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IMPROVED DEGRADATION OF N-NITROSOSOLASODINE TO PREGNANE DERIVATIVES

C.G. Bakker[1] and P. Vrijhof*

Diosynth B.V. (Akzo Pharma)
Organic Chemical Research Department
P.O. Box 20, Oss, The Netherlands

The Solanum spirosolane alkaloid solasodine (1) is a convenient starting material for the commercial synthesis of hormonal steroids[2]. Most degradations of solasodine (1) to 3β-hydroxypregna-5,16-dien-20-one-3β-acetate (7; 16-DPA) involve a 3,N-diacetylation, followed by a prototropic pseudomerization of the diacetate 4, oxidation of the 26-acetylaminofurosta-5,20(22)-diene derivative 15c and finally cleavage of the 16β-side chain moiety of 6 by treatment with boiling acetic acid to 7.

Another route to the degradation of spirosolane alkaloids to 20-oxopregnanes is the deamination of their N-nitroso derivatives in non-aqueous medium, followed by oxidation. The yield obtained with this route is only 30%[3].

In this paper we describe a potentially commercial synthesis of 16-DPA (7) via N-nitrososolasodine (2) and postulate a mechanism on the basis of isolated intermediates.

The N-nitroso-3-acetyl derivative 3 is prepared in almost quantitative yield according to known methods[4]. Conversion of 3 in acetic acid proceeds best under anhydrous conditions (with 5% acetic anhydride) and in the presence of a catalytic amount of p-toluenesulphonic acid at 45°C. At least 5 products are formed and after column chromatography with silica these were identified as (25R)-spirost-5-en-3β-ol-3β-acetate (8; diosgenine acetate, 8%), (22R)-22,25-oxidofurost-5-en-3β-ol-3β-acetate (9; 8%), (25R)-furosta-5,20(22)-diene-3β,26-diol-3β,26-diacetate (15b; 10%), furosta-5,20(22),25-trien-3β-ol-3β-acetate (16; 20%) and furosta-5,20(22)-diene-3β,25-diol-3β,25-diacetate (17b; 30%)[5]. In a direct synthesis starting with solasodine (1) the N-nitrosation, 3-acetylation, pseudomerization in acetic acid, oxidation with sodium dichromate and cleavage of the 16β-side chain are executed up to 16-DPA (7) pure (m.p. 172°-174°C) with 50% yield.

More insight in the mechanism of the isomerization and a higher overall yield are obtained when the reaction is carried out in methanol.

N-nitroso-3-acetylsolasodine (3; 10,95 g.) is suspended in 60 ml dry methanol at 65°C and 0,5 g. p-toluenesulphonic acid in 10 ml dry methanol is slowly added. After nitrogen evolution has ceased a clear solution results. The solution is neutralized with 1,0 g. of sodium acetate and the methanol is evaporated.

In the residue the following products can be detected: 2% diosgenine acetate (8) and mixtures of hemi-acetals and acetals resp. 12a and 12b (30%), 13a and 13b (15%), 14a and 14b (30%)[6]. When these mixtures were dissolved in acetic acid at 20°C more polar compounds were formed, as was noticed with t.l.c.. We postulate these intermediates to be the acylated hemi-acetals 12c, 13c and 14c. However we have not been able to isolate these labile intermediates and to confirm the configuration at C-22. By heating the acetic acid solution the furostadiene derivatives 15a, 16 and 17a[7] are formed. With this method the overall yield of the degradation of solasodine (1) to 16-DPA (7) is 60%.

Discussion.

The pseudomerization of 3 is an acid-catalyzed ring-opening of the N-nitroso-spiroaminoketal function. During this reaction the OH-group of the protonated nitroso function is directly shifted to C-22 without formation of a free carbonium ion. This is concluded from the retention of configuration at C-22 (22R) observed in the isolated diosgenine (8). The unstable diazonium ion 5 loses nitrogen and isomerization of carbonium ion 10 into 11 takes place (Demjanov rearrangement). In the weak nucleophilic acetic acid a considerable amount of ring closed products 8 and 9 is formed. With the more nucleophilic methanol the carbonium ions are rapidly captured and so ring closure is diminished. The hemi-acetals are slowly converted into the acetals with unknown configuration at C-22 (see footnote 11). The formation of carbonium ions 10 and 11 results in the 3 isomeric compounds 12a, 13a and 14a, which after dissolution in acetic acid at 20° are converted into acylated hemi-acetals 12c, 13c and 14c and at higher temperatures into the furostadiene derivatives 15a, 16 and 17a.

Acknowledgments.

