pound with N,N'-bis(triethylsilylmethyl)thiourea. In a similar reaction, bis(3-triethylsilylpropyl)amine yields N,N,N',N'-tetrakis(3-triethylsilylpropyl)thiourea, while bis(triethylsilylmethyl)amine yields a complex mixture of products.

2. The reaction of triethylsilylmethylamine with thiourea in the presence of ammonium sulfate yields N,N'-bis(triethylsilylmethyl)thiourea.

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TRANSFORMED STEROIDS. COMMUNICATION 130. EFFECT OF THE SUBSTITUENT AT POSITION 21 ON THE REACTION OF Δ^{16}-20-KETOSTEROIDS WITH DIPHENYLSULFYLIMINE

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The presence of oxygen-containing functional groups at position 21 of steroids is apparently a necessary condition for the manifestation of cortisone activity. But such 21-functionalization frequently encounters great difficulty, especially with compounds that are multi substituted in the D ring. In continuation of our investigations of 16,17-heterosubstituted pregnanes, we have attempted to synthesize 16,17α-epimino-21-hydroxyl(acetoxy)-20-ketopregnanes, using the two-step method [1] that had been used previously to synthesize 16,17α-epiminopregnenolone (IX). It turned out that the nature of the substituent at position 21 substantially affects both steps of the process. Thus, Michael condensation of pregn-5,16-dien-3β,21-diol-20-one diacetate (III) with methylhydroxylamine is better defined than in the case of the 21-methyl analog (I) that leads to the 16α-methoxyamine (VI). But the second step of the process, viz., ring closure to aziridine with removal of the 17α proton, which requires prolonged heating of amine VI with CH_3ONa to t-BuOK in DMFA, yields a complex mixture of products, in which aziridine was not detected. The only compound that was separated was the 16,20-diketone VIII, formed by the removal of the 16β proton. Seeking to moderate the cyclization conditions by carrying out the two reactions in one step, we replaced methylhydroxylamine by S,S-diphenylsulfylimine (DPSI) [2]; as recently discovered [3-6], this compound can react with electrophilic olefins by a kind of Michael reaction to form aziridines. Investigation of the reaction with ketones I and II in CH_3OH, C_6H_6, and $C_6H_5CH_3$ showed that it proceeds only with prolonged heating. The presence of another nucleophilic reagent that competes with the bulky DPSI at the step of addition to the sterically hindered Δ^{16} bond is undesirable. Thus, when I is heated with DPSI in CH_3OH, along with aziridine IX there is obtained the product of solvent addition, 16α-methoxypregn-5-en-3β-ol-20-one [7]. The optimum yield of IX was obtained (80%) when II was boiled with DPSI in C_6H_6 for 65-70 h. In order to accelerate the reaction we used high pressure (6000 atm). In this case IX was obtained in quantitative yield by heating II with excess DPSI in toluene for 6 h at 80°C in an ampul. The analogous reaction with 21-acetoxy(hydroxy)-Δ^{16}-steroids III-V is more complicated, and without high pressure does not take place at all: heating the reaction mixture thoroughly destroys the steroid molecule. Typical of the behavior of the 21-acetoxysteroids

