*Anal.* Calcd. for $C_{27}H_{26}O_9$: C, 65.58; H, 5.30. Found: C, 65.68; H, 5.29.

**3,4,5-Tri-*O*-benzoyl-D-*threo*-pentose Phenylosazone (V).**—A 50-ml. portion of the solution resulting from boiling III with dilute acetic acid was further refluxed for 4 hr. with 1 ml. of freshly distilled phenylhydrazine. The fine yellow needles which formed were filtered and recrystallized twice from water–ethanol; yield 10 mg., m.p. 196°. The X-ray powder diffraction pattern was identical with that of a sample prepared by benzoylation of D-xylose phenylosazone. D-Xylose phenylosazone (1 g.) was suspended in a mixture of 10 ml. of pyridine and 10 ml. of chloroform and treated with 2.0 g. of benzoyl chloride for 24 hr. at room temperature. The solution was poured into water, the chloroform layer separated, washed with water, dried and evaporated to a sirup. It was crystallized from abs. ethanol; yield 2 g., dec. 176–186°, $[\alpha]^{20}D$ +5° (*c* 0.85, chloroform); X-ray powder diffraction data[7]: 11.87m, 10.85w, 6.19vw, 5.25vs(1), 4.56vw, 4.36m(3), 4.21s(2), 3.96m, 3.63vw, 3.49vw, 3.42vw, 3.08w.

*Anal.* Calcd. for $C_{38}H_{32}N_4O_6$: C, 71.23; H, 5.03; N, 8.76. Found: C, 71.23; H, 5.16; N, 8.93.

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[7] Interplanar spacing, Å., CuK$\alpha$ radiation; intensity of lines estimated visually: s, strong; m, medium; w, weak; v, very; parenthetic numerals indicate three strongest lines; 1, strongest line.

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[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

# Potential Steroid Substitutes. I. Introductory Remarks. The Synthesis of Some Dioxoperhydroanthracenes

BY ROBERT L. CLARKE AND WILLIAM S. JOHNSON

RECEIVED APRIL 10, 1959

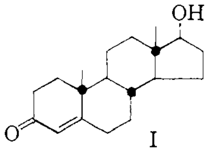
Perhydrogenation of 2,6-anthracenediol followed by oxidation of the crude product gave *cis-syn-cis*-perhydro-2,6-anthracenedione (IVa) and an isomer of IVa which had either the *cis-anti-cis* or *trans-anti-trans* configuration. Reduction of the latter isomer produced a new perhydroanthracene. Addition of two mole-equivalents of 2-ethoxy-1,3-butadiene to benzoquinone produced a mixture of 2,6- and 2,7-diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinones (XIIIa and XIIIb). Hydrolysis of XIIIa produced perhydro-2,6,9,10-anthracenetetraone (XVa).

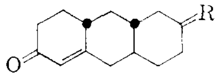
Following elucidation of the structure of a number of steroidal hormones and realization of their complexity, considerable effort was devoted to making simple steroid substitutes. It soon became evident that a wide variety of non-steroidal substances could possess estrogenic activity. On the other hand, non-steroidal substitutes for the androgenic and cortical hormones have been conspicuously scarce and of questionable activity.

In spite of numerous previous failures, the hope still remains that there may yet be found some simple skeletal structure which, when appropriately substituted by the functional groups known to invest specific activity in the steroid nucleus, will exhibit the corresponding hormonal action. Since androgenic and cortical hormones allow such little latitude in structural variation with retention of activity, it seemed best to test the over-all usefulness of various skeletal structures by making androgenic or cortical hormone analogs. The immediate goal of our work was to prepare a non-steroidal androgen.

As far as we are aware,[1] no non-steroidal compounds have been reported to show consistent androgenic activity with possibly two recent exceptions. A preliminary report by Khaletskii and Zaputryaef[2] declared that 1,2-bis-(1-carbethoxy-2-oxocyclopentyl)-ethane showed androgenic activity in rats, and Farinacci[3] has indicated that 2-aceto-13-methyl-7-oxo-1,2,3,4,5,6,7,9,10,11,12,13-dodecahydrophenanthrene promotes comb growth in capons.

