ON REACTION OF 3-(9'ß-ACETYL-DES-A,B-CHOLESTAN-8'α-YL)-PROPIONIC ACID WITH ETHANOLAMINE

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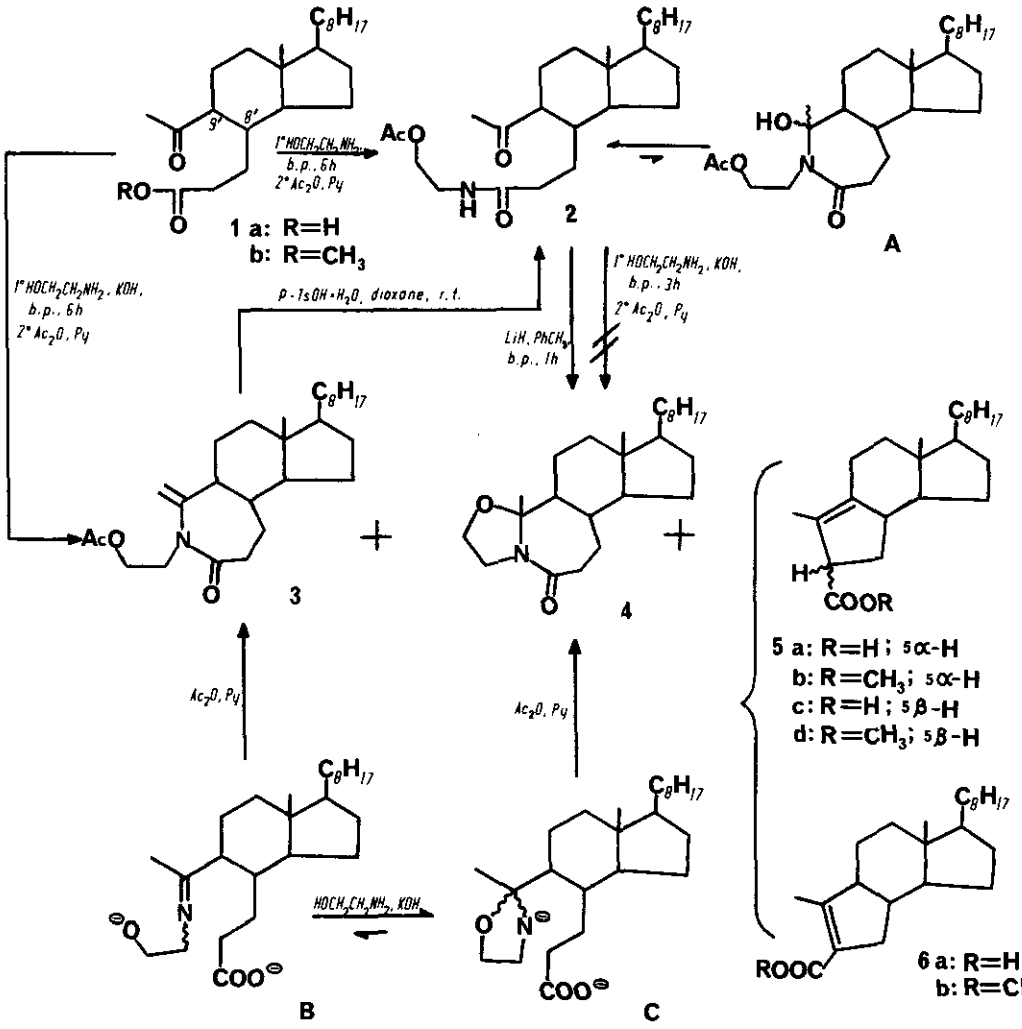
Abstract - Two procedures for the synthesis of A-oxazolidine compound 4 from keto-ester 1b have been elaborated. The two-step method involving keto-amide 2 preparation and its reaction with LiH seems to be superior to the direct synthesis from 1b and ethanolamine in the presence of KOH followed by Ac_2O/Py promoted cyclization.