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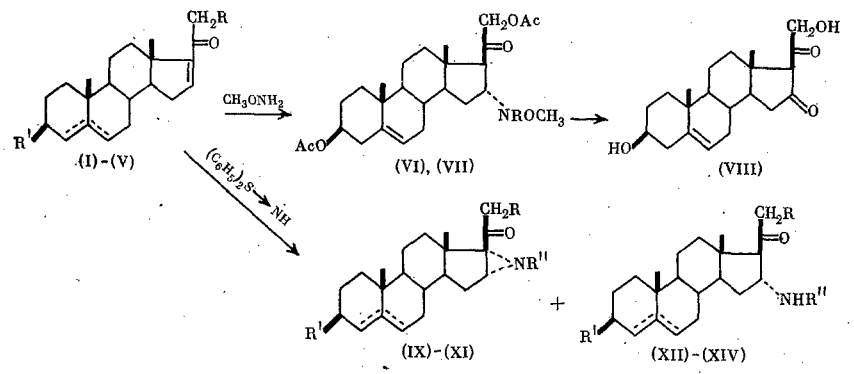
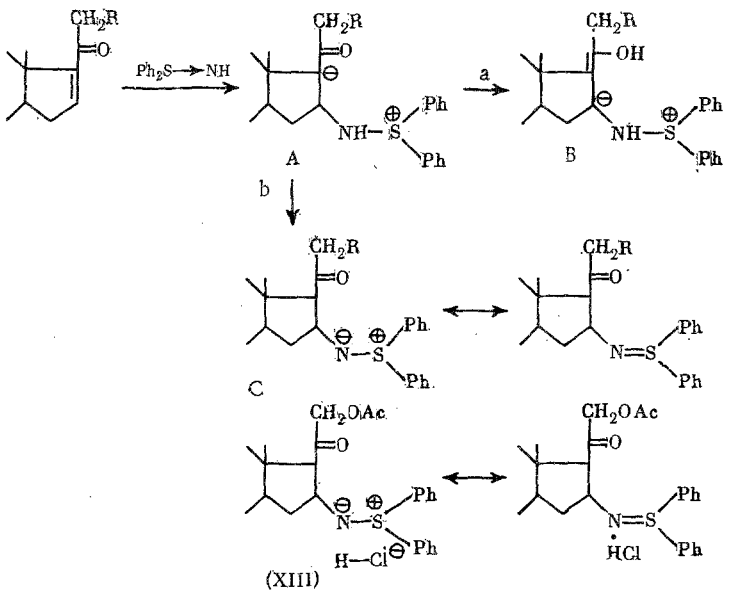
III and IV in this is the way in which it changes its course. Thus, holding the 3,21-diacetate III with DPSI at 20°C and 6000 atm for 24 h in toluene, followed by acetylation gives mainly the 3,16N,21-triacetate of 16α-aminopregn-5-en-3β-ol-20-one (XII), along with the triacetate of 16,17α-epiminopregn-5-en-3β,21-diol-20-one (X). In the analogous reaction with the Δ^4-3-keto analog (IV), significant amounts of aziridine were not detected, and the only product separated was the 16N,21-diacetate of 16α-aminopregn-4-en-3,20-dione (XIV), in 73% yield. On the other hand, in the reaction of DPSI with the 3,21-dihydroxy-Δ^{16}-20-diketone V, which is accompanied by intense tar formation and side reactions, aziridine X was obtained in 15% yield. The course of the reaction was estimated quantitatively by preparative TLC after acetylation of the reaction mixture. Primary products could be separated and characterized only in the reaction of the 21-acetate III with DPSI in CH_2Cl_2. Along with aziridine XI, we established the formation of the S-N-ylid hydrochloride XIII, which when acetylated gives the triacetate XII. (Apparently HCl is generated by the action of the reagent on CH_2Cl_2).



R = H, R′ = OAc, Δ^5 (I); R = H, R′ = OH, Δ^5 (II); R = R′ = OAc, Δ^5 (III); R = OAc, R′ = O, Δ^4 (IV); R = R′ = OH, Δ^5 (V); R = H(VI), Ac (VII); R = R″ = H, R′ = OH, Δ^5 (IX); R = R′ = OAc, R″ = Ac, Δ^5 (X); R = R′ = OAc; R″ = H (XI); R = R′ = OAc, R″ = Ac, Δ^5 (XII); R = R′ = OAc, R″ = $(C_6H_5)_2SCl$, Δ^5 (XIII); R = OAc, R′ = O, R″ = Ac, Δ^4 (XIV).