One of the more obvious approaches to an androgenic substance is to provide a rigid, flat scaffold to hold the functional groups of testosterone (I) in the correct spacial arrangement. Properly substituted hydroanthracenes with their rings fused in a *trans* manner (*cf.* II) seemed to fulfill the requirements, the oxygen functions being only slightly closer together than those in the natural androgens. The immediate objective was to synthesize *dl*-6$\beta$- and *dl*-6$\alpha$-hydroxy-2,3,4,4a$\beta$,5,6,7,8,8a$\alpha$,9,10,10a$\beta$-dodecahydro-2-anthracenone (IIa and IIb) for testing as androgens. Although IIa resembles testosterone in that the hydroxyl group is $\beta$-oriented, this hydroxyl group is, however, axially conformed; hence IIb with an equatorial hydroxyl might serve as a closer model of the hormone. The synthesis of these two compounds was ultimately accomplished[4] and they failed to show hormonal activity. The chemistry involved in the various approaches to these compounds, however, seems worth recording, and is the subject of this and the succeeding two papers.


I



IIa, R = H, $\beta$ OH
IIb, R = H, $\alpha$ OH

A direct approach to the synthesis of these hydroanthracenes appeared to be *via* the perhydrogenation of 2,6-anthracenediol, which was readily prepared by stannous chloride reduction of 2,6-dihydroxy-9,10-anthraquinone (anthraflavic acid) to 2,6,9-anthracenetriol[5] followed by aluminum

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[1] *Cf.* A. L. Wilds, C. H. Hoffman and T. H. Pearson, THIS JOURNAL, **77**, 647 (1955), and references therein.

[2] A. M. Khaletskii and B. A. Zaputryaef, *J. Gen. Chem.* (*USSR*), **26**, 3026 (1956).

[3] N. T. Farinacci, U. S. Patent 2,830,074, April 8, 1958.

[4] R. L. Clarke and C. M. Martini, THIS JOURNAL, **81**, 5716 (1959), Paper III of this group.

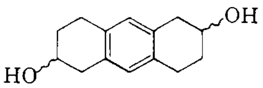
[5] According to the procedure of G. M. Badger and J. W. Cook, *J. Chem. Soc.*, 802 (1939), for the preparation of 1,2-benzanthrol.

amalgam reduction according to a modification of a known procedure.[6] It was necessary to purify this diol by converting it to its diacetate,[6] recrystallizing the latter, and regenerating the diol before satisfactory hydrogenation could be accomplished. The diacetate could not be perhydrogenated in our hands.

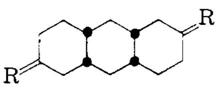
In an effort to minimize *cis* hydrogenation and obtain a product with the rings fused in a *trans* manner, the hydrogenation of 2,6-anthracenediol was conducted under relatively severe conditions. Treatment of the diol at 150° with hydrogen under 4200 p.s.i. for 3 hr. in the presence of W-4 Raney nickel and potassium hydroxide[7] resulted in the formation of 1,2,3,4,5,6,7,8-octahydro-2,6-anthracenediol (III) in 82% yield after purification. Only after III was purified would it accept further hydrogen under the conditions described and yield a perhydrogenated product. The presence of an appreciable quantity of pentane-soluble material in the reaction mixture indicated that some hydrogenolysis occurred.

The crude perhydrogenated product was oxidized to a mixture of 2,6-diketones in order to remove two of the six asymmetric centers. Chromatography of the oxidation product afforded a trace of a perhydro-2-anthracenone, m.p. 83.5–85.5°, of unknown configuration, a perhydro-2,6-anthracenedione, m.p. 128–130°, in 6.3% yield from III, and another stereoisomer, m.p. 247–250°, in 0.8% yield from III. Except for 0.8% of recovered III, no other crystalline product was isolated.

The configuration of the 130° diketone was established as the *cis-syn-cis* compound IVa by Clemmensen reduction to the known *cis-syn-cis*-perhydroanthracene IVb, m.p. 60–61°.[8] The dipole moment of IVa was found to be 4.0 D. which is in accord with its unsymmetrical structure.



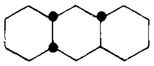
III



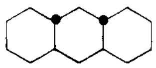
IVa, R = O
IVb, R = $H_2$

Clemmensen reduction of the 250° diketone gave a perhydroanthracene which melted at 122–122.5°. *cis-trans*-Perhydroanthracene (V), m.p. 39–40°,[8] and *trans-syn-trans*-perhydroanthracene (VI), m.p. 89–90°,[8,9] are the only other of the five possible perhydroanthracenes known. Therefore, the new hydrocarbon must be either *cis-anti-cis*-(VII) or *trans-anti-trans*-(VIII) perhydroanthracene. The non-identity of the 122° hydrocarbon with IVb and VI was confirmed by their infrared spectra.

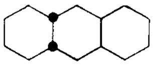
On the basis of stability considerations, the *all-chair* structure VII is preferred over the *chair-boat-chair* structure VIII for the 122° hydrocarbon.[10] In the hope of proving the configuration of the 122° hydrocarbon, efforts were directed toward the synthesis of the *cis-anti-cis* isomer VII by the stereorational approach described below. While this objective has not yet been realized, a number of observations were made which we consider worth recording.



