

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°;  $\nu^{\text{Nujol}}$  1710, 1665, and 1620  $\text{cm}^{-1}$ . The vinyl protons appeared in the nmr at  $\delta$  5.77 (s) and 7.01.

*Anal.* Calcd for  $\text{C}_{25}\text{H}_{32}\text{F}_6\text{O}_2$ : C, 63.56; H, 5.51; F, 24.15. Found: C, 63.31; H, 5.53; F, 23.92.

**14 $\alpha$ ,17 $\alpha$ -Ethano-15 $\beta$ ,16 $\beta$ -di(trifluoromethyl)pregn-5-en-3 $\beta$ -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<sup>2</sup> 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°;  $\nu^{\text{Nujol}}$  1730, 1707, and 1642  $\text{cm}^{-1}$ . The C-6 vinyl proton appeared in the nmr at  $\delta$  5.42 (m).

*Anal.* Calcd for  $\text{C}_{27}\text{H}_{34}\text{F}_6\text{O}_3$ : C, 62.30; H, 6.58; F, 21.92. Found: C, 62.54; H, 6.39; F, 22.02.

**14 $\alpha$ ,17 $\alpha$ -Ethano-15 $\beta$ ,16 $\beta$ -di(trifluoromethyl)pregn-5-en-3 $\beta$ -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°;  $\nu^{\text{Nujol}}$  3545, 1701, and 1643  $\text{cm}^{-1}$ . The C-6 vinyl proton appeared in the nmr spectrum at  $\delta$  5.40.

*Anal.* Calcd for  $\text{C}_{25}\text{H}_{32}\text{F}_6\text{O}_2$ : C, 62.76; H, 6.69. Found: C, 63.00; H, 6.57.

**14 $\alpha$ ,17 $\alpha$ -Ethano-15 $\beta$ ,16 $\beta$ -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°;  $\nu^{\text{Nujol}}$  1697, 1668, and 1616  $\text{cm}^{-1}$ . The C-4 vinyl proton appeared in the nmr spectrum at  $\delta$  5.71.

*Anal.* Calcd for  $\text{C}_{25}\text{H}_{30}\text{F}_6\text{O}_2$ : C, 63.02; H, 6.30. Found: C, 63.03; H, 6.11.

## Mammalian Antifertility Agents. V. 5,6-Diarylhydronaphthalenes<sup>1</sup>

DANIEL LEDNICER, D. EDWARD EMMERT, GORDON W. DUNCAN, AND STANLEY C. LYSER

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

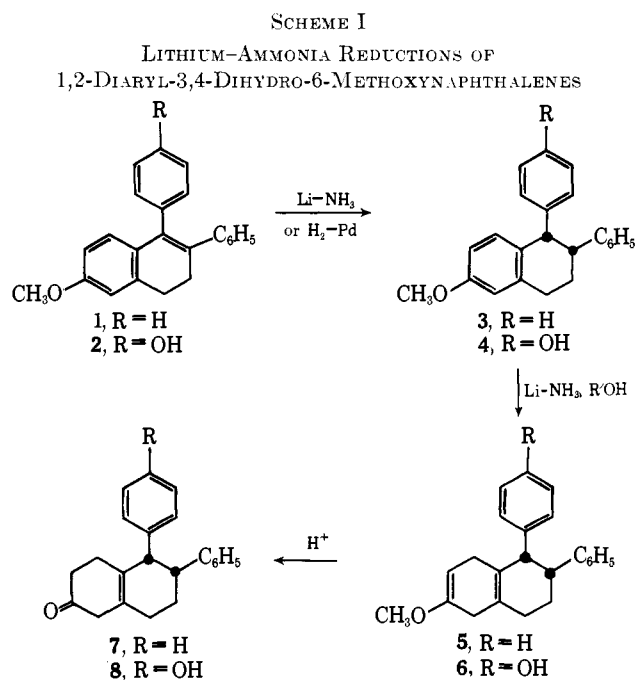
Received June 6, 1967

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 uterotrophic agents.

