TRANSFORMED STEROIDS

122. FUNCTIONALIZATION OF C^{17} CENTER OF 20-KETOSTEROIDS BY REDUCTIVE SPLITTING OF 16α,17α-CYCLOPROPANE RING

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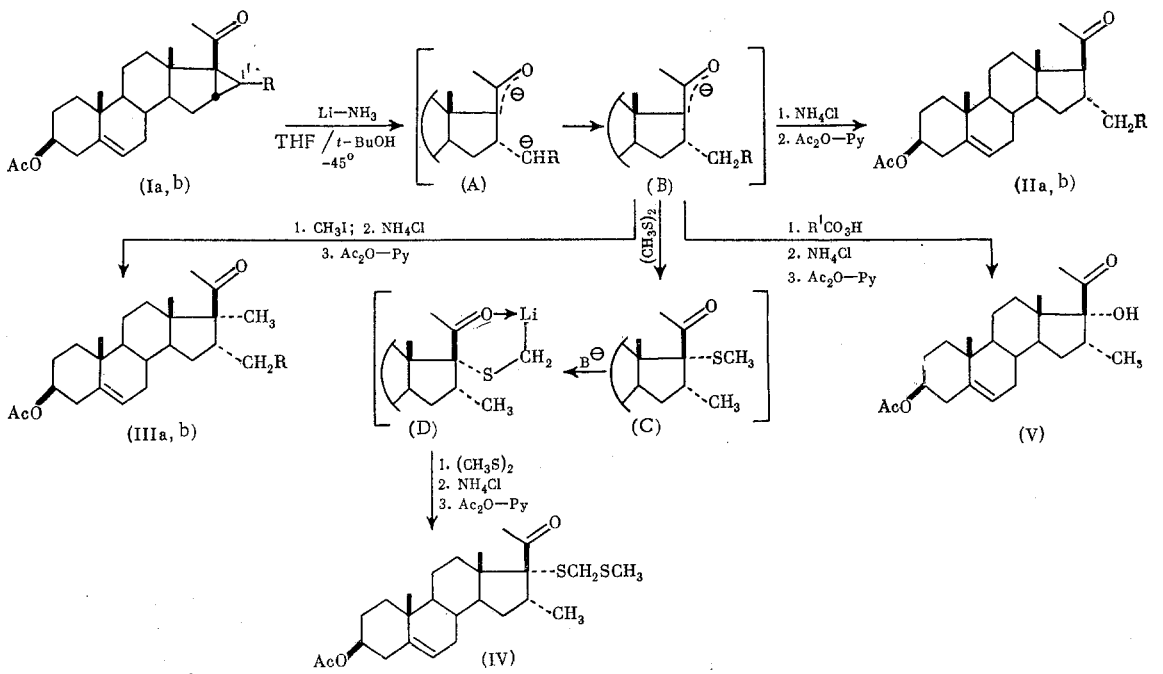
It has recently been shown [1, 2] that an acid-catalyzed nucleophilic opening of 16α,17α-methyleno-20-ketopregnanes leads to 17-unsubstituted steroids only, and depending on the reaction conditions and the nature of the nucleophile, both 16α derivatives with a normal structure and D-homo products are formed.

In continuation of our studies on the synthesis of 16α,17α-bifunctional pregnanes [3], it was interesting to study the opening of cyclomethylene derivatives (I) when a substituent was introduced in the C^{17} position. In the present work we investigated the reductive splitting of cyclopropanes conjugated with the carbonyl group, by means of Li in NH_3 [4]. We found that the reaction proceeds regio- and stereospecifically with cleavage of the $C^{17}-C^{1'}$ bond, which opens up a new route to the preparation of 17-substituted 20-ketopregnanes with a hydrocarbon substituent in the 16 position. The method consists in the action of electrophilic reagents on the 20-enolate formed during the opening of 16α,17α-cyclopropano-20-ketosteroids [5]. The initial steroids (Ia) and (Ib) were obtained by decomposition of the corresponding pyrazolines formed during the cycloaddition of diazomethane [6] and diazoacetic ester [7], respectively, to 16-dehydropregnenolone acetate. The reaction can be illustrated by the following scheme:



R = H (a), CO_2Et (b).

The anion-radical formed from ketone (I) by the action of solvated electron undergoes cleavage of the three-membered ring at the $C^{17}-C^{1'}$ bond, maximally overlapping the π orbital of the carbonyl group [4], and then reduction to dianion (A). The latter is transformed into (B) at the expense of the proton donor (t-BuOH) present in the reaction mixture. The enolate-anion (B) formed under kinetically controlled conditions [8] (−40 to −50°C, 5 min, 8-10 g-eq Li) can be stabilized by the action of excess of a selected electrophilic reagent. Treatment of the reaction mixture with NH_4Cl leads to 16-substituted 20-ketopregnanes (IIa, b) in high yields.

