SYNTHESIS OF 17β-PYRIDYL- AND 17β-PYRIDONYL-ANDROSTANE DERIVATIVES

Jerzy Wicha * and Marek Masnyk
Institute of Organic Chemistry of the Polish Academy of Sciences,
Kasprzaka 44, 01-224 Warszawa, Poland

Abstract - Bufadienolide analogues 11 - 14 were synthesized from the 17-oxocompound 3.

The medical utility of cardenolides and bufadienolides [1] (examplified by digitoxigenin 1 and bufalin 2 correspondingly) stimulated interest in the synthesis and chemical modifications of these compounds. [2] Recently it has been found that for cardiotonic activity of steroids the presence of the 17β-side chain containing moiety $-\overset{|}{C}=\overset{|}{C}-\overset{\vdots}{C}\equiv A$, where A is oxygen or nitrogen, rather than the presence of lactone ring is prerequisite. [3] Little is known, however, about the biological activities of nitrogen bufadienolide derivatives which comprise this structural element. [4] It appeared of interest, therefore, to develop a method of synthesis of pyridyl- and pyridonyl-bufadienolide analogues from easily available starting material. In the present communication we wish to report the synthesis of pyridine 11, and α-pyridone derivative 14 starting from the 17-oxocompound 3.

In the first approach to the synthesis of pyridone 14 the route involving the pyridine derivative 11 was examined. Ketone 3 was treated (-78°, ether-THF) with 3-pyridyllithium [5] and the reaction product was separated into basic and neutral fractions. From the basic fraction pyridylcarbinol 4 [6] was obtained (28-35% yield); the neutral fraction contained the starting material (30-50% of initial amount) and 17-n-butyl-carbinol 5 [6] (5-15% yield). The alcohol 4 was dehydrated (thionyl chloride - pyridine, 0° to 5°, 18h) to the unsaturated derivative 7 [6] (50% yield), which on hydrogenation over platinium catalyst (in ethanol) furnished 3β-methoxy-17β-(3'-pyridyl)-5α-androstane 11 [6] (60% yield). The expected β-orientation of pyridine ring in compound 11 is confirmed by the ^{13}C NMR spectra of this compound in which the signal for C_{18} appears at δ 12.8 ppm, and in relation to 3β-hydroxyandrostane acetate (C_{18} at 17.5 ppm) shows a typical „gamma" effect [7]

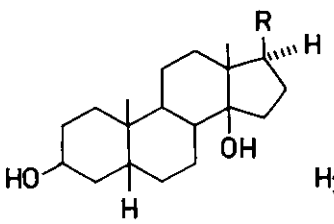
The pyridine derivative 11 was oxidized with m-chlorobenzoic acid (1.5

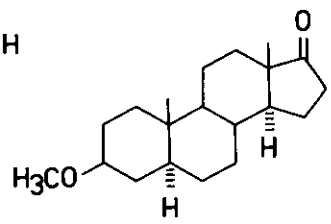
equiv., methylene chloride, 0°, 15h). The N-oxide 12 [6] thus obtained (quantitative yield) was heated with acetic anhydride (reflux, 3h), and the resulting product was hydrolyzed to the mixture of pyridones (83% yield). The mixture was separated by preparative TLC(4 developments benzene - chloroform - methanol, 4.5:4.5:1) to pure compounds 13 [6] (more mobile) and 14 in almost equal amounts. The structures of compounds 13 and 14 were ascribed on the basis of their pmr spectra in which protons of pyridone ring appeared: for 13 at δ6.13 ppm, triplet, J=4 Hz (1H, C_{23}-H, steroid numbering), δ7.27 multiplet (2H, C_{22}- and C_{24}-H), for 14 at δ6.52, doublet, J=10 Hz (1H, C_{23}-H), 7.20, doublet, J=2 Hz (1H, C_{21}-H) and 7.40 doublet of doublets J=10 and J=2 Hz (1H, C_{22}-H). It should be noted, that α-pyridone derivatives of type 13 can not be obtained by amminolysis of natural bufadienolides.