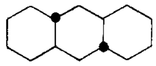
V



VI

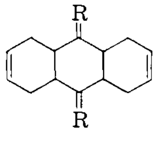


VII

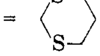


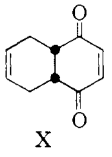
VIII

Alder and Stein[11] have combined two molecules of butadiene with one of benzoquinone to form *cis* - *cis* - 1,4,4a,5,8,8a,9a,10a - octahydro - 9,10-anthraquinone (IXa), a product in which the rings may be fused either in a *syn* or an *anti* manner.



IXa, R = O
IXb, R =

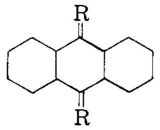




X

These authors favored the former configuration on the basis of presumptive evidence involving isomerization experiments. Molecular models suggest, however, a distinct steric hinderance to addition of the second molecule of butadiene in a *syn* manner to the intermediate 4a,5,8,8a-tetrahydro-1,4-naphthoquinone (X) and on this basis we prefer the *cis-anti-cis* structure.

Since reduction of the carbonyl groups of IXa *via* Raney nickel desulfurization of the corresponding bis-propylenethioketal (IXb) gave no satisfactory product, possibly due to a tendency toward aromatization, the double bonds of IXa were hydrogenated. Perhydro - 9,10 - anthracenedione[11] (XIa) could not be induced to form a bis-propylenethioketal when subjected to the conditions used to form IXb.



XIa, R = O
XIb, R = H, OH
XIc, R = H, OTs

The diketone XIa was reduced with lithium aluminum hydride with the expectation that reduction would occur before isomerization could destroy the *cis-cis* ring fusion.[12] The only crystalline product, isolated in 25–35% yield, m.p. 272–274°,[13] was presumed to be one of the desired *cis-cis*-perhydro-9,10-anthracenediols (XIb). Its infrared

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[6] J. Hall and A. G. Perkin, *J. Chem. Soc.*, 2029 (1923).

[7] To minimize hydrogenolysis; *cf.* H. E. Ungnade and F. V. Morriss, THIS JOURNAL, **72**, 2112 (1950).

[8] J. W. Cook, N. A. McGinnis and S. Mitchell, *J. Chem. Soc.*, 286 (1944).

[9] S. Bog, O. Hassel and E. H. Vihovde, *Acta Chem. Scand.*, **7**, 1308 (1953).

[10] W. S. Johnson, *Experientia*, **7**, 315 (1951).

[11] K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).

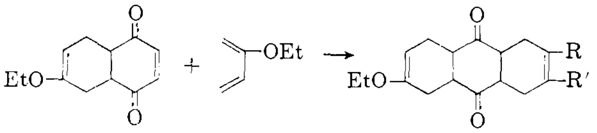
[12] *Cf.* D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950); D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

[13] K. H. Shah, B. D. Tilak and K. Venkataraman, *Proc. Indian Acad. Sci.*, **28A**, 142 (1948), reported that reduction of 9,10-anthraquinone with Raney nickel in boiling, aqueous sodium hydroxide gave a compound, m.p. 267°, which had analytical values corresponding to perhydro-9,10-anthracenediol.

spectrum showed strong bands at 9.57 and 9.70 μ which have been related to equatorial hydroxyl groups[4] but no band between 9.85 and 10.0 μ (axial hydroxyl).

The ditosylate XIc, m.p. 130° dec., of XIb was subjected to reduction with lithium aluminum hydride in the hope of producing a perhydroanthracene. When the reaction was carried out in refluxing tetrahydrofuran for 3 days, *sym*-octahydroanthracene[14] was isolated in 26% yield which is evidently a product of elimination[15] followed by aromatization.[16] Since axial attack by the lithium aluminum hydride in the present case (XIc) is strongly hindered, elimination of the elements of tosyl acid was not unexpected. The ditosylate also failed to react with sodium benzylthiol.

When the above efforts to obtain the *trans*-hydroanthracenones failed, attention was turned to another approach involving the Diels–Alder synthesis. 6 - Ethoxy - 4a,5,8,8a - tetrahydro - 1,4-naphthoquinone[17] (XII) was allowed to react with 2-ethoxybutadiene to give a mixture of 2,6-diethoxy-1,4,4a,5,8,8a,9a,10a - octahydro - 9,10 - anthraquinone (XIIIa), m.p. 169–172° dec., isolated in 14% yield and 2,7-diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIb), m.p. 148–150°, isolated in 2% yield.

