoxy-20-keto-5,14,16-pregnatriene (I) with hexafluoro-2-butyne led to the formation of 14α,17α-etheno-15,16-di(trifluoromethyl)pregna-5,15-dien-3β-ol-20-one acetate (IIa). The similarity in the vinyl hydrogen region of the nmr spectrum of IIa to those of closely related Diels–Alder adducts[1,5,15] supports its gross structure. The assumption of β-face attack on the D ring is, as is the case with our other adducts,[15] based on the fact that only one isomer could be isolated from the reaction and therefore presumably is formed by attack on the diene from the less hindered side. Both the appearance of models and the results of catalytic hydrogenation[16] indicate that the less hindered side of steroidal 14,16-diene systems is the β side. After the acetate group of IIa was removed by hydrolysis, the resulting alcohol was oxidized[17] to afford 14α,17α-etheno-15,16-di(trifluoromethyl)pregna-4,15-diene-3,20-dione (III).

Hydrogenation of II resulted in selective reduction of the ring D double bonds to afford 14α,17α-ethano-15β,16β-di(trifluoromethyl)pregn-5-en-3β-ol-20-one acetate (IVa) in 84% yield. The gross structure of IVa is supported by its nmr spectrum which indicates the continued presence of the 5-vinyl hydrogen but which shows no other vinyl hydrogens. The stereochemistry of IVa is that which would be predicted from a study of models and is in accord with the demonstrated result of catalytic reduction of 14α,17α-etheno-16-carbomethoxypregna-5,15-dien-3β-ol-20-one acetate.[18] The acetate group of IVa was hydrolyzed and the resulting alcohol was oxidized[17] to form 14α,17α-ethano-15β,16β-di(trifluoromethyl)pregn-4-ene-3,20-dione (V).

Results of Biological Testing.—Table I summarizes the results obtained by subcutaneous administration

(1) Part IV: A. J. Solo and B. Singh, *J. Med. Chem.*, **9**, 957 (1966).

(2) This work was supported in part by Grants AM-06900-03 and AM-06900-04 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(3) To whom inquiries concerning this work should be directed.

(4) A. J. Solo and B. Singh, *J. Org. Chem.*, **30**, 1658 (1965).

(5) A. J. Solo and B. Singh, *J. Med. Chem.*, **9**, 179 (1966).

(6) N. Appelzweig "Steroid Drugs," Vol. II, Holden-Day Inc., San Francisco, Calif, 1964.

(7) R. P. Graber, M. B. Meyers, L. G. Hickman, E. H. Borochoff, and A. D. Odell, *J. Med. Chem.*, **7**, 540 (1964).

(8) Z. Cekan, M. Seda, J. Mikalaskova, and K. Syhora, *Steroids*, **4**, 115 (1964).

(9) J. Runo, *Tetrahedron*, **3**, 37 (1958).

(10) B. Ellis, V. Petrow, and D. Wallake, *J. Chem. Soc.*, 3748 (1958).

(11) R. E. Putnam, R. J. Harder, and J. E. Castle, *J. Am. Chem. Soc.*, **83**, 391 (1961).

(12) C. G. Krespan, B. C. McKusick, and T. L. Cairns, *ibid.*, **83**, 3428 (1961).

(13) The 16α-fluoromethyl-, difluoromethyl-, and trifluoromethylprogesterones have been reported and are described as hypnotic agents and of use in the treatment of premenstrual tension.[14a] The preparation of other 16α-trifluoromethyl-substituted progesterone analogs has been described.[14b]