It is well known that estrogenic responses are elicited by many organic molecules devoid of the steroid nucleus;<sup>2</sup> 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.<sup>3</sup> Except for a few reports of nonsteroidal androgens,<sup>4</sup> 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-diphenylhydronaphthalenes are potent estrogens<sup>5</sup> 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



leads to the conclusion that each of these has the *cis* configuration.<sup>6</sup> 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).

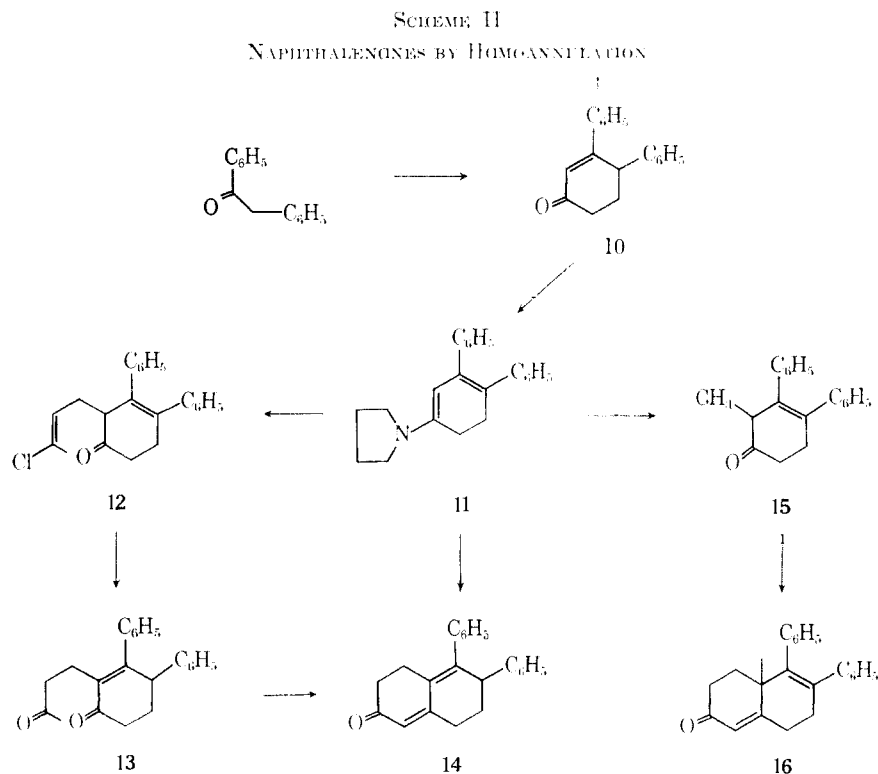
(2) J. A. Hogg and J. Korman, "Medicinal Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1956, p 34.

(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. Benzecr, 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.



usual<sup>7</sup> stereochemical path of metal reduction probably arises from peculiarities of the system involved.<sup>8</sup>

Subsequent treatment of the tetralins under the standard conditions for the Birch reduction gave the enol ethers **5** and **6**; acid hydrolysis of these ethers afforded the desired enones **7** and **8**.

The approach in which the A ring was elaborated by a variation of the Robinson homoannulation procedure seemed most suitable for the preparation of compounds incorporating steroid features such as **14** and **16**. Reaction of methyl vinyl ketone with deoxybenzoin followed by enamine formation gave the key intermediate **11**. The presence of a one-proton singlet at  $\delta$  4.75 in the nmr spectrum of this compound confirmed its formulation as **11**. Reaction of this with methyl vinyl ketone followed by hydrolysis gave a very low yield of the desired bicyclic product **14**. We next resorted to an enamine route analogous to the recently developed method involving the use of 1,3-dichloro-2-butene.<sup>9</sup> Alkylation of the enamine with this halide followed by hydrolysis led to the labile product **12**; interestingly, the infrared spectrum ( $\nu_{\max}$  1702  $\text{cm}^{-1}$ ) showed this to be the unconjugated ketone. Brief treatment in concentrated sulfuric acid gave a mixture of the hydrolysis product **13** and the cyclized product **14**. The former, obtained only in crude form, was treated with *p*-toluenesulfonic acid in benzene to afford additional naphthalenone. In practice it proved more convenient to carry out the sequence without isolation of intermediates.