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When other (different from proton) electrophiles are used, a regio- and stereospecific functionalization of the C^{17} center is achieved with the formation of 16α,17α-disubstituted 20-ketopregnanes (III)-(V). We used CH_3I, $(CH_3S)_2$, and peracide as electrophilic reagents. Following the alkylation of enolate (B) (R = H, CO_2Et) by CH_3I, acetates of the known [9] 16α,17α-dimethylpregn-5-en-3β-ol-20-one (IIIa) and its 16α-carbethoxymethyl-17α-methyl analog (IIIb) were obtained (after acetylation) in a high yield. The structure of these two compounds was confirmed by physicochemical methods. In the PMR spectrum of (IIIb), a three-proton singlet of 18-CH_3 at δ 0.65 ppm, a six-proton singlet of 17- and 19-CH_3 at δ 1.00 ppm, and two three-proton singlets at δ 2.0 and 2.10 ppm, corresponding to the 3-acetate and 21-CH_3 groups, are present.

By the action of an excess of $(CH_3S)_2$ on enolate (B) (R = H), followed by acetylation, a product containing two S atoms has been isolated in a satisfactory yield. Structure of (IV) has been ascribed to it from the data of physicochemical analysis. In fact, in the PMR spectrum of (IV), together with the singlets of the angular, 21-CH_3 and 3-CH_3COO groups, there is an additional three-proton singlet assigned to the CH_3S group signal. The assignment of the signals of the 21-CH_3 and SCH_3 groups in the 2.0-2.14 ppm region is difficult. In the spectrum there is also a single two-proton signal at δ 4.3 ppm, which was assigned to the SCH_2S group. The formation of (IV) can be represented in the following way. Compound (C) initially formed during the alkylation of the enolate (B) is probably readily deprotonated under the reaction conditions as the result of the formation of an intramolecularly stabilized Li salt (D), which under the action of an excess of $(CH_3S)_2$ converts into the final disulfide (IV).

Lastly, the use of peracids as an electrophilic reagent (m-chloroperbenzoic or p-methoxyperbenzoic) made it possible to synthesize 16α-methyl-17α-hydroxy-20-ketopregnane (V) (yield ~ 20%). Thus, together with (V), a 17-unsubstituted product (IIa) is formed in considerable amounts, clearly due to the protonation of enolate (B). Under optimizing conditions of the process, the above method may be interesting for introducing a 17α-hydroxyl group into the intermediate products in the synthesis of the important hormonal preparation dexamethasone.

EXPERIMENTAL

The melting points were determined on a Koffler block. The IR spectra were measured on a UR-10 apparatus (KBr), and the PMR spectra on Varian DA-60-IL and WP-90 spectrometers in $CDCl_3$ solutions, with reference to TMS. Thin-layer chromatography was carried out on microplates with brand L silica gel (5-40 μm). For columns, brand KSK silica gel (200-250 mesh), free from iron, was used.

16α-Methylpregn-5-en-3β-ol-20-one Acetate (IIa). A solution of 1.37 g (3.1 mmole) of (Ia) and 0.35 ml of t-BuOH in 50 ml of THF was rapidly added at −45°C to a solution of 170 mg (24 mg-atom) of Li in 50 ml of liquid NH_3, vigorously stirred in an argon atmosphere. After 5 min, the mixture was decomposed with an excess of NH_4Cl, and evaporated in vacuo. The residue was treated with 100 ml of $CHCl_3$ and 25 ml of H_2O, and the organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated in vacuo. The crystalline residue, without further purification, was acetylated with 6 ml of Ac_2O and 6 ml of pyridine. After 12 h, the mixture was poured into water, the oily precipitate was extracted with $CHCl_3$, and the extract washed with H_2O, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on 80 g of SiO_2. Elution with a mixture of petroleum ether and ether (95:5) gave 1.16 g (85%) of (IIa), mp 192-194°C (ether−hexane); comp. [10]. IR spectrum (ν, cm^{-1}): 1250, 1705, 1730. PMR spectrum (δ, ppm): 0.65 s (3H, 18-CH_3), 0.89 d (J = 7 Hz; 3H, 16-CH_3), 1.00 s (3H, 19-CH_3), 2.01 s (3H, 3-OAc), 2.11 s (3H, 21-CH_3), 5.33 m (1H, HC^6).

16α-Carbethoxymethylpregn-5-en-3β-ol-20-one Acetate (IIb). Similarly, from 420 mg (0.95 mmole) of (Ib), 70 mg (10 mg-atom) of Li in 40 ml of liquid NH_3, 0.15 ml of t-BuOH in 30 ml of THF, with subsequent acetylation, 310 mg (74%) of (IIb), mp 119-120.5° (petroleum ether), was obtained. IR spectrum (ν, cm^{-1}): 1250 br, 1690, 1725, 1735. PMR spectrum (δ, ppm): 0.65 s (3H, 18-CH_3), 1.00 s (3H, 19-CH_3), 1.20 t (J = 6 Hz, 3H, CH_2CH_3), 2.00 s (3H, 3-OAc), 2.10 s (3H, 21-CH_3), 4.03 m (4H, 16-$C\underline{H}_2CO_2C\underline{H}_2CH_3$), 5.33 m (1H, HC^6). Found: C 73.36; H 9.35%. $C_{29}H_{40}O_5$. Calculated: C 72.94; H 9.07%.

