

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY AND PHARMACY OF THE REED AND CARNICK INSTITUTE FOR MEDICAL RESEARCH]

## Synthetic Estrogens. I. 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene, 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-hexane and Some of their Organic Esters

BY V. NIEDERL, C. A. SICONOLFI, A. BLOOM AND C. T. VAN METER<sup>1</sup>

It is generally agreed that 3,4-bis-(*p*-hydroxyphenyl)-3-hexene (diethylstilbestrol) has been a valuable medicinal agent. Equally apparent for some time now, however, has been the fact that the administration of diethylstilbestrol is not infrequently accompanied by certain physiological disturbances commonly regarded as manifestations of toxicity. As in other similar instances, this situation has encouraged considerable research designed to produce related compounds which retain sufficient estrogenic activity to have practical value, and which at the same time are sufficiently non-toxic as to have favorable therapeutic indexes.

The structure of diethylstilbestrol suggests at once certain simple chemical alterations worthy of investigation. Thus various esters and ethers have been prepared and tested, as have also many other compounds differing from diethylstilbestrol primarily in degree of saturation, presence of alkyl and other substituents in the hexane residue, and points of attachment of the benzene nuclei to the aliphatic chain. Various closely related intermediates and by-products formed during the synthesis of such compounds have also been tested for estrogenic activity.<sup>2</sup>

To date, however, little attention has been given to the possibility of producing derivatives with improved properties through the introduction of alkyl groups on the benzene nuclei while at the same time retaining the six carbon aliphatic chain.

Kaiser and Svarz<sup>3</sup> have prepared the 3,3'-diallyl, and dipropenyl diethylstilbestrols and the 3,3'-diallyl, dipropenyl, and di-*n*-propyl hexestrols, but found them to be weakly estrogenic. Other somewhat similar compounds have been prepared and tested, but they differ from the compounds pertinent to this study either in length of the main aliphatic chain or in points of attachment of the benzene nuclei thereto.<sup>4-12</sup>

(1) Presented by C. T. Van Meter before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Illinois, Sept. 12, 1946.

(2) Solmssen, *Chem. Rev.*, **37**, 481 (1945).

(3) Kaiser and Svarz, *THIS JOURNAL*, **68**, 636 (1946).

(4) Bretschneider, Bretschneider and Ajtai, *Ber.*, **74**, 571 (1941).

(5) Baker, *THIS JOURNAL*, **65**, 1572 (1943).

(6) Campbell, *Proc. Roy. Soc. (London)*, **B129**, 528 (1940).

(7) Dodds and Lawson, *ibid.*, **B125**, 222 (1938).

(8) Easson, Harrison, McSwiney and Pyman, *Quart. J. Pharm. Pharmacol.*, **7**, 509 (1934).

(9) Harden and Reid, *THIS JOURNAL*, **54**, 4325 (1932).

(10) Linnell and Shaikhamud, *Quart. J. Pharm. Pharmacol.*, **15**, 384 (1942).

(11) J. B. Niederl, and co-workers, *THIS JOURNAL*, **61**, 345 (1939); **64**, 885, 2486 (1942).

(12) Hudson and Walton, *J. Chem. Soc.*, 85 (1946).

It is the primary aim of this research to prepare and investigate for estrogenic activity and toxicity derivatives containing one methyl group in each benzene ring, with and without simultaneous changes in the degree of saturation in the hexane residue. In this report *m*-methyl derivatives of 3,4-bis-(*p*-hydroxyphenyl)-2,4-hexadiene and 3,4-bis-(*p*-hydroxyphenyl)-hexane, along with some of their esters, are described.

### Pharmacology

In common with other groups of related estrogens the potency of individual members in the series herein reported varies considerably. Tested on ovariectomized rats by the vaginal smear method, the two dihydroxy compounds are more active on injection than when given orally, but this order of relative activity is reversed in at least some of the esters. As in the diethylstilbestrol and hexestrol series, esters of monobasic aliphatic acids higher than propionic show decreased activities, and certain special esters such as the alkylcarbonates, acid succinates, and *m*-sulfobenzoates show their usual relatively high activities. Hydrogenation of a potent hexadiene compound to the corresponding hexane compound increases the activity.

The estrogenic activities (rats, vaginal smear) of the more potent compounds are shown in Table I. These activities were determined according to the method of the League of Nations Health Organization.<sup>13</sup> Vaginal smears are regarded as positive (a) if cornified cells only are present, or (b) if a smear of many nucleated and some cornified cells and no leucocytes is followed by a smear showing many cornified and nucleated cells with few leucocytes. Control rats received U.S.P. Reference Estrone as the standard estrogenic substance.

