116. Steroids and Sex Hormones.

Part 245[1])

Partial Synthesis of Batrachotoxinin A

Preliminary communication[2])

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(23. 3. 72)

Zusammenfassung. Im Rahmen der vorliegenden Mitteilung wird über den erstmaligen partialsynthetischen Aufbau des Steroidalkaloids Batrachotoxinin A (**23**) [4] berichtet. Als Ausgangsmaterial der Synthese diente das 20-Oxo-pregnan-Derivat **2**, das von uns bereits früher [3] aus dem 18,20-Lacton **1** [2] dargestellt worden ist.

We have already described the 13-stage conversion of the lactone **1** [2] into compound **2** [3], the starting material for a synthesis of the steroidal alkaloid batrachotoxinin A (**23**)[3]), along lines developed in the course of earlier investigations [1] [5–7]. We now report the partial synthesis of batrachotoxinin A (**23**)[3]).

Compound **2** was acetylated under drastic conditions to give the triacetate **3**[4]), which was converted in two stages by repeated bromination (N-bromsuccinimide) and dehydrobromination *via* enone **4** into the dienone **5**. This could be selectively oxidized to the 14β,15β-epoxy derivative **6** by means of *p*-nitroperbenzoic acid. Catalytic hydrogen transfer (cyclohexene-Pd on $BaSO_4$) [6] then led to the 14β-hydroxy compound **7**, which was hydrolysed to the 14,18-diol **8**. Reaction with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid gave a quantitative yield of the acetonide **9**, which could be reduced with $NaBH_4$ in methanol at $-30°$ to the (20*S*)-alcohol **10**[5]) (60% yield[6])). The crude acetylation product **11** was converted by the usual acid treatment (*p*-toluensulfonic acid in methanol) into the 14,18-diol **12**, which was oxidized (dimethylsulfoxide/acetic anhydride [10] [1]) to the aldehyde **13**. The 18-N-methylamino group was now introduced by reacting **13** with methylamine at 80° and reducing the product **14**[7]) with $NaBH_4$ (→**15**)[7]). The crude product was converted into the chloroacetate **16**[7]) and subsequently into the free 14β-hydroxy derivative **17** by treatment with HCl in methanol (yield **12** → **17** ca. 60%).

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[1]) For part 244, see [1].

[2]) Full paper: Helv., in preparation.

[3]) For isolation and structure elucidation of **23** see [4].

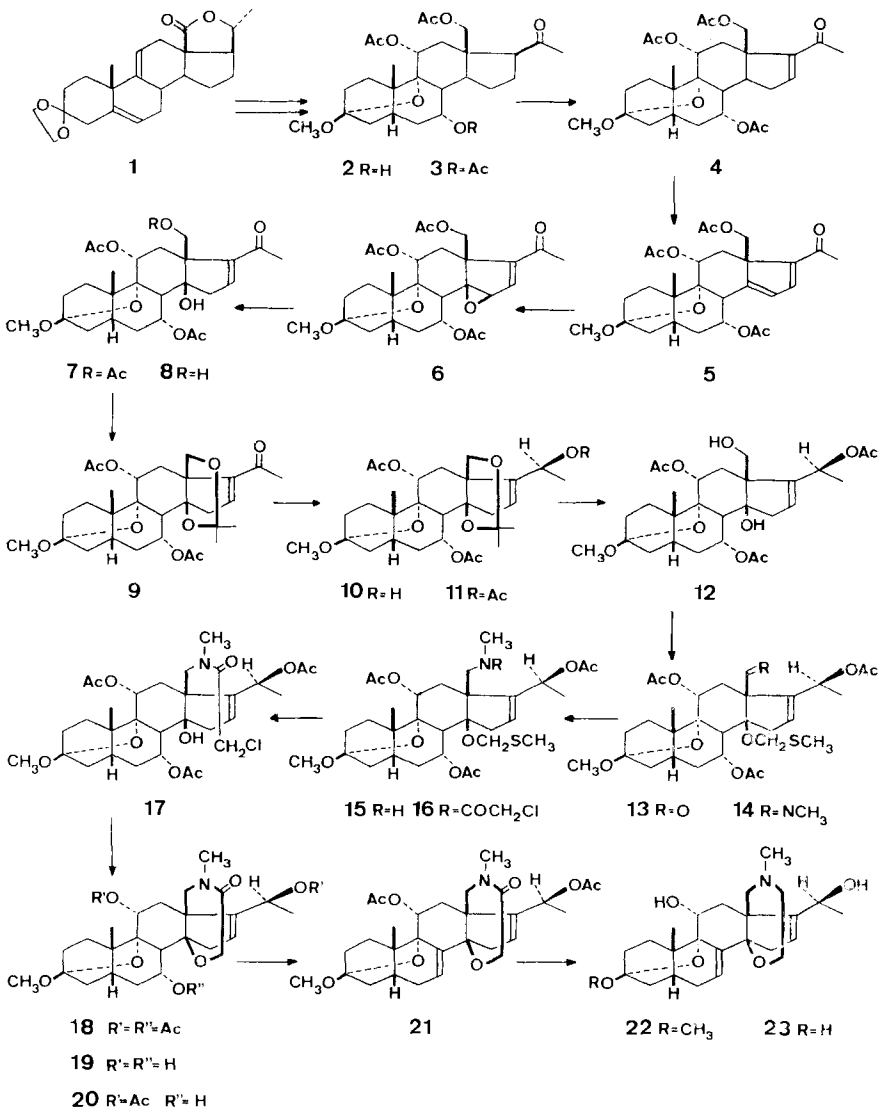
[4]) The new compounds were characterized by IR., NMR., and MS., and optical rotations. Satisfactory elemental analyses have been obtained for all crystalline derivatives.