16α,17α-Dimethylpregn-5-en-3β-ol-20-one Acetate (IIIa). A solution of 0.5 g (1.3 mmole) of (Ia) and 0.12 ml of t-BuOH in 30 ml of THF was added at −45°C to a solution of 90 mg (13 mg-atom) of Li in 40 ml of liquid NH_3, vigorously stirred in an argon atmosphere. After 1-2 min, 4 ml of CH_3I was rapidly added to the mixture, which was then stirred for 5 min. The mixture was treated as above, the residue was acetylated and chromatographed on 35 g of SiO_2. Elution with a petroleum ether−ether mixture (95:5) gave 390 mg (78%) of acetate (IIIa), mp 220-224°C (ether−hexane); comp. [9]. PMR spectrum (δ, ppm): 0.72 s (3H, 18-CH_3), 0.88 d (J = 7 Hz, 3H, 16-CH_3), 1.02 s and 1.05 s (6H, 17- and 19-CH_3), 2.00 s (2H, 3-OAc), 2.10 s (3H, 21-CH_3), 5.33 m (1H, HC^6).

16α-Carbethoxymethyl-17α-methylpregn-5-en-3β-ol-20-one Acetate (IIIb). Under similar conditions, from 0.5 g of steroid (Ib), 270 mg (59%) of (IIIb), mp 135-140°C (hexane), was obtained. PMR spectrum (δ, ppm): 0.64 s (3H, 18-CH_3); 1.00 s and 1.10 s (6H, 17- and 19-CH_3), 1.20 t (J = 7 Hz, 3H, $CH_2C\underline{H}_3$), 2.02 s (3H, 3-OAc), 2.10 s (3H, 21-CH_3), 3.48 q (J = 7 Hz, 2H, $C\underline{H}_2CO_2C_2H_5$), 4.03 q (J = 7 Hz, 2H, $OC\underline{H}_2CH_3$), 5.3 m (1H, HC^6). M^+ 458. $C_{30}H_{42}O_5$. Calculated: mol. wt. 458.62.

16α-Methyl-17α-(methylthio)methylthiopregn-5-en-3β-ol-20-one Acetate (IV). A solution of 0.5 g (1.3 mmole) of (Ia) and 0.13 ml of t-BuOH in 30 ml of THF was added at −45°C to a solution of 70 mg (10 mg-atom) of Li in liquid NH_3, vigorously stirred in an argon atmosphere. After 1-2 min, 1 ml of freshly distilled $(CH_3S)_2$ was rapidly added to the mixture, which was then stirred for 5 min, and treated as above. Elution with a mixture of petroleum ether and ether (99:1) gave 300 mg (47%) of disulfide (IV), mp 178-184°C (petroleum ether). IR spectrum (ν, cm^{-1}): 1250, 1700, 1735. PMR spectrum (δ, ppm): 0.74 s (3H, 18-CH_3), 0.98 d (J = 6.5 Hz, 3H, 16-CH_3), 1.04 s (3H, 19-CH_3), 1.98 s (3H, 3-OAc), 2.04 s and 2.14 s (6H, SCH_3 and 21-CH_3), 4.3 br. s (2H, SCH_2S), 5.33 m (1H, HC^6). Found: C 67.26; H 8.84; S 13.80%. $C_{26}H_{39}O_3S_2$. Calculated: C 67.38; H 8.42; S 13.82%.

16α-Methylpregn-5-en-3β,17α-diol-20-one Acetate (V). A solution of 0.5 g (1.3 mmole) of (Ia) and 0.15 ml of t-BuOH in 25 ml of THF was added at −45°C to a solution of 110 mg (15.7 mg-atom) of Li in 50 ml of liquid NH_3, vigorously stirred in an argon atmosphere. After 1-2 min, the temperature was increased to evaporation of NH_3, and the residues of NH_3 and THF were removed in vacuo. To the dry residue, 30 ml of THF was added. A 0.94-g portion of m-$ClC_6H_4CO_3H$ in 10 ml of THF was added to the suspension obtained, the mixture was stirred for 10 min at 20°C, and evaporated to dryness. To the residue, $CHCl_3$ and H_2O were added, the organic layer was separated, and the aqueous layer extracted with $CHCl_3$. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated in vacuo. The residue obtained after the above treatment was chromatographed on 35 g of SiO_2. Graded elution with a petroleum ether–ether mixture with an increasing amount of the latter gave 300 mg of acetate (IIa) and 100 mg (19%) of acetate (V), mp 183-187°C (acetone–hexane), which did not depress the melting point in a mixed probe with an authentic sample [11]. IR spectrum (ν, cm^{-1}): 1250, 1690, 1735, 3345.

Similarly, from 1 g of p-$CH_3OOCC_6H_4CO_3H$, 250 mg of (IIa) and 90 mg of (V) were obtained.

CONCLUSIONS

In reductive splitting of 16α,17α-cyclopropano-20-ketopregnanes with lithium in liquid ammonia, followed by an action of electrophilic reagents on the 20-enolate formed, a regio- and stereospecific functionalization of the C^{17} center takes place.

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