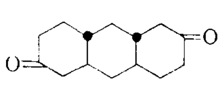


XII

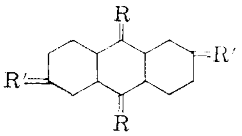
XIIIa, R = OEt, R′ = H
XIIIb, R = H, R′ = OEt

The position of the ethoxy groups in these compounds was established by their air oxidation to the corresponding known[18] 2,6- and 2,7-diethoxy-9,10-anthraquinones. The 2,6-compound was prepared from authentic 2,6-dihydroxy-9,10-anthraquinone for direct comparison.

The original plan for synthesis envisaged isomerization of XIIIa under alkaline conditions to form the stable *trans-trans* ring system, Wolff–Kishner reduction of the two carbonyl groups and, finally, acid cleavage of the enol ether groups to form *trans-syn-trans*-perhydro-2,6-anthracenedione[19] (XIV). The vigorous conditions required for the Wolff–Kishner reduction, however, decomposed XIIIa.



XIV



XVa, R = R′ = O
XVb, R = O R′ = H, OEt

Acid hydrolysis of XIIIa produced perhydro-2,6,9,10-anthracenetetraone (XVa), m.p. 236.5–238.5°. Catalytic hydrogenation of XIIIa produced a 2,6-diethoxyperhydro-9,10-anthracenedione (XVb), m.p. 177–179°.

## Experimental[20]

**2,6,9-Anthracenetriol (Anthraflavanol).**[5]—A mixture of 100 g. (0.42 mole) of 2,6-dihydroxy-9,10-anthraquinone, 1500 ml. of glacial acetic acid, 450 g. (2.37 moles) of stannous chloride and 900 ml. of concentrated hydrochloric acid was refluxed for 2 hr., cooled, and filtered. The crude product, dried at 100°, weighed 85 g. (90% yield).

The **triacetate**, prepared with acetic anhydride containing a trace of sulfuric acid, formed colorless prisms from acetone, m.p. 174–175.5° (reported[21] 165°).

*Anal.* Calcd. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.1; H, 4.6.

**2,6-Anthracenediol** was prepared according to the procedure of Hall and Perkin[6] with the modification that after the reflux period with ammonia, the reaction mixture from a 40-g. run was poured while hot into 1.1 l. of concentrated hydrochloric acid and the mixture was boiled for 30 min. before cooling and filtering. The dried filter cake of crude 2,6-anthracenediol was acetylated directly to give a 55% yield of the **diacetate**, m.p. 265–268° from pyridine (reported[6] m.p. 260–261° from acetic acid).

The sketchy procedure of Hall and Perkin[6] for hydrolysis of this diacetate has been detailed as follows. To a boiling mixture of 1400 ml. of glacial acetic acid and 70 g. (0.238 mole) of the above diol diacetate were added 100 ml. of water and 100 ml. of concentrated hydrochloric acid. The mixture was boiled for 1 hr., a second 100-ml. portion of hydrochloric acid was added, and boiling was continued for 1 hr. The cooled mixture was filtered and the air-dried, green solid recrystallized from 500 ml. of acetone. Concentration of the mother liquor to a 100-ml. volume afforded further product giving a total of 40 g. (80% yield) of yellow crystals of 2,6-anthracenediol, m.p. 295° dec., which darkened upon standing in contact with air.

**Hydrogenation of 2,6-Anthracenediol.**—A mixture of 117 g. (0.56 mole) of 2,6-anthracenediol purified as described above, 1.8 l. of absolute ethanol, 2 g. of potassium hydroxide[7] and 3 teaspoonfuls of W-4 Raney nickel catalyst was treated with hydrogen under 4200 p.s.i at 150° for 3 hr. The hot mixture was filtered, evaporated to a 600-ml. volume and chilled to give 93.2 g. of **1,2,3,4,5,6,7,8-octahydro-2,6-anthracenediol** (III). Concentration of the mother liquor to a 75-ml. volume furnished a further 13.8 g. This 107 g. of product was recrystallized from 1800 ml. of absolute ethanol to give 74.4 g. of white solid, m.p. 200–205°. The solvent was evaporated and the residue sublimed at 185–200° (0.9 mm.). This yielded a further 24.9 g., m.p. 205–209°, making a total of 99.3 g. (82% yield). A further recrystallization from absolute ethanol gave an analytical sample, m.p. 211.8–212.5°.

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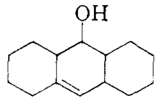
[14] M. P. Lambert and M. J. Lecompte, *Ann. combustibles liquids*, **9**, 979 (1934).