Treatment of the enamine **11** with methyl iodide followed by hydrolysis gave the methylated product **15**. The presence of a three-proton doublet at  $\delta$  1.16

showed that here again the double bond had not isomerized under the conditions of the enamine alkylation. Treatment of this ketone with methyl vinyl ketone in the presence of alcohol-free sodium methoxide gave the desired ketone **16**.

**Biological Activity.**—Compounds **3**, **7**, **14**, and **16** completely inhibited pregnancy at 2, 0.5, 1, and 10 mg/rat/day, respectively, when tested for antifertility effects in mature female rats.<sup>1</sup> Each of these induced an estrogenic response in the rat uterine-weight assay (Table I); the magnitude of the response and the relative potencies of these compounds in this assay strongly suggest that their estrogenic effects are sufficient to account for the observed antifertility activity. It is of interest that **16**, which has an angular methyl group, was substantially less potent than its close analog **14**.

Both **14** and **16** were assayed for androgenic and antiandrogenic activity. Compound **16** was without effect in either assay; **14**, inactive in the androgenic assay, caused slight enhancement of seminal vesicle

TABLE I  
ANTIFERTILITY AND UTEROTROPIC ACTIVITY

Compd	AF MED <sub>50</sub> <sup>a</sup>	Daily dose, $\mu\text{g}$	Uterine wt <sup>b</sup> $\mu\text{g}$
3	2	0.1	110
		0.2	127
		0.025	87
7	0.5	0.05	105
		0.1	119
		0.01	73
14	1	0.02	83
		0.1	129
		0.4	145
16	10	1	94
		2.5	105
		5	124

<sup>a</sup> Minimum effective antifertility dose in mg/rat/day orally; 10 days consecutive treatment. <sup>b</sup> Average of five rats/dose. Vehicle controls averaged 26 mg.

(7) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 50 ff.

(8) Protonation of the metalation product would lead to a benzhydryl anion at the 1 position; a transient red color was observed in the course of the reduction. Molecular models suggest that the least hindered approach to that carbanion site is from the side leading to the *cis* product.

(9) L. Veluz, G. Nomine, and G. Mathien, *Angew. Chem.*, **72**, 725 (1960).

weights when administered concomitantly with testosterone propionate (probably a reflection of its estrogenic activity).

### Experimental Section<sup>10</sup>

**cis-1,2-Diphenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (3).**—Dihydronaphthalene **1** (0.63 g) in 20 ml of THF and 1 ml of *t*-BuOH was added to 100 ml of  $\text{NH}_3$  redistilled from Li. To this was added 28 mg of Li wire; the color faded very quickly. After 5–10 min, an additional 28 mg was added. The blue color, this time, persisted for 20 min. After the addition of 1 g of  $\text{NH}_4\text{Cl}$ , the mixture was taken to dryness under  $\text{N}_2$ . The residue was then washed with ether and  $\text{CH}_2\text{Cl}_2$ . The solid which remained when the extracts were taken to dryness was recrystallized from EtOH to give 0.53 g of **3**, mp 160–162°. Another crystallization gave a sample, mp 166–168°.

*Anal.* Calcd for  $\text{C}_{23}\text{H}_{22}\text{O}$ : C, 87.86; H, 7.05. Found: C, 87.30; H, 7.13.

**1-(*p*-Hydroxyphenyl)-2-phenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene (4).** **A. By Reduction with Lithium-Ammonia.**—One gram of **2** was reduced with 84 mg of Li in exactly the same manner as above. The gummy solid which remained when the solvents had been removed from the reaction mixture was suspended in  $\text{H}_2\text{O}$  and made acidic with acetic acid. The solid was collected and recrystallized twice from MeOH to yield 0.40 g of **4**, mp 188–190°.

*Anal.* Calcd for  $\text{C}_{23}\text{H}_{22}\text{O}_2$ : C, 83.60; H, 6.71. Found: C, 83.45; H, 6.89.

