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Note

Ketalization of 3-Keto Group of 4-Pregnene-21-ol-3,20-dione and Syntheses of 21-Phenyl-4-pregnene-3,20-dione

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20-Ketosteroids react with ethylene glycol in the presence of acids more quickly than the Δ^4-3-keto group. It has been found that the Δ^4-3-keto group of 4-pregnene-21-ol-3,20-dione (I) reacts with ethylene glycol in the presence of pyridine hydrochloride and anhydrous sodium sulfate more quickly than the 20-keto group. From the so obtained pregnene-21-ol-3,20-dione-3-ethyleneketal (IV) 21-phenyl-4-pregnene-3,20-dione (VII) was prepared.

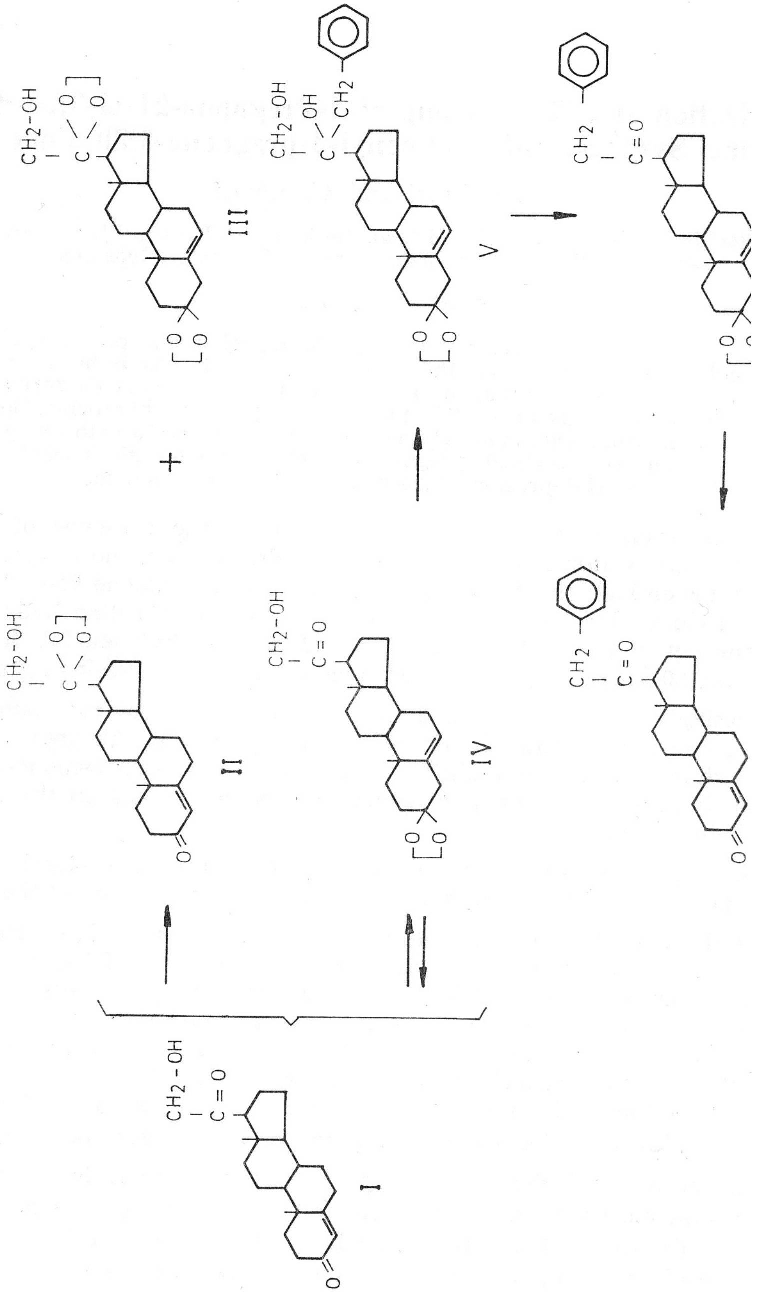
20-Ketosteroids react with ethylene glycol in the presence of an acid, such as *p*-toluenesulfonic acid or pyridine hydrochloride, more quickly than the Δ^4-3-ketosteroids[1]; therefore in the reaction of 4-pregnene-21-ol-3,20-dione (I) with ethylene glycol and *p*-toluenesulfonic acid or pyridine hydrochloride in benzene, only 20-ethyleneketal (II) and 3,20-diethyleneketal (III) were obtained, the 20-keto group being more reactive than the Δ^4-3-keto group[2].

