3ζ,17β-Diacetoxy-4-oxa-5α-androstane (Ie).—Acetylation of hemiacetal Ia (0.4 g) was repeated (see Id). In this case the crude product weighed 0.45 g and melted at 120–122°. Recrystn from Me_2CO–pentane gave needles melting at 141–144°. Further recrystn from the same solvent provided an analytical sample of diacetate Ie, mp 142–144°. *Anal.* ($C_{22}H_{34}O_5$) C, H, O.

Comparison of acetal Id, mp 141–143°, with diacetate Ie, mp 141–144°, by mixture melting point determination showed a depression to 115°.

17β-Acetoxy-4-oxa-2-androstene (III).—A soln of acetal Id (0.2 g) in C_6H_6 (25 ml) containing *p*-TosOH (0.04 g) was heated at reflux 20 hr. The mixture was washed successively with H_2O, aq $NaHCO_3$, and H_2O. Following removal of solvent, the residue was chromatographed on activated alumina. Elution with 1:1 hexane–C_6H_6 led to 0.14 g of III. The oily product crystd from MeOH as small needles melting at 118–120°. Recrystallization from MeOH gave a pure sample, mp 120–121°. *Anal.* ($C_{20}H_{30}O_3$) C, H, O.

Formation of III was monitored by tlc (1:1 C_6H_6–$CHCl_3$, mobile phase) and extended reaction periods (for example, 66 hr) were shown to yield a series of products.

3ζ,17β-Bis(dihydropyranyloxy)-4-oxa-5α-androstane (If).—A soln prepared from C_6H_6 (12 ml), hemiacetal Ia (0.21 g), dihydropyran (2 ml), and *p*-TosOH (0.05 g) was stirred 1 hr at room temp. The soln was washed with aq $NaHCO_3$ and H_2O. Removal of solvent *in vacuo* gave a semisolid which crystd from MeOH–Me_2CO as small needles weighing 0.10 g, mp 165–169°. Recrystallization from the same solvent afforded thick needle clusters melting at 176–179°. *Anal.* ($C_{28}H_{46}O_5$) C, H, O.

3ζ-Acetoxy-4-oxa-5α-cholestane (IIb).—A sample (0.25 g) of 3ζ-hydroxy-4-oxa-5α-cholestane (IIa)[2b] was acetylated as summarized in the case of Ia (see Ie). The crude acetate crystd from pentane as thick needles melting at 103–107° (sintering at 90°). An anal. sample, recrystd from pentane, melted at 105–108° (sintering at 95°); tlc 1:2 C_6H_6–$CHCl_3$. *Anal.* ($C_{28}H_{48}O_2$)C, H, O.

Oxidation of 12α,15-Epoxy-12-nor-13β-methyl-11β,14α-abietane (IVa). Method A.—A soln of XXIa (0.20 g)[4] in glacial AcOH (6 ml) was treated with a slight excess of an 8 *N* CO_3 reagent[3] at 60°. Heating was continued at steam bath temp for 10 min. Excess oxidizing agent was removed by adding MeOH. Following diln with H_2O and extraction with Et_2O containing $CHCl_3$, the extract was washed well with H_2O, aq $NaHCO_3$, and H_2O. Removal of solvent gave 0.17 g of solid which was chromatographed in pentane on activated alumina. Elution with pentane removed 0.03 g of starting material. A fraction eluted by 1:1 pentane–C_6H_6 provided 0.12 g of dihydroabietic γ-lactone (IVb)[4] melting at 125–127°. Recrystallization from MeOH gave long needles melting at 126–128°.

Method B.—Oxidation of IVa (1.1 g)[3] was repeated in a soln composed of glacial AcOH (16 ml), C_6H_6 (6 ml), and $Na_2Cr_2O_7 \cdot 2H_2O$ (2.1 g).[5] The soln was stirred and maintained at approx 75° for 30 hr. The product was isolated and purified as noted directly above. In this case, 0.87 g of starting ether IVa was recovered and 0.26 g of lactone IVb was isolated.

