

the extent of binding to protein of the four adenosine adamantates have been initiated in our laboratories.<sup>48</sup>

In conclusion, the nucleoside adamantates as well as the adamantane-containing agents earlier described may derive their high efficacy, at least in part, through a process of precise and specific binding of the adamantane moiety to complementary, lipid regions of the protein receptor site molecule.

Naturally, binding to protein of adamantane-containing agents acting *in vivo* may also affect their absorption and their distribution (transport) in the animal host. The effect of protein binding on these processes may be responsible for the quantitative differences seen between the *in vivo* activities, on the one hand, of the monomethylated analogs relative to the adamantane agent in the sulfonylurea series<sup>7</sup> (about 25%) and the nortestosterone esters<sup>2</sup> (about 15–20%), and on the

other hand, the activity of adenosine monomethyladamantate relative to the adamantate (about 130%) in inhibiting platelet aggregation *in vitro* (Table X).

The study of a different class of adamantane-containing agents which display a structure-activity relationship opposite to that reported in this paper and which presumably do not benefit from binding to protein will be the subject of a forthcoming publication.

**Acknowledgments.**—The authors are grateful to Mr. W. L. Brown and associates for microanalyses; to Mr. D. O. Woolf for physicochemical data; to Dr. Richard E. Holmes for the interpretation of nmr data; to Dr. Irving S. Johnson, Mr. G. A. Poore, Dr. R. L. Stone, and associates for the generous cooperation in obtaining the varied biological results;<sup>40</sup> and to Dr. Alex L. Nussbaum<sup>17</sup> and Dr. William E. Razzell<sup>19</sup> for contributions to the chemical experimental work. The special efforts of Dr. R. G. Herrmann and associates<sup>37</sup> to obtain reproducible results in the platelet aggregation studies are gratefully remembered.

(48) Preliminary results indicate the possibility that the effect of methyl substitution on partition values parallel the test results obtained in the platelet aggregation studies (Table X). The help of Mr. M. M. Marsh and associates, Analytical Research and Development Division, The Lilly Research Laboratories, in obtaining these results is gratefully acknowledged.

## Totally Synthetic Steroid Hormones. XIII.<sup>1</sup> The Chemical Resolution of Some Racemic Estrane, 13 $\beta$ -Ethylgonane, and 13 $\beta$ -*n*-Propylgonane Derivatives and the Preparation of Some Estrane and 13 $\beta$ -Ethylgonane Derivatives of Unnatural Configuration

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The following six racemic steroids have been resolved into optical antipodes by salt formation between the corresponding hemisuccinate esters and various optically active bases: 3-methoxyestra-1,3,5(10),8,14-pentaen-17 $\beta$ -ol, 3-methoxyestra-1,3,5(10),8-tetraen-17 $\beta$ -ol, 3-methoxyestra-1,3,5(10)-trien-17 $\beta$ -ol, 13 $\beta$ -ethyl-3-methoxygon-1,3,5(10)-trien-17 $\beta$ -ol, 13 $\beta$ -ethyl-3-methoxygon-1,3,5(10),8-tetraen-17 $\beta$ -ol, and 3-methoxy-13 $\beta$ -*n*-propylgon-1,3,5(10)-trien-17 $\beta$ -ol. Racemic 3-benzyloxy-13 $\beta$ -ethylgon-1,3,5(10)-trien-17 $\beta$ -ol has been chemically resolved by separation of its diastereoisomeric (–)-menthoxyacetates. Chemical transformations of several of the steroidal enantiomorphs are reported. Results of biological testing are given for some of the steroids of unnatural configuration.

Previous parts of this series have reported efficient, stereoselective total syntheses of various racemic estrone, estrane (19-norandrostane), and 13 $\beta$ -polycarbonalkylgonane derivatives.<sup>3,4</sup> These researches have already provided a possible basis for the commercial production of estrone, and, therefore, of those of its derivatives which are medicinally important as estrogenic, progestational, anabolic, and antifertility agents, and have also led to a variety of biologically interesting racemic 13 $\beta$ -polycarbonalkylgon-1,3,5(10)-trienes and gon-4-en-3-ones of potential or actual clinical utility.<sup>4b</sup>

This paper describes resolution procedures of the purely chemical type which lead from our previously described racemates<sup>3–6</sup> to enantiomorphs in the estrane, 13 $\beta$ -ethylgonane, and 13 $\beta$ -*n*-propylgonane series. Such studies were undertaken to furnish the final links in our totally synthetic chain to *d*-estrone,<sup>7</sup> to permit a more detailed examination of the properties of the biologically

(5) G. A. Hughes and H. Smith, German Patents 1,213,404, 1,213,405, and 1,214,679 (Feb 19, 1960, June 22, 1961, and Feb 29, 1961, respectively).

(6) G. A. Hughes and H. Smith, Japanese Patent 40-20700 (May 16, 1962).

(7) We denote the absolute configuration of enantiomorphs of steroids according to a convention proposed by L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 336, by which estrane and gon-1,3,5(10)-trienes are defined as *d* steroids if they have the same configuration as cholesterol at C-13 and as *l* steroids if they have the opposite configuration at that center. The graphic formulas correspond to enantiomorphs of the *d* series but are used to denote the structure and absolute configuration of any steroid by use of the appropriate prefix *d*, *l*, or *dl*. The prefixes (+) and (–) are used, where necessary, to denote dextro- or levorotatory compounds, respectively.

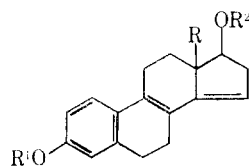
(1) Part XII: G. A. Hughes and H. Smith, *Steroids*, **8**, 547 (1966).

(2) Postal address, P. O. Box 8299, Philadelphia, Pa. 19101.

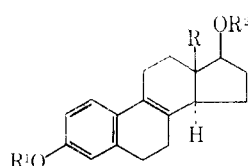
(3) G. A. Hughes and H. Smith, *Chem. Ind. (London)*, 1022 (1960); G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).

(4) (a) H. Smith, *et al.*, *Experientia*, **19**, 394 (1963); (b) *J. Chem. Soc.*, 4472 (1964).

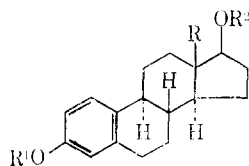
active *d* enantiomorphs<sup>8</sup> corresponding to the most interesting *dl*-13 $\beta$ -ethyl- and *n*-propylgonanes, and to provide for a systematic exploration for biological activity of selected estrane and 13 $\beta$ -ethyl- and *n*-propylgonane derivatives of *l* ("unnatural") configuration. Parts VIII<sup>9</sup> and IX<sup>10</sup> of this series have described resolutions employing microorganisms leading to compounds in the last two classes, two Japanese publications have described independent chemical resolutions of *dl*-3-methoxyestra-1,3,5(10),8,14-pentaen-17 $\beta$ -ol<sup>11</sup> and *dl*-13 $\beta$ -ethylgon-1,3,5(10),8-tetraen-17 $\beta$ -ol,<sup>12</sup> and a German publication<sup>13</sup> has reported a modification of one of our estradiol 3-methyl ether syntheses<sup>3</sup> which, through the introduction of an elegant asymmetric reduction using microorganisms, leads exclusively to natural *d*-estradiol 3-methyl ether without formation of unwanted enantiomorphs.