Surprisingly it has been found that in the reaction of compound I with ethylene glycol and pyridine hydrochloride in benzene in the presence of anhydrous sodium sulfate, the main product of the reaction is 3-mono-ethyleneketal (IV). It is not clear what influence sodium sulfate has on the reactivity of the 3-keto group.

Work is in progress to see if sodium sulfate increases the reactivity of the Δ^4-3-keto group of other steroids and to elucidate the mechanism of the reaction.

UV and IR spectra were used to elucidate the presence of 20-keto and the absence of Δ^4-3-keto groups in compound IV. Compound IV does not show the UV absorbance of the Δ^4-3-keto group which usually appears in 240—250 nm range[2]. It also does not have the IR band at 1610 cm^{-1} which is characteristic of the Δ^4-3-keto group[3-5]. However, compound IV does show an IR band at 1720 cm^{-1} characteristic of the presence of the 20-keto group. It also reduces (like other 20-keto-21 hydroxysteroids) a solution of 2,3,5-triphenyltetrazolium chloride while acetic acid-water mixture gives compound I.

It has been found that a better yield of compound II is obtainable by reacting compound I with ethylene glycol and *p*-toluenesulfonic acid in benzene to give the mixture of II and III: this mixture was converted into 21-acetates the 3-ethyleneketal group was selectively hydrolyzed with aqueous acetic acid (the 20-ketal group being hindered by the 21-acetate group) and finally the 21-acetate group was removed with potassium carbonate.


SCHEME

It is known[6] that some electron-rich groups (like alkenyl or alkynil or acetoxy groups) near to the 20-keto function increase the progestational activity of some steroids.

For this reason (in order to investigate the influence on the progestational activity of a phenyl group near to the 20-keto one), it seemed interesting to prepare the 21-phenyl-4-pregnene-3,20-dione (VII) starting from easily obtainable compound IV.

Compound IV by means of reaction with benzylmagnesium chloride, was converted into 20-benzyl derivative V: the configuration at carbon C_{20} was not determined.

Compound V was oxidized with periodic acid[7] into compound VI which was then hydrolyzed with aqueous acetic acid into 21-phenyl-4-pregnene-3,20-dione (VII). The progestational activity of compound VII will be tested.

EXPERIMENTAL

Melting points are uncorrected, UV spectra were determined in methanol, IR spectra were recorded on Perkin-Elmer 137 infrared spectrophotometer, optical rotation in chloroform at 1% concentration.

5-Pregnene-21-ol-3,20-dione 20-ethyleneketal (II)

A solution of I (10 g.) in a mixture of benzene (720 ml.) and ethylene glycol (80 ml.) containing 0.3 g. of *p*-toluenesulfonic acid was refluxed with stirring for 6 hours removing water continuously with a Dean-Stark trap.[8] The solution was washed with 10% aqueous sodium bicarbonate and water, evaporated *in vacuo:* 11 g. of a mixture of II and III were obtained. The mixture was dissolved in pyridine (110 ml.) and treated with acetic anhydride (33 ml.) for 20 hours at room temperature. After dilution with 1 l. of ice-water, filtration and washing with water 21-acetates of II and III were obtained (10.2 g.) which were treated with acetic acid—water (9 : 1, 400 ml.) at 63° for 2 hours. After dilution with 2 l. of water, neutralization with sodium carbonate to *p*H 8, extraction with ethyl acetate, evaporation of the solvent, the residue was dissolved in methanol (840 ml.), aqueous solution of potassium carbonate was added (10. 2 g. in 102 ml. of water), and the mixture was refluxed for 6 hours. After evaporation of methanol, dilution with water, extraction with ethyl acetate, and evaporation of the solvent, the crude product (8 g.) was obtained. It was chromatographed on a column of Florisil (300 g.) eluated with benzene-ether (1 : 4) and ether—ethyl acetate (3 : 2); the residue of these fractions was crystallized from methanol—water to give pure II (7.0 g. 10.5%) m. p. 150—152°, $[\alpha]_D$ 105°; UV max. 242 nm (»ε« near 16.200); IR bands at 3550, 1670 and 1610 cm^{-1}; no reaction with 2,3,5-triphenyltetrazolium chloride [lit.[2] m. p. 154—158°, $[\alpha]_D^{25} = 105.1 \pm 3°$ (c = 0.7323 in chloroform)].

5-Pregnene-21-ol-3,20-dione 3-ethyleneketal (IV)

Into a solution of I (50 g.) in benzene (4.86 l.) were added ethylene glycol (500 ml.) pyridine hydrochloride (7.2 g.) and anhydrous sodium sulfate (10 g.), and the mixture was stirred and boiled under reflux for 24 hours; water being continuously removed with a Dean-Stark trap. The solvent was evaporated and the residue was treated with 50% aqueous sodium hydroxide (5. ml.) and 3.5 l. of ice-water. After extraction with benzene, evaporation of the solvent and crystallization from methanol the compound IV was obtained (6.7 g., 12%): m. p. 180—183°, $[\alpha]_D + 38°$, no UV max; IR band at 3300 and 1720 cm^{-1}; reduction of 2,3,5-triphenyltetrazolium chloride.