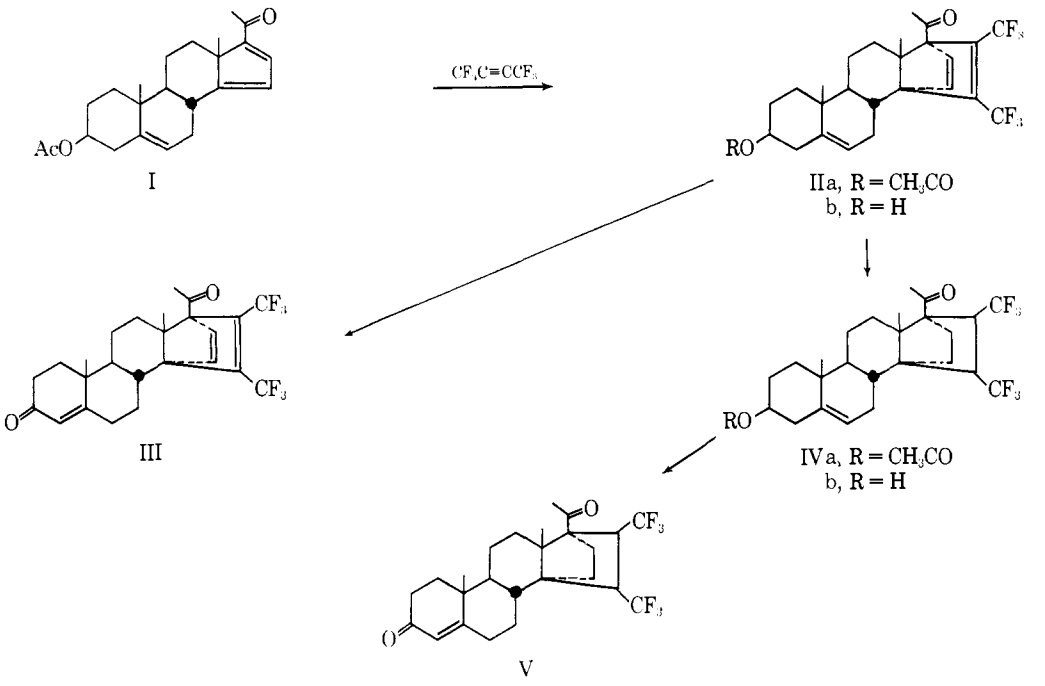
(14) (a) A. Bowers and J. A. Edwards, U. S. Patent 3,151,132 (Sept 29, 1964); *Chem. Abstr.*, **62**, 618 (1965); (b) Syntex, British Patent 994,743 June 10, 1965); *Chem. Abstr.*, **63**, 16422 (1965).

(15) A. J. Solo, H. S. Sachdev, and S. S. H. Gilani, *J. Org. Chem.*, **30**, 765 (1965).

(16) P. A. Plattner, H. Heusser, and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

(17) C. Djerassi, *Org. Reactions*, **6**, 207 (1951).

(18) A. J. Solo and B. Singh, unpublished results.



of 14α,17α-ethenopregn-4-ene-3,20-dione,[1] III, and V to immature estrogen-primed rabbits under the conditions of the modified Clauberg assay.[19] Histological preparations of uterine tissue were examined and graded from 0 to 4+ for degree of progestational proliferation.[19] The more extensive testing, reported here, indicates that 14α,17α-ethenopregn-4-ene-3,20-dione is only about 54%[20] as effective as progesterone in the Clauberg assay, rather than several times as effective, as found in the preliminary assay.[1] Introduction of the 15,16-di(trifluoromethyl) groups results in a loss in activity, but the effect is not as great as that produced by a 16α-carbomethoxy group.[5]

Discussion

The low Clauberg activity of 14α,17α-ethenopregn-4-ene-3,20-dione compared to that of 17α-ethylprogesterone[21] was at first surprising in that the activity of these compounds supports the view[22] that interaction of a gestagen with a Clauberg receptor does not involve the α side of the gestagen, at least in the vicinity of the D ring. Moreover, both compounds should be resistant to metabolic degradation of the side chain, and they should have comparable polarities. However, insertion of a two-carbon bridge between the 14α and 17α positions of progesterone requires a small deformation of the D ring which results in the 17-acetyl group being deflected toward the α side. Consideration of possible reasons why such a deformation might result in a lowering of Clauberg activity led us to the following hypothesis: if a plane, parallel to the average plane of a gestagen, is imagined to pass through the critical A ring and C-17 substituents,[23] then, for maximum Clauberg activity, the protrusion of the molecule above the plane, in the vicinity of the A/B junction, should be minimal. Activity seems to decrease as the bulk in this region increases and to disappear entirely as the height of the protrusion exceeds that of the 10β-methyl group of progesterone. On the other hand, in the vicinity of the C/D junction, optimum activity requires that a group protrude above the plane at least as far as the 13β-methyl group of progesterone and preferably as far as a 13β-ethyl group. This rule is concerned only with the fit of the gestagen to the Clauberg receptor site and not with the shape of the molecule in its most stable conformation. Therefore, in applying this rule, the molecule must be viewed in that conformation which places the critical A- and D-ring substituents closest to the positions which they would occupy in progesterone or in ethisterone.