I, R = R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = H  
IV, R = R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = CO(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H

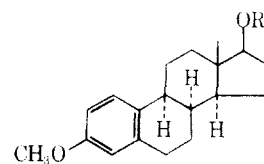


II, R = R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = H  
V, R = R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = CO(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H  
VII, R = C<sub>2</sub>H<sub>5</sub>; R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = H  
IX, R = C<sub>2</sub>H<sub>5</sub>; R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = CO(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H

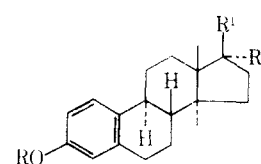


III, R = R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = H  
VI, R = R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = CO(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H  
VIII, R = C<sub>2</sub>H<sub>5</sub>; R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = H  
X, R = C<sub>2</sub>H<sub>5</sub>; R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = CO(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H  
XI, R = *n*-C<sub>3</sub>H<sub>7</sub>; R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = H  
XII, R = *n*-C<sub>3</sub>H<sub>7</sub>; R<sup>1</sup> = CH<sub>3</sub>;  
R<sup>2</sup> = CO(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H  
XIII, R = C<sub>2</sub>H<sub>5</sub>; R<sup>1</sup> = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>;  
R<sup>2</sup> = H  
XIV, R = C<sub>2</sub>H<sub>5</sub>; R<sup>1</sup> = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>;  
R<sup>2</sup> = C<sub>12</sub>H<sub>25</sub>O<sub>2</sub>  
XV, R = C<sub>2</sub>H<sub>5</sub>; R<sup>1</sup> = R<sup>2</sup> = H

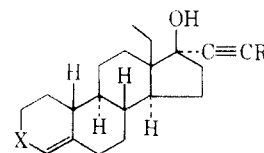
**Resolution of 17-Alcohols through Their Hemisuccinates.**—*dl*-Estrone can be resolved by separation of its diastereoisomeric (–)-menthoxyacetates.<sup>14</sup> However, since our syntheses proceed through intermediates of types I, II, and III, we believed that resolution at any of these stages would be more convenient and potentially more economic. Notably, estradiol methyl



XVII, R = COCH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H  
XVIII, R = H



XIX, R = CH<sub>3</sub>; R<sup>1</sup>, R<sup>2</sup> = O  
XX, R = H; R<sup>1</sup>, R<sup>2</sup> = O  
XXI, R = H; R<sup>1</sup> = OH;  
R<sup>2</sup> = H  
XXII, R = CH<sub>3</sub>; R<sup>1</sup> = OH;  
R<sup>2</sup> = C≡CH  
XXIII, R = H; R<sup>1</sup> = OH;  
R<sup>2</sup> = C≡CH



XXIV, X = CO; R = H  
XXV, X = CHOH; R = H  
XXVI, X = CHOCOCH<sub>3</sub>; R = H  
XXVII, X = CO; R = Cl

ether III may be converted to clinically important hormones of the 19-nortestosterone class<sup>15</sup> in two stages less than *d*-estrone.

The alcohols I–III have all been satisfactorily resolved through the formation of diastereoisomeric salts between the corresponding hemisuccinate esters IV–VI, respectively, and appropriate bases,<sup>16</sup> which have included (+)- and (–)-1-(1-naphthyl)ethylamine, (–)-ephedrine, and the (+)-dehydroabietylamine (XVI).<sup>17</sup> The last gives the most efficient resolution of the series when 0.5 equiv of its acetate salt is added to IV in ethyl acetate containing 1 equiv of triethylamine to selectively precipitate the salt of *d*-IV and XVI. A somewhat less efficient resolution is obtained under similar conditions with XVI and 0.5 equiv of triethylamine. In both cases *l*-IV is separated from mother liquors through formation of its salt with (–)-ephedrine. To secure reproducible results, wherever possible the experimental conditions were adjusted to allow the separation of one diastereoisomeric salt from its pair in a stirred solution or suspension. The same consideration applies to the resolution of the *dl*-hemisuccinates IX, X, and XII (below). The results are summarized in the collective Table I. In processes 1, 4, and 5, both enantiomorphs were obtained, in 4 by use of a single base [(–)-ephedrine] for salt formation with each, and in 1 and 5, by use of a second resolving base after initial precipitation of the salt of one enantiomorph hemisuccinate salt.

**Resolution of *dl*-13 $\beta$ -Ethyl- and *n*-Propylgonane Derivatives.**—Chemical resolution of the *dl*-13 $\beta$ -ethylgon-1,3,5(10)-triene series was first effected through formation of diastereoisomeric esters of the *dl*-alcohol XIII with (–)-menthoxyacetyl chloride. The ester XIV, after saponification and catalytic hydrogenolysis, gave the enantiomorph diols XV, whose absolute configurations have been previously defined.<sup>4b</sup>

The *dl*-hemisuccinates IX, X, and XII have all been resolved by salt formation with the bases indicated in

(8) R. A. Edgren, H. Smith, G. A. Hughes, L. L. Smith, and G. Greenspan, *Steroids*, **2**, 731 (1963).

(9) L. L. Smith, G. Greenspan, R. Rees, and T. Foell, *J. Am. Chem. Soc.*, **88**, 3120 (1966).

(10) G. Greenspan, L. L. Smith, R. Rees, T. Foell, and H. E. Alburn, *J. Org. Chem.*, **31**, 2512 (1966).

(11) T. Miki, K. Hiraga, and T. Asako, *Proc. Chem. Soc.*, 139 (1963); *Chem. Pharm. Bull.* (Tokyo), **13**, 1285 (1965).

(12) K. Hiraga, *ibid.*, **13**, 1289 (1965).

(13) H. Gibian, K. Kieslich, H.-J. Koch, H. Kosmol, C. Rufer, E. Schröder, and R. Vössing, *Tetrahedron Letters*, 2321 (1966).

(14) G. Anner and K. Miescher, *Helv. Chim. Acta*, **33**, 1379 (1950).

(15) L. F. Fieser and M. Fieser, ref 7, p 588.

(16) These resolutions have already been referred to by our Schering AG colleagues<sup>12</sup> to whom they were privately disclosed before publication.

