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OLEFINE-FORMING ELIMINATION OF THE AMIDO GROUP

K. Syhora and H. Bočková

The Research Institute for Natural Drugs
Prague 9, Czechoslovakia

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Whereas the acid-catalyzed elimination of oxygen substituents leading to the formation of a carbon-carbon double bond is a general, well-established reaction, only a very limited attention has been hitherto paid to the possible parallelism in analogously substituted nitrogen compounds (1). In all known experiments in this direction, excess reagent (phosphorus pentoxide) was used, and the results available did not allow any conclusion concerning scope or mechanism of the reaction.

We wish now to report about our observations on olefine-forming elimination of the amido group under acid catalysis, which seem to contribute to the general scope of this reaction: On refluxing cyclohexylamine with excess acetic anhydride in the presence of catalytic amounts of sulfosalicylic acid, cyclohexene was formed in good yield (over 70 %). Similar results were obtained with N-acetylcyclohexylamine. In the absence of an acid catalyst, the reaction did not proceed.

Analogously, various N-acyl derivatives of funtumine (3α-amino-5α-pregnan-20-one), i.e. N-acetylfuntumine

(Ia) (2); N-benzoylfuntumine (Ib), m.p. 219-220° C, $[\alpha]_D^{20}$ +90.5° (c 1.0, $CHCl_3$)*; and N-carbobenzoxyfuntumine (Ic), m.p. 135-137° C, $[\alpha]_D^{20}$ +74.5° (c 1.0, $CHCl_3$) were treated with acetic anhydride and sulfosalicylic acid in refluxing toluene as an inert solvent affording, under concomitant enol-acetylation of the 20-keto group, 20-acetoxy-5α-pregna-2,17(20)-diene (II), m.p. 150-153°, $[\alpha]_D^{20}$ +59° (c 1.0, $CHCl_3$), probably as a mixture of 17,20-cis- and -trans- forms. Omitting the isolation of the enol acetate II and hydrolyzing the crude reaction product directly with methanolic potassium hydroxide, we achieved excellent yields (over 75 %) of the known (2) 5α-pregn-2-en-20-one (III). (Probably, this substance is contaminated with a small unseparable admixture of the Δ^3-isomer, cf. (3,4,5).) In the absence of the acid catalyst, no reaction occured even at the temperatures of boiling xylene or acetic anhydride.

Analogous results were also shown for the similarly substituted derivatives of the androstane series: both 3α-carbobenzoxyamino-17β-acetoxy-5α-androstane (IVa), m.p. 164-166°, $[\alpha]_D^{20}$ +25.5° (c 1.1, $CHCl_3$), and 3α-acetamino--17β-acetoxy-5α-androstane (IVb) (6) gave 17β-acetoxy-5α--androst-2-ene (V) (7), and 3α-acetamino-5α-androstan-17--one (VI), m.p. 200-205°, $[\alpha]_D^{20}$ +114° (c 1.0, EtOH) afforded, after alkaline hydrolysis of the crude primary 17-enol

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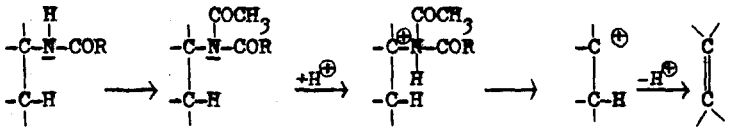
* Correct elemental analyses were obtained for all new substances; the described ones were identified by comparison with the respective authentic samples.

acetate, the known (8) 5α-androst-2-en-17-one (VII).

Additional light was thrown onto the possible mechanism of this elimination by the cleavage of N-acetyl derivatives of bornylamine (VIII) and neobornylamine (IX), which both gave rise to a neutral volatile fraction consisting of 87 (81) % of camphene (X), 9 (11) % of tricyclene (XI), 3 (1) %) of bornylene (XII) (and 6 % of an unidentified lower-boiling matter) as estimated by gas chromatography*.

On the basis of these results, we assume that the following reaction mechanism of a monomolecular acid-catalyzed elimination seems to be plausible: The amide group (A) is acetylated under the reaction conditions to give a secondary amide (B), which is in turn protonated, in a



A B C D E

fast reaction, on the nitrogen atom. The intermediate onium kation (C) dissociates then spontaneously into the carbonium ion (D), which stabilizes itself in the usual manner, known from the chemistry of acid-catalyzed dehydration, according to its individual character depending on the rest of the molecule. No decisive results concerning the fate of

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the nitrogen-containing portion have been achieved so far.