We believe that this hypothesis not only correlates the activities of all normal progesterone and ethisterone analogs, but that it also accommodates skeletal isomers, such as the retroprogesterones.[24] In addition, it accounts for the fact that 14-iso-17-isoprogesterone is inactive[25] while the corresponding 19-nor compound is highly active,[26] since in these compounds both the 10 and 14 positions are unusually far above the hypothetical plane. The presence of a 10β-methyl group in such a situation presumably leads to prohibitive steric interaction with the receptor. The shape of the β face of our 14α,17α-ethenopregn-4-ene-3,20-dione is strikingly similar to that of 14-iso-17-isoprogesterone, thus suggesting that the low activity of our ring-D-bridged compounds is due, at least in part, to greater than normal unfavorable interaction of the 10β-methyl group with the receptor.

A corollary of the above hypothesis is that the 13β substituent is not a specific binding point for the Clau-

(19) Biological testing was performed at the Endocrine Laboratory, Madison, Wis.

(20) Graphical estimate at 2.0+ response level.

(21) (a) R. Deghenghi, C. Revesz, and R. Gaudry, *J. Med. Chem.*, **6**, 301 (1963); (b) M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr., and C. J. Coscia, *Chem. Ind.* (London), 118 (1963).

(22) H. J. Ringold in "Mechanism of Action of Steroid Hormones," C. A. Villee and L. L. Engel, Ed., Pergamon Press, Oxford, 1961, p 200.

(23) The critical C-17 substituent is usually the oxygen either of an acetyl group or of a tertiary alcohol. The A-ring substituent is generally a double bond at the 4 position. Both of the critical groups must be available for β-face binding.

(24) H. F. L. Scholer, *Acta Endocrinol.*, **35**, 188 (1960).

(25) P. A. Plattner, H. Heusser, and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

(26) G. W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957).

TABLE I
PROGESTATIONAL ACTIVITY IN A MODIFIED CLAUBERG ASSAY (SUBCUTANEOUS INJECTION)[a]

Material administ	Total dose, mg	No. of rabbits	Mean uterine wt, g	Range of proliferation index	Mean proliferation index
Progesterone	0.2	7	1.19	0.5[b]–2.0[b]	0.86[b]
	0.5	5	2.10	3.0[b]–4.0[b]	3.5[b]
	1.0	2	2.24	4.0[b]	4.0[b]
14α,17α-Ethenopregn-4-ene-3,20-dione	0.05	2	1.30	0.0	0.0
	0.1	2	1.42	0.0	0.0
	0.2	9	1.17	0.0–2.0[b]	0.44[b]
	0.5	7	1.62	0.5[b]–3.5[b]	1.9[b]
	1.0	2	2.64	4.0[b]	4.0[b]
	5.0	2	3.69	4.0[b]	4.0[b]
III	0.1	2	1.10	0.0	0.0
	0.2	2	0.90	0.0	0.0
	0.5	2	0.91	0.0	0.0
	1.0	2	0.72	0.0	0.0
	5.0	2	1.16	0.0	0.0
	20.0	2	2.36	2.5[b]–3.0[b]	2.8[b]
	0.1	2	1.09	0.0	0.0
	0.2	2	1.00	0.0	0.0
	0.5	2	0.92	0.0	0.0
	1.0	2	1.05	0.0	0.0
	5.0	2	1.78	3.0[b]–3.5[b]	3.3[b]