(17) (a) W. J. Gottstein and L. C. Cheney, U. S. Patent 2,787,637 (1957); (b) *J. Org. Chem.*, **30**, 2072 (1965); (c) B. Sjöberg and S. Sjöberg, *Arkiv Kemi*, **22**, 147 (1964).

TABLE I  
 CHEMICAL RESOLUTION OF 13 $\beta$ -ALKYLGNAPOLYEN-17 $\beta$ -OLS

Substrate	Process	Resolving agent	Product	Mp, °C	$[\alpha]_D$ , deg	Crystn <sup>a</sup> solvent	Yield, % <sup>b</sup>	Formula	Calcd, % C H	Found, % C H
<i>dl</i> -IV				136-140	0		82	C <sub>23</sub> H <sub>26</sub> O <sub>5</sub>	72.23 6.85	71.70 6.83
<i>dl</i> -IV·NEt <sub>3</sub>	1 <sup>c</sup>	XVI·HOOCCH <sub>3</sub>	<i>d</i> -IV	148-150	-146	A + B	81.4	C <sub>23</sub> H <sub>26</sub> O <sub>5</sub>	72.23 6.85	72.32 6.69
		(-)-Ephedrine	<i>d</i> -I <sup>d</sup>	110-111	-132.8	C + D	60.5	C <sub>19</sub> H <sub>22</sub> O <sub>2</sub>	80.81 7.85	81.05 7.60
			<i>l</i> -IV	149-152	+154.6	A + B	55	C <sub>23</sub> H <sub>26</sub> O <sub>5</sub>	72.23 6.85	72.11 6.70
			<i>l</i> -I	110-112	+135	C + D	69	C <sub>19</sub> H <sub>22</sub> O <sub>2</sub>	80.81 7.85	80.96 7.56
<i>dl</i> -IV	2	(-)-Ephedrine	<i>l</i> -IV	149-151	+146	C + D	73	C <sub>23</sub> H <sub>26</sub> O <sub>5</sub>	72.23 6.85	72.11 6.70
<i>dl</i> -IV	3	(+)-1-(1-Naphthyl)-ethylamine	<i>l</i> -IV	150-152	+151	C + D	40	C <sub>23</sub> H <sub>26</sub> O <sub>5</sub>	72.23 6.85	72.35 6.73
<i>dl</i> -V				149-154	0	C + D	70	C <sub>23</sub> H <sub>26</sub> O <sub>5</sub>	71.85 7.34	71.76 7.18
<i>dl</i> -V	4 <sup>e</sup>	(-)-Ephedrine	<i>l</i> -V	Gum						
			<i>l</i> -II	125-126	+5.1	D + E	76	C <sub>19</sub> H <sub>24</sub> O <sub>2</sub>	80.24 8.51	80.42 8.48
		(-)-Ephedrine	<i>d</i> -V	Gum						
			<i>d</i> -II <sup>f</sup>	118-121	-4.0	D + E	36	C <sub>19</sub> H <sub>24</sub> O <sub>2</sub>	80.24 8.51	79.74 7.94
<i>dl</i> -VI				178.5-180.5	0		86.5	C <sub>23</sub> H <sub>30</sub> O <sub>5</sub>	71.48 7.82	71.20 7.52
<i>dl</i> -VI	5 <sup>e</sup>	(-)-1-(1-Naphthyl)-ethylamine	<i>d</i> -VI	Gum						
			<i>d</i> -III <sup>g,h</sup>	117-118	+74.4	F + G	65	C <sub>19</sub> H <sub>26</sub> O <sub>2</sub>	79.68 9.15	79.75 9.07
		(+)-1-(1-Naphthyl)-ethylamine	<i>l</i> -VI	Gum						
			<i>l</i> -III	91-93 <sup>k</sup>	-69.5	F + G	47	C <sub>19</sub> H <sub>26</sub> O <sub>2</sub>	79.68 9.15	79.55 8.83
<i>dl</i> -IX				164-166	0		85	C <sub>24</sub> H <sub>30</sub> O <sub>5</sub>	72.33 7.59	72.32 7.48
<i>dl</i> -IX	6 <sup>e</sup>	(-)-Ephedrine	<i>l</i> -IX	Gum						
			<i>l</i> -VII <sup>i</sup>	115-118	+59	F	43.5	C <sub>20</sub> H <sub>26</sub> O <sub>2</sub>	80.49 8.78	80.15 8.72
		(-)-Ephedrine	<i>d</i> -IX	Gum						
			<i>d</i> -VII <sup>j</sup>	113-115	-54	F	30	C <sub>20</sub> H <sub>26</sub> O <sub>2</sub> ·0.5Et	79.43 8.94	79.45 8.54
<i>dl</i> -X				160-161.5	0		91	C <sub>24</sub> H <sub>32</sub> O <sub>5</sub>	71.97 8.05	71.98 7.81
<i>dl</i> -X	7 <sup>e</sup>	XVI	<i>l</i> -X	Gum						
			<i>l</i> -VIII <sup>k</sup>	105-108	-56.6	F + G	46	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub>	79.95 9.39	79.74 9.13
		(-)-1-(1-Naphthyl)-ethylamine	<i>d</i> -X	Gum						
			<i>d</i> -VIII	103-106	+49.5	F + G	39	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub>	79.95 9.39	79.49 9.01
	8 <sup>e</sup>	XVI	<i>l</i> -VIII	103-106	-56	F + G	63			
		(+)-Amphetamine	<i>d</i> -VIII	103-107	+59	F + G	57.5			
<i>dl</i> -XII				149-153	0	C + D	98	C <sub>25</sub> H <sub>34</sub> O <sub>5</sub>	72.43 8.27	72.20 8.11
<i>dl</i> -XII	9 <sup>e</sup>	(-)-Ephedrine	<i>d</i> -XII	145-146	+26	C + D		C <sub>25</sub> H <sub>34</sub> O <sub>5</sub>	72.43 8.27	72.26 7.74
			<i>d</i> -XI	101-103	+69	D	49.4	C <sub>21</sub> H <sub>30</sub> O <sub>2</sub>	80.21 9.62	80.25 9.61
		(-)-Ephedrine	<i>l</i> -XII	145-146	-23	C + D		C <sub>25</sub> H <sub>34</sub> O <sub>5</sub>	72.43 8.27	72.47 8.02
			<i>l</i> -XI <sup>l</sup>	102-104	-65	D	34.2	C <sub>21</sub> H <sub>30</sub> O <sub>2</sub>	80.21 9.62	80.21 9.90
<i>dl</i> -XIII				123-124	0	F	83	C <sub>26</sub> H <sub>32</sub> O <sub>2</sub>	82.93 8.57	82.89 8.34
<i>dl</i> -XIII	10	(-)-Menthoxycarbonyl chloride	<i>l</i> -XIV	143-143.5	-51	H	23.6	C <sub>38</sub> H <sub>52</sub> O <sub>4</sub>	79.68 9.15	79.54 9.15
			<i>l</i> -XIII	121-122.5	-42.2	I	91	C <sub>26</sub> H <sub>32</sub> O <sub>2</sub>	82.93 8.57	82.69 8.50
			<i>l</i> -XV <sup>m</sup>	189-190.5	-55.2	I	76			
			<i>d</i> -XIV	91-91.5	-20.7	I	20	C <sub>38</sub> H <sub>52</sub> O <sub>4</sub>	79.68 9.15	79.40 8.98
			<i>d</i> -XIII	120.5-122	+42.6	I	87.5			
			<i>d</i> -XV <sup>n</sup>	188.5-189.5	+58	I	68			