[15] *Cf.* E. J. Corey, M. G. Howell, Alma Boston, R. L. Young and R. A. Sneen, THIS JOURNAL, **78**, 5036 (1956).

[16] Stirring this reaction mixture at room temperature for 7 days, on the other hand, produced in 13% yield, a substance, m.p. 129–132°, which gave analytical values corresponding to 1,2,3,4,4a,5,6,7,8,8a,9,9a-dodecahydro-9-anthrol (i) or an isomer in which the double bond migrated. Its infrared spectrum confirmed the presence of a hydroxyl group.



(i)

[17] T. R. Lewis, W. B. Dickinson and S. Archer, THIS JOURNAL, **74**, 5321 (1952).

[18] E. Schunk and H. Roemer, *Chem. Ber.*, **9**, 379 (1876).

[19] Initially it was believed that under equilibrating conditions the *trans-syn-trans* configuration, *i.e.*, that most stable in the hydrocarbon series (ref. 10), would be assumed. However, evidence reported by P. A. Robins and J. Walker, *J. Chem. Soc.*, 1789 (1955), concerning eclipsed carbonyl-methylene interactions lends considerable support to the possibility that the *trans-anti-trans* configuration (*chair-boat-chair*) is the more stable when carbonyl groups are present at C-9 and C-10. This matter is being investigated.

[20] All melting points are corrected for stem exposure. The infrared spectra were determined with a Perkin–Elmer model 21 double beam recording spectrophotometer equipped with a sodium chloride prism. Appreciation is expressed to Dr. F. C. Nachod, Miss Catherine Martini and Mrs. M. Becker for the spectral determinations and to Mr. Kenneth D. Fleischer and his associates for the analytical data.

[21] C. Liebermann, *Chem. Ber.*, **21**, 435 (1888).

*Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31. Found: C, 77.1; H, 8.2.

**The diacetate of III**, twice recrystallized from absolute ethanol, melted at 152–153.5°.

*Anal.* Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.3; H, 7.2.

The 99 g. (0.45 mole) of compound III, 1800 ml. of absolute ethanol, 1 g. of potassium hydroxide and 2 teaspoonfuls of Raney nickel were treated with hydrogen under 4200 p.s.i. at 150° for 3 hr. Shaking of the mixture was not started until the indicated temperature had been reached. The filtered mixture was diluted with 1.3 l. of ether and the precipitated solid was collected (37.1 g., m.p. 152–175°). The solvent was evaporated and the oily residue was extracted with 500 ml. of pentane which dissolved 13.8 g. of material considered to be largely hydrocarbon and mono-oxygenated products. The pentane-insoluble oil was dissolved in 500 ml. of acetone and chilled for two days whereupon 7.3 g. of solid, m.p. 148–175°, separated. The solvent was removed from the filtrate and the residual oil taken up in 300 ml. of ether, whereupon 3.5 g. of solid, m.p. 138–167°, separated after standing for one week. This 47.9 g. represented a 46.5% yield of a crude mixture of **perhydro-2,6-anthracenediols** called **mixture A**. Removal of the ether from the filtrate gave 34.8 g. of crude, oily perhydroanthracenes called **mixture B**.

**Oxidation of the Mixture of Perhydro-2,6-anthracenediols.**—To a suspension of 30 g. (0.134 mole) of the crude mixture of crystalline perhydro-2,6-anthracenediols (mixture A) in 500 ml. of benzene was added dropwise with stirring in 40 min. at 25–30° a mixture containing 49 g. of sodium dichromate, 38 ml. of acetic acid, 67 ml. of concentrated sulfuric acid, and 203 ml. of water. The reaction mixture was stirred for 2 hr., the layers were separated, and the aqueous layer was extracted once with benzene. The combined organic layers were washed with water and with potassium carbonate solution, and dried over anhydrous potassium carbonate. The solution was concentrated to a 60-ml. volume and kept at 7° for 3 days. There separated 2.38 g. of white crystals, m.p. 185–230° (the filtrate is referred to below as filtrate A), which was chromatographed on 250 g. of unwashed alumina. Pure ether eluted a **perhydro-2,6-anthracenedione** which, after crystallization from acetone, amounted to 0.60 g., m.p. 247–250°.

*Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.2; H, 8.9.

Further elution of the column with 1:1 acetone–methanol afforded **1,2,3,4,5,6,7,8-octahydro-2,6-anthracenediol** (III) which, after recrystallization from methanol, amounted to 0.75 g., m.p. 208–210° (8% recovery).