The estrogenic activities in Table I assume added importance when considered in conjunction with the following typical toxicity data. Compounds (2) and (7) have been administered orally to mice, daily over a three week period, in doses up to five times the toxic dose for diethylstilbestrol with no abnormal findings on autopsy.

Injected intraperitoneally as suspensions in acacia, the M.L.D.<sub>50</sub>'s (mice) are: diethylstilbestrol 18 mg., compound no. (2) 36 mg., and compound no. (7) 36 mg.

Favorable therapeutic indexes for these compounds are thus to be expected and early clinical work verifies this expectation.<sup>14</sup>

(13) League of Nations *Bull. Health Organization*, **4**, 622 (1935).

(14) S. H. Sturgis, *Am. J. Obstet. Gynecol.*, **53**, 678 (1947).

TABLE I

Compound	Dose, mcg.	Method of administration	Response <sup>b</sup>
(1) 3,4-bis-( <i>m</i> -Methyl- <i>p</i> -hydroxyphenyl)-2,4-hexadiene	5	Inj.	100
	2.5	Inj.	30
	15	Oral	10
	5	Oral	0
(2) Diacetate of (1)	15	Inj.	80
	15	Oral	65
(3) Dipropionate of (1)	15	Inj.	0
	15	Oral	85
	10	Oral	30
	5	Oral	0
(4) Dibutyrate of (1)	15	Oral	15
(5) 3,4-bis-( <i>m</i> -Methyl- <i>p</i> -hydroxyphenyl)-hexane	1.5	Inj.	90
	1.0	Inj.	70
	0.6	Inj.	30
	15	Oral	65
(6) Diacetate of (5)	15	Inj.	95
	5	Inj.	75
	2.5	Inj.	10
	10	Oral	70
	5	Oral	30
	2.5	Oral	0
(7) Dipropionate of (5)	15	Inj.	60
	10	Oral	90
	5	Oral	50
	2.5	Oral	0
(8) Dibutyrate of (5)	15	Oral	60
(9) Dibenzoate of (5)	5	Oral	85
(10) Di- <i>m'</i> -sodiumsulfo- benzoate of (5)	10	Oral	50
	6	Inj.	100
(11) Diacid succinate of (5)	15	Oral	100
	5	Oral	30
(12) Diethocarbonate of (5)	50	Oral	100
	15	Oral	70

<sup>a</sup> Solutions in oil except (10) which was given in aqueous solution. <sup>b</sup> Per cent. of rats showing smears consisting predominantly of cornified cells.

The general plan of synthesis involves a Fries isomerization of *o*-cresyl propionate, esterification of the resulting *p*-hydroxyphenone, reduction of this phenone ester to the corresponding pinacol, dehydration of the pinacol to a 2,4-hexadiene derivative and finally hydrogenation to a hexane type of compound.

### Experimental

***o*-Cresyl Propionate.**<sup>14</sup>—One mole of *o*-cresol was esterified with 1.1 moles of propionyl chloride. That fraction distilling at 104–106° (14 mm.) was collected as the ester; b. p. 218° (1 atm.); yield, quantitative.

**3-Methyl-4-hydroxypropionophenone.**<sup>14</sup>—One mole of *o*-cresyl propionate dissolved in 500 cc. of nitrobenzene was subjected to a typical Fries rearrangement at room temperature using 1.1 moles of anhydrous aluminum chloride. After hydrolysis of the aluminum complex the nitrobenzene solution was extracted with 10% sodium hydroxide. Acidification of this extract precipitated a mixture of the *o*- and *p*-hydroxypropionophenones which was collected, dried and distilled under vacuum. The fraction boiling at 150–155° (1 mm.) was collected as 3-

methyl-4-hydroxypropionophenone; m. p. 86°; yield, 75%.

The 2,4-dinitrophenylhydrazine was prepared; m. p. 238°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub>: N, 16.28. Found: N, 16.13.

**3-Methyl-4-propionoxypropionophenone.**—One-half mole of 3-methyl-4-hydroxypropionophenone was placed in a 500-cc. round-bottom flask fitted with a reflux condenser and a dropping funnel through which 0.55 mole of propionic anhydride was slowly added. The mixture was heated gently with a small flame during this addition and strongly enough thereafter to maintain gentle ebullition for one hour. Propionic acid and excess propionic anhydride were then distilled from the reaction mixture. The residual oil on cooling yielded 109 g. (99%) of solid material, m. p. 48–50°. Recrystallization from petroleum ether gave small white crystals, m. p. 52–53°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>16</sub>O<sub>5</sub>: C, 70.88; H, 7.32. Found: C, 70.69; H, 7.43.