berg receptor.[27] This view is supported both by the fact that homologation of the 13β-methyl group of progesterone or of norethisterone results in an increase in activity,[28] and by the fact that compounds such as 19-nor-14-iso-17-isoprogesterone[26] demonstrate that high activity can be retained in compounds in which the angular relationship between the 13β-methyl group and the acetyl side chain differs greatly from that of progesterone. Since it has been shown that 18-norprogesterone derivatives have little Clauberg activity,[29] the 13β-alkyl group must have some important role in conferring such activity. One possibility is that the 13β substituent acts as a wedge to prevent too strong an interaction between the 17 substituent and its receptor site.[30] Support for this view is provided by the recent report that 2-(1-ethynyl-1-hydroxyethyl)-7-oxo-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene has appreciable Clauberg activity.[31] The lack of an intact D ring increases the entropy of the "C-17" substituent and may thus compensate for the lack of a "13β-substituent" in this compound. A second possible explanation of the role of the 13β substituent is that it acts as a wedge in the sense that it protrudes into the receptor site in such a way as to force a conformational change in the receptor molecule.[32,33] Such a conformational change might result either in the creation or destruction of other types of receptor (or "active") sites on that molecule, thus explaining how the gestagen initiates the chain of action which is manifest as Clauberg activity. Attempts to test these various proposals are currently underway in this laboratory.

Experimental Section[34]

14α,17α-Etheno-15,16-di(trifluoromethyl)pregna-5,15-dien-3β-ol-20-one Acetate (IIa).—A mixture of 6.05 g of 3β-acetoxy-20-keto-5,14,16-pregnatriene[4] (I), 7–8 ml of hexafluoro-2-butyne, and 30 mg of hydroquinone was sealed in a steel bomb with a glass liner (capacity 85 ml) and heated at 120° for 164 hr. The crude product was chromatographed over 100 g of Merck acid-washed alumina. Elution with 400 ml of 1:1 hexane–benzene afforded the adduct IIa in a yield of 5.15 g (57%) as a light yellow semi-solid: ν_{max}^{neat} 1735, 1715, 1650 cm^{-1}. The vinyl protons appeared in the nmr spectrum at δ 5.40 (m), 6.97 (d), and 7.06 (d).

Anal. Calcd for $C_{27}H_{30}F_6O_3$: C, 62.70; H, 5.81. Found: C, 62.62; H, 5.82.

14α,17α-Etheno-15,16-di(trifluoromethyl)pregna-5,15-dien-3β-ol-20-one (IIb).—A solution of 295 mg of 14α,17α-etheno-15,16-di(trifluoromethyl)pregna-5,15-dien-3β-ol-20-one acetate (IIa), 500 mg of KOH, and 2.25 ml of water in 20.0 ml of methanol was stirred at room temperature for 25 hr. Standard work-up gave IIb as a pale yellow foam, in a yield of 235 mg (85%): ν_{Nujol}^{max} 3440, 1715, and 1650 cm^{-1}. The vinyl protons appeared in the nmr spectrum at δ 5.41 (m), 6.97 (doublet, J = 5.3 cps), and 7.06 (doublet, J = 5.3 cps).

Anal. Calcd for $C_{25}H_{28}F_6O_2$: C, 63.29; H, 5.91. Found: C, 63.40; H, 6.05.

14α,17α-Etheno-15,16-di(trifluoromethyl)pregna-4,15-diene-3,20-dione (III).—A solution of 1.88 g of IIb and 12.0 ml of cyclohexanone in 200 ml of toluene was azeotroped under a Dean-Stark head until water stopped coming off. After the solution had cooled to room temperature, 1.85 g of aluminum isopropoxide was added. Refluxing was resumed for 2 hr. After standard work-up, the crude product was purified by chromatography

(27) It is not a specific binding point in the sense that it does not bind by van der Waals forces.

(28) (a) R. A. Edgren, H. Smith, D. L. Peterson, and D. L. Carter, *Steroids*, **2**, 319 (1963); (b) G. A. Hughes, T. Y. Jen, and H. Smith, *ibid.*, **8**, 947 (1966).