An 11.9-g. (0.053 mole) sample of the crude mixture of oily perhydro-2,6-anthracenediols (mixture B) was oxidized in a similar manner. The benzene solution of the total product was combined with filtrate A described above and the solvent removed. The residual oil was chromatographed on 400 g. of acid-washed alumina in an ether–pentane mixture. Ether–pentane (3:7) eluted ***cis-syn-cis*-perhydro-2,6-anthracenedione (IVa)** which was recrystallized from ether to give 6.25 g. (6.3% yield from III), m.p. 128–130°.

*Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.6; H, 8.9.

Pure ether eluted a further 190 mg. of the 250° dione, described above, m.p. 244–250°, (total yield, 790 mg., 0.8% yield from III).

Rechromatography on 400 g. of unwashed alumina of the material eluted just prior to the dione IVa gave, after recrystallization from pentane, 50 mg. of a **perhydro-2-anthracenone** of unknown configuration, m.p. 83.5–85.5°.

*Anal.* Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.5; H, 10.8.

**Reduction of *cis-syn-cis*-perhydro-2,6-anthracenedione (IVa).**—A mixture of 20 g. of zinc which had been amalgamated,[22] 1.45 g. of *cis-syn-cis*-perhydro-2,6-anthracenedione (IVa), m.p. 123–128°, 10 ml. of 95% ethanol, 5 ml. of water and 14 ml. of concentrated hydrochloric acid was refluxed for 65 hr. The reaction mixture was extracted twice with pentane, the solvent was removed from the extracts, and the residue was steam distilled. The steam distillate was extracted twice with pentane, the solvent removed from the dried extracts, and the residue recrystallized from absolute ethanol. The ***cis-syn-cis*-perhydroanthracene** so obtained, 320 mg. (25% yield), melted at 60–61° (reported[8] 61.5–63°).

*Anal.* Calcd. for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.1; H, 12.6.

**Reduction of the 250° Perhydro-2,6-anthracenedione.**—A mixture of 20 g. of zinc which had been amalgamated,[22] 0.43 g. of the perhydro-2,6-anthracenedione of m.p. 247–250°, 15 ml. of 95% ethanol, and 15 ml. of concentrated hydrochloric acid was refluxed for 3 hr.; then 5 ml. more acid was added and refluxing continued for 15 hr., followed by 5 ml. more acid and 10 ml. of 95% ethanol and refluxing for 2 hr. The mixture was extracted 3 times with pentane and the product isolated as described above for the *cis-syn-cis* isomer. The new perhydroanthracene so obtained formed colorless needles from acetone, m.p. 122–122.5° (sealed tube), 50 mg., 13% yield.

*Anal.* Calcd. for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.3; H, 12.6.

**1,4,4a,5,8,8a,9a,10a-Octahydro-9,10-anthraquinone Bis-propylenethioketal (IXb).**—A mixture of 3.1 g. (0.0143 mole) of 1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone[11] (IXa), m.p. 150–153°, 25 ml. of acetic acid, 12.4 g. (0.115 mole) of propylene dithiol and 15 drops of 45% boron trifluoride etherate was allowed to stand at room temperature for 13 days. The precipitated prisms, washed with ether, weighed 3.8 g. A portion, recrystallized once from toluene, melted at 306–311°.

*Anal.* Calcd. for $C_{20}H_{28}S_4$: C, 60.55; H, 7.11; S, 32.33. Found: C, 59.9; H, 6.9; S, 32.2.

***cis-cis*-Perhydro-9,10-anthracenediol (XIb).**—A solution of 2.0 g. (0.0091 mole) of *cis-cis*-perhydro-9,10-anthracenedione[11] (XIa), m.p. 180–185°, in 85 ml. of anhydrous tetrahydrofuran was added to 0.38 g. (0.01 mole) of lithium aluminum hydride in 15 ml. of tetrahydrofuran and the mixture was stirred for 10 min. Thirty-five ml. of 2 *N* hydrochloric acid was added and the organic layer was concentrated to a 20-ml. volume. Cooling gave 0.7 g. of solid, m.p. 265–274° and working up the filtrate gave an additional 0.15 g. Recrystallization from absolute ethanol gave 0.51 g. (25% yield) of white needle clusters, m.p. 272–274°; $\lambda_{\max}^{\mathrm{KBr}}$ 2.97, 5.97 and 9.70 μ with no band in the 9.90–10.1 μ region.

*Anal.* Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.1; H, 10.9.

