m.p. 173.5–178.5°. Recrystallization from acetone–hexane furnished IVb (1.05 g.), m.p. 176–178.5°, $[\alpha]D$ +43°, λ^{KBr} 2.93, 5.68 μ.

Anal. Calcd. for $C_{20}H_{29}FO_2$: C, 74.96; H, 9.12; F, 5.93. Found: C, 74.79; H, 9.14; F, 5.73.

16α-Fluoro-16β-methyl-4-androstene-3,17-dione (Vb).—The chromic acid oxidation[8] of IVb, 1 g., in acetone at 5° yielded 980 mg. of crystals, m.p. 198–202°. Recrystallization from ether gave Vb, 950 mg., m.p. 204–205°, λ_{max}^{EtOH} 241 mμ (ϵ 16,400), $[\alpha]D$ +203°, λ^{KBr} 5.69, 6.01, 6.20 μ.

Anal. Calcd. for $C_{20}H_{27}FO_2$: C, 75.43; H, 8.55; F, 5.97. Found: C, 75.66; H, 8.40; F, 5.77.

16α-Fluoro-16β-methyl-3-ethoxyandrost-3,5-diene-17-one (VI) and 16α-Fluoro-16β-methyl-androst-4-ene-17β-ol-3-one (VII). (a)—A mixture of Vb (950 mg.), 10 ml. of dry tetrahydrofuran and 0.6 ml. of triethyl orthoformate was heated to reflux. Then 0.4 ml. of absolute ethanol containing 2 drops of concentrated sulfuric acid was added. After refluxing for 30 min., an additional 0.4 ml. of triethyl orthoformate was added, then the mixture was refluxed for an additional hr. The mixture was then diluted with water, extracted with ethyl acetate, the organic layer was washed with water, dried over magnesium sulfate, filtered, and concentrated to give 1.1 g. of oil, λ^{CCl_4} 2.78, 6.04, and 6.13 μ. This crude oil was dissolved in 25 ml. of anhydrous tetrahydrofuran and then 8.2 ml. of water, 0.125 ml. of 2.5 *N* sodium hydroxide, and 520 mg. sodium borohydride were added with stirring, and the mixture was refluxed for 5 hr. After cooling to room temperature, the mixture was extracted with ethyl acetate, and the organic layer was washed to neutrality, dried, and concentrated to give 900 mg. of a foamy glaze. This crude product was dissolved in 30 ml. of absolute ethanol and 5.2 ml. of water. Then 10.5 ml. of 0.12 *N* hydrochloric acid was added and the mixture was kept at room temperature overnight. The mixture was further diluted with 300 ml. of water and extracted with ethyl acetate. The organic layer was washed with 5% sodium bicarbonate solution and water to neutrality, dried, and concentrated to give 800 mg. of foam, λ^{KBr} 2.91, 6.0, and 6.18 μ. Employing a 30 g. Florisil column, elutions with 10% ether in methylene chloride yielded 485 mg. of crystals, m.p. 128–133°. Recrystallization from ether gave a first crop of VII (315 mg.), m.p. 134–135°, $[\alpha]D$ +31°, λ_{max}^{EtOH} 241 mμ (ϵ 11,500), λ^{KBr} 2.92, 6.01, and 6.19 μ.

Anal. Calcd. for $C_{20}H_{29}FO_2$: C, 74.96; H, 9.12; F, 5.93. Found: C, 74.94; H, 9.10; F, 5.94.

(b).—A solution of 16α-fluoro-16β-methyl-3-ethoxyandrost-3,5-diene-17-one (350 mg.) in 30 ml. of anhydrous ether was added during a period of 15 min. to a stirred solution of 300 mg. of lithium aluminum hydride in 30 ml. of anhydrous ether. The mixture was refluxed for 30 min., cooled to 0°, and the excess lithium aluminum hydride was decomposed with water, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, dried, and concentrated to give 229 mg. of solid. The solids were redissolved in a mixture of 5 ml. of ethanol, 10 ml. of water, and 10 ml. of 0.1 *N* hydrochloric acid and then kept at room temperature overnight. Extraction with ethyl acetate followed by a Florisil column chromatography (elutions with methylene chloride) gave 166 mg. of crystals, m.p. 126–135°. Recrystallization from ether gave a first crop of VII (121 mg.), m.p. 134–135°, identical with the compound obtained by sodium borohydride reduction.