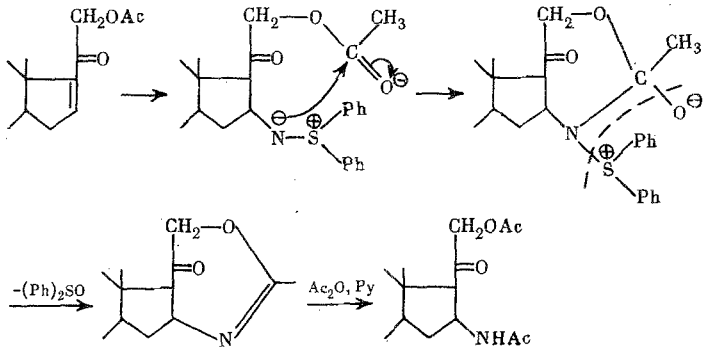
The structure of the reaction products follows from the physical chemical analytical data. The mass spectra of aziridines X and XI have molecular peaks of 471 and 429, respectively, and show fragmentation corresponding to the removal of the aziridine ring that is confirmed by metastable peaks. The IR spectrum of XI shows strong absorption in the region of N–H valence vibrations, 3315 cm^{-1}, and that of its N-acetate, X, shows a highly intense tertiary amine band at 1688 cm^{-1}. The aziridine structure of X and XI is confirmed by the PMR signals of the aziridine ring proton at 3.39 and 2.8 ppm respectively. The angular methyl proton signals are quite close together, which is typical of 20-ketopregnanes with a three-membered ring at the 16α and 17α positions. The mass spectra of amines XII and XIV also show molecular peaks and fragmentation corresponds to the removal of an amide group. The IR spectra of these compounds show the assortment of absorption bands that is typical of secondary amines. The position and configuration of the NHAc group follows from the PMR spectra, in which the angular Me signals appear in the region that is typical of 16α-substituted pregnanes, viz., 0.64 and 0.68 ppm for XII and XIV, respectively. The downfield signal of the nitrogen proton in XII apepars as a doublet, which characterizes its interaction with the C-16 proton [8]. The following data support the structure assigned from XIII: The PMR spectrum has two multiplet signals with δ 7.6 and 7.98 ppm, each corresponding to 5 proton units. The UV spectrum in C_2H_5OH is almost identical with that of DPSI, and has two absorption maxima in the region that is typical for such ylides [9]: λ_{max} 225, log ε 4.24, and λ_{max} 270, log ε 3.46. The mass spectrum does not show a molecular ion; the main peaks correspond to the removal of Ph_2S + HCl (m/z 429). Furthermore, the spectrum is practically the same as that of XI, indicating that the latter is formed by fragmentation of XIII; the main peak has m/z 186 (Ph_2S) [9]. These data plus the elemental analyses show that the molecule has retained the diphenylsulfide group in a valence state close to that of the original ylide. The IR spectrum shows a high intensity band of the NH^+ valence vibrations (ν 2650 cm^{-1}) of the ylide hydrochloride.

According to the accepted views [3, 4], the reaction of DPSI with these unsaturated ketones must proceed through intermediate A which is stabilized by elimination of diphenyl sulfide to form aziridine, or through resonance structure B to form enaminoketone. In none of the reactions that we studied was any aminoketone or its derivative detected. Apparently, besides proceeding by path "a," the reaction can also proceed by path "b" to form the ylide B, the stable form of which is the hydrochloride XIII that was isolated.



(XIII)

The features of the reaction that were noted for the 21-acetates III and IV can be explained by the following scheme, according to which stabilization of ylide C occurs with the participation of the 21-acetate group. The concluding step of the reaction has been completely substantiated, since the easy splitting of the steroid methyloxazolines by Ac_2O and Py is established [8].



EXPERIMENTAL

Melting points were determined on a Kofler block. PMR spectra were obtained on a Tesla BS-497 spectrometer (100 MHz) in $CDCl_3$ solution, with HMDS as the internal standard. IR spectra were obtained on a UR-20 apparatus. Mass spectra were obtained on a Varian MAT CH-6 apparatus with direct introduction of the sample into the ion source at 70 eV ionization voltage.

3,21-Diacetate of 16α-Methoxyaminopregn-5-en-3β,21-diol-20-one (VI). A solution of 0.3 g of 3,21-diacetate III [9] and 0.08 ml of freshly distilled CH_3ONH_2 in 3 ml of alcohol was boiled for 3.5 h, after which two 0.08-ml portions of CH_3ONH_2 were added during 5-h boiling. The mixture was cooled, and the crystalline precipitate was filtered off and washed with cold CH_3OH. There was obtained 0.24 g of methoxyamine VI, mp 147-153°C. Crystallization of the mother liquor from CH_3OH yielded an additional 0.3 g of VI, analytical sample mp 157-159°C. IR spectrum (ν, cm^{-1}, KBr): 1242, 1725, 1748. PMR spectrum (δ, ppm): 0.77 s (18-CH_3), 0.94 s (19-CH_3), 2.09 s (21-CH_3), 3.40 s (OCH_3), 4.78 q (21-CH_2), 5.26 br.l. (6-H). Mass spectrum (m/z): 461 $(M)^+$, 430 $(M-OCH_3)^+$, 401 $(M-HOAc)^+$, 386 $(M-HOAc-CH_3)^+$, 370 $(M-HOAc-OCH_3)^+$, 358.