The 2,4-dinitrophenylhydrazone was prepared; m. p. 179–180°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>: N, 14.00. Found: N, 14.05.

Instead of separating the isomeric hydroxyphenones obtained in the Fries rearrangement and then propionylating the desired isomer as described above, the mixture of hydroxyphenones may be subjected to the propionylation reaction and the mixture then fractionally distilled. The 4-propionoxy isomer distills at 141–143° (2 mm.). Less thermal decomposition occurs in this alternative procedure.

**3,4-bis-(*m*-Methyl-*p*-propionoxyphenyl)-3,4-hexanediol.**—This pinacol was first prepared by the reduction of 3-methyl-4-propionoxypropionophenone according to the method of Dodds, *et al.*,<sup>16</sup> for *p*-methoxypropionophenone, using aluminum amalgam and moist ether. The following method, however, was much more convenient and gave much higher yields.

One hundred grams of 3-methyl-4-propionoxypropionophenone was dissolved in 750 cc. of ethyl acetate which previously had been saturated with water. Forty grams of aluminum foil (strips, 2" × 1½") was etched with 10% sodium hydroxide solution, thoroughly amalgamated with 0.5% mercuric chloride solution, and washed successively with water, ethanol and ethyl acetate. The amalgam was then added quickly to the reaction flask and the mixture stirred for thirty minutes. During this time the temperature of the mixture had risen to a maximum of about 70° and had started to fall. After cooling aluminum hydroxide and unreacted aluminum were filtered off and washed several times with fresh portions of ethyl acetate. Removal of the ethyl acetate by distillation yielded a very sticky viscous oil which solidified slowly on long standing. Trituration of this solidified mass with a small quantity of cold isopropyl ether facilitated the separation of a white solid. After washing with isopropyl ether and recrystallizing from 70% ethanol, small white crystals of the pinacol were obtained; m. p. 152–153°.

*Anal.* Calcd. for C<sub>26</sub>H<sub>34</sub>O<sub>6</sub>: C, 70.56; H, 7.74. Found: C, 70.73; H, 7.91.

In the over-all synthesis it is unnecessary to separate the pure pinacol as described above. Instead, the viscous oil remaining after removal of ethyl acetate may be subjected directly to the dehydration reaction to form the hexadiene compound. In this manner over-all yields of 50% (phenone ester to diene) were obtained.

**3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-3,4-hexanediol.**—This compound was prepared by reducing 75 g. of 3-methyl-4-hydroxypropionophenone with 40 g. of aluminum foil as described above; yield, 26 g. (35%) of crystalline pinacol; m. p. 180–183°. Recrystallization from dilute acetic acid gave small white crystals of the pinacol, m. p. 182–183°.

(15) Hartung, Munch, Miller and Crossley, *THIS JOURNAL*, **53**, 4149 (1931).

(16) Dodds, Goldberg, Lawson and Robinson, *Proc. Roy. Soc. (London)*, **B127**, 140 (1939).

*Anal.* Calcd. for  $C_{20}H_{28}O_4$ : C, 72.70; H, 7.93. Found: C, 72.57; H, 7.69.

The *p,p'*-dibenzoate of this pinacol, prepared by the Schotten-Baumann reaction, was obtained as small white needles, m. p. 252°.

*Anal.* Calcd. for  $C_{24}H_{34}O_6$ : C, 75.81; H, 6.36. Found: C, 75.59; H, 6.53.

**3,4-bis-(*m*-Methyl-*p*-acetoxypheyl)-2,4-hexadiene.**—Five grams of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-3,4-hexanediol was suspended in a mixture of 15 cc. of acetic anhydride and 10 cc. of acetyl chloride, and the mixture refluxed gently for thirty minutes. After cooling the reaction mixture was poured into ice-water and allowed to stand with occasional stirring for two hours. The solid which separated was filtered, washed with water and then triturated with about 10 cc. of cold methanol. After filtering and drying 4.4 g. (80%) of solid material remained, m. p. 160–163°. Recrystallization from ethanol gave white crystals, m. p. 166–168°.

The tetrabromo derivative, prepared by bromination in carbon tetrachloride and purified by recrystallization from ethanol, formed white crystals, m. p. 148° dec.

