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CYCLOPENTANOPHENANTHRENE DERIVATIVES AND COMPOUNDS

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The present invention relates to certain novel cyclopentanophenanthrene derivatives and to processes for the production thereof.

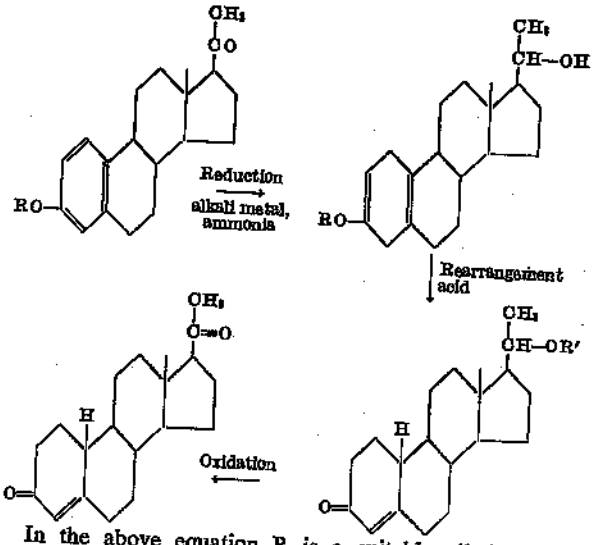
More particularly the present invention relates to a novel Δ^4-19-norpregnen-3,20-dione (19-norprogesterone), a novel homologue of progesterone lacking the angular methyl group in position 10 of progesterone and having superior progestational activity.

A 19-norprogesterone has been disclosed and previously synthesized by Ehrenstein (J. Org. Chem. 9, 435 (1944). The compound obtained by Ehrenstein is described as a resin $(\alpha)_D+89°$ supposedly consisting of a mixture of isomers with a predominance of the 14-iso-17-iso configuration (Ehrenstein et al., Chem. Rev. 42, 475 (1948); J. Org. Chem. 16, 355 (1951); Plattner et al., Helv. Chim. Acta., 31, 249 (1948).

In accordance with the present invention a 19-norprogesterone has been obtained which is clearly different from the compound obtained by Ehrenstein. In addition to having a distinct melting point and an entirely different optical rotation, $(\alpha)_D^{20}+147°$, the present compound possesses the same natural configuration at C-14 and C-17 as progesterone. Further, it is believed that the configuration at the 10 carbon atom is β, since this is the most stable configuration produced in accordance with the hereinafter set forth process. Further, the novel 19-norprogesterone of the present invention has a progestational activity from 3–5 times greater than that of progesterone itself. In addition to the high biological and therapeutical potency of the present novel compound, it is further desired to point out that the 19-norprogesterone is a valuable intermediate for the total synthesis of progestational and cortical hormones.

The novel process according to the present invention may form a part of a total synthesis of 19-norprogesterone, since the starting material, 3-alkyloxy-17-acetyl-1,3,5(10)-estratriene, is conventionally obtained by the etherification of the known 3-hydroxy-17-acetyl-1,3,5(10)-estratriene (Djerassi, Rosenkranz, Iriarte, Berlin and Romo, J. Am. Chem. Soc. 73, 1523 (1950), this compound having also been prepared from estrone, (Velluz and Muller, Bull. Soc. Chim. France, 166 (1950). Since estrone has been totally synthesized (Johnson et al., J. Am. Chem. Soc., 72, 1426 (1950) and Anner and Miescher, Helv. Chim. Acta., 31, 2173 (1948), it is evident that the present process forms a valuable step in the total synthesis of 19-norprogesterone.

In addition, the present invention relates to certain other novel intermediates possessing the $\Delta^{2,5(10)}$-19-norpregnen structure and the Δ^4-19-norpregnen structure. The novel process according to the present invention may be illustrated by the following equation:



In the above equation R is a suitable alkyl group, preferably a lower alkyl group, such as methyl or ethyl, and R^1 represents hydrogen or the residue of an organic acid, preferably a lower fatty acid, such as acetic or propionic, although any organic acid commonly used for esterification of steroid hormones may be thus designated and the corresponding compound employed in the present process.

In practicing the present invention according to the above equation, the starting compound, as for example 3-methoxy-17-acetyl-1,3,5(10)-estratriene was added to an alkali metal, such as lithium or sodium dissolved in liquid ammonia. Preferably the starting material is previously dissolved in a suitable solvent, such as absolute ethanol and anhydrous ether, and is added to the liquid ammonia solution of the alkali metal dropwise over a period of time of approximately 15 minutes, followed by the addition of additional solvent, such as absolute ethanol. The novel blue color produced disappears when the reaction is complete, and water is then added. Thereafter the reaction mixture is left to evaporate overnight at room temperature to remove excess ammonia and the residue is collected with water and extracted with a suitable solvent, such as a mixture of ether and ethyl acetate. The extract is then washed until neutral, dried and evaporated to dryness to produce a pale yellow oil which, upon crystallization from acetone, gave $\Delta^{2,5(10)}$-19-nor-3-methoxy - 20 - hydroxypregnadiene (the corresponding estradiene derivative of 3-methoxy-17-acetyl-1,3,5(10)-estratriene), as indicated above. However, it was unnecessary to crystallize the compound indicated, the pale yellow oil being preferably used directly for the second step, i. e. rearrangement in acid medium. For the second step the oil was refluxed for a short period of time with a lower alcohol, preferably methanol, and concentrated mineral acid, preferably hydrochloric. The reaction mixture resulting was then purified and extracted and after drying passed through a column of alumina and diluted with a suitable solvent, such as a mixture of benzene and ether. The product was Δ^4-19-norpregnen-20-ol-3-one. The corresponding 20-esters of this compound could be obtained by conventional acylation with an organic acid, as for example acetic or propionic to produce the corresponding 20-acetate or propionate.