Under very favourable structural features enabling an additional weakening of the carbon-nitrogen bond, the formation of the secondary amide (B) is not indispensable, and the elimination of an acyl derivate of a secondary amine can occur as well. This was demonstrated by the cleavage of N-acetyl-3α-methylaminocholest-5-ene (XIII) (9), which afforded, though in moderate yield, cholesta--3,5-diene (XIV) (10). In this case, the elimination was probably favoured by the axial position of the amido group as well as by the ability of the intermediate to form a conjugated diene system. - On the contrary, the closely related 3α-methylamino-17β-acetoxy-5α-androstane (XVa), m.p. 87-90° C, $[\alpha]_D^{20}$ +59°, lacking the activating influence of the Δ^5-double bond, formed merely the corresponding N-acetyl derivative (XVb), but was not cleaved at all.

Another interesting example in support of the above mechanism was experienced with 3β-aminocholest-5--ene (XVIa) (11). Under the standard conditions, this substance was merely converted to its N,N-diacetyl derivative (XVIb), m.p. 165-166° C, $[\alpha]_D^{20}$ -21° (c 1.0, $CHCl_3$); this afforded, by a prolonged treatment, a moderate yield of 3β-acetoxycholest-5-ene (cholesterol acetate, XVII). This result is in accordance with the ability (12,13) of the original carbonium ion XVIII to be stabilized in a non--classical ionic structure XIX, which undergoes the sub-

sequent substitution reaction with the acetate anion. These three last mentioned examples allow to assume that the formation of the double bond occurs prior to a full development of a planar carbonium ion prefering thus a diaxial trans-elimination mechanism (cf. 14). In this way, the smooth elimination of the axial 3α- substituent contrasting with the limited reactivity of the 3β-amido group could be explained.

In view of the above considerations, it is not surprising that elimination of an amido group attached to a primary carbon atom did not take place. This was demonstrated with N-acetyl-n-octylamine, N-acetyl-n-dodecylamine, and ε-caprolactam, which all afforded only the corresponding higher acetylated products but not a trace of an olefin even under forcing conditions. Also, in the case of 3β-acetoxy-17β-acetamidoandrost-5-ene (XX) (15), where the amido group was linked to a cyclopentane ring, the elimination experiment was unsuccessfull. This failure can be explained by the usual resistance of the five-membered ring to form an endocyclic double bond; similarly, previous attempts (16) to eliminate an analogously situated hydroxyl group in this molecule were accompanied with rearrangements and led to deeper structural changes.

In the most general terms, the acid-catalyzed olefine-forming elimination of N-acyl (or N,N-diacyl) amides closely resembles that of analogous hydroxy derivatives, and follows similar rules. The basic character of the nitro-

gen atom is here suppressed by acylation to such an extent that the electron shift due to the protonation is sufficient enough to loose the carbon-nitrogen bond. The outlined general scheme is also consistent with the prior experience (1 and references cited herein): a very striking example in support of our hypothesis is the ready elimination of amido groups attached to a tertiary carbon atom (the "reverse Ritter reaction") (17).

Full experimental details of this work will appear at a later date in Coll. Czech. Chem. Comm.

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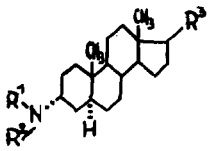
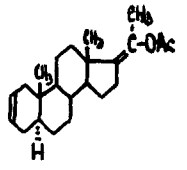
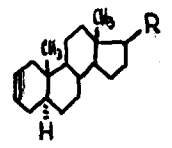


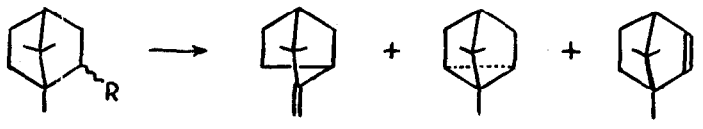
Ia R^1=H; R^2=Ac; R^3= β-$COCH_3$
Ib R^1=H; R^2=Bz; R^3= β-$COCH_3$
Ic R^1=H; R^2=$PhCH_2OCO$; R^3= β-$COCH_3$
IVa R^1=H; R^2=$PhCH_2OCO$; R^3= β-OAc
IVb R^1=H; R^2=Ac; R^3= β-OAc
VI R^1=H; R^2=Ac; R^3= =O
XVa R^1=Et; R^2=H; R^3= β-OAc
XVb R^1=Et; R^2=Ac; R^3= β-OAc



II

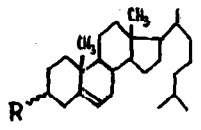


III R= β-$COCH_3$
V R= β-OAc
VII R= =O

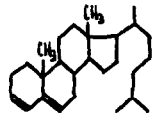


VIII R= α-NH_2
IX R= β-NH_2

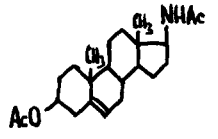
X XI XII



XIII R= α-$N\langle^{Me}_{Ac}$

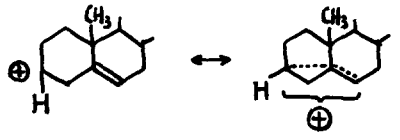


XIV



XX

XVIa R= β-NH_2
XVIb R= β-NAc_2
XVII R= β-OAc



XVIII XIX