**B. By Catalytic Reduction.**—A mixture of 1.0 g of **2** and 0.10 g of 10% Pd-C in 50 ml of ethanol was stirred under  $\text{H}_2$  to the absorption of 1 mole of hydrogen (1 hr). The filtered solution was evaporated to dryness. The residual solid was recrystallized from methanol to give 0.71 g of **4**, mp 188.5–190°, alone or in mixture with **4** prepared by the Birch reduction.

**1,2-Diphenyl-6-methoxy-1,2,3,4,5,8-hexahydronaphthalene (5).**—Tetralin **3** (3.4 g), in 110 ml of THF and 11 ml of *t*-BuOH, was added to 500 ml of  $\text{NH}_3$  redistilled from Li. Li wire (0.76 g) was added in seven equal portions to the mixture at 5-min intervals. The mixture was stirred for 30 min, and 33 ml of *t*-BuOH was added. Following an additional 25 min (stirring), 30 g of  $\text{NH}_4\text{Cl}$  was added. The solvent was evaporated under  $\text{N}_2$  and the residue was treated with  $\text{H}_2\text{O}$ . The solid was collected on a filter and recrystallized from ligroin to afford 2.62 g of **5**, mp 138–142°. The analytical sample, mp 132–134°, was obtained from another run.

*Anal.* Calcd for  $\text{C}_{23}\text{H}_{24}\text{O}$ : C, 87.30; H, 7.65. Found: C, 87.02; H, 7.90.

**1-(*p*-Hydroxyphenyl)-2-phenyl-6-methoxy-1,2,3,4,5,8-hexahydronaphthalene (6).**—Proceeding as above, 0.66 g of **4** was reduced with 154 mg of Li. The product was recrystallized from aqueous MeOH to give 0.58 g of **6**, mp 184.5–187.5°. The analytical sample melted at 183–185°.

*Anal.* Calcd for  $\text{C}_{23}\text{H}_{24}\text{O}_2$ : C, 83.10; H, 7.28. Found: C, 83.07; H, 7.40.

**4,5-Diphenyl-3,4,5,6,7,8-hexahydro-2(1H)-naphthalenone (7).**—A suspension of 2.0 g of **5** in 400 ml of methanol and 20 ml of 2.5 *N* HCl was stirred for 20 min in an ice bath and 1 hr at room temperature. The now homogeneous solution was neutralized with saturated aqueous  $\text{NaHCO}_3$  and the bulk of the solvent was removed on the rotary evaporator. Ether was added, and the organic layer was washed with  $\text{H}_2\text{O}$  and brine. The residual gum was recrystallized three times from a small amount of ligroin to give 0.82 g of **7**, mp 124–129°. The analytical sample,  $\nu_{\text{max}}$  1705  $\text{cm}^{-1}$ , melted at 128–132°.

*Anal.* Calcd for  $\text{C}_{22}\text{H}_{22}\text{O}$ : C, 87.37; H, 7.33. Found: C, 87.77; H, 7.42.

**5-(*p*-Hydroxyphenyl)-6-phenyl-3,4,5,6,7,8-hexahydro-2(1H)-naphthalenone (8).**—A suspension of 1.65 g of **6** in 83 ml of methanol containing 3.3 ml of 1 *M* oxalic acid was stirred to solution at room temperature (40 min) and taken to dryness at

reduced pressure; the residue was dissolved in ether- $\text{CH}_2\text{Cl}_2$ . This solution was washed ( $\text{H}_2\text{O}$ , aqueous  $\text{NaHCO}_3$ , brine). The residue which remained when the solvent was removed was recrystallized from methanol to give a first crop of 0.53 g of **8**, mp 209–216°; the second-crop material was recrystallized from aqueous MeOH to give an additional 0.90 g of **8**, mp 213–216°. The analytical sample,  $\nu_{\text{max}}$  3310 and 1705  $\text{cm}^{-1}$ , melted at 215–224°.

*Anal.* Calcd for  $\text{C}_{23}\text{H}_{22}\text{O}_2$ : C, 82.98; H, 6.96. Found: C, 82.72; H, 7.28.