In the course of our studies on nitrogen analogs of steroids we have synthesized a number of azasteroids by multi-step transformations of natural products such as cholesterol[1], testosterone[2] and dehydroepiandrosterone[3]. These syntheses were successfully accomplished but in the most cases the total yields were not very impressive though each individual step was fairly efficient. Very often the direct, "one pot" procedures are superior in respect of yield to other methods, sometimes quite elegant but longer. Recently we have worked out relatively short and efficient methods of preparation of some des-A,B-steroids, particularly 3-(9'ß-acetyl-des-A,B-cholestan-8'α-yl)-propionic acid (1a) and its methyl ester (1b)[4]. In this report the results of our investigation on the compound 1 reaction with ethanolamine are presented. We have examined this reaction with a view to inserting of two heteroatoms to the steroid nucleus (oxygen and nitrogen in the positions 1 and 5, respectively) with a simultaneous closure of two rings A and B. Such A-oxazolidine compound 4 would be a bridge between stereoids and veatchine type alkaloids[5]. Keto-ester 1b was heated under reflux in ethanolamine solution for 6 h. After removing of excess ethanolamine under reduced pressure the residue was treated with acetic anhydride in pyridine (the primary product was very polar and therefore difficult to isolate). The usual work-up and silica gel column chromatography afforded the product in a pure form in about 75 % yield. On the basis of 1H-NMR and IR data it appeared to be a simple keto-amide 2. Since compound 2 was the only isolated product there was no evidence for equilibrium (shown on the Scheme) existing between 2 and a cyclic form A.



Compound 2, m.p. 88.5–90°C; $[\alpha]_D^{24}$ = +16.4°; $\nu_{max}^{CHCl_3}$: 1673 (amide C=O), 1699 (ketone C=O), 1742 cm^{-1} (acetate C=O); $\delta(CDCl_3)$: 6.09 (bs, 1H, -NH), 4.19 (t, J = 6 Hz, 2H, $-CH_2-OAc$), 3.55 (m, 2H, $-CH_2-NH-$), 2.19 (s, 3H, CH_3CO-), 2.09 (s, 3H, CH_3COO-), 0.72 (s, 18-H); m/e: 449 (M^+; 30%), 389 (M^+-HOAc; 18%), 364 ($M^+-C_4H_7NO$; 50%), 145 ($C_6H_{11}NO_3^+$; 100%), 85 ($C_4H_7NO^+$; 62%).

Compound 3, an oil, $[\alpha]_D^{24}$ = -55.7°; $\nu_{max}^{CHCl_3}$: 1635 (lactam C=O), 1661 (C=C), 1742 cm^{-1} (acetate C=O); λ_{max}^{MeOH}: 223 nm (ε = 3500); $\delta(CDCl_3)$: 5.17 and 5.08 (2xs, 2x1H, $\overset{H}{H}\!>\!C\!=\!C\!<$), 4.18 (m, 2H, $-CH_2-OAc$), 3.97 and 3.64 (2xm, 2x1H, $-CH_2-\overset{4}{N}-$), 2.02 (s, 3H, CH_3COO-), 0.73 (s, 18-H).

Compound 4, m.p. 125.5–127°C; $[\alpha]_D^{25}$ +71.6°; $\nu_{max}^{CHCl_3}$: 1630 cm^{-1} (lactam C=O); $\delta(CDCl_3)$: 3.50–4.30 (m, 4H, oxazolidine protons), 1.51 (s, 19-H), 0.71 (s, 18-H); m/e: 389 (M^+; 2%), 86 (C_4H_8NO ; 100%)