16α-Fluoro-16β-methyl-dihydrotestosterone (VIII).—A mixture of VII (250 mg.) in 10 ml. of ethanol and 31.3 mg. of 10% palladium on charcoal was hydrogenated at room temperature during a period of 25 min. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give 245 mg. of foam, λ^{KBr} 2.92, and 5.85 μ. The crude product was purified by Florisil (10 g.) chromatography. Elutions with methylene chloride containing 5% ether gave 180 mg. of crystals, m.p. 154–156°. Recrystallization from ether furnished the analytical sample of VIII, 120 mg., m.p. 156–157°, λ^{KBr} 2.92, and 5.85 μ.

Anal. Calcd. for $C_{20}H_{31}FO_2$: C, 74.49; H, 9.68; F, 5.89. Found: C, 73.82; H, 9.51; F, 5.85.

Acknowledgment.—The author wishes to express his sincere appreciation to Dr. A. D. Odell for his encouragement and helpful discussions. Thanks are extended to Mr. L. G. Hickman of these Laboratories for his assistance in performing some of the experiments.

A Tautomer of a 2-Thienol Analog of Stilbestrol[1,2]

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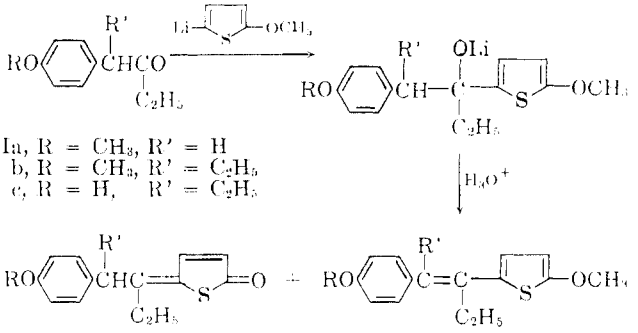
Following the discovery of the high estrogenic potency of diethylstilbestrol,[3] numerous related compounds were prepared for hormonal assay.[4] More recently the search has turned toward the development of compounds which might possess antihormonal action[5]; relatively few of these compounds have included heterocyclic groupings. However, several stilbestrol-like compounds bearing the thiophene nucleus in place of one or both of the benzene rings have been reported.[6]

In an attempt to prepare a 2-thienol analog of stilbestrol, we have now succeeded in synthesizing its more stable tautomeric α,β-unsaturated thiolactone form as the crystalline acetate, (IId). Preliminary work, resulting in the synthesis of the related methyl ethers (IIa and IIb), was also conducted. A recently developed synthesis[7] of 5-substituted 2(5*H*)-thiophenones has been utilized.



Ia, R = CH_3, R′ = H
b, R = CH_3, R′ = C_2H_5
c, R = H, R′ = C_2H_5

IIa, R = CH_3, R′ = H
b, R = CH_3, R′ = C_2H_5
c, R = H, R′ = C_2H_5
d, R = CH_3CO, R′ = C_2H_5

IIIa, R = CH_3, R′ = H
b, R = CH_3, R′ = C_2H_5

Ketones Ia and Ib were prepared from the appropriate acyl chlorides and diethylcadmium or by the method of Myers, *et al.*[5a] The phenolic ketone (Ic) was prepared from α-(*p*-acetoxyphenyl)-butyryl chloride[8] and diethylcadmium, followed by hydrolysis (65% yield) or by hydrobromic acid demethylation of the methoxy ketone (Ib).

(1) This investigation was supported by a research grant, T-114, from the American Cancer Society and a grant, AM 03388, from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, United States Public Health Service.

(2) Presented in part before the Medicinal Chemistry Division, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(3) E. C. Dodds, L. Golberg, W. Lawson, and R. Robinson, *Nature*, **141**, 247 (1938); *Proc. Roy. Soc.* (London), **B 127**, 140 (1939).