Anal. $C_{23}H_{34}O_4$ (374.50) calc'd.: C 73.76; H 9.15%
found: C 73.88; H 9.41%

The mother liquor was chromatographed on a colum of Florosil (1000 g.) using hexane—ethyl acetate (3 : 2) for elution to give an additional crop of IV (23.3 g.); m. p. 179—182°. Total yield: 53.6%.

A sample of IV (0.5 g.) was dissolved in pyridine (5 ml.) and treated with acetic anhydride (1 ml.) at room temperature overninght. The mixture was worked up in a standard way to prepare 21-acetate in a good yield. Crystallized from acetone: m. p. 207—209°; no UV max; IR bands at 1730, 1720 and 1240 cm^{-1}.

Anal. $C_{25}H_{36}O_5$ (416.54) calc'd.: C 72.10; H 8.65%
found: C 72.15 H 8.73%

0.5 g. of IV was treated with acetic acid—water (9 : 1) (40 ml.) for 2 hours at 63° and after dilution with water, treatment with sodium carbonate to *p*H 8, extraction with ethyl acetate, evaporation and crystallization from methanol—water, gave 0.2 g. of I.

20-Benzyl-5-pregnene-20,21-diol-3-one 3-ethyleneketal (V)

To a solution of benzylmagnesium chloride [(obtained from 1.7 g. of Mg, 50 ml. of benzene—ether (1 : 2) and 8.9 g. of benzyl chloride in 30 ml. benzene—ether (1 : 2) at 45°)], a solution of IV (3.74 g.) in benzene (60 ml.) was added. The mixture was refluxed with stirring for 20 hours and, at 10°, saturated aqueous ammonium chloride was added. The aqueous phase was separated and extracted with ether; the combined organic phases were washed with water and evaporated *in vacuo*. The residue, on standing in ether, gave a solid which was filtered and crystallized from methanol—water: 1 g. of V was obtained; m. p. 245—248°; no UV max; IR bands at 3560 and 3450 cm^{-1} and no bands between 2000 and 1500 cm^{-1}; no reaction with 2,3,5-triphenyltetrazolium chloride.

Anal. $C_{30}H_{42}O_4$ (466.64) calc'd.: C 72.21; H 9.07%
found: C 72.18; H 9.15%

21-Phenyl-4-pregnene-3,20-dione (VII)

A solution of V (1 g.) in dioxane (95 ml.) was treated under stirring with a solution of periodic acid (1.1 g.) in water (25 ml.) for 20 hours at 20°. After dilution with 5% aqueous potassium carbonate (400 ml), extraction with methylene chloride, evaporation of the solvent, 0.9 g. of crude VI were obtained: no hydroxyl bands in IR but a carbonyl band at 1720 cm^{-1}. Crude VI (0.8 g.) was treated with a mixture of acetic acid and water (9 : 2, 80 ml.) for 2 hours at 68°. The solution was diluted with 10% aqueous potassium carbonate (400 ml.) extracted with methylene chloride, evaporated and chromatographed on a column of Florisil (30 g.) eluted with benzene—ether (1 : 2), (1 : 5), and with ether: 300 mg. of VII obtained, when crystallized from ether gave 200 mg., m. p. 139—141°; UV max. 241 nm (»ε« near 15.800); IR bands at 1720, 1680, 1620, 1310, 1270, 1230, 1190, 1080, 860, 770, 720 and 700 cm^{-1}; no reaction with 2,3,5-triphenyltetrazolium chloride.

Anal. $C_{27}H_{34}O_2$ (390.54) calc'd.: C 83.03; H 8.77%
found: C 82.98; H 8.85%

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IZVLEČEK

Ketalizacija 3-keto skupine 4-pregnen-21-ol-3,20-diona in sinteza 21-fenil-4-pregnen-3,20-diona

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20-Ketosteroidi reagirajo z etilenglikolom v prisotnosti kislin hitreje kakor Δ^4-3-keto skupine. Odkrili smo, da reagira Δ^4-3-keto skupina 4-pregnen-21-ol-3,20-diona z etilenglikolom v prisotnosti piridin hidroklorida in brezvodnega natrijevega sulfata hitreje kot 20-keto skupina. Iz tako pripravljenega 5-pregnen-21-ol-3,20-dion-3-etilenketala smo pripravili 21-fenil-4-pregnen-3,20-dion.

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