Acetylation of VI with Ac_2O and Py at 20°C yielded 3,16N,21-triacetate of 16α-methoxyaminopregn-5-en-3β,21-diol-20-one (VII), mp 173-174°C (from CH_3OH). IR spectrum (ν, cm^{-1}, KBr): 1245, 1660, 1730, 1740. PMR spectrum (δ, ppm): 0.67 s (18-CH_3), 0.98 s (19-CH_3), 1.98 s (3-OAc), 2.04 s (21-OAc), 2.12 s (NAc), 3.64 s (OCH_3), 4.66 q (21-CH_2), 5.63 br.l. (6-H).

Pregn-5-en-3β,21-diol-16,20-dione (VIII). A solution of 0.1 g of 16α-methoxyamine VI in 0.3 ml of 2 N CH_3ONa was boiled 5 h. The mixture was treated with water and neutralized with AcOH, and the precipitate was filtered off, washed with water, and dried. There was obtained 0.08 g of a complex mixture, from which 0.011 g of VIII was separated by TLC (SiO_2, C_6H_6:CH_3OH 7:1), decomp. ∿329-335°C (from CH_3OH—C_6H_6). IR spectrum (ν, cm^{-1}, KBr): 1660 sh, 1720, 1755, 3080, 3180, 3330. Mass spectrum (m/z), 346 $(M)^+$.

16,17α-Epiminopregn-5-en-3β-ol-20-one (IX). 1) A solution of 0.1 g of II and 0.3 g of DPSI in 1 ml of C_6H_6 was boiled for 65 h and evaporated in vacuum. The residue was purified by TLC (SiO_2, ether:hexane 3:1), yielding 0.08 g of IX, mp 187-190°C (from CH_3OH), identical with the sample previously obtained [1].

2) A solution of 0.06 g of II and 0.18 g DPSI in 3.2 ml of toluene was kept in a high-pressure ampul at 80°C for 6 h at 6000 atm; IX, 0.051 g, was separated by the method described above.

3) A solution of 0.05 g of I and 0.15 g of DPSI in 2 ml of CH_3OH was boiled for 30 h, and there were separated by TLC, along with 0.009 g of II, 0.028 g of IX and 0.011 g of 16α-methoxypregn-5-en-3β-ol-20-one, mp 159-160°C (from CH_2Cl_2—C_6H_{14}) [7].

Triacetate of 16,17α-Epiminopregn-5-en-3β,21-diol-20-one (X), and Triacetate of 16α-Aminopregn-5-en-3β,21-diol-20-one (XII). A solution of 0.1 g of diacetate III and 0.1 g DPSI in 3.2 ml of abs. toluene was kept for 1 day in an ampul at 20°C and 6000 atm pressure. The solvent was distilled off in vacuum, and the residue was dissolved in 1.5 ml of Ac_2O and 3 ml of Py and left at 20°C for 48 h. CH_3OH was added, the solvent was partially distilled off in vacuum, water was added to the residue, and the mixture was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and evaporated. TLC of the residue (ether:hexane 2:1) yielded, along with 0.055 g of unreacted III, 0.013 g of aziridine X, mp 160-162°C (from ethyl acetate—hexane). IR spectrum (ν, cm^{-1}, KBr); 1240, 1688, 1722, 1750. PMR spectrum (δ, ppm): 0.91 s (18-CH_3), 0.96 s (19-CH_3), 1.95 s (3-OAc), 2.01 s (NAc), 2.08 s (21-OAc), 3.39 br.t. (16-H), 4.68 q (21-CH_2). Mass spectrum (m/z): 471 $(M)^+$, 429 $(M - COCH_2)^+$, 414 $(429 - NH)^+$, *399.5 = (428 → 414), 386 $(M - COCH_2 - COCH_3)^+$, 369 $(M - COCH_2 - HOAc)^+$, 354 $(369 - NH)^+$ *347.3 (429 → 386). Besides X there was separated 0.03 g of 16α-N-acetylamine XII; mp 150-157/173-178°C (from CH_3OH—H_2O). IR spectrum (ν, cm^{-1}, $CHCl_3$): 1260, 1515, 1659, 1722, 1745 sh, 3450. PMR spectrum (δ, ppm): 0.64 s (18-CH_3), 0.94 s (19-CH_3), 1.82 s (NHAc), 1.94 s (3-OAc), 2.08 s (21-OAc), 4.60 q (21-CH_2), 5.94 d (NH). Mass spectrum (m/z): 473 $(M)^+$, 430 $(M - COCH_3)^+$, 415 $(M - NHAc)^+$, 413 $(M - HOAc)^+$, 402, 400, 371 $(M - HOAc - COCH_2)^+$, 354 $(M - HOAc - NH_2Ac)^+$, *303.4 = (143 → 354).