In the next experiment to the solution of keto-ester 1b in ethanolamine potassium hydroxide (6 eq) was added and the reaction mixture was refluxed for 6 h. After removing of ethanolamine from the reaction mixture, the residue was acetylated as in the first experiment. TLC showed the presence of the major product and several by-products. The rough chromatography afforded consecutively fractions a, b and c. IR of the least polar fraction a showed the characteristic bands of carboxylic acids. Before further chromatographical purification fraction a was treated with diazomethane. The less polar methyl ester appeared to be β,γ -unsaturated ester 5d with a quasi-equatorial carbometoxyl group. The more polar ester proved to be a chromatographically unseparable mixture of 5α -H epimer 5b and α,β -unsaturated ester 6b (λ_{max} = 228 nm). Products 5 and 6 were apparently formed as a result of aldol like intramolecular condensation and existed in a very low concentration in the reaction mixture. Rechromatography of fraction b led to isolation of two products - egzo-methylene lactam 3 and an unidentified compound containing presumably two ethanolamine units. To confirm the structure of the former compound it was treated with p-TSOH.H_2O in dioxane. Within 6 h at room temperature compound 3 disappeared and keto-amide 2 was formed in quantitative yield. The reaction probably proceeded via water addition to the highly reactive acylimmonium ion[6] followed by an isomerization of the intermediary hydroxylactam A to the thermodynamically favourable keto-amide 2. The main fraction c consisted of the major reaction product, A-oxazolidine compound 4, and the traces of the more polar keto- amide 2. The overall yield of 4 was 37 %, whereas the yields of the by-products described were in the range 5-10 %. To elucidate a mechanism of compound 4 formation some additional experiments were carried out. In order to check a hypothesis that keto-amide 2 was an intermediate in the process it was heated in ethanolamine solution in the presence of KOH and then, after a removal of $HOCH_2CH_2NH_2$, treated with Ac_2O in pyridine. In the separate experiment keto-ester 1b was refluxed in ethanolamine in the absence of KOH (to generate in situ keto-amide 2 and to avoid the base-catalyzed formation of the by-products 5 and 6), then potassium hydroxide was added and the further proceeding was as above. However in both cases TLC showed no spot corresponding to compound 4. In another experiment the reaction with $HOCH_2CH_2NH_2$ and KOH was repeated in exactly the same manner as in the successful experiment but the acetylation step was omitted. TLC of the reaction mixture showed the presence of small amounts of compounds 5 and 6, only traces of 4 and the most of material at the base spot. In the light of this result "the acetylation" seems to be essential in compound 4 formation. We assume that during the reaction with $HOCH_2CH_2NH_2$ in the presence of strong base there is an equilibrium between an open form B and a cyclic form C, the carboxylic group probably does not participate directly in the reaction (the most likely, however, it has an effect on the stereochemistry of the process) remaining as a carboxylate. Only after the removal of ethanolamine and addition of AC_2O in pyridine a carboxylate reacts to give a mixed anhydride

and it acylated intramolecularly either the form B or C thus quenching an equilibrium. From the open form B the major byproduct 3 is formed by a proton abstraction exclusively from the angular methyl group - it may be also an intramolecular process. The cyclic form C becomes transformed to A-oxazolidine compound 4. Formation of 4 is the highly stereospecific reaction. The compound isolated was homogenous in TLC, had a sharp melting point, a single signal of 19-H protons in 1H-NMR and beyond doubt it was a pure stereoisomer. The inspection of Dreiding stereomodels suggested R configuration at C-10 but unfortunately there was no additional proof from spectral data. However 10R configuration was strongly supported by the following expriment.
Keto-amide 2 was treated with lithium hydride (4 eq) in refluxing toluene. The reaction was completed within 1 h. Unexpectedly the only product isolated (in about 70 % yield) was identical in all respects (including the stereochemistry at C-10) with the previously obtained compound 4.
A mechanism of this reaction seems to be clear - the tertiary alkoxide anion deriving from the cyclic form A of keto-amide 2 substitutes intramolecularly the acetate thus closing an oxazolidine ring.The cyclic form A is a mixture of two stereoisomers of different chirality at C-10, but only one of them, with a quasi equatorial hydroxyl group (10R) is capable to attain a suitable conformation for S_N2 type reaction. In the case of the epimeric form A an approach to a bonding distance would be rather difficult and would require transition states of much higher energy. However, it easily equilibrates via the open keto-amide 2 providing the form A which is able to cyclize to oxazolidine 4. The total yield of 4 from keto-ester 1b according to the procedure involving two steps, keto-amide 2 formation and LiH initiated cyclization of 2, exceeds 50 % and is superior to the direct method.

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