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(4) G. R. Pettit, B. Green, T. R. Kasturi, and U. R. Ghatak, *Tetrahedron*, **18**, 953 (1962).

(5) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4386 (1953).

Hypocholesteremic Agents. 2. Cyclohexane and Indan Derivatives

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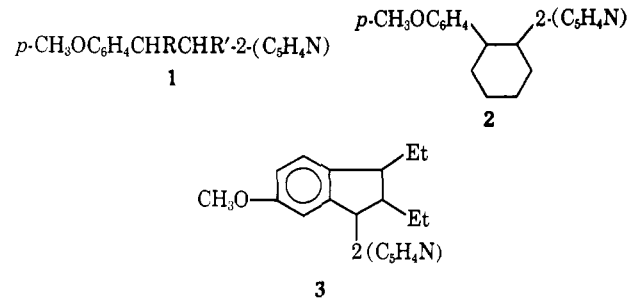
Maximum hypocholesteremic activity and minimal estrogenic potency was found in the dihydrostilbazole series containing lower alkyl substituents on both carbons of the ethylenic bridge (**1**).[1] It was of interest to study the hypocholesteremic activity of compounds in which R and R[1] are fused in a cyclohexane ring (**2**) or are part of an indan structure (**3**).



Compounds of formulas **2** and **3** were prepared by treating the appropriately substituted cyclic ketone with pyridyllithium, followed by dehydration of the tertiary carbinol and hydrogenation of the resulting double bond. 2-*p*-Methoxyphenyl-1-(2-pyridyl)-1-cyclohexanol having OH on C α to 2-pyridyl, as in the cases previously reported,[1] resisted dehydration by the usual acid dehydrating agents. However, fusion of this carbinol with potassium pyrosulfate gave a mixture of the 1,2- and 2,3-cyclohexenes (**4**).[2,3] The addition of 2-pyridyllithium to **6** gave the tertiary carbinol which was converted into the indene derivative **8a** by heating with H_3PO_4. In contrast, the addition of 3-pyridyllithium to **6** gave the unsaturated compound **8b** directly and provides further evidence for the stability of the 2-pyridyl carbinol moiety.

At the screening dose of 50 mg/kg orally and 10 mg/kg subcutaneously,[4] these compounds were ineffective in lowering the serum cholesterol levels in both male and female rats. The compounds were devoid of estrogenic activity even at higher doses. Previous investigators[5a,b] have shown that 1,2-bis(*p*-methoxyphenyl)cyclohexane has definite but weak estrogenic activity.

Experimental Section[6]

β-Ethyl-*p*-methoxycinnamic Acid.—The Reformatsky ester (160 g), bp 125–155° (1 mm), obtained from 164 g (1 mole) of *p*-methoxypropiophenone, 167 g of ethyl bromoacetate, and 85 g of Zn (20 mesh) was saponified with 160 g of KOH in 1600 ml of EtOH and 800 ml of H_2O to give the trans acid, mp 132–134, and cis acid, mp 68–70°. *Anal.* ($C_{12}H_{14}O_3$) C, H.

β-Ethyl-*p*-methoxyhydrocinnamic Acid (7).—In 4 portions a solution of 84 g of the above acids in 1 l. of EtOH was reduced in a Parr hydrogenator in presence of 20 g of 5% Pd-C. The catalyst was filtered, the solvent removed *in vacuo*, and the residue triturated with pet ether. The product was crystd from hexane: yield 73 g; mp 81–83°. *Anal.* ($C_{12}H_{16}O_3$) C, H.

3-Ethyl-6-methoxyindan-1-one (5).—Acid **7** (35 g) and 1700 g of polyphosphoric acid were heated with stirring on the steam

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(1) F. J. Villani, C. A. Ellis, R. F. Tavares, M. Steinberg, and S. Tolksdorf, *J. Med. Chem.*, **13**, 359 (1970).

(2) The mixture was not separated into its components but was used directly in the hydrogenation.

(3) The composition of the mixture was determined by nmr and contained approximately equal amounts of both isomers. We are indebted to Mr. James Morton of the Physical Analytical Department of the Schering Corp. for his interpretations of the nmr spectrum.