<sup>a</sup> A = acetone, B = heptane, C = ether, D = hexane, E = ethyl acetate, F = ethanol, G = water, H = petroleum ether (bp 40-60°), I = methanol. <sup>b</sup> Yields for each stage were calculated by taking into account, where applicable, recovered substrate. <sup>c</sup> Stirring at stage involving separation of diastereoisomeric salts. <sup>d</sup> Miki, *et al.*,<sup>11</sup> give mp 55°,  $[\alpha]_D^{25}$  -126°. <sup>e</sup> No stirring at stage of separation of diastereoisomeric salts. <sup>f</sup> Miki, *et al.*,<sup>11</sup> give mp 125°,  $[\alpha]_D^{25}$  -3°. <sup>g</sup> Miki, *et al.*,<sup>11</sup> give mp 98°,  $[\alpha]_D^{25}$  +80°. <sup>h</sup> A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953), give for enantiomorphs mp 97-98, 118-119, and 120.5-121.5°,  $[\alpha]_D^{25}$  +77.4°. <sup>i</sup> Hiraga<sup>12</sup> gives mp 118°,  $[\alpha]_D$  +64°. <sup>j</sup> Hiraga<sup>12</sup> gives mp 118°,  $[\alpha]_D$  -64°. <sup>k</sup> Lit.<sup>4b</sup> mp 107.5-109.5°,  $[\alpha]_D$  -51°. <sup>l</sup> Lit.<sup>4b</sup> mp 101-103°,  $[\alpha]_D$  -58.7°. <sup>m</sup> Lit.<sup>9</sup> mp 189.5-190°,  $[\alpha]_D$  -53.4°. <sup>n</sup> Lit.<sup>9</sup> mp 106 and 187-189°,  $[\alpha]_D$  +58.5°.

Table I. The absolute configurations of the enantiomorphs VIII and XI, corresponding to X and XII, respectively, have also been elucidated in our earlier work.<sup>4b</sup> The absolute configurations of the enantiomorphs of VII were revealed by showing that reduction of the (-)-VII with lithium and aniline in liquid ammonia, gave *d*-VIII. Hiraga<sup>12</sup> has independently described the resolution of *dl*-IX through salt formation with brucine, but, apparently using the *d* and *l* prefixes to denote the sign of the optical rotation rather than the absolute configuration, did not define the absolute configuration of the enantiomorphs.

**Transformations of *d*- and *l*-Estrapolyenes and 13 $\beta$ -Ethylgonapolyenes.**—The absolute configuration as-

signed<sup>12</sup> to *d*-I and -II has been confirmed by selectively hydrogenating *d*-IV to *d*-V, saponifying the product to *d*-II, and reducing the latter with lithium in liquid ammonia-aniline<sup>4</sup> to authentic *d*-estradiol 3-methyl ether III. Also, various *l*-estrane and *l*-13 $\beta$ -ethylgonane derivatives have been prepared for biological evaluation, including *l*-III, prepared by the same sequence as *d*-III, and the *l* series XVII-XXIII and XXIV-XXVII. The *l*-8 $\alpha$ -estratriene XVIII, corresponding to the antilipemically active racemate,<sup>18</sup> was obtained from *l*-IV by catalytic hydrogenation in

(18) G. C. Buzby, Jr., E. Capaldi, G. H. Douglas, D. Hartley, D. Herbst, G. A. Hughes, K. Ledig, J. McMenamin, T. Pattison, H. Smith, C. R. Walk, and G. R. Wendt, *J. Med. Chem.*, **9**, 338 (1966).

ethyl acetate-benzene over Pd-C to XVII and saponification. *l*-XIX-XXIII, corresponding to the estrogenically active *d* enantiomorphs, were obtained by straightforward procedures from *l*-IV (see Experimental Section). *l*-XXV and -XXVI were prepared from *l*-XXIV, and *l*-XXVII was made from *l*-VIII by Birch reduction, Oppenauer oxidation, addition of lithium chloroacetylde to the resulting ketone, and acid hydrolysis. *l*-XXVI and -XXVII are enantiomorphs corresponding to potent racemic progestational-anti-estrogenic agents.<sup>19</sup> The molecular rotational difference between the *l*-XXVI and *l*-XXIV is +170° as compared to +397 and -209°, respectively, for those between *d*-3 $\alpha$ - and -3 $\beta$ ,17 $\beta$ -diacetoxyestr-4-ene<sup>20</sup> and *d*-17 $\beta$ -acetoxyestr-4-en-3-one,<sup>21</sup> which suggests that XXVI has the *l*-3 $\beta$ -acetoxy configuration.

**Biological Testing Data.**—We deemed it of interest to determine whether steroids of the *l* ("unnatural") configuration could possess any of the biological activities associated with corresponding hormones in the *d* ("natural") series, and, in particular, to ascertain whether any *l*-estratriene would display the antilipemic properties characteristic of the natural estrogens without retaining their usual feminizing activities. A substance with the appropriate separation of such activities would be of potential use in the treatment of atherosclerosis (*cf.* ref 22). Estrogenic activity was determined in a standard mouse uterotrophic<sup>23</sup> test (A) and antilipemic activity in blood cholesterol lowering tests in normal<sup>22</sup> and hypocholesterolemic<sup>24</sup> rats (B and C, respectively), and from the alteration by the drug of the serum cholesterol:phospholipid ratio in cholesterol-fed cockerels (test D).<sup>22</sup> Notably, *l*-estradiol XXI showed 90, 8, and 50% of the antilipemic activity of estrone in tests B, C, and D, respectively, with only 0.06% of the feminizing activity of the same hormone in test A. The last value could conceivably represent a trace of *d*-XXI present as an impurity. Similarly, the *l*-8 $\alpha$ -estradiol methyl ether XVIII displayed 300 and 6% of the antilipemic activity of estrone in tests B and C, respectively, with slight feminizing activity in the former test as indicated by regression of testicular weight. Although conversion of *d*-estradiol to *d*-ethynylestradiol potentiates normal estrogenic activity, the same conversion in the *l*-series abolishes antilipemic activity almost completely. Thus, the *l*-ethynyl alcohol XXIII has only a trace of antilipemic activity in test C and low activity (<5% of the activity of estrone) in test D. Also, the corresponding methyl ether XXIII is devoid of activity in tests B, C, and D.

