

Title	Synthesis of isomeric 5 α -androstane-3, 15, 17 β -triols
Sub Title	
Author	松井, 道夫(Matsui, Michio) 絹山, 優子(Kinuyama, Yuko)
Publisher	共立薬科大学
Publication year	1976
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.21 (1976.) ,p.104- 105
JaLC DOI	
Abstract	
Notes	抄録
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000021-0104

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Synthesis of isomeric 5 α -androstane-3,15,17 β -triols*

松井道夫, 絹山優子

MICHIO MATSUI and YUKO KINUYAMA

In a paper dealing with the biliary metabolites of testosterone sulphate in the rat, we reported the production of considerable quantities of disulphates of 5 α -androstane-3 α ,17 β -diol and polar hydroxylated steroids in the female. Gustafsson and Ingelman-Sundberg recently described the 15 β -hydroxylation of the 3,17-disulphates of 5 α -androstane-3 α ,17 β -diol and the corresponding 3 β -epimer in female rat liver microsomes. These results strongly suggest the occurrence of 15 β -hydroxylated steroids in biliary metabolites. As authentic standards, 5 α -androstane-3,15,17 β -triols were prepared by incubation of 15 α - and 15 β -hydroxyandrost-4-ene-3,17-dione with rat liver microsomes, and the respective trimethylsilyl ethers were subjected to glc-mass spectrometric analysis. Of the four isomeric 3,15,17 β -triols, 5 α -androstane-3 β ,15 α ,17 β -triol (15) has been prepared by Nussim and his co-workers. We now describe the synthesis of 5 α -androstane-3 α ,15 β ,17 β -triol(8), -3 β ,15 β ,17 β -triol(10), and -3 α ,15 α ,17 β -triol(13).

The 15 β -hydroxy-group has been introduced into the steroid nucleus by nucleophilic addition of a benzyl alcohol to a Δ^{15} -17-oxo steroid, followed by catalytic hydrogenolysis, and 15 α -hydroxysteroids have been prepared by hydroboration of Δ^{14} -steroids. We have applied these reactions to the synthesis of the 5 α -androstane-3,15,17 β -triols.

3 α -Acetoxy-16 α -bromo-5 α -androstan-17-one (1) was acetalised with ethylene glycol; dehydrobromination of the bromo-acetal (2) with potassium *t*-butoxide in refluxing xylene then gave the unexpected 3 β -epimerisation product, 3 β -hydroxy-5 α -androstan-15-en-17-one (3) (after hydrolysis of the acetal with toluene-*p*-sulphonic acid). The structure (3) was confirmed by catalytic hydrogenation to give 3 β -hydroxy-5 α -androstan-17-one (4), identical with an authentic sample. However, mild dehydrobromination of the bromo-acetal (2) with potassium *t*-butoxide in dimethyl sulphoxide at 37°C and subsequent deacetalisation provided a route to 3 α -hydroxy-5 α -androstan-15-en-17-one (5), catalytic hydrogenation of the 15,16-double bond affording 3 α -hydroxy-5 α -androstan-17-one (6). Base-catalysed addition of benzyl alcohol to the Δ^{15} -3 α -ol (5) followed by hydrogenolysis over palladium-charcoal gave 3 α ,15 β -dihydroxy-5 α -androstan-17-one (7), which was converted into the 3 α ,15 β ,17 β -triol (8) with sodium borohydride. Similarly, condensation of the Δ^{15} -3 β -ol (3) with benzyl alcohol and hydrogenolysis yielded 3 β ,15 β -dihydroxy-5 α -androstan-17-one (9), which was reduced

* 本報告はJ. Chem. Soc. Perkin I, 1429 (1976) に発表

with sodium borohydride to the $3\beta,15\beta,17\beta$ -triol (10).

3α -Hydroxy- 5α -androst-14-en-17-one (11), prepared by acid-catalysed epimerisation of the 4^{15} - 3α -ol (5), was reduced with sodium borohydride to give 5α -androst-14-ene- $3\alpha,17\beta$ -diol (12). Hydroboration followed by oxidation with alkaline hydrogen peroxide then afforded the $3\alpha,15\alpha,17\beta$ -triol (3). The $3\beta,15\alpha,17\beta$ -triol (15) was also prepared from 5α -androst-14-ene- $3\beta,17\beta$ -diol (14) by the hydroboration method.

The spectral properties of the isomeric $3,15,17\beta$ -triols are markedly affected by the configuration of the C-15 hydroxy-group. Molecular rotation analysis indicated that the 15α -ols [(13) and (15)] were more dextrorotatory than the 15β -epimers [(8) and (10)], in accord with other epimeric 15-hydroxy-steroids. The ^1H n.m.r. data showed a large downfield shift of the 13-methyl signal of the 15β -ols due to pseudo-1,3-diaxial deshielding by the 15β -hydroxy-group. The mass spectrometric fragmentations provided strong evidence for the configuration of the 15-hydroxy-group. Prominent ions at m/e 107 and 264 are characteristic of 15α -ols, whereas the mass spectra of the 15β -ols are dominated by fragments of m/e 107, 217, and 290. Generally the 15α -hydroxy-group confers greater polarity than does the 15β -hydroxy-group. Tlc showed that the 15β -ols were more mobile than the 15α -ols. Glc of the trimethylsilyl ether derivatives on 0.5% CHDMS (or 1.5% SE-30) gave retention times (relative to 5α -cholestane) of 0.34(0.70), 0.43 (0.71), 0.55 (0.90), and 0.68(0.99) for the $3\alpha,15\beta,17\beta$ -triol (8), the $3\alpha,15\alpha,17\beta$ -triol (13), the $3\beta,15\beta,17\beta$ -triol (10), and the $3\beta,15\alpha,17\beta$ -triol (15), respectively.