(29) (a) G. Stork, H. N. Khastigir, and A. J. Solo, *J. Am. Chem. Soc.*, **80**, 6457 (1958); (b) W. F. Johns, *ibid.*, **80**, 6456 (1958); (c) R. Anliker, M. Muller, M. Perelman, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, **42**, 1071 (1960); (d) H. A. Salhanick and J. Swanson, *Acta Endocrinol. Suppl.*, **51**, 903 (1960).

(30) Such a requirement might exist if the gestagen must be adsorbed and then desorbed before its activity could be manifest or if, in the absence of such a steric wedge, strong interaction between the 17 substituent and its receptor could pull the gestagen into a position in which a necessary, but weak, interaction between a remote substituent and its receptor would be impossible.

(31) (a) A. Boris, *Endocrinology*, **76**, 1062 (1965); (b) A. Boris and R. H. Stevenson, *ibid.*, **78**, 549 (1966).

(32) The second proposed mechanism would require that 2-(1-ethynyl-1-hydroxyethyl)-7-oxo-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene exerts its activity by means of some mechanism other than interaction with the normal Clauberg receptor.

(33) We do not intend to convey the impression that no other explanations are conceivable.

(34) Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The infrared spectra were determined on a Perkin-Elmer Infracord Model 137 or on a Beckman IR-8 spectrophotometer. Nmr spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer and are reported in ppm downfield from Me_4Si (internal standard).

over a column of 100 g of Merck acid-washed alumina. Fractions containing the product were eluted by benzene containing up to 10% ethyl acetate. Crystallization from acetone–hexane gave III in a yield of 988 mg (62%) as fine white needles: mp 184.5–185.5°; ν^{Nujol} 1710, 1665, and 1620 cm^{-1}. The vinyl protons appeared in the nmr at δ 5.77 (s) and 7.01.

Anal. Calcd for $C_{25}H_{26}F_6O_2$: C, 63.56; H, 5.51; F, 24.15. Found: C, 63.31; H, 5.53; F, 23.92.

14α,17α-Ethano-15β,16β-di(trifluoromethyl)pregn-5-en-3β-ol-20-one Acetate (IVa).—A solution of 2.46 g of IIa in 200 ml of methanol plus 5 ml of water was hydrogenated over 256 mg of 10% Pd–C at 3.66 kg/cm^2 and room temperature for 12 hr. After the catalyst had been filtered off, the solvent was removed under reduced pressure. The residue was crystallized from hexane to afford IVa, in a yield of 2.14 g (84%), as granular particles: mp 145–146°; ν^{Nujol} 1730, 1707, and 1642 cm^{-1}. The C-6 vinyl proton appeared in the nmr at δ 5.42 (m).

Anal. Calcd for $C_{27}H_{34}F_6O_3$: C, 62.30; H, 6.58; F, 21.92. Found: C, 62.54; H, 6.39; F, 22.02.

14α,17α-Ethano-15β,16β-di(trifluoromethyl)pregn-5-en-3β-ol-20-one (IVb).—A solution of 2.01 g of IVa, 2.05 g of KOH, and 5 ml of water in 55 ml of methanol was stirred at room temperature for 24 hr. After standard work-up the crude product was crystallized from acetone–hexane to afford IVb, in a yield of 1.61 g (88%), as tiny white rods: mp 194–195°; ν^{Nujol} 3545, 1701, and 1643 cm^{-1}. The C-6 vinyl proton appeared in the nmr spectrum at δ 5.40.

Anal. Calcd for $C_{25}H_{32}F_6O_2$: C, 62.76; H, 6.69. Found: C, 63.00; H, 6.57.

14α,17α-Ethano-15β,16β-di(trifluoromethyl)pregn-4-ene-3,20-dione (V).—A solution of 1.24 g of IVb, 12.0 ml of cyclohexanone, and 150 ml of toluene was azeotroped as described for III, 1.24 g of aluminum isopropoxide was added, and refluxing resumed for 2 hr. After standard work-up the residue was partitioned between ether and HCl. The residue from the ether solution was chromatographed over 40 g of Merck acid-washed alumina. Fractions eluted by passage of 400 ml of benzene followed by 400 ml of benzene containing 5% ethyl acetate gave 882 mg of crude product. Crystallization from acetone–hexane gave V, in a yield of 785 mg (64%), as light yellow flakes: mp 159–161°; ν^{Nujol} 1697, 1668, and 1616 cm^{-1}. The C-4 vinyl proton appeared in the nmr spectrum at δ 5.71.