(4) U. V. Solmssen, *Chem. Rev.*, **37**, 481 (1945); J. Grundy, *ibid.*, **57**, 281 (1957); J. A. Hogg and J. Korman, in "Medicinal Chemistry," Vol. 2, F. F. Blicke and C. M. Suter, Ed., John Wiley and Sons, New York, N. Y., 1956, p. 34.

(5) (a) T. C. Myers, R. J. Pratt, R. L. Morgan, J. O'Donnell, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 5655 (1955); (b) R. L. Morgan, P. Tannhauser, R. J. Pratt, T. C. Myers, and E. V. Jensen, *ibid.*, **77**, 5658 (1955); (c) R. J. Pratt and E. V. Jensen, *ibid.*, **78**, 4430 (1956).

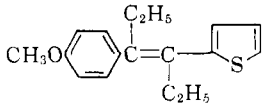
(6) Bun-Hoï and Hiong-Ki-Wei, *Compt. rend.*, **220**, 175 (1945); W. R. Biggerstaff and O. L. Stafford, *J. Am. Chem. Soc.*, **74**, 419 (1952); J. Sicé and M. Mednick, *ibid.*, **75**, 1628 (1953).

(7) W. R. Biggerstaff and K. L. Stevens, *J. Org. Chem.*, **28**, 733 (1963).

(8) A. L. Wilds and W. R. Biggerstaff, *J. Am. Chem. Soc.*, **67**, 789 (1945).

When 1-(*p*-methoxyphenyl)-2-butanone (Ia) was treated with an equimolar quantity of 5-methoxy-2-thienyllithium,[7,9] followed by hydrolysis of the intermediate lithium salt, a mixture of products was obtained as an oil. Extensive chromatographic separation of the material on silica or Florisil[10] led to a 16% yield of the oily α,β-unsaturated thiolactone (IIa) and 46% of the 2-methoxythiophene derivative (IIIa), also as an oil; the latter compound arose from the normal dehydration of the intermediate carbinol. These results are in agreement with previous work in which ketones possessing α-hydrogens were studied.[7]

The reaction of 4-(*p*-methoxyphenyl)-3-hexanone (Ib) with the lithium reagent, followed by acidic hydrolysis, led, upon chromatographic separation of the product, to the α,β-unsaturated thiolactone (IIb) (30%), as an oil; only a trace amount of dimethyl ether (IIIb) was detected. In one run a small early crystalline fraction (*ca.* 1%), eluted from a silica column with petroleum ether, was identified by its infrared spectrum and comparison with an authentic sample as the previously reported 4-(*p*-methoxyphenyl)-3-(2-thienyl)-3-hexene (IV).[5b]



IV

When two molar equivalents of the 5-methoxy-2-thienyllithium reagent was added to phenolic ketone Ic and the resulting lithium salt was hydrolyzed, the phenolic α,β-unsaturated thiolactone (IIc) was obtained as an oil which failed to crystallize; however, treatment with acetic anhydride and pyridine led to the crystalline acetate (IId) in 34% yield. Evaporative distillation of the filtrate produced the geometrical isomer of IId as an oil (49%). The presence of a phenolic stilbene analog corresponding to IIIb was not detected.

In both of the methoxyl series the fractions from the columns were identified by their infrared spectra and were finally evaporatively distilled to produce analytically pure samples. Previous work has established that absorptions at 5.97 and 8.32 μ are consistent with the five-membered α,β-unsaturated thiolactone and the 2-methoxythienyl groups, respectively.[7,11]

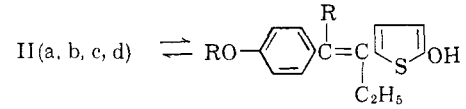
Although geometrical isomers of the thiolactones (IIa–d) and of the stilbene analogs (IIIa and b) were probably present, there were only two instances in which separation was achieved; the acetoxythiolactone (IId) in which the oily isomer was probably contaminated with the crystalline form, and the methoxythiolactone (IIa) in which case two definite yellow bands developed on the silica column. Fractional elution produced samples which gave essentially identical infrared spectra. Only one band produced sufficient material for analysis.