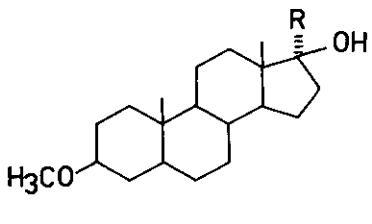
The further experiments were directed towards specific synthesis of "bufadienolide like" pyridone 14. The ketone 3 was treated with 6-bromo-3-pyridyllithium [8] to give bromopyridyl-carbinol 6 [6] (50% yield). The bromo-compound 6 was heated in acetic acid in the presence of potassium acetate (34h) followed by water work-up and neutralization with sodium hydrogen carbonate. At these conditions dehydration and substitution of bromine by hydroxyl took place to give the pyridone 10 [6] (80% yield) having a double bond at C-16. Careful hydrogenation of 16,17-double bond (5% palladium on carbon, ethanol) gave saturated pyridone (72% yield) identical with the sample previously obtained. Alternatively, dehydration of carbinol 6 to olefin 8 [6] was accomplished with thionyl chloride in pyridine (0°to 5°,18h,60% yield) and the compound 8 was transformed to pyridone 10 [6] (80% yield) by means of acetic acid - potassium acetate.

Finaly, we synthesized the pyridone 14 via the alternate pathway which does not involve oxidative or acid induced transformations. Bromopyridine derivative 8 was reacted with sodium benzylate in benzyl alcohol (150°, 12h) to give benzyl ether 9 [6] (90% yield). Catalytic hydrogenation of compound 9 (5% palladium on carbon, ethanol - THF) lead to saturation of its 16,17-double bond and hydrogenolysis of benzyl ether moiety to give pyridone 14 (58% yield) identical with the sample previously obtained.

The work on synthesis of pyridine and pyridone analogues of 14β-hydroxybufadienolides is in progress. [9]







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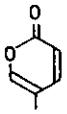
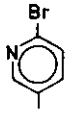
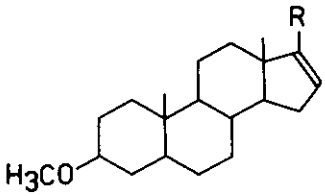
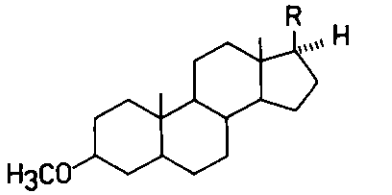
2 R = 

6 R = 





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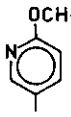
9 R = 

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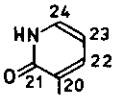
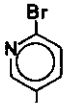
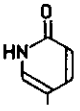
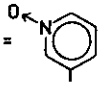
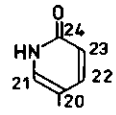
13 R = 

8 R = 

10 R = 

12 R = 

14 R = 

REFERENCES AND FOOTNOTES

1) These compounds show wide spectrum of pharmacological activity, among others cardiotonic and cytostatic.

2) For the leading references see: L.F.Fieser and M.Fieser,"Steroids",Reinhold Publishing Corp.,New York,1959, Chapter 20; F.Sondheimer, Chem.Brit.,1965,1,454; T. Thomas, J.Boutagy and A.Gelbart, J.Pharm.Sci.,1974,63,1648

3) For review see: Th.W.Günter and H.H.Linde,Experientia,1977,33,697

4) The report on the preparation and activity of some pyridone derivatives of bufadienolides is given by R.Megges, H.Timm, H.J.Portius, E.Glusa and K.Repke Pat.GDR 129795 (Feb.8,1978), see also F.C.Uhle and H.Schröter, J.Org.Chem.,1961, 26,4169