Anal. Calcd for $C_{25}H_{30}F_6O_2$: C, 63.02; H, 6.30. Found: C, 63.03; H, 6.11.

Mammalian Antifertility Agents. V. 5,6-Diarylhydronaphthalenones[1]

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A series of derivatives of 5,6-diphenyltetra- and -hexahydronaphthalenes was prepared, incorporating such features as carbonyls in the 2 position and an angular methyl group at 4a. Several of the compounds are active as antifertility and uterotropic agents.

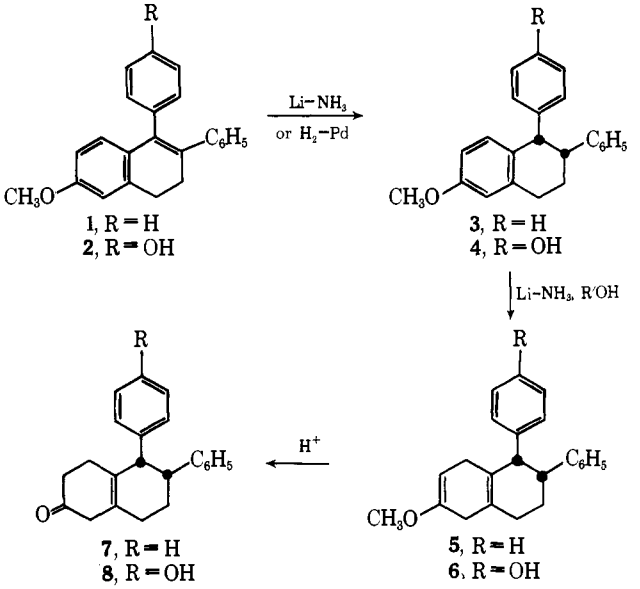
It is well known that estrogenic responses are elicited by many organic molecules devoid of the steroid nucleus;[2] suitable modification of such structures has led to the development of an impressive array of structures which, at least in laboratory animals, will act as estrogen antagonists.[3] Except for a few reports of nonsteroidal androgens,[4] no similar success has met attempts to prepare nonsteroidal counterparts of the other gonadal hormones.

In the steroid series, reduction of the aromatic A ring of ethynylestradiol to the corresponding 3-oxo derivative leads from a potent estrogen to a compound which exhibits many of the properties of a progestin. The observation that certain derivatives of 1,2-diphenyldihydronaphthalenes are potent estrogens[5] prompted us to prepare the counterparts of those compounds in which the moiety corresponding to the steroid A ring was reduced to a ketone.

Our initial approach consisted in the straightforward reduction of the conjugated double bond by lithium in liquid ammonia (see Scheme I). Compounds **1** and **2** were treated with a controlled amount of the metal in ammonia to afford the tetralins **3** and **4**; the observed 5-cps splitting constant for the proton at position 1

Scheme I

Lithium–Ammonia Reductions of 1,2-Diaryl-3,4-Dihydro-6-Methoxynaphthalenes



leads to the conclusion that each of these has the *cis* configuration.[6] Support for this stereochemical assignment comes from the observation that catalytic reduction of **2** leads to a sample of the reduced product identical in all respects with that obtained from the lithium–ammonia reduction. This departure from the

(1) Previous paper in this series: D. Lednicer, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **10**, 78 (1967).

(2) J. A. Hogg and J. Korman, "Medicinal Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1956, p 34.

(3) For a recent review see D. Lednicer, *Ann. Rept. Med. Chem.*, **2**, 199 (1966).

(4) See, for example, R. I. Dorfman and D. Stevens, *Endocrinology*, **67**, 394 (1960).

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

(6) W. L. Bencze, R. W. J. Carney, L. I. Barsky, A. A. Renzi, L. Dorfman, and G. deStevens, *Experientia*, **21**, 261 (1965); these authors report a J value of 5 cps for an analogous system.