The *l*-13-ethylgonenone XXVII was inactive in the Claiberg test,<sup>25</sup> in agreement with previous tests in these laboratories which have demonstrated that the progestational, antiestrogenic, and androgenic proper-

ties of various *dl*-13-ethylgonane derivatives are confined to the enantiomorphs corresponding in absolute configuration to the natural steroids.<sup>5</sup>

## Experimental Section<sup>26</sup>

Data on the substrates, intermediates, and end products of various resolution experiments (processes 1-10) are assembled in Table I. The conditions required for the successful separation of diastereoisomeric salts (including those made from mother liquors) are quite critical and are therefore given in detail for each process. Distilled water was used throughout all resolution processes, being particularly necessary in those involving XVI or its acetate to avoid precipitation of the insoluble sulfate which would otherwise be formed from the sulfate anion present in tap water.

***dl*-13 $\beta$ -Alkylgonapolyen-17 $\beta$ -ol Hemisuccinates.**—The *dl*-gonapolyen-17 $\beta$ -ol (0.23 mole) was refluxed with succinic anhydride (0.65 mole) in pyridine (100 ml) under nitrogen for 5-20 hr. For the preparation of *dl*-IV, benzene (400 ml) was also added to the reaction mixture. The cooled solution was poured into excess aqueous HCl containing crushed ice and the mixture was extracted with CHCl<sub>3</sub>. Evaporation of the washed and dried extract gave a residue which was triturated with ether. The crystals were filtered off, washed thoroughly with ice-cold ether, and dried to give the hemisuccinate.

**Hydrolysis of 13 $\beta$ -Alkylgonapolyen-17 $\beta$ -ol Hemisuccinate Amine Salts.**—(a) The salt (0.043 mole) was stirred at 50° with four teaspoonfuls of Amberlite IR 120 ion-exchange resin<sup>27</sup> in methanol-water (900:100 ml). Four additional teaspoonfuls of resin was added at intervals of 30 min, and after 3.5 hr the cooled mixture was filtered. Water (500 ml) was added, and the precipitated crystals of the hemisuccinate were filtered off, dried, and recrystallized. (b) The salt was shaken with 3 *N* HCl and ether until dissolved and the ether layer was washed, dried, and evaporated to give the hemisuccinate.

**Hydrolysis of 13 $\beta$ -Alkylgonapolyen-17 $\beta$ -ol Hemisuccinates.**—The hemisuccinate (15 g) was refluxed in 95% ethanol-20% aqueous NaOH (250:25 ml) for 1 hr. If a cloudiness developed during this period, sufficient water (*ca.* 20 ml) was added to clarify. The cooled solution was acidified to pH 6 with 3 *N* HCl or acetic acid, and water was added dropwise to precipitate the 13 $\beta$ -alkylgonapolyen-17 $\beta$ -ol which was filtered off and dried.

**Resolution of *dl*-3-Methoxyestra-1,3,5(10),8,14-pentaen-17 $\beta$ -ol Hemisuccinate (IV).**—(1) A mixture of the hemisuccinate (43.2 g, 0.113 mole), triethylamine (11.4 g, 0.113 mole), and the acetate salt of base XVI<sup>28</sup> (20.6 g, 0.0565 mole) was stirred in ethyl acetate (750 ml) at 50° until a clear solution was obtained. The mixture was then stirred in an ice bath for 1.5 hr and filtered. The solid was washed with hexane and dried, and the resulting salt (34 g), mp 126-131°, was recrystallized from methanol-water to give the salt of *d*-IV with the base XVI (28.5 g), mp 126-131°, which was decomposed by method a to the *d*-hemisuccinate IV (14 g), mp 148-150°. To the mother liquors from the initial formation and recrystallization of the salt of *d*-IV and base XVI, was added (–)-ephedrine (0.0565 mole), and the solution was kept at room temperature for 16 hr. The crystals were filtered off, washed with ethyl acetate, and dried to give the (–)-ephedrine salt of *l*-IV (20 g), mp 144-147°, which was decomposed by method b to afford a residue which was recrystallized from acetone-heptane to give *l*-IV (12 g), mp 149.5-152°. The mother liquors from the precipitation and recrystallization of the (–)-ephedrine salt of *l*-IV were washed with HCl and brine and evaporated. The residue was stirred for 2.5 hr at 0° with ethyl acetate (250 ml), triethylamine (2.0 g, 0.0198 mole), and XVI (5.63 g, 0.0198 mole). Recrystallization of the precipitate from methanol-water gave a second crop of the salt of *d*-IV and -XVI (9.5 g, mp 127-131°) which was decomposed by method a to give further *d*-IV (3.6 g), mp 148-150° (from acetone-heptane).

(2) The hemisuccinate IV (1.5 g) was stirred for 2 hr at 40° in ethyl acetate (18 ml) containing triethylamine (0.187 g) and (–)-ephedrine (0.371 g). Stirring was continued for a further

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(26) Melting points were determined in capillary tubes (Thomas-Hoover apparatus) and are uncorrected. Ultraviolet absorption spectra were determined in 95% ethanol solutions. Optical rotations were determined with the Zeiss 0.005° Photoelectric polarimeter on 0.5-1% solutions in CHCl<sub>3</sub> at 25° unless stated otherwise.

(27) Mallinckrodt Chemical Co., St. Louis, Mo.

2 hr while the temperature fell to 30°. The precipitated *l*-IV (–)-ephedrine salt (0.425 g), mp 144–147°, was filtered off and decomposed by method b to give *l*-IV (0.25 g), mp 149–151° (from ether–hexane).

(3) (+)-1-(1-Naphthyl)ethylamine was added dropwise with swirling to a suspension of IV (0.5 g) in ethyl acetate (10 ml) until solution was effected. The mixture was kept overnight at room temperature and filtered. Recrystallization of the precipitate from ethyl acetate gave the *l*-IV (+)-1-(1-naphthyl)ethylamine salt (0.2 g), mp 136–138°, which was decomposed by method b to give *l*-IV (0.1 g), mp 150–152° (from ether–hexane).

