SYNTHESIS OF INDOLIZIDINE AZASTEROIDS

Jacek W. Morzycki* and Władysław J. Rodewald
Department of Chemistry, University of Warsaw,
02093 Warszawa, Poland

Abstract - A synthesis of some indolizidine azasteroids (hydroxylactam 4, unsaturated lactam 5, aldehyde 6, diol 8 and imide 9)‡ by contraction of ring B in unsaturated lactam 1 is described.

In our previous communication[1] we described, among others, a convenient route to the synthesis of unsaturated lactam 1. Now we report ring B contraction in this compound. We hope that some azasteroids containing an indolizidine system could possess interesting biological activity.

Hydroxylation of unsaturated lactam 1 with osmium tetroxide yielded a single product - diol 2 (m.p. 144-145°C, $[\alpha]_D^{25}$ +33.3°). Inspection of Dreiding models of compound 1 showed that it may exist in two rigid conformations. However, only one of them has the lactam carbonyl and the double bond in approximately the same plane therefore permitting effective interaction of the nitrogen lone pair orbital and the π-orbitals of the adjacent unsaturated atoms. A strong absorption at 237 nm confirms the planar character of the -CO-N-CH=CH- grouping. In such a conformation rings C and D (particularly the axial protons 9α-H and 14α-H) considerably hinder OsO_4 attack from the α side of the steroid molecule. In accordance with this the obtained cis-diol 2 has the β-configuration of hydroxyl groups (in ^{1}H-NMR spectrum C-19 methyl protons resonance was strongly shifted downfield to δ1.49 by β-substituents at C-6 and C-7).

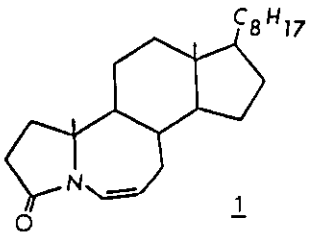
Reaction of 2 with periodic acid gave seco-aldehyde 3 (an oil, $[\alpha]_D^{17}$ +69.7°), which in turn was converted into the indolizidine system by two methods. On heating 3 with concentrated hydrochloric acid in dioxane solution a cyclization of ring B took place and unsaturated aldehyde 6 (m.p. 117-119°C, $[\alpha]_D^{17}$ +92.5°) was obtained in

‡ Yields of all transformations described were over 70%.

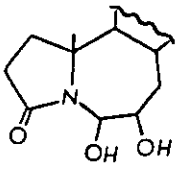
good yield. The highly conjugated structure 6 was indicated by its absorption band at 291 nm.

Reaction of seco-aldehyde 3 with potassium hydroxide in dioxane under reflux afforded hydroxylactam 4 (amorphous solid, $[\alpha]_D^{25}$ +17.9°), the product being isolated directly from the reaction mixture without acidification. During the course of the reaction loss of the N-formyl group occurs to give seco-aldehyde 7 which undergoes rapid cyclization to compound 4 (the 2-pyrrolidinone ring is quite resistant towards basic hydrolysis). The β-configuration of the hydroxyl group in hydroxylactam 4 was deduced from its ^{1}H-NMR spectrum. The chemical shift of C-19 methyl protons (δ1.43) as well as a narrow signal of 6α-H (δ5.54, $\frac{w}{2}$ = 9 cps) indicated a β-position (axial) of a hydroxyl group at C-6. In the case of acid work-up (HCl aq) of the reaction mixture or treatment of compound 4 with an acid, dehydrated product 5 (m.p. 103°C, $[\alpha]_D^{17}$ -30.4°) was obtained in good yield. Dehydration (complete or partial) under acidic conditions is a common feature of hydroxylactams[1-3]. The UV absorption band of 5 was shifted, in comparison with 1, to a longer wavelength (247 nm). Oxidation of hydroxylactam 4 with ruthenium tetroxide afforded the known compound - imide 9, (m.p. 159°C, $[\alpha]_D^{19}$ +34.5°; lit.[4] m.p. 159°C, $[\alpha]_D^{25}$ +40.8°).