A solution of 0.05 g of diol V [10] and 0.1 g of DPSI in 3 ml of abs. THF was kept in a high-pressure ampul at 20°C and 6000 atm for 48 h. The solvent was distilled off in vacuum and the residue was acetylated in 2 ml of Ac_2O and 4 ml of Py. The mixture was subjected to repeated TLC (ether—hexane, ethyl acetate—hexane, etc.). There was obtained 0.007 g of X, identical with that described above.

3,21-Diacetate of 16,17α-Epiminopregn-5-en-3β,21-diol-20-one (XI) and 3β,21-Diacetoxy-16α-S,S-diphenylsulfyliminopregn-5-en-20-one Hydrochloride (XIII). A solution of 0.3 g of III and 0.3 g of DPSI in 1.5 ml of dry CH_2Cl_2 was kept for 1 day in an ampul at 20°C and 6000 atm. The reaction mixture was subjected to repeated TLC (C_6H_6:CH_3OH 8-15:1). Along with 0.03 g of unreacted III, 0.021 g of XI was separated, mp 195-200°C (from aqueous CH_3OH) [IR spectrum (ν, cm^{-1}, KBr): 1238, 1250 sh, 1710 sh, 1728, 1750, 3315. Mass spectrum (m/z): 429 $(M)^+$, 414 $(M - NH)^+$, *399.5 = (429 → 414), 386 $(M - COCH_3)^+$, 369 $(M - HOAc)^+$, 354 $(M - HOAc - NH)^+$, *347.3 = (429 → 386), 326 $(M - HOAc - CH_3CO)^+$] and 0.06 g of XIII, mp 210-221°C (from ethyl acetate). IR spectrum (ν, cm^{-1}, KBr): 1040, 1240, 1250 sh, 1725, 2650. PMR spectrum (δ, ppm): 0.57 s (18-CH_3), 0.91 s (19-CH_3), 1.94 s (3-OAc), 2.06 s (21-OAc), 4.56 q (21-CH_2), 7.6 br.s (C_6H_5), 7.98 br.s (C_6H_5). Raman spectrum (C_2H_5OH): λ_{max} 285 (Δε 5.01). Mass spectrum (m/z): 429, 414, *399.5, 386, 369, 354, 343, 313, 294, 281, 253. Found: S 4.83; Cl 5.32%. $C_{37}H_{46}O_5SNCl$. Calculated: S 4.92; Cl 5.44%.

Diacetate of 16α-Aminopregn-4-en-21-ol-3,20-dione (XIV). A solution of 0.15 g of the 21-acetate IV [11] and 0.3 g of DPSI in 3 ml. of abs. toluene was kept in a high-pressure ampul at 20°C and 6000 atm for 48 h; the solution was evaporated and the residue was acetylated with 3.2 ml of Ac_2O and 6.6 ml of Py. After the workup as described above and TLC (ether:hexane 4:1, ethyl acetate: methanol 15:1). along with unreacted IV (0.022 g) there was separated 0.11 g of XIV, mp 227-232°C (from ethyl acetate—hexane). IR spectrum (ν, cm^{-1}, KBr): 1240, 1530, 1612, 1660, 1670 (sh), 1735, 1750, 3370. PMR spectrum (δ, ppm): 0.68 s

(18-CH_3), 1.1 s (19-CH_3), 1.84 s (NHAc), 2.08 s (21-OAc), 4.6 q (21-CH_2), 5.8 br.ℓ. (4-H), 6.18 br.ℓ. (NH). Mass spectrum (m/z): 429 $(M)^+$, 386 $(M - COCH_3)$, 369 (M − HOAc), 356, 354, 328 $(M-NHAc - COCH_3)^+$, 310 $(M - HOAc - NH_2Ac)^+$, *317.2 = (429 → 386), 297.

CONCLUSIONS

The course of the reaction of Δ^{16}-20-ketosteroids with S,S-diphenylsulfylimine depends on the substituent at position 21; it may proceed with cyclization to the 16,17α-epimino-20-ketosteroids, or with formation of 16α-substituted S–N steroidal ylides.

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