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1. Research Fellow 1977-1978. Present address: Department of Organic Chemistry, Roman Catholic University, Nijmegen, The Netherlands.
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5. Analytical details:
   8 M.p. 196-198°. Identical with an authentic sample.
   9 M.p. 196-200° (lit. 192-195°)[8]. M.s.: $\frac{m}{e}$ 456 (M). IR (cm^{-1}; CCl_4): 1731 (C=O acetate).

PMR (δ in ppm, TMS as internal ref., $CDCl_3$): 0.79 s 18-CH_3, 0.96 d (J=7 Hz) 21-CH_3, 1.04 s 19-CH_3, 1.19 s $OCCH_3$, 1.34 s $OCCH_3$, 2.02 s $OCOCH_3$, 4.3-4.8 m 3α-H and 16α-H, 5.36 broad d (J=5 Hz) 6-H.

15b M.p. 100-102° (lit. 98-100°)[9]. M.s.: $\frac{m}{e}$ 498 (M). IR (cm^{-1}; CCl_4): 1732 (C=O acetate), 1690 (C=C,Δ^{20}). PMR (idem): 0.69 s 18-CH_3, 0.92 d (J=7 Hz) 27-CH_3, 1.03 s 19-CH_3. 1.58 s 21-CH_3, 2.02 s $OCOCH_3$, 2.04 s $OCOCH_3$, 3.91 d (J=7 Hz) 26-CH_2, 4.4-4.9 m 3α-H and 16α-H, 5.36 broad d (J=5 Hz) 6-H.

16 M.p. 113-118° (lit. 126-131°)[10]. M.s.: $\frac{m}{e}$ 438 (M). IR (cm^{-1}; CCl_4): 3080 (=CH_2), 1730 (C=O acetate), 1690 (C=C,Δ^{20}), 1648 (C=C,Δ^{25}), 895 (=CH_2). PMR (idem): 0.70 s 18-CH_3, 1.03 s 19-CH_3, 1.60 s 21-CH_3, 1.72 s 27-CH_3, 2.02 s $OCOCH_3$, 4.4-4.9 m 3α-H and 16α-H, 4.70 broad s 26-CH_2=, 5.38 broad d (J=5 Hz) 6-H.

17b M.p. 126-130°. M.s.: $\frac{m}{e}$ 498 (M). IR (cm^{-1}; CCl_4): 1730 (C=O acetate), 1691 (C=C,Δ^{20}) PMR (idem): 0.69 s 18-CH_3, 1.04 s 19-CH_3, 1.44 s $OC(CH_3)_2$, 1.58 broad s 21-CH_3, 1.98 s $OCOCH_3$, 2.03 s $OCOCH_3$, 4.4-4.9 m 3α-H and 16α-H, 5.35 broad d (J=5 Hz) 6-H.

6. Only the relevant spectroscopic data are given. Further analogous to the structures given in footnote 5.

Mixture 12a and 12b:
M.s.: $\frac{m}{e}$ 470 (M- H_2O or CH_3OH). IR(cm^{-1}; CCl_4): 3608 (OH), 2833 (OCH_3), 1103 (OCH_3). PMR (δ in ppm, TMS as internal ref., $CDCl_3$): 3.12 s 22-OCH_3 (30% present), 3.29 s 26-OCH_3, 3.18 probably d, hidden by singlets 26-CH_2.

Mixture 13a and 13b:
M.s.: $\frac{m}{e}$ 470 (M), $\frac{m}{e}$ 456 (M), $\frac{m}{e}$ 438 (M- H_2O or CH_3OH). IR (idem): 3607 (OH), 3080 (=CH_2), 1649 (C=C,Δ^{25}). PMR (idem): 1.75 broad s 27-CH_3, 3.14 s 22-OCH_3 (30% present), 4.65 broad s 26-CH_2=.

Mixture 14a and 14b:
M.s.: $\frac{m}{e}$ 470 (M- H_2O or CH_3OH). IR (idem): 3608 (OH), 2834 (OCH_3), 1091 (OCH_3). PMR (idem): 1.14 s $OCCH_3$, 1.17 s $OCCH_3$, 3.15 and 3.17 2s 22-OCH_3 (90% present)[11], 3.28 s 25-OCH_3.

7. 15a. M.p. 97-100°. M.s.: $\frac{m}{e}$ 470 (M).
17a. M.p. 129-132°. M.s.: $\frac{m}{e}$ 470 (M).
Structural data analogous to 12ab, 14ab, 15b and 17b.