**3,4-Diphenyl-2-cyclohexen-1-one (10).**—Deoxybenzoin (10.0 g) in 100 ml of benzene was added to methanol-free  $\text{NaOCH}_3$  prepared from 1.15 g of Na. The resulting yellow mixture was cooled in ice. During 20 min, there was added 4.0 g of methyl vinyl ketone in 40 ml of benzene. The mixture was heated under reflux for 30 min, cooled in ice, and decomposed with 50 ml of saturated aqueous  $\text{NH}_4\text{Cl}$ . The organic layer was separated and washed with  $\text{H}_2\text{O}$ , then brine. The viscous oil which remained when the solvent was removed was chromatographed over Florisil (elution with 2.5% followed by 5% acetone in ligroin). There was obtained first 4.12 g of starting material, followed by 6.1 g of crude product which was recrystallized from ligroin to yield 5.6 g of **10**, mp 96–99°. The analytical sample melted at 96.5–98.5°.

*Anal.* Calcd for  $\text{C}_{15}\text{H}_{16}\text{O}$ : C, 87.06; H, 6.50. Found: C, 86.52; H, 6.38.

**3,4-Diphenyl-1-pyrrolidino-1,3-cyclohexadiene (11).**—A solution of 6.1 g of **10**, 6 ml of pyrrolidine, and 150 ml of benzene was heated overnight under a Dean-Stark trap. The excess reagent and solvent were removed *in vacuo*. The residue (from ether) afforded 6.2 g of bright yellow solid, mp 128–130°. The analytical sample melted at 128–131.5°; nmr spectrum, vinyl proton as a singlet at  $\delta$  4.75.

*Anal.* Calcd for  $\text{C}_{22}\text{H}_{23}\text{N}$ : C, 87.66; H, 7.69. Found: C, 87.62; H, 7.64.

**5,6-Diphenyl-4,6,7,8-tetrahydro-2(3H)naphthalenone (14).** **A. By Reaction of 11 with Methyl Vinyl Ketone.**—During 30 min, 0.8 g of freshly distilled methyl vinyl ketone in 30 ml of THF was added to 3.0 g of **11** in 60 ml of THF. The mixture was stirred under  $\text{N}_2$  at room temperature for 30 min and at reflux for 4 hr. Sodium acetate (2 g) in 2 ml of AcOH and 4 ml of  $\text{H}_2\text{O}$  was then added, and reflux was continued overnight. The bulk of the solvent was removed *in vacuo*; the residue was dissolved in ether. The solution was washed ( $\text{H}_2\text{O}$ , 2.5 *N* HCl,  $\text{H}_2\text{O}$ , brine). The gum which remained when the solvent was removed was chromatographed over Florisil (elution with 2.5 then 5% acetone in ligroin) to give as a first fraction 0.66 g of recovered ketone, mp 95–97°, followed by a succession of gums. The latter were combined and rechromatographed on Woelm neutral alumina (elution 1:1 benzene-ether). The crystalline fractions were combined and recrystallized twice from MeOH to give 31.8 mg of **14**, mp 141–143.5°;  $\lambda_{\text{max}}^{\text{alc}}$  235  $\mu$  ( $\epsilon$  4780), 307  $\mu$  ( $\epsilon$  11,800).

**B. By the Sequence 11, 12, 13.**—To a suspension of 3.0 g of **11** and 1.7 g of finely powdered KI in 20 ml of DMF under  $\text{N}_2$  was added 2.05 g of 1,3-dichloro-2-butene in 5 ml of DMF. After 30 min (stirring) at room temperature, 10 ml of  $\text{H}_2\text{O}$  was added. After an additional 2 hr (stirring), ether was added. The organic layer was separated, washed well ( $\text{H}_2\text{O}$ , brine), and taken to dryness. Chromatography over Florisil (elution with 1.25% acetone in ligroin) afforded **12** as waxy crystals. This was recrystallized twice from ligroin to yield 1.3 g, mp 70–80°,  $\nu_{\text{max}}$  1702  $\text{cm}^{-1}$ , strong Beilstein test.