The infrared spectrum of the crystalline acetoxythiolactone exhibited characteristic absorption for the α,β-unsaturated thiolactone group at 5.95 μ, as well as absorption at 5.66 and 8.32 μ, expected of a phenyl acetate group. The infrared spectrum of the oily isomer of IId was identical in most respects with that of the solid isomer. The ultraviolet spectrum of the solid isomer exhibited a shoulder at 280 mμ and λ_{max} 325 mμ.[12]

The benzoate of the hydroxythiolactone (IIc) was prepared by the simultaneous addition to the acetate (IId) of 2 molar equivalents of dilute base and 1 molar equivalent of benzoyl chloride. Absorption in the infrared was characteristic of aryl benzoates[13] in addition to that predicted for the α,β-unsaturated thiolactone group (5.98 μ). The ultraviolet spectrum remained consistent with an extended conjugated carbonyl system.

Although anhydrous ether was used as the solvent during the work with methoxy ketones (Ia and Ib), it was found that tetrahydrofuran was a superior solvent for the reaction involving the phenolic ketone (Ic); the lithium salt in the latter case appeared to lack solubility in diethyl ether and resulted in incomplete reaction.

Although it might be expected that the α,β-unsaturated thiolactones (IIa–d) would establish equilibrium with their corresponding tautomeric 2-thienol forms (V), no evidence was obtained that the 2-thienols exist



V

in detectable amounts. Hydroxyl absorption in the infrared region was absent for the two methoxyl derivatives (IIa and b), and attempts to prepare the 2-thienyl methyl ethers of the possible enol forms of IIa or b using dimethyl sulfate in dilute base, diazomethane, or methanol catalyzed by *p*-toluenesulfonic acid failed. It has already been noted, however, that the methyl ethers of the enol forms of IIa and b were produced during the main reaction by dehydration of the intermediate carbinol; derivatives of 2-methoxythiophene can be readily characterized by their absorption at 8.32 μ. Similar attempts to prepare the enol acetates using acetic anhydride and pyridine, or isopropenyl acetate also met with failure.

Testing Results.—Estrogenic and antiestrogenic tests were performed under the direction of Dr. Roy Hertz of the Endocrinology Branch of the National Cancer Institute, Bethesda, Maryland. The thiolactone (IIb) and the dimethyl ether (IIIa) were each *ca.* 10^{-6} as estrogenic as estrone in the uterine assay with castrated mice. The acetoxythiolactone (IId) was *ca.* 10^{-5} as estrogenic as estrone. None of the compounds exerted an antiestrogenic effect against just maximally effective doses of estrone.

Experimental[14]

4-(*p*-Methoxyphenyl)-3-hexanone (Ib).—A mixture of 35.9 g. (0.185 mole) of α-(*p*-methoxyphenyl)-butyric acid,[8] 70 ml. of

(9) J. Sicé, *J. Am. Chem. Soc.*, **75**, 3697 (1953).

(10) Florisil, ® a magnesia–silica gel adsorbent.

(11) C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **72**, 5543 (1950).

(12) Absorption in the 320–350 mμ (log ϵ 4.0–4.5) region has been observed for related thiolactones possessing an extended conjugated system; *cf.* ref. 7.

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 179.

(14) Melting points of analytical samples were determined by means of the Hershberg apparatus; Anschütz, total immersion thermometers were used. Infrared spectra were determined on a Beckman IR-5 spectrophotometer using carbon disulfide as solvent. Ultraviolet spectra were obtained by means of a Beckman DK-2 spectrophotometer; 95% ethanol was the solvent.

thionyl chloride, and 0.5 ml. of pyridine in a previously dried 250-ml. filter flask was allowed to react overnight at room temperature. The excess thionyl chloride was then removed under reduced pressure (steam bath); several portions of benzene were alternately added and evaporated to remove completely the thionyl chloride.