*Anal.* Calcd. for  $C_{24}H_{28}Br_4O_4$ : Br, 45.79. Found: Br, 45.60.

**3,4-bis-(*m*-Methyl-*p*-propionoxypheyl)-2,4-hexadiene.**—This compound was prepared as described above for the acetoxy analog using 5 g. of 3,4-bis-(*m*-methyl-*p*-propionoxypheyl)-3,4-hexanediol, 15 cc. of acetic anhydride and 10 cc. of acetyl chloride; 4.1 g. (90%) of solid material was collected, m. p. 132–135°; recrystallization from ethanol gave white crystals; m. p. 139–140°.

**3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene.**—Two grams of 3,4-bis-(*m*-methyl-*p*-propionoxypheyl)-2,4-hexadiene was suspended in 20 cc. of Claisen solution (100 g. of potassium hydroxide dissolved in 100 cc. of water and diluted, after cooling, with an equal volume of methanol). The mixture was warmed on a steam-bath until the solid was completely dissolved and then allowed to stand at room temperature overnight. After diluting to 150 cc. with water, the mixture was filtered and then acidified with 10% hydrochloric acid to a pH of about 3. The white flocculent precipitate which separated was filtered, washed with water and dried; yield, 1.4 g. (95%), m. p. 180–185°. Recrystallization from 50% ethanol gave white needles, m. p. 187–189°.

**3,4-bis-(*m*-Methyl-*p*-butyroxypheyl)-2,4-hexadiene.**—One gram of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was dissolved in 10 cc. of anhydrous pyridine, 1.1 g. of butyric anhydride added and the mixture refluxed gently for ninety minutes. After cooling the reaction mixture was poured into 150 cc. of water and stirred for thirty minutes. The solid which separated was collected, washed with water and recrystallized from methanol, yielding one gram of small white crystals, m. p. 123–124°.

**3,4-bis-(*m*-Methyl-*p*-palmitoxypheyl)-2,4-hexadiene.**—One and one-half grams of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was dissolved in 10 cc. of anhydrous pyridine, 3 g. of palmityl chloride added and the mixture refluxed gently for thirty minutes. After cooling, the reaction product was poured into 100 cc. of water and allowed to stand for fifteen minutes. The mixture was then extracted with 150 cc. of ether and the ether solution then washed successively with 40 cc. of 10% hydrochloric acid, 40 cc. of 5% sodium hydroxide and then with water until the washings were neutral to litmus. After drying over anhydrous calcium chloride the ethereal solution was filtered, evaporated to dryness and the residue then recrystallized from ethanol, giving a white amorphous powder, m. p. 69–70°.

**3,4-bis-(*m*-Methyl-*p*-benzoxypheyl)-2,4-hexadiene.**—This compound was prepared by the Schotten-Baumann method using 1 g. of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene. Recrystallization from ethanol gave white needles, m. p. 207–208°.

**Disodium Salt of 3,4-bis-(*m*-Methyl-*p*-(*m'*-sulfo benzoyl)-phenyl)-2,4-hexadiene.**—Three grams of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was added slowly to a solution of 5 g. of benzoic acid-*m*-sulfochloride in 15 cc. of pyridine maintained at 80°. After all the hydroxy compound had been added, the mixture was heated for two hours at 80° and then poured into 150 cc. of water. The solution was then filtered, treated with saturated aqueous sodium chloride and centrifuged. The solid thus obtained was then dissolved in a minimum of water and the resulting solution was again treated with sodium chloride and centrifuged. This process was repeated once more and this time the resulting precipitate was pressed between filter papers and dried over sulfuric acid. The dried material was dissolved in a minimum of hot ethanol and the solution treated with benzene, whereupon the compound was obtained as a white, flocculent precipitate which was collected and dried. The compound decomposed at high temperatures.

**bis-Acid Succinate of 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene.**—One gram of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was dissolved in 10 cc. of pyridine, 1 g. of succinic anhydride added, and the mixture gently refluxed for two hours. After cooling the reaction mixture was diluted with 40 cc. of acetone and an excess of concentrated hydrochloric acid added. A viscous oil separated which was washed with water and recrystallized from dilute acetic acid to give small white crystals, m. p. 193°.

**bis-Methylcarbonate of 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene.**—One gram of 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene was dissolved in 15 cc. of pyridine and cooled to 0° in an ice-bath. Four cc. of methyl chlorocarbonate was added dropwise with shaking and cooling. The mixture was then allowed to come to room temperature and was poured into 100 cc. of water. The solid which separated was collected, washed first with water, and then with several small portions of ethanol and dried. Recrystallization from ethanol gave small white crystals, m. p. 171–172°.