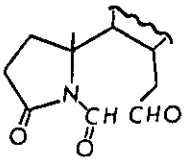
An alternative route to the synthesis of indolizidine azasteroids provided a rearrangement of diol 2 proceeding under basic conditions. During heating of compound 2 in boiling dioxane with potassium hydroxide a formation of isomeric diol 8 (m.p. 190-192°C, $[\alpha]_D^{19}$ -11.0°) containing a 6-membered ring B took place in almost quantitative yield. It is well known[5,6] that hydroxylactams exist in equilibrium with the so-called open form i.e. seco-aldehyde 10. In this tautomeric equilibrium the structure 2 is by far the preferred form. However, the open form 10 is stabilized in alkaline medium and furthermore undergoes a rearrangement via enol 11 to hydroxyketone 12. This conversion (10→12) is similar to the often observed isomerizations in carbohydrate chemistry (for instance: glucose→fructose). The 2-pyrrolidinone ring remained intact during reaction. At the last step of the reaction hydroxyketone 12 cyclized to diol 8. The configuration of substituents at C-6 in diol 8 was established on the basis of its ^{1}H-NMR spectrum. The C-19 methyl protons resonance was strongly deshielded (δ1.46), probably as a result of its 1,3-diaxial relationship with the hydroxyl group at C-6. The equatorial $-CH_2OH$ grouping gave three signals at δ: 5.46 (dd, J_{H_A-OH} = 12 cps, J_{H_B-OH} = 4.5 cps, O-H),


C_8H_{17}
N
O

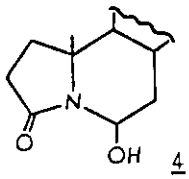
1


N
O
OH
OH

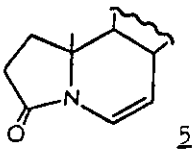
2


N
CH
CHO
O
O

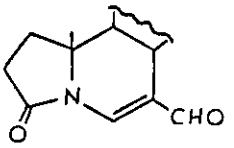
3


N
O
OH

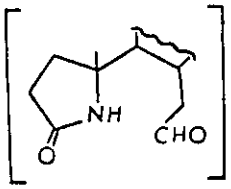
4


N
O

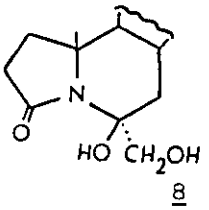
5


N
CHO
O

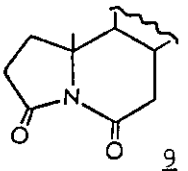
6


NH
CHO
O

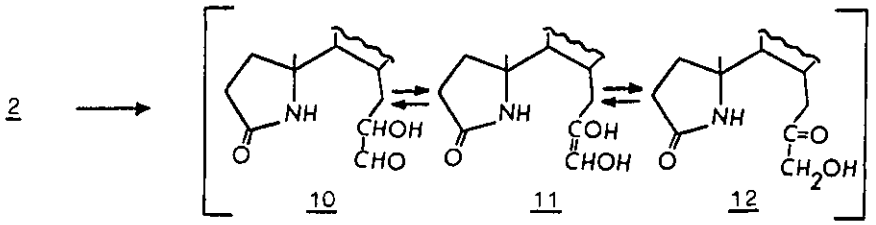
7


N
O
HO
CH_2OH

8


N
O
O

9


2
NH
CHOH
CHO
O
10
NH
COH
CHOH
O
11
NH
C=O
CH_2OH
O
12
8

3.83 (dd, $J_{H_A-H_B}$ = 12 cps, J_{H_B-OH} = 4.5 cps, $-CH_A\underline{H}_B-OH$) and 3.12 (t, $J_{H_A-H_B}$ = = J_{H_A-OH} = 12 cps, $-C\underline{H}_AH_B-OH$). The unusually well resolved O-H signal at δ5.46 disappeared upon shaking the sample with D_2O and at the same time the methylene protons gave a normal AB system. This primary hydroxyl group is likely to be intramolecularly H-bonded. Compound 8 exhibited a sharp absorption band at 3483 cm^{-1} in dilute CCl_4 solution and a relatively high mobility by thin layer chromatography (silica-gel). To definitively confirm the assigned structure the oxidation of 8 with periodic acid was carried out. The product hereby obtained, imide 9, was identical with its authentic sample[4].

References

1. J. W. Morzycki, W. J. Rodewald, Heterocycles, preceding communication.
2. N. J. Doorenbos, C. L. Huang, C. R. Tamorria, M. T. Wu, J. Org. Chem., 26, 2546 (1961).
3. J. C. Hubert, J. B. P. A. Wijnberg, W. N. Speckamp, Tetrahedron, 31, 1437 (1975).
4. W. J. Rodewald, J. Wicha, Roczniki Chem., 40, 1069 (1966).
5. J. J. J. de Boer, W. N. Speckamp, Tetrahedron Letters, 1975, 4039.
6. R. E. Valter, Usp. Khim., 42, 1060 (1973).

Received, 10th March, 1981