Concentrated  $\text{H}_2\text{SO}_4$  (10 ml) was added to the above chloro ketone in 5 ml of ether. After 5 min, the mixture was neutralized with  $\text{Na}_2\text{CO}_3$ . The organic material was dissolved in ether- $\text{CH}_2\text{Cl}_2$ . This solution was washed well ( $\text{H}_2\text{O}$ , brine) and taken to dryness. The gum which remained was chromatographed over Florisil (elution with 5% acetone in ligroin) to yield 0.22 g of crude crystalline **14** and 0.38 g of a gum which (neat) showed infrared bands at 1705 and 1655  $\text{cm}^{-1}$ . The crystalline fraction was recrystallized twice from MeOH to afford 0.10 g of **14**, mp 144–145.5°, alone or in mixture with **14** obtained above.

*Anal.* Calcd for  $\text{C}_{22}\text{H}_{21}\text{O}$ : C, 87.96; H, 6.71. Found: C, 87.78; H, 6.98.

The gummy **13** obtained above in 10 ml of benzene containing 100 mg of *p*-toluenesulfonic acid was heated under reflux for 1.5 hr. The solution was allowed to cool, washed with aqueous  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$ , and taken to dryness. The residual solid was recrystallized once from MeOH to give an additional 0.32 g of **14**, mp 139–142°.

(10) The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Co. for elemental and spectral determinations. Nmr spectra were obtained on a Varian A-60 spectrometer in  $\text{CDCl}_3$ . Infrared spectra were as Nujol mulls unless otherwise specified.

In another run, 7.3 g of the enamine was taken through this reaction sequence without the isolation or purification of any intermediates. The gum which was obtained following the last step was chromatographed on Florisil. Recrystallization of the crystalline fractions from cyclohexane gave 3.3 g of **14**, mp 140–143°.

**3,4-Diphenyl-2-methyl-3-cyclohexen-1-one (15).**—A mixture of 3.0 g of the enamine and 2 ml of MeI in 20 ml of DMF was stirred under N<sub>2</sub> at room temperature for 18 hr. Water (10 ml) was added, and stirring was continued for 3 hr. Ether was added, and the organic layer was washed well (H<sub>2</sub>O, brine). The solid which remained when the solvent was removed was recrystallized twice from ligroin to give 1.2 g of **15**, mp 66–70°,  $\nu_{\max}$  1705 cm<sup>-1</sup>, doublet at  $\delta$  1.16.

*Anal.* Calcd for C<sub>15</sub>H<sub>15</sub>O: C, 86.98; H, 6.91. Found: C, 86.98; H, 7.17.

**5,6-Diphenyl-4a-methyl-1,4a,7,8-tetrahydro-2(3H)-naphthalenone (16).**—A solution of 1.19 g of the cyclohexenone **15**, 0.51 ml of methyl vinyl ketone, and 20 ml of benzene was added during 30 min to a suspension of methanol-free NaOCH<sub>3</sub> (from 0.10 g of Na metal) in 10 ml of benzene. After 2 hr (stirring) at room temperature and 1 hr at reflux, the mixture was worked up as in the case of **10**. The residual gum was chromatographed over Florisil (elution with 2.5% acetone in ligroin). The crystalline fractions were recrystallized twice from MeOH to afford 0.72 g of **16**, mp 131–134°,  $\lambda_{\max}^{\text{obs}}$  238 m $\mu$  ( $\epsilon$  11,800).

*Anal.* Calcd for C<sub>23</sub>H<sub>23</sub>O: C, 87.86; H, 6.85. Found: C, 87.54; H, 6.85.

## Stereochemical Aspects of Analgesics. Preparation of 10-Methyl-5-phenyl-5-propionoxy-*trans,syn,trans*-tetradecahydroacridine<sup>1</sup>