**The ditosylate XIc** of XIb was prepared by adding 0.95 g. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine to a solution of 0.40 g. of XIb, m.p. 272–274°, in 10 ml. of pyridine and letting the mixture stand for 23 hr. The mixture was poured into water, stirred thoroughly, and filtered. Recrystallization of the solid (0.76 g.) from benzene gave 0.33 g. (35% yield) of long prisms, decomposition point 130°.[23]

*Anal.* Calcd. for $C_{28}H_{36}O_6S_2$: C, 63.13; H, 6.81; S, 12.04. Found: C, 62.8; H, 7.0; S, 12.2.

**Attempted Detosylation of Compound XIc.**—A solution of 1.0 g. of lithium aluminum hydride in 50 ml. of anhydrous tetrahydrofuran was added to a hot solution of 1.87 g. of the ditosylate XIc, decomposition point 132°, in 200 ml. of tetrahydrofuran. The mixture was refluxed for 72 hr. Sixty ml. of 2 *N* hydrochloric acid was added and the organic layer was separated and dried ($Na_2SO_4$). The solvent was removed by distillation through a Vigreux column and the residue was triturated with pentane. Removal of the solvent from the pentane solution gave a solid which was recrystallized from absolute ethanol to furnish 92 mg. (26% yield), m.p. 72.5–74.5°. Its ultraviolet spectrum showed bands characteristic of a benzene ring and its infrared spectrum corresponded completely with the detailed band values reported by Lambert and Lecompte[14] for 1,2,3,4,5,6,7,8-octahydroanthracene, m.p. 73–74°.

*Anal.* Calcd. for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found C, 90.4; H, 9.5.

In a second experiment a mixture of 1.5 g. of lithium aluminum hydride, 3.0 g. of the ditosylate XIc and 500 ml. of anhydrous tetrahydrofuran was stirred at room temperature for a week and the crude product, isolated as described im-

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[22] Procedure described in "Organic Reactions," Vol. I, Roger Adams, *et al.*, John Wiley and Sons, New York, N. Y., 1942, p. 163.

[23] Subsequent runs have shown that the initially precipitated tosylate is quite pure. The decomposition point has varied to as high as 142° and is dependent upon the rate of heating.

mediately above, was chromatographed on 75 g. of unwashed alumina. Ether–pentane (1:1) eluted needles of what appeared to be 1,2,3,4,4a,5,6,7,8,8a,9,9a-dodecahydro-9-anthracenol (i). After recrystallization from 5 ml. of pentane, it melted at 129–132° (0.15 g., 13% yield), $\lambda_{\max}^{CS_2}$ 2.82 and 9.75 $\mu$.

*Anal.* Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75; O, 7.75. Found: C, 81.5; H, 10.5; O, 7.7.

**2,6- and 2,7-Diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa and XIIIb).**—A mixture of 50 g. (0.24 mole) of the quinone adduct XII,[17] 150 ml. of benzene and 35.6 g. (0.36 mole) of 2-ethoxy-1,3-butadiene was refluxed for 110 hr., then kept at 0° for 4 hr. The precipitated solid (12.5 g.) was recrystallized from benzene to give 10.2 g. (14% yield) of white, heavy needles, m.p. 169–172° dec., of **2,6-diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone** (XIIIa).

*Anal.* Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95; OEt, 29.65. Found: C, 71.2; H, 8.1; OEt, 28.9.

The filtrate from the separation of XIIIa was washed twice with 10% aqueous potassium hydroxide and twice with water. It was dried ($K_2CO_3$), concentrated to a 75-ml. volume under an inert atmosphere, and diluted with 150 ml. of pentane. The precipitated solid was recrystallized 3 times from ethanol to give 1.42 g. (2% yield) of faintly yellow spherulites, m.p. 148–150°, of **2,7-diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone** (XIIIb).

*Anal.* Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.0; H, 7.7.

**Oxidation of 2,6-Diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa).**—Air was bubbled through a refluxing solution of 0.30 g. of XIIIa in 10 ml. of 15% alcoholic potassium hydroxide for 30 min. A dark gel formed initially which was soon replaced by a crystalline precipitate. The cooled mixture was filtered and the precipitate washed with cold 95% ethanol. Two recrystallizations of the precipitate (0.28 g.) from benzene gave 0.17 g. of yellow, heavy needles of 2,6-diethoxy-9,10-anthraquinone, m.p. 239.6–240.6° (reported[18] 232°). This material showed no depression in melting point upon admixture with a sample, m.p. 237–239°, prepared from 2,6-dihydroxyanthraquinone as described below.

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.9; H, 5.3.