5)H.Gilman and S.M.Spatz,J.Org.Chem., 1951,16,1485

6)All new compounds obtained had satisfactory combution analyses or high resolution mass spectra. NMR spectra were taken in $CDCl_3$ solution on Jeol 100MHz (6,8-14) and Bruker HX-270MHz(4,7);values are given in ppm; 4,mp 179-80°, δ 8.50 (1H,d,$J_{21,22}$=1.6Hz,C_{21}-H), 8.44(1H,dd,$J_{24,23}$=5Hz,$J_{24,22}$=1.2Hz,C_{24}-H), 7.52(1H, dq,$J_{22,23}$=9Hz,$J_{22,21}$=1.6Hz,$J_{22,24}$=1.2Hz,C_{22}-H), 7.23(1H,dd,$J_{22,23}$=9Hz,$J_{23,24}$=5Hz, C_{23}-H),1.06(3H,s) and 0.79(3H,s) angular CH_3; 5,mp 117-119°; 6,mp 231-232°, δ 8.25(1H,d,J=3Hz,C_{21}-H), 7.61(1H,dd,$J_{22,23}$=8Hz,$J_{22,21}$=3Hz,C_{22}-H), 7.40(1H,d,J=8Hz, C_{23}-H), 1.16(3H,s) and 0.89(3H,s) angular CH_3; 7,mp 101-103°,δ 8.62(1H,d,$J_{21,22}$= 2Hz,C_{21}-H),8.45(1H,dd,$J_{24,23}$=5Hz,$J_{24,22}$=1,3Hz,C_{24}-H), 7.64(1H,dt,$J_{22,23}$=8Hz, $J_{22,24}$=1.3Hz,$J_{22,21}$=2Hz,C_{22}-H), 7.21(1H,dd,$J_{23,24}$=5Hz,$J_{23,22}$=8Hz,C_{23}-H), 5.97 (1H,t,J=2.4Hz,C_{16}-H),1.00(3H,s) and 0.85(3H,s) angular CH_3; 8,mp 146-147°,δ 8.35 (1H,d,J=2Hz,C_{21}-H), 7.51(1H,dd,$J_{22,23}$=9Hz,$J_{22,21}$=2Hz,C_{22}-H), 7.37(1H,d,J=9Hz,C_{23}- -H), 0.98(3H,s) and 0.84(3H,s) angular CH_3; 9,mp 157-159°,δ8.20(1H,d,J=2Hz,C_{21}- -H),7.57(1H,dd,$J_{22,23}$=9Hz,$J_{22,21}$=2Hz,C_{22}-H), 7.40(5H,m,-C_6H_5), 6.76(1H,d,J=9Hz, C_{23}-H), 5.85(1H,br.d,J=2Hz,C_{16}-H), 5.38(2H,s-O$CH_2C_6H_5$), 1.00(3H,s) and 0.87(3H, s) angular CH_3; 10,mp 220°(decomp.),δ7.50(1H,dd,$J_{22,23}$=10Hz,$J_{22,21}$=2Hz,C_{22}-H), 7.39(1H,br.s,C_{21}-H), 6.53(1H,d,$J_{23,22}$=10Hz,C_{23}-H), 5.74(1H,br.s,C_{16}-H), 0.93(3H, s) and 0.84(3H,s) angular CH_3; 11,mp 134-135°,δ8.44(2H,m,C_{21}- and C_{24}-H), 7.47 (1H,m,C_{22}-H), 7.18(1H,dd,J=8Hz,J=5Hz,C_{23}-H), 0.86(3H,s) and 0.52(3H,s) angular CH_3; 12,mp 242-246°,δ8.13(2H,m) and 7.16(2H.m) pyridine H, 0.82(3H,s) and 0.50 (3H,s) angular CH_3; 13,mp 265-268°; 14,mp 290-294°.

7)The authors are indebted to Dr. Helmut Duddeck for this measurement.

8)W.E.Parham and R.M.Piccirilli,J.Org.Chem.,1977,42,257

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