**Resolution of *dl*-3-Methoxyestra-1,3,5(10),8-tetraen-17 $\beta$ -ol Hemisuccinate (V).**—(4) (–)-Ephedrine (from the hydrochloride, 3 g) was added with swirling to a suspension of *dl*-V (3.0 g) in ethyl acetate (80 ml) and the clear solution was kept at room temperature without disturbance for 1.5 hr. The resulting crystals were slurried with hot ethyl acetate, to give the (–)-ephedrine *l*-V salt (1.66 g), mp 166–168°, which was decomposed by method b to give *l*-V as a gum which was hydrolyzed to *l*-II (0.84 g), mp 125–126°. The combined mother liquors from the initial precipitation of the (–)-ephedrine *l*-V salt and its suspension in ethyl acetate were concentrated to half volume and gave, on standing, further crystals, mp 140–150°, which were recrystallized from ethyl acetate. A first crop (0.17 g), mp 135–150°, was filtered off and discarded. The mother liquors then deposited a second crop (1.01 g), mp 136–139°, which was recrystallized from ethyl acetate to give the (–)-ephedrine *d*-V salt (0.825 g), mp 139–141°. This was decomposed by method b and the resulting hemisuccinate was hydrolyzed to *d*-II (0.390 g), mp 118–121°. One further recrystallization raised the melting point to 129–131°,  $[\alpha]_D^{25} -4.8^\circ$  (*c* 3, CHCl<sub>3</sub>).

**Resolution of *dl*-3-Methoxyestra-1,3,5(10)-trien-17 $\beta$ -ol Hemisuccinate (VI).**—(5) (–)-1-(1-Naphthyl)ethylamine (30 ml) was added with swirling to a suspension of *dl*-VI (30 g) in ethyl acetate (500 ml). The resulting solution was seeded with authentic *d*-VI–XVI salt and kept for 65 hr. The precipitate was filtered off, washed with ethyl acetate and ether, and recrystallized from ethyl acetate (200 ml) to give the (–)-1-(1-naphthyl)ethylamine *l*-VI salt (21 g), mp 113–119°, which was decomposed by method b. The product was suspended in ice-cold ether (150 ml), filtered off, and dried to give recovered *dl*-VI (5 g), mp 178–181°. Evaporation of the ethereal mother liquors gave *d*-VI as a gum which was hydrolyzed to *d*-III (6.0 g), mp 117–118°. The mother liquors from the original precipitation of the *d*-VI salt and from its recrystallization were combined, washed with 10% aqueous HCl, dried, and evaporated. The residue was triturated with ice-cold ether to give recovered *dl*-VI (7.0 g), mp 175–178°. The ethereal filtrate was evaporated, and the residue was kept for 20 hr in ethyl acetate (154 ml) with (+)-1-(1-naphthyl)ethylamine (11 ml). The precipitate was filtered off and washed with ethyl acetate and ether to give (+)-1-(1-naphthyl)ethylamine *l*-VI salt (9.5 g), mp 127–128°, which was decomposed by method b. Hydrolysis of the resulting *l*-VI gave *l*-III (4.34 g), mp 91–93° (from aqueous ethanol).

**Resolution of *dl*-13 $\beta$ -Ethyl-3-methoxygona-1,3,5(10),8-tetraen-17 $\beta$ -ol Hemisuccinate (IX).**—(6) The hemisuccinate IX (4 g) was dissolved in ethyl acetate (70 ml) containing (–)-ephedrine (from the hydrochloride, 4 g) and the solution was kept overnight. The precipitated salt was filtered off and recrystallized twice from ethyl acetate to give the (–)-ephedrine *l*-IX salt (2 g), mp 147–149°, which was decomposed by method b. Hydrolysis of the resulting *l*-IX and recrystallization of the product gave *l*-VII (0.65 g). The combined mother liquors from the original precipitation and the recrystallizations of (–)-ephedrine *l*-IX salt were concentrated to half volume and kept for 16 hr. Recrystallization of the precipitate from ethyl acetate gave the (–)-ephedrine *d*-IX salt (1.75 g), mp 125–128°, which was decomposed by method b. Hydrolysis of the resulting gummy *d*-IX then gave *d*-VII (0.445 g), mp 113–115°.

**Resolution of *dl*-13 $\beta$ -Ethyl-3-methoxygona-1,3,5(10)-trien-17 $\beta$ -ol Hemisuccinate (X).**—(7) The amine XVI (17.78 g, 0.0625 mole) was added at room temperature to *dl*-X (50.7 g, 0.125 mole) in ethyl acetate (875 ml) containing triethylamine (6.31 g, 0.0625 mole), and the mixture was stirred at 0° for 1.5 hr. The precipitate was filtered off, washed with ethyl acetate, and recrystallized from ethanol–water to give the XVI *l*-X salt (24.5 g), mp 167–169°, which was heated on the steam bath for 3 hr in aqueous ethanolic NaOH. The cooled solution was acidified with acetic acid and diluted with water. The precipitate was filtered off, washed with water, and dried to give *l*-VIII (8.8 g),

mp 105–108°. (–)-1-(1-Naphthyl)ethylamine (30 ml) was added to the mother liquors from the precipitation of the XVI–*l*-X salt, and the solution was kept for 16 hr. The precipitate was filtered off, washed with ether, and recrystallized twice from ethyl acetate to give the (–)-1-(1-naphthyl)ethylamine *d*-X salt (16.0 g), mp 117–118.5°, which was decomposed with hot aqueous ethanolic NaOH as before to give the *d*-VIII (7.4 g), mp 103–106°.

(8) The *dl*-hemisuccinate X (10 g) was treated with XVI as in (7) to remove the *l*-enantiomorph, and to the mother liquors (+)-amphetamine (2 ml) was added, and the solution was stirred at 0° for 2 hr. Recrystallization of the precipitate from ethyl acetate gave the (+)-amphetamine *d*-X salt (4.4 g), mp 158–165°, which was decomposed by aqueous ethanolic NaOH as in (7) to give *d*-VIII (2.15 g), mp 103–107°.

**Resolution of *dl*-17 $\beta$ -Hydroxy-13 $\beta$ -n-propyl-3-methoxygona-1,3,5(10)-trien Hemisuccinate (XII).**—(9) The *dl*-hemisuccinate XII (38 g) was added with swirling to ethyl acetate (700 ml) containing (–)-ephedrine (from the hydrochloride, 38 g). After standing for 2 hr, the mixture was filtered and the precipitate was recrystallized from ethyl acetate to give the (–)-ephedrine *d*-XII salt (18.8 g), mp 152–154°,  $[\alpha]_D^{25} +3^\circ$  (*c* 2, CHCl<sub>3</sub>), which was decomposed by method b to *d*-XII, mp 145–146°. The latter was hydrolyzed to *d*-XI (8.5 g), mp 101–103° (from ether–hexane). The mother liquors from the (–)-ephedrine *d*-XII salt were concentrated to half volume and filtered. The precipitate was recrystallized from ethyl acetate to give the (–)-ephedrine *l*-XII salt (14.5 g), mp 139–141°,  $[\alpha]_D^{25} -23.4^\circ$ , which was converted *via l*-XII, mp 145–146°, to *l*-XI (5.0 g), mp 102–104°.