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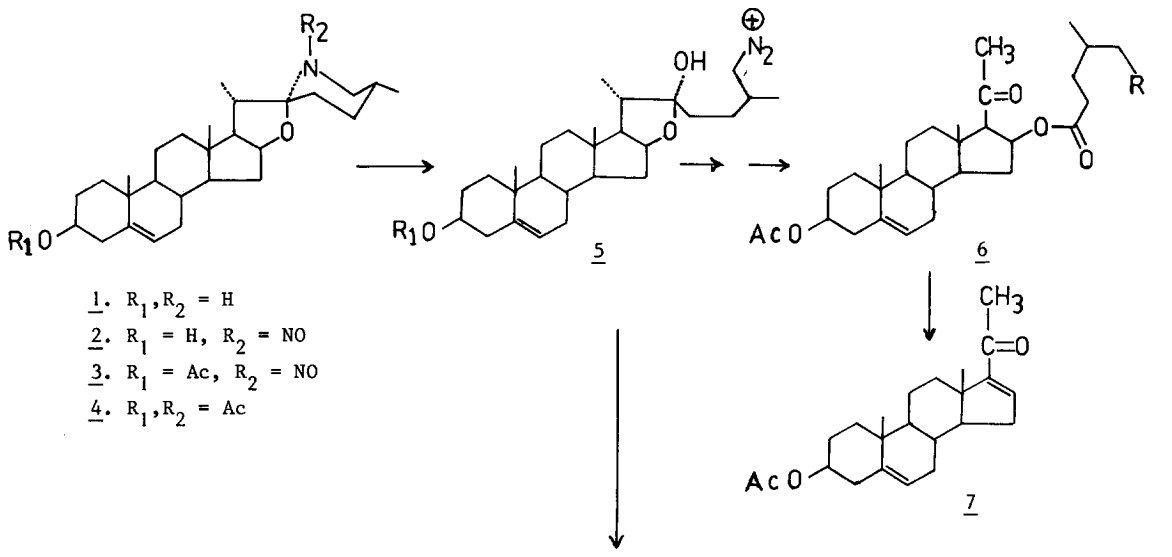
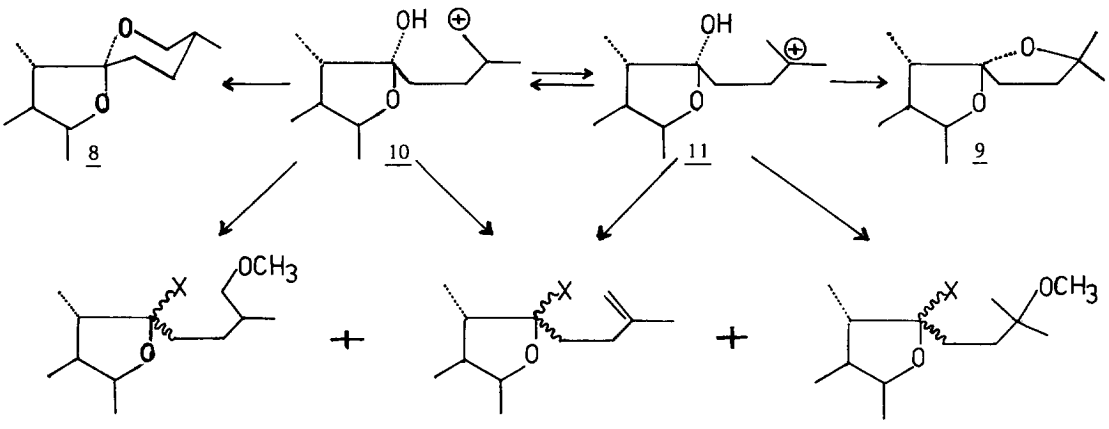
11. Probably a mixture of 22S and 22R derivative. The almost complete formation of the acetal 14b is incomprehensible.



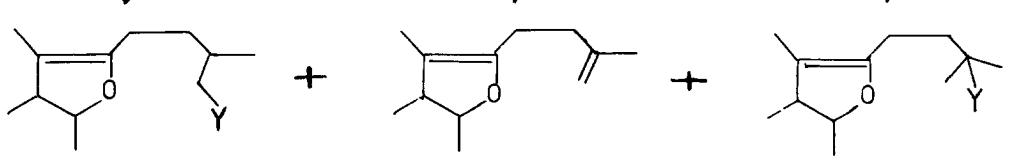
1. R_1, R_2 = H
2. R_1 = H, R_2 = NO
3. R_1 = Ac, R_2 = NO
4. R_1, R_2 = Ac



12a (22R, X = OH)
b (X = OCH_3)
c (X = OAc)

13a (22R, X = OH)
b (X = OCH_3)
c (X = OAc)

14a (22R, X = OH)
b (X = OCH_3)
c (X = OAc)



15a (Y = OCH_3)
b (Y = OAc)
c (Y = NHAc)

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17a (Y = OCH_3)
b (Y = OAc)

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