(4) The authors are indebted to Drs. S. Tolksdorf and M. Steinberg of the Department of Endocrinology of the Schering Corp. for the biological data.

(5) (a) G. P. Mueller and D. Pickens, *J. Amer. Chem. Soc.*, **72**, 3626 (1950); (b) G. P. Mueller and R. May, *ibid.*, **71**, 3313 (1949).

(6) Melting point are uncorrected and were obtained on a Thomas Hoover open capillary melting point apparatus. Where analyses are indicated only by the symbols of the elements, analytical values are within 0.4% of the theoretical values.

bath for 3.5 hr, poured into ice, and extracted with Et_2O. The extracts were washed and distd to give 20.5 g (63.5%) of an oil: bp 130–133° (1 mm); $n^{25}D$ 1.5548; ir, strong band at 5.85 μ.

2,3-Diethyl-6-methoxyindan-1-one (6).—To 70 g of NaOMe was added with stirring 80 g (0.42 mole) of **5**. With cooling 400 g of EtI was added rapidly and the mixture was stirred for 30 min and then heated on the steam bath for 3 hr. Excess EtI was removed by distn, H_2O added, and the mixture extracted (Et_2O). The solvent was evapd after drying (Na_2SO_4) and the residue was distd: yield 74.5 g (81%); bp 155–160° (1 mm); $n^{25}D$ 1.5393. *Anal.* ($C_{14}H_{18}O_2$) C, H.

Pyridyllithium Reactions. 2-(*p*-Methoxyphenyl)-1-(2-pyridyl)-cyclohexanol.—To an Et_2O soln (400 ml) of BuLi prepared under N_2 at −10° from 4.1 g (0.6 mole) of Li and 41.1 g (0.3 mole) of BuBr was added at −40°, 47.4 g (0.3 mole) of 2-bromopyridine in 200 ml of Et_2O. After 1 hr, a soln of 30.6 g (0.15 mole) of 2-(*p*-methoxyphenyl)cyclohexanone[3b] in 500 ml of Et_2O was added dropwise with stirring and the mixture was allowed to warm to room temp. Stirring was continued for 6 hr. H_2O was cautiously added, the organic layer was sepd and combined with an additional Et_2O extract. The combined Et_2O soln were extracted with 10% HCl and, after preliminary washing (Et_2O), the acid soln was basified (NH_4OH) and extracted ($CHCl_3$). The $CHCl_3$ soln was washed (H_2O) and coned on the steam bath to an oil which was triturated with pet ether (bp 30–60°) and recrystd from hexane: yield 24.7 g (58%); mp 74–75°. The ir spectrum showed a typical OH band at 3 μ. *Anal.* ($C_{18}H_{21}NO_2$) C, H, N.

1-(2-Pyridyl)-2,3-diethyl-6-methoxy-indan-1-ol was prepared by a similar procedure: yield 74%; bp 183–189° (1 mm); $n^{25}D$ 1.5722; strong OH in ir at 3.0 μ. *Anal.* ($C_{19}H_{23}NO_2$) C, H, N.

1-(3-Pyridyl)-2,3-diethyl-6-methoxy-1-indene (8b).—This compound was obtained from 3-bromopyridine by the above procedure in 61% yield: bp 180–185° (1 mm); $n^{25}D$ 1.5923; log $\epsilon_{265\ m\mu}$ 4.05. *Anal.* ($C_{19}H_{21}NO$) C, H, N.

Dehydration Procedure (Mixture 4).—A mixture of 10 g (0.035 mole) of 2-(*p*-methoxyphenyl)-1-(2-pyridyl)cyclohexanol and 40 g of powdered potassium pyrosulfate was placed in a bath at 240° and the temp raised to 240–260° with manual stirring until the fusion was completed and held at this temp for 1 min. The mixture was allowed to cool somewhat and poured into ice, made basic (NH_4OH), and extracted ($CHCl_3$), washed, and distd: bp 172–175° (2.5 mm); yield 5.8 g (63%); $n^{25}D$ 1.6063. *Anal.* ($C_{18}H_{19}NO$) C, H, N.