A solution of diethylcadmium was prepared by adding in portions 25.3 g. (0.138 mole) of dry cadmium chloride to 0.28 mole of ethylmagnesium bromide in 500 ml. of ether solution. After refluxing for 30 min., approximately three-fourths of the ether was replaced by 250 ml. of benzene, and a benzene solution of the previously prepared α-(*p*-methoxyphenyl)-butyryl chloride was added dropwise with stirring. The mixture was stirred and refluxed for an additional hour, cooled, and acidified with dilute hydrochloric acid, and washed with two 30-ml. portions of 5% sodium bicarbonate followed by 2 portions of water. The benzene solution was dried over anhydrous sodium sulfate, the solvent was removed, and the product distilled. The methoxy ketone weighed 20.21 g. (53%), b.p. 160–165° (20 mm.), $n^{22}D$ 1.5094, semicarbazone m.p. 130–132° (lit.[5a] b.p. 158–160° (19 mm.), $n^{22}D$ 1.5094, semicarbazone m.p. 132°). In subsequent runs yields as high as 65% were obtained.

When *p*-methoxyphenylacetic acid was the starting material, the diethylcadmium method led to 1-(*p*-methoxyphenyl)-2-butanone (Ia) in 63% yield, b.p. 110–115° (1 mm.), $n^{23}D$ 1.5172 (lit.[5a] b.p. 93–96° (0.5 mm.); $n^{25}D$ 1.5178). The two methoxy ketones (Ia and Ib) were also prepared by the method of Meyers and co-workers.[5a]

4-(*p*-Hydroxyphenyl)-3-hexanone (Ic).—Conversion of 10.00 g. of the previously reported α-(*p*-acetoxyphenyl)-butyric acid[8] to the acid chloride and reaction with diethylcadmium by the foregoing procedure led to the 4-(*p*-acetoxyphenyl)-3-hexanone as an oil which was hydrolyzed directly in methanolic potassium hydroxide. Acidification of the basic solution and extraction with ether produced 8.90 g. of hydroxyphenyl ketone Ic.[15] Recrystallization from benzene–petroleum ether gave, in two crops, 6.34 g. (73.3%) of the phenolic ketone m.p. 63–66.5°; lit.[16] m.p. 67–68°. The phenolic ketone (Ic) was also conveniently obtained by demethylation of the previously prepared methoxy ketone, (Ib). In a typical run 9.88 g. of ketone Ib, 170 ml. of 47% hydrobromic acid, and 170 ml. of glacial acetic acid were refluxed for 6 hr. After cooling, dilution, and extraction with ether, the ether solution was washed with 5% sodium bicarbonate solution, water, and then dried and the ether removed. The remaining oil was crystallized from benzene–petroleum ether to give 8.70 g. (95.3%), m.p. 57–60°. A second recrystallization raised the m.p. to 65–67°.

5-[1-(*p*-Methoxyphenyl)-2-butylidene]-2(5*H*)-thiophenone (IIa).—Ten grams (0.056 mole) of 1-(*p*-methoxyphenyl)-2-butanone (Ia) dissolved in 100 ml. of anhydrous ether was added to an ether solution (150 ml.) of the 5-methoxy-2-thienyllithium reagent (prepared from 0.061 mole of phenyllithium and 0.062 mole of 2-methoxythiophene)[7,9]; the reaction product was worked up in the previously described manner. Following treatment with *N* hydrochloric acid to complete the demethylation rearrangement to the thiolacetone structure, 11.6 g. of an oily mixture was obtained which was separated into 20 fractions using a silica column and petroleum ether (b.p 30–60°)–benzene for elution. Fractions 1, 2, and 3 contained mainly 2-methoxythiophene, biphenyl, and the dimethyl ether (IIIa) fractions 4–19 contained IIIa. Fraction 20 (eluted with anhydrous ether) contained the thiolacetone (IIa). Rechromatography of the thiolactone (IIa) (5.95 μ) and the dimethyl ether (IIIa) (8.0 and 8.3 μ) fractions led to two homogeneous portions which were finally purified by evaporative distillation. In this manner 7.07 g. (46%) of the **dimethyl ether (IIIa)** b.p. 120–125° (0.2 mm.) was obtained. Redistillation at 120° (0.2 mm.) produced the analytical sample as a viscous yellow oil; infrared absorption at 8.0 μ (methoxyphenyl), and 8.3 μ (2-methoxythienyl).