**2,6-Diethoxy-9,10-anthraquinone from 2,6-Dihydroxy-9,10-anthraquinone.**—To a mixture of 20 g. (0.082 mole) of 2,6-dihydroxyanthraquinone, 6.6 g. (0.166 mole) of sodium hydroxide and 200 ml. of water was added dropwise with stirring at room temperature 25.6 g. (0.166 mole) of diethyl sulfate over a period of 10 min. This mixture was heated for 1 hr. on the steam-bath, cooled, and filtered. The solid was boiled with 1 l. of 95% ethanol and the mixture filtered while hot. After treatment with Darco G-60, the filtrate, on cooling, gave a product which was recrystallized once from pyridine (Darco G-60) and once from benzene to give yellow needles, m.p. 237–239°.[18]

**Oxidation of 2,7-Diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa).**—The oxidation was performed on 0.30 g. of XIIIb in the manner described above for XIIIa. The product was recrystallized twice from absolute ethanol to give 0.15 g. of yellow needles, m.p. 193.8–194.4° (reported[18] m.p. 193–194°).

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.7; H, 5.4.

**Perhydro-2,6,9,10-anthracenetetraone (XVa).**—A mixture of 1.20 g. of XIIIa, m.p. 169–172° dec., 10 ml. of 95% ethanol and 2 ml. of concentrated hydrochloric acid was refluxed for 30 min., then an additional 5 ml. of ethanol and 2 ml. of acid were introduced, and refluxing was continued for 1 hr. On cooling, 0.61 g. of colorless, powdery material precipitated which was recrystallized from acetone to give 0.23 g. of white plates, m.p. 236.5–238.5°, $\lambda_{\max}^{KBr}$ 5.84 $\mu$ (very strong).

*Anal.* Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.5; H, 6.7.

**2,6-Diethoxyperhydro-9,10-anthracenedione (XVb).**—A mixture of 1.4 g. (0.0046 mole) of 2,6-diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa), 0.2 g. of 10% palladium-on-charcoal and 250 ml. of absolute alcohol was treated with hydrogen under 45 p.s.i. at room temperature for 2 hr. The filtered mixture was concentrated to a 7-ml. volume whereupon 0.35 g. of crystals separated. Recrystallization once from ethanol and once from Skellysolve C afforded 0.135 g. (10% yield) of XVb, m.p. 177–179°.

*Anal.* Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.4; H, 9.1.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Potential Steroid Substitutes. II.[1] The Formation of a Spiro Compound in the Attempted Preparation of 6-Hydroxy-2,3,4,4a$\beta$,5,6,7,8,8a$\alpha$,9,10,10a$\beta$-dodecahydro-2-anthracenone

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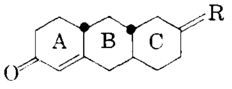
Success in the preparation of the potentially androgenic compounds 6$\alpha$- and 6$\beta$-hydroxy-2,3,4,4a$\beta$,5,6,7,8,8a$\alpha$,9,10,10a$\beta$-dodecahydro-2-anthracenone (Ia and Ib) by the synthetic route shown in Table I depended primarily upon the reaction of ethyl $\beta$-anisoyl-$\beta$-bromopropionate (IIIa) with sodium diethyl malonate to produce diethyl $\beta$-anisoyl-$\alpha$-carbethoxyglutarate (A). Actually, this bromoester (IIIa) was dehydrohalogenated under the reaction conditions and the ethyl $\beta$-anisoylacrylate so produced immediately added diethyl malonate to form diethyl $\alpha$-(anisoylmethyl)-$\alpha'$-carbethoxysuccinate (IVa). Performance on compound IVa of the chemical operations planned for compound A produced spiro-[cyclopentanone-3,2'-(1',2',3',4',4a',5',6',7'-octahydro-7'-naphthalenone)] (XVIII). Several compounds related to the intermediates in this synthetic series are described.

In the first paper of this series[1] certain approaches were described to the synthesis of 6$\alpha$- and 6$\beta$-hydroxy-2,3,4,4a$\beta$,5,6,7,8,8a$\alpha$,9,10,10a$\beta$-dodecahydro-2-anthracenone (Ia and Ib), potential nonsteroidal androgens. These involved the hydrogenation of appropriately substituted anthracenes, and attachment of the A and C rings to the B ring. The present paper presents the details of an attempt to build the B and C rings consecutively onto the A ring.



Ia, R = H, $\alpha$-OH
Ib, R = H, $\beta$-OH

The starting material, $\beta$-anisoylpropionic acid,[2] was brominated by a modification of a known

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[1] Paper I, R. L. Clarke and W. S. Johnson, THIS JOURNAL, **81**, 5706 (1959).

[2] L. F. Fieser and E. B. Hershberg, *ibid.*, **58**, 2314 (1936).