***dl*-3-Benzoyloxy-13 $\beta$ -ethylgona-1,3,5(10)-trien-17-one.**—*dl*-13 $\beta$ -Ethyl-3-hydroxygona-1,3,5(10)-trien-17-one<sup>4b</sup> (4g) was refluxed with benzyl chloride (8 ml) and K<sub>2</sub>CO<sub>3</sub> (9 g) in ethanol–water (200:10 ml) for 16 hr. Water (50 ml) was added and the mixture cooled at 0° (bath) for 4 hr. The precipitate was filtered off and recrystallized from ethanol to give the benzyl ether (4.2 g), mp 145–148°. The analytical sample, a polymorph, had mp 125.5–126° (from ethanol),  $\lambda_{\max}$  277 and 284.5 m $\mu$  ( $\epsilon$  2300 and 2100).

*Anal.* Calcd for C<sub>26</sub>H<sub>30</sub>O<sub>2</sub>: C, 83.4; H, 8.1. Found: C, 83.2; H, 8.0.

***dl*-3-Benzoyloxy-13 $\beta$ -ethylgona-1,3,5(10)-trien-17 $\beta$ -ol (XIII).**—(a) *dl*-3-Benzoyloxy-13 $\beta$ -ethylgona-1,3,5(10)-trien-17-one (7 g) was refluxed with NaBH<sub>4</sub> (2.5 g) in ethanol (120 ml) for 2 hr. The solution was evaporated to dryness, water and ether were added, and the mixture was acidified with 3 N HCl. Evaporation of the washed and dried ether solution gave a residue which was recrystallized from ethanol to give the alcohol (5.8 g), mp 123–124°.

(b) *dl*-13 $\beta$ -Ethylgona-1,3,5(10)-trien-3,17 $\beta$ -diol (1.74 g) was refluxed with NaOC<sub>2</sub>H<sub>5</sub> (from the metal, 0.2 g) in ethanol for 15 min. Benzyl bromide (5 ml) was added to the cooled solution, and the mixture refluxed for 5 hr. Water was added and the product was extracted with ether. The ether solution was washed with aqueous 2 N NaOH, water, and brine. The product was chromatographed on Florisil, elution with benzene giving crystals which were recrystallized from methanol to give the alcohol (0.25 g), mp 120.5–121°,  $\lambda_{\max}$  277 and 288.5 m $\mu$  ( $\epsilon$  2200 and 1900).

**Resolution of *dl*-3-Benzoyloxy-13 $\beta$ -ethylgona-1,3,5(10)-trien-17 $\beta$ -ol (XIII).**—Freshly distilled (–)-menthoxyacetyl chloride (23 g) was added with stirring and external cooling (<10°) to *dl*-XIII (15 g) in pyridine (100 ml). The mixture was stirred for 2 hr at 10°, for 15 hr at room temperature, then added to ice-cold 3 N HCl. The mixture was extracted with ether, and the ether extracts, after washing and drying, were evaporated. The residue, which crystallized on trituration with petroleum ether (bp 60–80°) was recrystallized five times from the same solvent to give the (–)-menthoxyacetyl ester, *l*-XIV (5.45 g), mp 143–143.5°,  $\lambda_{\max}$  285.5 and 277 m $\mu$  ( $\epsilon$  1900 and 2200). The foregoing ester was refluxed with KOH (10 g) in methanol (600 ml) for 2 hr, and the mixture was evaporated to dryness. Water was added to the residue, and the mixture was extracted with ethyl acetate. The product was recrystallized from methanol to give *l*-XIII (3.2 g), mp 121–122.5°.

The mother liquor from the first recrystallization of the (–)-menthoxyacetyl ester *l*-XIV was evaporated and the residue recrystallized five times from methanol–ether (4:1, v/v) to give the (–)-menthoxyacetyl ester, *d*-XIV (4.5 g), mp 91–91.5°. The foregoing ester was hydrolyzed with methanolic KOH as above to give *d*-XIII, mp 120.5–122°.

***l*-13 $\beta$ -Ethylgona-1,3,5(10)-triene-3,17 $\beta$ -diol (XV).**—The (–)-ether, *l*-XIII (162 mg), was shaken with hydrogen at atmospheric pressure in ethanol (30 ml) containing 10% Pd-C (74 mg) until hydrogen uptake ceased. The catalyst was filtered off, the filtrate was evaporated to dryness, and the residue was recrystallized from methanol to give the diol (105 mg), mp 189–190.5°.

***d*-13 $\beta$ -Ethylgona-1,3,5(10)-triene-3,17 $\beta$ -diol (XV).**—obtained by hydrogenolysis, as before, of the (–)-ether, *d*-XIII (55 mg), formed crystals (28 mg), mp 188.5–189.5° (from methanol).

**Conversion of *d*- and *l*-IV to *d*- and *l*-III, Respectively.**—(a) The *d*-hemisuccinate IV (2 g) in benzene (100 ml) was shaken at atmospheric pressure in hydrogen with 2% Pd-SrCO<sub>3</sub> (0.5 g) until 1 mole of gas had been absorbed (10 min). The gummy product was hydrolyzed to give *d*-II (1.225 g), mp 127–129°, [ $\alpha$ ]<sub>D</sub> –8° (*c* 3, CHCl<sub>3</sub>). Lithium (60 mg) was added with stirring to *d*-II in liquid ammonia–aniline (400:10 ml), and, after 1 hr, NH<sub>4</sub>Cl was added to discharge the blue color. Recrystallization of the product from 95% ethanol gave *d*-III (0.575 g), mp 117–118.5°, [ $\alpha$ ]<sub>D</sub> +74.5° (*c* 1, CHCl<sub>3</sub>).

(b) The same sequence using *l*-IV gave *l*-II, mp 129–131°, [ $\alpha$ ]<sub>D</sub> +5.0° (*c* 1, CHCl<sub>3</sub>) and *l*-III, mp 118–119.5°, [ $\alpha$ ]<sub>D</sub> –73° (*c* 1, CHCl<sub>3</sub>).

***l*-3-Methoxy-8 $\alpha$ -estra-1,3,5(10)-trien-17 $\beta$ -ol (XVIII).**—The hemisuccinate *l*-IV (2 g) was shaken with hydrogen at atmospheric pressure in ethyl acetate–benzene (50:50 ml) containing 10% Pd-C (0.5 g) until 2 moles of gas had been absorbed (2 hr). Recrystallization of the product from ether–hexane gave the hemisuccinate XVII (1.05 g), mp 131–133°,  $\lambda_{\text{max}}$  282 m $\mu$  ( $\epsilon$  2100), [ $\alpha$ ]<sub>D</sub> +8.0°.

*Anal.* Calcd for C<sub>23</sub>H<sub>30</sub>O<sub>5</sub>: C, 71.5; H, 7.85. Found: C, 71.4; H, 8.3.