Anal. Calcd. for $C_{15}H_{18}O_2S$: C, 70.04; H, 6.61. Found: C, 69.84; H, 6.77.

The thiolactone fraction finally led upon evaporative distillation at 120° (0.2 mm.) to 2.30 g. (16%) of IIa (5.95 μ) as a yellow oil which turned green on standing. A representative sample was redistilled and analyzed.

Anal. Calcd. for $C_{15}H_{16}O_2S$: C, 69.30; H, 6.20. Found: C, 69.53; H, 6.78.

5-[4-(*p*-Methoxyphenyl)-3-hexylidene]-2(5*H*)-thiophenone (IIb).—Into a dry 500 ml. flask in an atmosphere of dry nitrogen was placed 5.00 g. (0.0242 mole) of 4-(*p*-methoxyphenyl)-3-hexanone (Ib) dissolved in 40 ml. of anhydrous ether. Through the dropping funnel was added dropwise a solution of 5-methoxy-2-thienyllithium (0.0264 mole, prepared from 2-methoxythiophene and *n*-butyllithium in hexane); the mixture was stirred at room temperature for 2 hr. and was then washed with water, the organic layer separated, and the ether evaporated. The oily residue was dissolved in 30 ml. of methanol, 25 ml. of *N* hydrochloric acid was added, and mixture heated on the steam bath for 7 min. After dilution with water, the product was extracted with three portions of ether; the ethereal solution was washed successively with two portions of water, one of 5% sodium bicarbonate, water, and dried over anhydrous sodium sulfate. Evaporation of the ether left an oily product showing absorption at 5.85 and 5.98 μ characteristic of the starting ketone and the α,β-unsaturated thiolactone, respectively; lack of hydroxyl (2.8 μ) and 2-methoxythienyl absorption (8.32 μ) was evidence of complete demethylation rearrangement. The product was placed on a Florisil[16] packed column and eluted with successively enriched portions of benzene in petroleum ether and finally anhydrous ether. Following the fractions containing the unchanged starting ketone there was obtained a series of fractions, combined on the basis of their infrared spectra, which yielded 1.99 g. (30%) of the *p*-methoxyphenyl α,β-unsaturated thiolactone (IIb) as a yellow oil. Evaporative distillation at 130–135° (0.1 mm.) produced an analytically pure yellow oil. Infrared absorption was exhibited at 5.98 μ (α,β-unsaturated thiolactone), 8.05 μ (*p*-methoxyphenyl).

Anal. Calcd. for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.99. Found: C, 71.21; H, 7.30.

In a previous run followed by chromatographic separation of the products, 50 mg. of 4-(*p*-methoxyphenyl)-3-(2-thienyl)-3-hexene (IV), m.p. 71–75°, was isolated. The compound (lit.[5b] m.p. 75–78°) showed no melting point depression when mixed with an authentic sample. Also obtained from early fractions in trace amounts was a yellow oil which gave an infrared spectrum consistent with that expected for 4-(*p*-methoxyphenyl)-3-(5-methoxy-2-thienyl)-3-hexene (IIIb). Absorption was exhibited at 8.05 μ (*p*-methoxyphenyl) and 8.32 μ (2-methoxythienyl); none at 5.98 and 2.8 μ. Repeated distillation of this fraction failed to produce an analytically pure sample of IIIb; the contaminant, probably a hydrocarbon, led to consistently high carbon values.

