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UNITED STATES PATENT OFFICE

2,248,284

DERIVATIVES OF PREGNANE AND PREGNENE

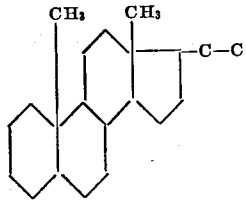
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No Drawing. Original application March 10, 1938, Serial No. 195,161. Divided and this application February 9, 1939, Serial No. 255,483. In Switzerland March 22, 1937

16 Claims. (Cl. 260—239)

This invention relates to the preparation of derivatives of pregnane and pregnene and particularly to the 21-diazo ketone derivatives, these compounds being especially useful as intermediate products for the synthesis of certain biologically active compounds.

Compounds with a pregnane or pregnene skeleton (see Formula I) have heretofore either been isolated from natural sources or produced by oxidative decomposition from higher molecular substances. The production of such derivatives as are substituted in the carbon C_{21} so as to form a diazo ketone has not been described.

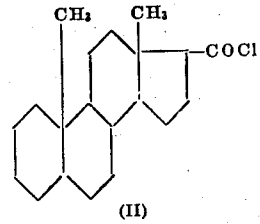


(I)

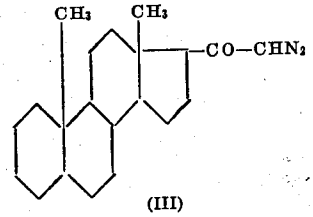
It has now been found that valuable derivatives having the characteristic pregnane structure with at least two carbon atoms in the side chain attached to the cyclopentane ring can be formed from etiocholanic acid or etiocholenic acid or their derivatives by first forming the acid chloride or other acid halide of the derivative, then forming the 21-diazo ketone derivative and from this the desired derivative having a pregnane structure. To form the 21-diazo ketone derivative is somewhat of a problem since the structures of etiocholanic and etiocholenic acid are rather delicate and those of their derivatives are even more so. It has been found, however, that if in the case of oxygenous derivatives such as those having additional hydroxy groups, the compounds are first protected by acylating or alkylating at the additional oxygen, the resulting compounds or the etiocholanic or etiocholenic acid, can then be converted into acid halides by treatment with a mild halogenating agent such as thionyl chloride.

Upon reaction of the acid halides with diazo methane, either the 21-diazo ketone or the 21-halogen ketone is obtained depending on whether from the beginning an excess of diazo methane is used or whether this is added in successive portions to the acid halide. By careful alkaline hydrolysis a diazo ketone that is acylated in the nucleus may be converted into the free hydroxy diazo ketone.

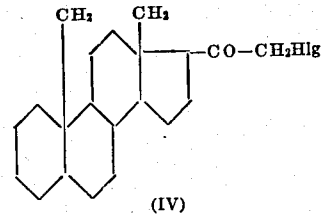
Type formulas for the 21-acid chloride (II) the 21-diazo ketone (III) and the 21-halogen ketone (IV) are given below.



(II)



(III)



(IV)

By treatment of a diazo ketone acylated in the nucleus, with an aqueous oxygenous inorganic acid, e. g. sulphuric acid and phosphoric acids, or with organic sulphonic acids, e. g. toluene sulphonic acid, and eventually adding suitable diluents, derivatives with a free hydroxyl group in the side chain and a protected one in the ring system may be obtained. On the other hand treatment of an hydroxy diazo ketone with organic acids, in absence of water and at temperatures ranging from about 60–120° C. leads to derivatives in which the hydroxyl group in the ring system is free and the one in the side chain is acylated.

As an example of the preparation of the new type of compounds the following is given:

1. *Production of diazo ketones.*—The 3-oxy-aetio-cholenic acid or its derivatives acylated or alkoxylated in the hydroxyl group used as a starting material can be obtained by oxydative decomposition of 3-oxy-bis-nor-cholenic acid (Fernholz, Liebigs, Ann. 507, 128, 1933) by way of a number of intermediate products. The free oxy-acid forms colorless crystals melting with decomposition at 280–288° C. (corrected) differ-

ences being observed at different velocities of heating. Its methylester forms needles from benzene melting at 180° C. (corrected). The acylated acid melts at 240–242° C. (corrected), its methylester at 153–154° C. (corrected).

One g. of 3-acetoxy-aetio-cholenic acid is boiled with reflux for 3 hours with 5 ml. of benzene and 5 g. of very pure thionyl chloride. Then the mixture is evaporated, humidity being excluded, upon which the acid chloride soon crystallizes. The weakly yellow product does not show a distinct melting point but decomposes at different temperatures depending on the velocity of heating. Sometimes melting at 160° C. may be observed followed by resolidifying and eventually melting again of the decomposed mass at a temperature over 300° C. The chloride is dissolved in 80 ml. of dry ether and poured into a dry ethereal solution of 1–1.5 g. of diazomethane, the temperature being —10° C.