Hydrolysis of the hemisuccinate and recrystallization of the product from ethyl acetate–hexane gave the 8 $\alpha$ -estratrienol (0.41 g), mp 92–94°, [ $\alpha$ ]<sub>D</sub> –18° (*c* 1, CHCl<sub>3</sub>).

*Anal.* Calcd for C<sub>19</sub>H<sub>26</sub>O<sub>2</sub>: C, 79.85; H, 9.16. Found: C, 79.97; H, 9.10.

***l*-3-Methoxyestra-1,3,5(10)-trien-17-one (XIX).**—Chromic acid<sup>28</sup> (2.5 ml, 8 N) was added dropwise to *l*-III (2.5 g) in acetone (100 ml). Recrystallization from methanol gave the product (1.55 g), mp 171–173°, [ $\alpha$ ]<sub>D</sub> –155.6° (*c* 1, CHCl<sub>3</sub>).

*Anal.* Calcd for C<sub>19</sub>H<sub>24</sub>O<sub>2</sub>: C, 80.24; H, 8.51. Found: C, 80.00; H, 8.45.

***l*-Estrone (XX).**—The ketone *l*-XIX (5 g) was fused under nitrogen for 45 min with pyridine hydrochloride (bath 185–195°). HCl (1 N) was added to the cooled melt, and the product was filtered off, dried, and recrystallized from chloroform–ether to give *l*-XX (3.4 g), mp 257–260°, [ $\alpha$ ]<sub>D</sub> –148.4° (*c* 1, CHCl<sub>3</sub>).

*Anal.* Calcd for C<sub>18</sub>H<sub>22</sub>O<sub>2</sub>: C, 79.66; H, 8.20. Found: C, 79.82; H, 8.55.

The acetate had mp 124–126°, [ $\alpha$ ]<sub>D</sub> –145° (*c* 1, CHCl<sub>3</sub>) (from hexane).

*Anal.* Calcd for C<sub>20</sub>H<sub>24</sub>O<sub>3</sub>: C, 76.89; H, 7.74. Found: C, 76.82; H, 7.30.

***l*-Estra-1,3,5(10)-triene-3,17 $\beta$ -diol (XXI).**—Sodium borohydride (0.75 g) was added piecemeal over 30 min to *l*-XX (2.5 g) in

ethanol 10% aqueous NaOH (50:3 ml). The mixture was heated to boiling point, cooled, acidified with dilute HCl, and diluted with water. The precipitate was filtered off, dried, and recrystallized from 80% aqueous ethanol to give *l*-XXI (1.58 g), mp 177–178°.

*Anal.* Calcd for C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>·0.5C<sub>2</sub>H<sub>5</sub>OH: C, 77.25; H, 9.21. Found: C, 77.21; H, 8.70.

***l*-17 $\alpha$ -Ethyne-3-methoxyestra-1,3,5(10)-trien-17 $\beta$ -ol (XXII).**

The *l*-ketone XIX (2 g) was stirred under acetylene for 4 hr with lithium acetylide–ethylenediamine complex (1.5 g) in dimethylacetamide (35 ml) for 4 hr. The mixture was poured onto crushed ice and extracted with ether. Recrystallization of the product from acetone–hexane gave *l*-XXII (1.12 g), mp 147–149°.

*Anal.* Calcd for C<sub>21</sub>H<sub>26</sub>O<sub>2</sub>: C, 81.25; H, 8.44. Found: C, 81.36; H, 8.40.

***l*-17 $\alpha$ -Ethyne-estra-1,3,5(10)-triene-3,17 $\beta$ -diol (XXIII).**—*l*-Estrone in tetrahydrofuran (40 ml) was added to a solution of LiAlH<sub>4</sub> (2 g) in THF (40 ml) which had previously been saturated with acetylene gas. After standing for 18 hr at room temperature water was added. Recrystallization of the product from ethanol–water gave *l*-XXIII, mp 96–99°.

*Anal.* Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>2</sub>·0.5H<sub>2</sub>O: C, 78.7; H, 8.5. Found: C, 78.9; H, 8.2.

***l*-3 $\beta$ -Acetoxy-13 $\beta$ -ethyl-17 $\alpha$ -ethynylgon-4-en-17 $\beta$ -ol (XXVI).**

*l*-13 $\beta$ -Ethyl-17 $\alpha$ -ethynyl-17 $\beta$ -hydroxygon-4-en-3-one (XXIV),<sup>29</sup> 4.6 g, mp 237–239°, [ $\alpha$ ]<sub>D</sub> +32.8°,<sup>29</sup> was stirred at room temperature for 4.5 hr with lithium tri-*t*-butoxyaluminum hydride (3.6 g) in THF (55 ml). The resulting *l*-XXV (1.1 g), mp 168–178°, was kept for 70 hr with acetic anhydride–pyridine (1.1:22 ml). Recrystallization of the product from ether gave *l*-XXVI (0.75 g), mp 98–105°, raised to 104–108°, [ $\alpha$ ]<sub>D</sub> +76.2, after recrystallization from ethyl acetate (charcoal).

*Anal.* Calcd for C<sub>23</sub>H<sub>32</sub>O<sub>5</sub>·0.5CH<sub>3</sub>COOC<sub>2</sub>H<sub>5</sub>: C, 74.96; H, 9.06. Found: C, 74.73; H, 9.3.

***l*-17 $\alpha$ -Chloroethynyl-17 $\beta$ -hydroxygon-4-en-3-one (XXVII).**

*l*-13 $\beta$ -Ethyl-3-methoxygon-2,5(10)-dien-17-one (5.6 g, prepared as described previously<sup>3</sup> from *l*-VIII) was added with stirring to lithium chloroacetylide<sup>30</sup> [from *cis*-dichloroethylene (5 ml) and 1.36 M ethereal methylolithium (50 ml)] in ether (200 ml). The mixture was stirred for 2 hr at room temperature and treated with water. The product was recrystallized from methanol to give *l*-17 $\alpha$ -chloroethynyl-3-methoxygon-2,5(10)-dien-17 $\beta$ -ol (5.85 g), mp 141–147°, which was stirred under nitrogen in methanol–water (90:4 ml) containing 11 N HCl (6 ml) for 30 min. Recrystallization of the product from methanol gave *l*-XXVII (2.5 g), mp 214–215°,  $\lambda_{\text{max}}$  243 m $\mu$  ( $\epsilon$  16,800), [ $\alpha$ ]<sub>D</sub> +43°.

*Anal.* Calcd for C<sub>21</sub>H<sub>22</sub>O<sub>2</sub>Cl: C, 72.60; H, 7.66; Cl, 10.22. Found: C, 72.92; H, 7.99; Cl, 10.15.

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(29) Part II<sup>4b</sup> erroneously states that (–)-XXIV was prepared from (–)-VIII. In fact (–)-XXIV, having the *d* absolute configuration, is prepared from (+)-VIII of the *d* series.

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