5-[4-(*p*-Acetoxyphenyl)-3-hexylidene)]-2(5*H*)-thiophenone (IId).—Into a 250-ml. flask fitted with a stirrer, dropping funnel, and drying tube was placed 7.17 g. (0.0374 mole) of 4-(*p*-hydroxyphenyl)-3-hexanone dissolved in 25 ml. of anhydrous tetrahydrofuran. Two equivalents plus 30% excess (0.0972 mole) of 5-methoxy-2-thienyllithium, freshly prepared from 58.6 ml. of 1.658 *N* *n*-butyllithium (hexane solution), was transferred into the dropping funnel under an atmosphere of dry nitrogen and added dropwise to the ketone with vigorous stirring. The mixture was stirred at room temperature for 4 hr.; a fine precipitate formed and more tetrahydrofuran was added, enough to maintain a fluid state. When the reaction was complete, the solvent was evaporated while warming in a stream of dry nitrogen. Water was added followed by dilute hydrochloric acid to pH 4. The mixture was extracted with ether; the ether layer was washed with water and then dried. Removal of the ether left a brown oil which was warmed with 30 ml. of *N* HCl on a steam bath for 10 min. to complete demethylation and rearrangement to the α,β-unsaturated thiolactone. After dilution with water and extraction with three portions of ether, the combined ether solution was washed successively with water, 5% sodium bicarbonate, and water, and then dried over anhydrous sodium sulfate. An infrared analysis at this stage showed absorption at 2.8 (hydroxyl) and 5.97 μ (α,β-unsaturated thiolactone). Attempts to purify a sample of the phenolic thiolactone by fractional elution from a Florisil-packed column met with only partial success; the color remained dark and attempts to crystallize the product failed. The reaction product consisting mainly of **5-[4-(*p*-hydroxyphenyl)-3-hexylidene]2(5*H*)-thiophenone (IIc)** was dissolved in 33 g. of acetic anhydride and 4.23 g. of pyridine. The solution was allowed to stand overnight at room temperature; the excess reagents were then evaporated on the steam bath under a stream of dry nitrogen, and the remaining brown oil was dis-

(15) This compound was prepared by Donald M. Lynch.

(16) E. Adler, H. v. Euler, and G. Gie, *Arkiv Kemi, Mineral., Geol.*, **18A**, 21 (1944).

solved in methanol and decolorized with Norit. After filtration and concentration of the filtrate, 3.95 g. (33.4%) of the yellow crystalline acetate, m.p. 111–114°, was obtained. Repeated recrystallization from methanol produced an analytical sample in the form of yellow, blunt prisms, m.p. 120–120.5°; infrared absorption at 5.66, 5.95, and 8.32 μ; ultraviolet λ_{max} 325 mμ (log ϵ 4.22), shoulder 280 mμ (log ϵ 3.88).

Anal. Calcd. for $C_{18}H_{20}O_3S$: C, 68.30; H, 6.40. Found: C, 68.12; H, 6.22.

The yellow oil obtained from the filtrate, which remained after removal of the crystalline acetate, was evaporatively distilled between 120 and 140° (0.05 mm.). Nine fractions were collected which exhibited identical absorption in the infrared region, consistent with the acetoxy-α,β-unsaturated thiolactone structure; the combined fractions weighed 5.86 g. (49.5%); a center fraction was chosen for analysis.

Anal. Calcd. for $C_{18}H_{20}O_3S$: C, 68.30; H, 6.40. Found: C, 68.15; H, 6.28.

The **benzoate** of the phenolic thiolactone (IIc) was prepared by dissolving 200 mg. (0.634 mmole) of the crystalline acetoxyphenyl thiolactone (IId) in tetrahydrofuran, followed by the simultaneous addition of 11.64 ml. of 0.1089 *N* sodium hydroxide (1.27 mmole) and 0.089 g. (0.634 mmole) of benzoyl chloride. The mixture was allowed to shake overnight, followed by evaporation of the tetrahydrofuran. The product was taken up in ether, washed with water, and dried. Evaporation of the ether left a brown oil which was dissolved in benzene and decolorized with Norit. The benzoate crystallized from benzene–petroleum ether in the form of pale yellow prisms, m.p. 90–95°. Further recrystallization produced an analytical sample, m.p. 98–98.5°; infrared absorption at 5.77, 5.98, 7.95, and 8.32 μ; ultraviolet λ_{max} 232 mμ (log ϵ 4.33), 280 mμ (log ϵ 4.00), and 326 mμ (log ϵ 4.22).