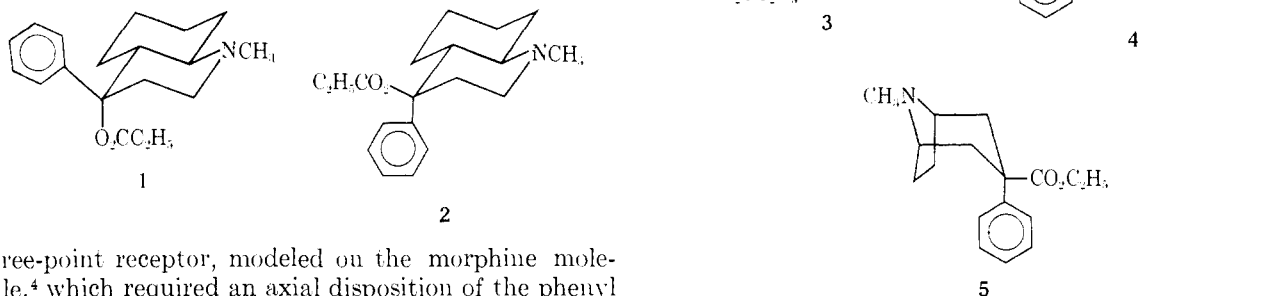
EDWARD E. SMISSMAN AND MARTIN STEINMAN<sup>2</sup>

Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas 66044

Received May 2, 1967

10-Methyl-5(e)-phenyl-5(a)-propionoxy-*trans,syn,trans*-tetradecahydroacridine (**13a**) was prepared by the reaction of 10-methyl-*trans,syn,trans*-dodecahydroacridone (**11**) with phenyllithium followed by esterification of the resulting alcohol, **12a**. The compound was tested for analgesic activity and was found inactive.

It has been shown that there is relatively no difference in analgesic activity between the rigid analogs of prodine, the 1-methyl-4-phenyl-*trans*-decahydro-4-propionoxyquinolines (**1** and **2**).<sup>3</sup> Beckett, in his original postulate of the analgesic receptor site, proposed a



three-point receptor, modeled on the morphine molecule,<sup>4</sup> which required an axial disposition of the phenyl ring, an amino group, and a two-carbon chain to fit a receptor-site cavity. The piperidine ring of prodine or meperidine-type analgesics can be substituted with small alkyl functions and still fit such a cavity.

The purpose of this work was to design an analgesic in which large bulky groups were placed in the 2, 3, 5, and 6 positions of the piperidine nucleus of a prodine-type system and to maintain rigid conformations of the phenyl and ester functions at the 4 position. The molecule selected for this purpose was 10-methyl-5-phenyl-5-propionoxy-*trans,syn,trans*-tetradecahydroacridine with the phenyl being equatorial (**3**) and axial (**4**).

Bell and Archer have reported ethyl 3- $\alpha$ -phenylpropane-3- $\beta$ -carboxylate (**5**) to be slightly more active than meperidine.<sup>5</sup> However, in this system there is

no unequivocal control of the conformation of the phenyl ring and no steric barrier to the approach of the phenyl ring to the receptor site.

In analogy to the preparation of the 1-methyl-4-phenyl-*trans*-decahydro-4-propionoxyquinolines (**1** and **2**),<sup>3</sup> it was assumed that the axial and equatorial isomers of 10-methyl-5-phenyl-5-hydroxy-*trans,syn,trans*-tetradecahydroacridine (**12a** and **e**) could be obtained by the reaction of the corresponding acridone **11** with either phenyllithium or phenylmagnesium bromide (Chart I). The scheme devised for the preparation of 10-methyl-*trans,syn,trans*-dodecahydroacridone (**11**) involved the reduction of anthranilic acid (**6**). The catalytic reduction of **6** utilizing 5% rhodium on alumina had been reported but solvent conditions were not specified.<sup>6</sup> Freifelder<sup>7</sup> had reported that pyridinealkanoic acids could be reduced in dilute aqueous ammonia and this solvent system was found to be useful for the reduction of anthranilic acid.

(1) Taken in part from the dissertation presented by Martin Steinman, June 1965, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Ph.D. degree.

(2) National Institutes of Health Predoctoral Fellow, 1964–1965.

(3) E. E. Smismman and M. Steinman, *J. Med. Chem.*, **9**, 455 (1966).

(4) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954); *Nature*, **173**, 1231 (1954).

(5) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 4638 (1960).

(6) N. A. LeBel, M. E. Post, and J. J. Whang, *ibid.*, **86**, 3750 (1964).

(7) M. Freifelder, *J. Org. Chem.*, **28**, 602 (1963).