**bis-Ethylcarbonate of 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexadiene.**—This compound was prepared as described immediately above by using ethyl chlorocarbonate. Recrystallization from ethanol yielded white crystals, m. p. 150–151°.

**3,4-bis-(*m*-Methyl-*p*-propionoxypheyl)-hexane.**—Two grams of 3,4-bis-(*m*-methyl-*p*-propionoxypheyl)-2,4-hexadiene was dissolved in 200 cc. of hot absolute ethanol and hydrogenated at 70° and about 70 atm. in the presence of Raney nickel. The mixture was then cooled, filtered and evaporated to dryness, whereupon 2 g. of solid material remained. Recrystallization from ethanol gave 1.6 g. (80%) of white crystals, m. p. 114–115°.

This compound was also prepared by hydrogenating the same quantity of the diene compound dissolved in 20 cc. of acetone, using 20 mg. of palladium black and an initial gage pressure of 48 lb. per sq. in. The theoretical pressure drop was attained in ten minutes; yield, 80% of pure product.

A study of the stereochemical aspects is in progress and will be reported later.

**3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-hexane.**—Two grams of 3,4-bis-(*m*-methyl-*p*-propionoxypheyl)-hexane was saponified by treatment with 20 cc. of Claisen solution as described under 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-2,4-hexadiene. Recrystallization from dilute acetic acid gave white crystals, m. p. 145°.

**Esters of 3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-hexane.**—Using identical methods, the same esters described in the hexadiene series were prepared.

Analytical data for all new compounds are summarized in Table II.

**Acknowledgment.**—Grateful acknowledgment is hereby expressed to Miss E. F. Deckert, Director of the Division of Pharmacology of the Reed and Carnrick Institute for Medical Re-

TABLE II

Compound	Molecular formula	M. p., °C.	Carbon, %		Hydrogen, %	
			Calcd.	Found	Calcd.	Found
3,4-bis-( <i>m</i> -Methyl- <i>p</i> -hydroxyphenyl)-2,4-hexadiene	C <sub>20</sub> H <sub>22</sub> O <sub>2</sub>	187-189	81.60	81.73	7.53	7.41
Diacetate	C <sub>24</sub> H <sub>26</sub> O <sub>4</sub>	166-168	76.16	76.30	6.93	6.96
Dipropionate	C <sub>30</sub> H <sub>30</sub> O <sub>4</sub>	138-139	76.82	76.78	7.44	7.56
Dibutyrate	C <sub>28</sub> H <sub>34</sub> O <sub>4</sub>	123-124	77.39	77.40	7.89	8.05
Dipalmitate	C <sub>52</sub> H <sub>82</sub> O <sub>4</sub>	69-70	80.98	80.70	10.72	10.66
Dibenzoate	C <sub>34</sub> H <sub>30</sub> O <sub>4</sub>	207-208	81.25	81.26	6.02	6.06
Dimethocarbonate	C <sub>34</sub> H <sub>30</sub> O <sub>6</sub>	171-172	70.22	70.20	6.38	6.61
Diethocarbonate	C <sub>26</sub> H <sub>30</sub> O <sub>6</sub>	150-151	71.21	71.19	6.90	7.17
Diacid succinate	C <sub>26</sub> H <sub>30</sub> O <sub>8</sub>	193	68.00	68.03	6.11	6.35
Di- <i>m'</i> -sulfobenzoate (disodium salt)	C <sub>34</sub> H <sub>30</sub> O <sub>10</sub> Na <sub>2</sub> S <sub>2</sub>	<sup>b</sup>	S, 9.07	8.79	Na, 6.51	6.41
3,4-bis-( <i>m</i> -Methyl- <i>p</i> -hydroxyphenyl)-hexane	C <sub>20</sub> H <sub>24</sub> O <sub>2</sub>	145	80.50	80.89	8.78	8.44
Diacetate	C <sub>24</sub> H <sub>26</sub> O <sub>4</sub>	132	75.36	75.21	7.91	7.82
Dipropionate	C <sub>30</sub> H <sub>34</sub> O <sub>4</sub>	115	76.06	76.09	8.35	8.28
Dibutyrate	C <sub>28</sub> H <sub>38</sub> O <sub>4</sub>	100-101	76.67	77.32	8.73	8.76
Dipalmitate	C <sub>52</sub> H <sub>58</sub> O <sub>4</sub>	68-69	80.56	80.67	11.18	10.77
Dibenzoate	C <sub>34</sub> H <sub>34</sub> O <sub>4</sub>	199-200	80.60	80.54	6.61	6.56
Dimethocarbonate	C <sub>34</sub> H <sub>38</sub> O <sub>6</sub>	148-149	69.54	69.34	7.30	7.24
Diethocarbonate	C <sub>26</sub> H <sub>34</sub> O <sub>6</sub>	138	70.56	70.69	7.74	7.28
Diacid succinate	C <sub>28</sub> H <sub>34</sub> O <sub>8</sub>	198-200	67.45	67.60	6.87	6.91
Di- <i>m'</i> -sulfobenzoate (disodium salt)	C <sub>34</sub> H <sub>38</sub> O <sub>10</sub> Na <sub>2</sub> S <sub>2</sub>	<sup>b</sup>	S, 9.02	8.98	Na, 6.47	6.62