Anal. Calcd. for $C_{23}H_{22}O_3S$: C, 72.99; H, 5.86. Found: C, 73.01; H, 5.79.

Acknowledgment.—We wish to express our appreciation to Drs. D. E. Clark, D. C. Burtner, and R. P. Ciula of this department for helpful discussions during the course of the work and to Dr. Roy Hertz for the physiological tests.

Hypocholesteremic Agents. I. Pyridyl Carbinols

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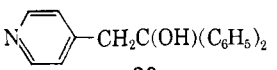
In a search for compounds showing tranquilizing properties, α,α-diphenyl-β-(4-pyridyl)ethanol (**20**) was



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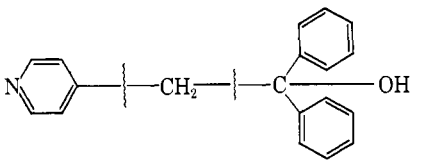
prepared by the action of benzophenone on 4-picolyl sodium.[1] This material when examined by our pharmacologists showed a marked activity in reducing serum cholesterol levels in the normal mouse. This observation stimulated our interest in the preparation and testing of other pyridyl carbinols. We were also interested in determining, if possible, what portions of the molecule were necessary for this observed diminution of the serum cholesterol content. The structure of the initial compound was divided into three portions with the



A B C

thought that a revamping of each portion would help to determine the site of activity. These variations were prepared by methods A and B in the Experimental.

Initially, we prepared and tested 1,1,2-triphenylethanol[2] and 1,2,2-triphenylethanol, two nonnitrogenous congeners. They showed little or no activity in our test and indicated the necessity for a basic ending in the molecule. Two compounds were prepared with a reduced hetero ring connected in the 1-position (**1**, **2**, Table I and II). Neither of these compounds had any activity. The substitution of 2-methylpyrazine for γ-picoline resulted in a product (**3**) that had no activity.

In our examination of the B portion of the molecule, branched chain condensation products were obtained by using 4-*n*-propylpyridine or 4-ethylpyridine, although the yields were poor. These products (**4**, **5**) showed some effectiveness at an intermediate dose, but at the lower dosage no activity was observed.

Other variations prepared involved the pyridyl grouping (α, β, or γ) adjacent to the hydroxyl and the phenyl substituent or the *p*-chloro derivative on the methylene carbon. None of these variations (**12**, **13**, **14**, **15**, **19**) conferred any cholesterol-lowering properties on the compounds except **15**. This material showed activity at a high dose level, but when the dosage was lowered, all activity disappeared.

When a substitution in portion C was made by 2-pyridyl, 3-pyridyl, methyl, and/or 4-pyridyl, the compound **16** was inactive, **8** was moderately active, while **17** and **18** showed activity only at a high dose level.

However, when one of the phenyl rings was replaced with a *p*-tolyl group, a very high dose of the compound (**6**) was active in the screening procedure. If the dosage was reduced, the activity disappeared.

If the methyl group was substituted only in the pyridyl portion of the molecule, some activity was observed. When the methyl substituent was present in both of the phenyl rings and not in the pyridyl, the compound was again inactive. Finally, if a methyl group was introduced into the *para* position of one of the phenyl rings and another methyl group *ortho* in the pyridyl nucleus, activity was present when the compound was examined at a high and an intermediate dosage (see **11**, **10**).

Method of Screening.—The compounds were mixed intimately with ground mouse diet at the concentrations shown. By calculation using a typical mouse weight at 20 g. and the average daily food consumption per mouse 3 g. diet (found in previous experiments), the approximate daily dose in mg./kg./day can be determined. (For example a concentration of 0.067% in the diet equals approximately 100 mg./kg./day). The mice were housed in groups of six, weighed once as a group at the beginning of the experiment and once at the end. Control groups (usually at least 2) were given plain ground diet, and treated groups got ground diet containing drug. Access to diet and water was un-

(1) A. W. Weston and R. W. DeNet, personal communication.

(2) C. Hell and Fr. Weigandt, *Ber.*, **37**, 1429 (1904).