1-(2-Pyridyl)-2,3-diethyl-6-methoxy-1-indene (8a).—A mixture of the 2-pyridyl carbinol (10 g) and 7 ml of 85% H_3PO_4 was heated under reflux for 6 hr and poured into ice. The solution was made basic (NaOH) and extracted ($CHCl_3$). The solvent was removed and the residue was distd: yield 7 g (76%); bp 173–178° (1 mm); $n^{25}D$ 1.5838; log $\epsilon_{268\ m\mu}$ 4.08. *Anal.* ($C_{19}H_{21}NO$) C, H, N.

***p*-Methoxyphenyl-2-(2-pyridyl)cyclohexane (2).**—A soln of 5.0 g (0.019 mole) of mixture **4** in 250 ml of EtOH was hydrogenated in a Parr hydrogenator in presence of 0.5 g of PtO_2. The reduction required 20–22 hr. The catalyst was filtered and the residue after removal of the solvent was distd: yield 4.3 g (85%); bp 190–192° (3 mm); $n^{25}D$ 1.5766. *Anal.* ($C_{18}H_{21}NO$) C, H, N.

1-(2-Pyridyl)-2,3-diethyl-6-methoxyindane (3).—The indene **8a** (5.5 g, 0.02 mole) in 150 ml of EtOH was reduced for 20 hr in a Parr hydrogenator using Raney Ni catalyst. The catalyst was removed and the product was distd: yield 3.8 g (83%); bp 185–190° (1 mm); $n^{26}D$ 1.5696. *Anal.* ($C_{18}H_{23}NO$) HN, calcd: C, 81.10; found: C, 80.68.

New Compounds

1-Dodecylpyridinium Dodecyl Sulfate

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When a mixture of 1-decanol and *N*-bromoacetamide in pyridine is treated with SO_2 under the conditions described for the dehydration of certain steroid alcohols[1] an excellent yield of 1-dodecylpyridinium dodecyl sulfate is obtained. The same compound is obtained when didodecyl sulfate is reacted with pyridine. Evidently this fact had been observed some years ago by Sementsov, *et al.*,[2] but their "S-containing salt of pyridine" had not been characterized.

Experimental Section[3]

A solution of 18.6 g of 1-dodecanol and 27.6 g of *N*-bromoacetamide (NBA) in 160 ml of pyridine was treated with SO_2 at about 25° until all of the NBA had been destroyed. Upon pouring the solution into an ice–water slurry, 20.23 g of 1-dodecylpyridinium dodecyl sulfate, mp 88–90°, precipitated. Recrystallization from EtOAc gave an analytical sample, mp 90–90.5°. Ir and nmr spectra supported the structure. *Anal.* ($C_{29}H_{55}NO_4S$) C, H, N, S.

The sample prepared by dissolving didodecyl sulfate in pyridine, followed by addition to H_2O, had mp 91–92° and spectral properties identical with those of the material prepared by the other route.

(1) See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 75.

(2) A. Sementsov, R. J. Kiesel, M. E. McGreal, and W. F. Hart, *J. Org. Chem.*, **23**, 2020 (1958).

(3) Melting points are uncorrected. Where analyses are indicated only by the symbols for the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

SH Analog of the Estrogen Hexestrol

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The synthetic estrogen *meso*-hexestrol (I) is frequently used in the clinic. A great number of analogous compounds have been prepared.[1] The thiophenol isostere II should at least be useful in making decisions about bonding forces in estrogen–receptor complexes[2] and could be expected to show some interesting biological properties. The synthesis of II by a method similar to one previously described[3] is reported.

Biological Activity.—The thiophenol analog II was

(1) U. V. Solmssen, *Chem. Rev.*, **37**, 481 (1945); J. Grundy, *ibid.*, **57**, 281 (1957).

(2) H. G. Mautner, *Pharm. Rev.*, **19**, 107 (1967).

(3) S. F. Torf and N. V. Khromov-Borisov, *Zh. Obshch. Khim.*, **31**, 2102 (1961). They report II to have mp 155–157°.