The mixture is left to stand for some hours at 0° C., then for 6 hours at room temperature after which it is concentrated. Petroleum ether is added until a turbidity occurs. The diazo ketone crystallizes. From the mother liquor additional amounts are obtained in analogous ways. Yield 0.7 g. of a pure product, weakly, pale yellow leaflets, melting point approaching 150° C. somewhat different depending on the velocity of heating.

For the preparation of the free diazo-21-pregnene-5-ol-3-one-20-one g. of the above acetate is suspended in 30 ml. of methanol, 16 ml. of a 5% solution of potassium hydroxide in methanol are added and the mixture is left to stand at room temperature for 6 hours with occasional agitation. The crystals dissolve after about half an hour. Then some water is added and after concentration in vacuo the oxy-diazo ketone crystallizes. It is filtered with suction washed with water and dried in vacuo; it can be recrystallized from ether-petroleum ether, it then being obtained in yale yellow lustrous grains melting at 144° C. with vigorous decomposition; upon slow heating the melting point can be found lower. The yield is almost quantitative. The product is distinguished from the acylated diazo ketone by its being precipitated by digitonine from an 80–90% alcoholic solution.

Analogous reactions may be carried out starting with 3-oxy-aetio-allo-cholanic acid and with other substituted derivatives of the aetio-cholanic and cholenic acids series carrying further substituents in the ring system besides those at the carbon atom C_3 especially oxygen in a hydroxyl, acyloxyl, or alkoxyl group.

Many other compounds may be manufactured from the types exemplified and some of these are described in application 195,161, of which this application is a division.

I claim:

1. The diazo-ketones of the cyclopentanodimethylpolyhydrophenanthrene series, in which the group —CO—CHN_2 is attached to the carbon atom C_{17}.

2. The diazo-ketones of the cyclopentanodimethylpolyhydrophenanthrene series having a group .CO.CHN_2 at the seventeenth position and a nuclear substituent at the three position selected from the class consisting of hydroxyl, acyloxyl and alkoxyl groups.

3. The diazo-ketones of the cyclopentanodimethylpolyhydrophenanthrene series having a group .CO.CHN_2 at the seventeenth position and a nuclear substituent at the three position selected from the class consisting of hydroxyl, acyloxyl and alkoxyl groups, and having a double bond between the fifth position carbon atom and a carbon atom occupying an adjoining position.

4. The compounds of claim 2 wherein the substituent at the third position is a hydroxyl group.

5. The compounds of claim 2 wherein the substituent at the third position is an acetoxy group.

6. The compounds of claim 2 wherein the substituent at the third position is an alkoxy-group.

7. The compounds of claim 3 wherein the substituent at the third position is a hydroxyl group.

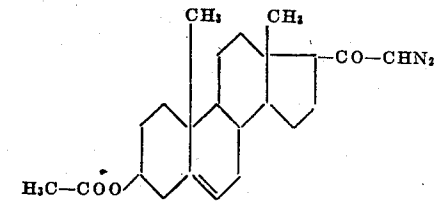
8. The compounds of claim 3 wherein the substituent at the third position is an acetoxy group.

9. The compounds of claim 3 wherein the substituent at the third position is an alkoxy-group.

10. As a new compound diazo-21-acetoxy-3-pregnene-5-one-20 having the formula

$C_{23}H_{32}O_3N_2$

and the structure

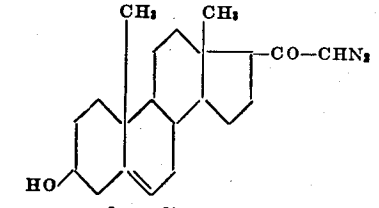


which compound melts at about 150° C. with vivid decomposition and is soluble in ether.

11. As a new compound hydroxy-3-diazo-21-pregnene-5-one-20 having the formula

$C_{21}H_{30}O_2N_2$

and the structure



which compound melts at about 144° C. with vivid decomposition, is soluble in ether and is precipitated with digitonine in an 80–90% solution.

12. A process for the preparation of diazoketones of the cyclopentanodimethylpolyhydrophenanthrene series, which comprises treating the acid halides of the carboxylic acids of said series with an excess of diazo methane.

13. A process for the preparation of diazoketones of the cyclopentanodimethylpolyhydrophenanthrene series, which comprises treating the acid halides of the carboxylic acids of said series, in which the carboxylic group is attached to the carbon atom C_{17}, with an excess of diazo methane.

14. A process for the preparation of diazoketones of the cyclopentanodimethylpolyhydrophenanthrene series, which comprises converting the carboxylic acids —17 of the cyclopentanodimethylpolyhydrophenanthrene series into the corresponding acid halides and treating these with an excess of diazo methane.

15. A process of claim 14 in which the conversion of the acids to the acid halides is effected with the aid of thionyl chloride.

16. A process of claim 13, further characterized in that the reaction product is subjected to alkaline saponification.

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