<sup>a</sup> All melting points are uncorrected. <sup>b</sup> Melts with decomposition at about 300°.

search, under whose guidance all determinations of estrogenic potency and toxicity on experimental animals have been conducted.

#### Summary

3,4-bis-(*m*-Methyl-*p*-hydroxyphenyl)-2,4-hexa-

diene, 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)-hexane and some of their organic esters have been prepared. Many of these compounds are active estrogens.

JERSEY CITY, N. J.

RECEIVED AUGUST 11, 1947

[CONTRIBUTION FROM THE RESEARCH DIVISION, THE UPJOHN COMPANY]

### Steroid Acids and their Transformation Products. I. Thiol Esters<sup>1a</sup>

BY ROBERT H. LEVIN, A. VERN MCINTOSH, JR., GEORGE B. SPERO, DOUGLAS E. RAYMAN AND ELIZABETH M. MEINZER

The use of Raney nickel catalyst for the desulfurization and reduction of sulfur compounds has recently been extended to the preparation of aldehydes<sup>1</sup> and alcohols<sup>2</sup> from carboxylic acids via the corresponding thiol compounds. Among the acids used by Jeger and co-workers<sup>2a</sup> were 3 $\beta$ -acetoxy-*etio*-*allo*-cholanolic acid and 3 $\beta$ -acetoxy- $\Delta^5$ -*etio*-cholenic acid. For the broader use of the thiol esters as starting materials for the side chain degradation of steroids we have prepared a number of these previously unreported esters.

The steroid thiol esters were prepared by two methods:<sup>3</sup> (A) reaction of the acid chloride with

an excess of mercaptan in pyridine; and (B) treatment of the acid chloride with a suspension of lead mercaptide<sup>4</sup> in ether. Generally speaking method A gave slightly better yields of crystalline thiol ester, but the products from B were easier to purify to constant m. p. Table I summarizes our data. Several of these compounds were chromatographed over alumina. It was found that the acetoxy thiol esters could be readily purified in this way. However, a number of the crystalline formoxy compounds became oily when put over the column, probably because of deformylation at the 3-position.

Ethyl 3 $\alpha$ -hydroxy-12 $\alpha$ -acetoxy-*nor*-thiolcholanate (III) was obtained from 3 $\alpha$ -hydroxy-12 $\alpha$ -acetoxy-*nor*-cholanolic acid (II)<sup>5</sup> using method A. This involves the interesting preparation of a non-aromatic hydroxy acid chloride by the use of thi-

(1a) Presented before the Division of Medicinal Chemistry, 112th A. C. S. Meeting, New York, N. Y., September 17, 1947.

(1) M. L. Wolfson and J. V. Karabinos, *THIS JOURNAL*, **68**, 1455 (1946).

(2) (a) V. Prelog, J. Norymberski and O. Jeger, *Helv. Chim. Acta*, **29**, 360 (1946). (b) O. Jeger, J. Norymberski, S. Szpilfogel and V. Prelog, *ibid.*, **29**, 684 (1946). (c) L. Ruzicka, S. Szpilfogel and O. Jeger, *ibid.*, **29**, 1520 (1946).

(3) A. W. Ralston, E. W. Segebrecht and S. T. Bower, *J. Org. Chem.*, **4**, 502 (1939), have reviewed the literature.

(4) P. Borgstrom, L. M. Ellis, Jr., and E. E. Reid, *THIS JOURNAL*, **51**, 3649 (1929).

(5) Byron Riegel and A. Vern McIntosh, Jr., *ibid.*, **66**, 1102 (1944).