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6-THIASTEROIDS

A NOVEL STEREOSELECTIVE PREPARATION OF 6-HETEROSTEROIDS

by

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The biological activity patterns of several A-nor- and A-homo-thiasteroids[2] and 6-thiaestrogens[3] have prompted the search for efficient routes for other analogues. In spite of numerous 6-heterosteroids known to-day no satisfactory and general procedure for the partial synthesis of 6-thiasteroids has been reported. In this letter a short and stereoselective synthesis of 6-thiaandrostanes and 6-thiacholestanes is presented.

Starting from the t-butylether of cholesterol[4] the corresponding keto-acid 1a[5] was obtained in 85% yield by modification of existing procedures. CH_2N_2-esterification followed by $NaBH_4$-reduction afforded 5α-H lactone 2a in quantitative yield. However, as the future reaction at C-5 with nucleophiles is expected to proceed with inversion at this centre the preparation of 5β-H lactone 3a was also necessary in order to obtain 6-thiasteroids of natural configuration. The latter goal could be achieved in yields over 80% by $NaBH_4$/DME reduction at -10°C of acid 1a or alternatively by B_2H_6/THF/r.t. reduction of the Na-salt of 1a. This dramatic change in stereoselectivity of the C-5 carbonyl reduction is accounted for by assuming a hydride transfer to C-5 from the β-face of the intermediate carboxylate-borane addition complex 4. Additional support for this explanation is found in the fact that B_2H_6 reduction of the ester of 1a gives exclusively 2a which is also formed in the $NaBH_4$/DME reduction of the Na-salt of 1a.

With the 5α- and 5β-lactones at hand the synthesis of 6-oxa- and 6-thia-steroids is straightforward. LAH-reduction of 2a and 3a afforded the corresponding diols 5a and 6a which were cyclized to 6-oxacholestanes 7a and 8a upon p-TsCl/pyridine treatment. Removal of the tBt function by p-TsOH/C_6H_6 reflux and CrO_3 or Ag_2CO_3/celite[6] oxidation gave the corresponding 6-oxa-cholestanones 11a and 12a. The 6-thiaderivatives were obtained as follows: mesylation of 6a in pyridine at -15 C°(24 hr) followed by additional stirring at 0°C (24 hr) gave the oily dimesylate[7] which upon treatment with Na_2S (anhydrous) in EtOH[8] afforded 6-thiacholestanol butylether 9a [mp. 144-146°C, pmr δ($CDCl_3$) 0,65 s (18-CH_3) and 1.02 s (19-CH_3)].

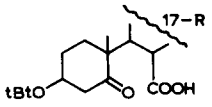
The same procedure applied to diol 5a afforded 10a [mp. 90-92°C, pmr δ($CDCl_3$) 0.66 s (18-CH_3) and 1.18 s (19-CH_3), 2.66 m (5-H; $J_{4a,5}$ = 13 Hz, $J_{4e,5}$ = 3.5 Hz)]. It should be emphasized that the success of latter cyclization completely depends upon the choice of the t-Bu ether at C-3 as protecting group.

In addition the ethers 9a and 10a were converted into the corresponding alcohols (p-TsOH) and oxidized with Ag_2CO_3/celite to the ketones 13a [mp. 147.5-149.5°C, pmr δ($CDCl_3$) 0.70 s (18-CH_3), 1.22 s (19-CH_3)] and 14a [mp. 148-154°C, pmr δ($CDCl_3$) 0.69 s (18-CH_3) and 1.27 s (19-CH_3)].

In a similar series of reactions androstane-3,17-diol di-t-butylether gave the corresponding 6-oxasteroids 11c and 12c while the diols 5b and 6b were converted into 6-thiasteroids 9b [mp. 236-238°C, pmr δ($CDCl_3$) 0.71 s (18-CH_3) and 1.04 s (19-CH_3)] and 10b [mp. 162-163°C, pmr δ($CDCl_3$) 0.71 s (18-CH_3) and 1.20 s (19-CH_3)] which upon ether cleavage and Ag_2CO_3 oxidation gave the 3-oxo-compounds 13c [mp. 197°C (dec), pmr δ($CDCl_3$) 0.78 s (18-CH_3) and 1.24 (19-CH_3)] and 14c [mp. 147-152°C, pmr δ($CDCl_3$) 0.79 s (18-CH_3) and 1.30 s (19-CH_3)].

Interestingly during the Na_2S cyclization of the dimesylate of 5b the unsaturated seco-sulfide 15 was formed in ca. 15% yield. However, the latter product upon irradiation in benzene (Philips SP-500 High Pressure) could be also converted into the 5β-derivative 10b.

All of the 6-thiasteroids synthesized were oxidized to the corresponding



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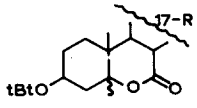
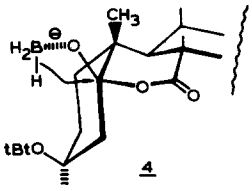


2 5α-H
3 5β-H



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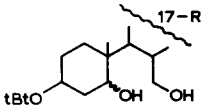
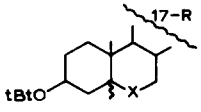
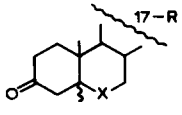


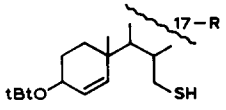
5 5α-H
6 5β-H



7 5α-H, X = O
8 5β-H, X = O
9 5α-H, X = S
10 5β-H, X = S



11 5α-H, X = O
12 5β-H, X = O
13 5α-H, X = S
14 5β-H, X = S



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a. R = C_8H_{17}
b. R = OtBt
c. R = OH

sulfoxides and sulfones. Furthermore the present procedure could also be applied in the synthesis of the corresponding 6-aza-derivatives.

Complete results will be published in our full paper.

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