[5]) The (20*S*)-configuration of **10** follows from transformation into **23**, whose structure and configuration have been established by X-ray analysis [8].

[6]) Beside **10** the (C-20)-epimeric compound was obtained (25% yield) and was reoxidized to **9** by MnO_2 [9].

[7]) Compounds **14–16** were not isolated.

The hydroxylactam **20** was then obtained by usual reaction of **17** with NaH (→**18**) [1] [5] [7] followed by direct base hydrolysis (→**19**) and subsequent acetylation at room temperature [yield **17** → **20**: 70%; IR.: 3510, 1730, 1635, 1240 cm^{-1} ($CHCl_3$); NMR. among other signals δ = 2.84 + 3.97, 2*d*, *J* = 14, CH_2(18), 3.07, *s*, NCH_3, 4.04 + 4.29,



2*d*, *J* = 18 CH_2(1') ($CDCl_3$ + D_2O)]. Compound **20** was dehydrated with thionyl chloride in pyridine at room temperature to give the doubly unsaturated lactam **21** [NMR.: among other signals δ = 5.96 + 6.16, 2*m*, CH(16) + CH(7)], which has not so far been crystallized. Reduction with $LiAlH_4$ in boiling ether gave amorphous 3-O-Methyl-batrachotoxinin A (**22**) [NMR.: among other signals δ = 0.88, *s*, CH_3(19),

1.42, *d*, $J = 7$, $CH_3(21)$, 2.36, *s*, NCH_3, 2.70, *s*, $CH_2(18)$, 3.30, *s*, 3-OCH_3,, 3.84, *d*, $J_{11,12\alpha} = 7$ (further splitting by $J_{11,12\beta} = 4$) CH(11), 4.45, *q*, $J = 7$ CH(20), 5.67, *t*, $J = 2$ CH(16), 6.25, *d*, $J_{6\beta,7} = 6$ (further splitting by $J_{6\alpha,7} = 2$) CH(7) ($CDCl_3 + D_2O$), identical according to MS. and thin-layer chromatography (3 different systems) with a sample prepared from natural batrachotoxinin A (**23**) by HCl/methanol treatment[8]). Finally **22** was converted (*p*-toluenesulfonic acid) to **23**, identical with natural batrachotoxinin A[8]) according to IR., NMR.[9]), MS., and thin-layer chromatography.

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[8]) A generous gift of natural batrachotoxinin A (**23**) by Professor Dr. *B. Witkop*, National Institutes of Health, Bethesda/USA, is gratefully acknowledged.

[9]) The NMR. spectrum for both natural[8]) and synthetic batrachotoxinin A is as follows: $\delta =$ 0.88/*s* CH_3-19, 1.40/*d*/$J = 7$ CH_3-21, ca. 2.00–4.20/several *m* CH_2-1′+CH_2-2′, 2.32+3.21/2*d*/$J_{15,15} = 19$ (further splitting by $J_{15,16} = 2$) CH_2-15, 2.35/*s* NCH_3, 2.71/*s* CH_2-18, 3.78/*d*/$J_{11,12\alpha} = 9$ (further splitting by $J_{11,12\beta} = 4$) CH-11, 4.46/*q*/$J = 7$ CH-20, 5.66/*t*/$J = 2$ CH-16, 6.24/*d*/$J_{6\beta,7} = 6$ (further splitting by $J_{6\alpha,7} = 2$) CH-7 ($CDCl_3 + D_2O$), somewhat different from the original description [4].

117. Le blocage de la lysine par la réaction de Maillard
II. Propriétés chimiques des dérivés N-(désoxy-1-D-fructosyl-1) et N-(désoxy-1-D-lactulosyl-1) de la lysine

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Summary. Lysine is often inactivated by 'Maillard-type' reactions in food proteins; the values obtained for it by different methods cannot be compared because the chemical behaviour of inactivated lysine is unknown. In this paper, the behaviour of an important form of inactivated lysine, namely its 1-deoxyketosyl derivatives, during acid hydrolysis as well as on the different assays for available lysine (F-DNB, TNBS, pipsylchloride and guanidination) is studied. The relative proportions of regenerated lysine and of formed furosine and pyridosine are established as a function of the conditions of hydrolysis. The validity of the methods used to estimate available lysine from its 1-deoxyketosyl derivatives is discussed.