Tetrahedron Letters No.47, pp. 4673-4676, 1967. Pergamon Press Ltd. Printed in Great Britain.

STRUCTURE OF SPIROETHERS DERIVED FROM PRODUCTS OF THE YEAST FERMENTATION OF THE 3-METHOXY-14-SECO-D-HOMO-1,3,5(10),9(11)-ESTRATETRAENDIONE-14,17a

Leonid M.Kogan, V.E.Gulaya, I.V.Torgov

Institute for the Chemistry of Natural Compounds,
USSR Academy of Sciences, Moscow, U.S.S.R.

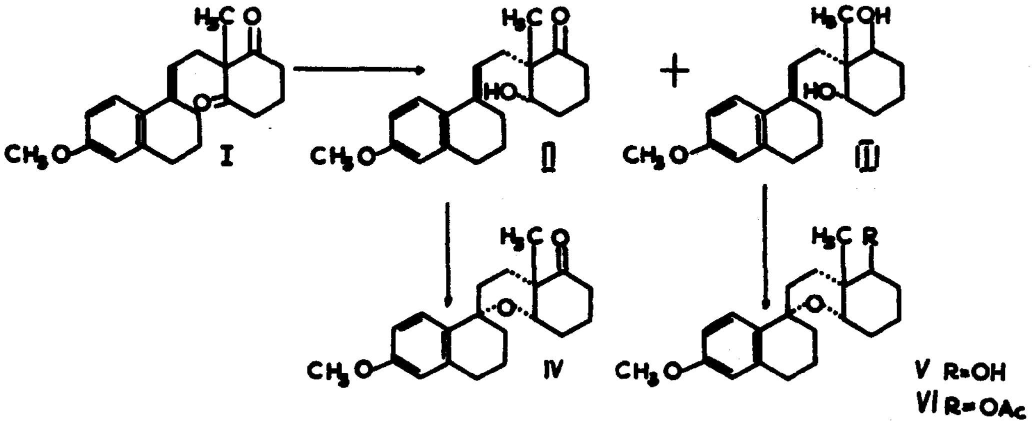
(Received in UK 2 August 1967)

It is widely known that the total synthesis of steroids leads to racemic compounds. Subsequent chemical or enzymic resolution into optical enantiomeres is accompanied by the loss of 50% of the substance.

Gibian, Kieslich et al./1,2/ in 1966 succeeded in transforming an optically inactive intermediate into d-estrone derivatives using microorganisms. This method gave an essential increase of the total yield of estrone because almost all the starting material was transformed into the compound of natural configuration, without l-compound formation. Mathieu and others /3/ had used Rhizopus arrhizus in the reduction of 2-methyl-2-(6'-carbomethoxy-3'-ketohexyl)-cyclopentandione-1,3 to an optically active ketol.

The application of microbial methods for the preparation of optically active D-homo steroids is of great significance /4/.

We carried out the reduction of 3-methoxy-8,14-seco-D-homo-1,3,5(10),-9(11)-estratetraendione-14,17a (I) to ketol (II) (oil, R_f=0,43) and diol (III), m.p. 125-131° /5/, $(\alpha)_D^{20}$ -13°; λ_{max} 262 mμ (ε 35200); ν_{max}^{muj} 3460 (OH); R_f=0,21 by yeasts particulary Saccharomyces carlsbergensis var.valdensis Dekker and baker's yeast.



Unlike corresponding hydroxy compounds with 5-membered ring D /6/, the ketol (II) and diol (III) are extremly unstable and rearrange into the chromatographically more mobile substances (IV) and (V) even on standing at room temperature (may be due to traces of acid in solvents).

The ketone (IV) has R_f=0,71, m.p. 149–153° (ethyl acetate), $(\alpha)_D^{20}$ −60°, λ_{max} 275, 282 mμ (ε 1800; 1750), ν_{max}^{mujol} 1708 (C=O), 1607 and 1590 (aromatic ring), 1090 cm^{-1} (C–O–C); NMR spectra: δ^{CDCl_3} 1,2 (18-CH$_3$), 3,76 (CH$_3$O–), 4,09 ppm (14-H); $\delta^{CDCl_3}_{40°}$: 1,12, 3,65 and 3,9 ppm; mol.w. 314.

The carbinol (V), oil, has R_f=0,53, $(\alpha)_D^{20}$ −33°, λ_{max} 276, 284 mμ (ε 1730; 1750), ν_{max}^{film} 3460 (OH), 1050 cm^{-1} (C–O–C); NMR spectra: δ^{CCl_4} 0,79 (18-CH$_3$), 3,6 (CH$_3$O–), 4,15 ppm (multiplet, 17-H); $\delta^{benzene}$ 0,76 (18-CH$_3$), 3,3 (CH$_3$O–), 3,5 (14-H), 4,1 ppm (multiplet, 17a-H), mol.w.316.

The usual acetylation of carbinol (V) gave acetate (VI), R_f=0,62, m.p. 145–148° (ethyl acetate), ν_{max}^{mujol} 1740 cm^{-1} (C=O in OCOCH$_3$); NMR spectra: δ^{CCl_4} 0,93 (18-CH$_3$), 2,0 (CH$_3$ in OCOCH$_3$), 3,72 (CH$_3$O–), 5,55 (multiplet, 17a-H); $\delta^{benzene}$ 0,87 (18-CH$_3$), 1,7 (CH$_3$ in OCOCH$_3$), 3,3 (CH$_3$O–), 3,55 (14-H), 5,8 (multiplet, 17a-H).

The structures of (IV) and (V) have been elucidated on the basis of the following considerations. The infrared spectrum of the ketone (IV) indicates the absence of hydroxy group. The lack of vinyl proton peaks in the n.m.r. spectra and infra red data confirm the structure of spiroether for the compound (IV). The oxygen is joined to 9-C-atom (and not to II-C-atom) because the area of the peak at 4,09 ppm (the proton on the oxygen-bearing carbon atom) corresponds to one proton. The narrow width (6 cps) of this signal indicates that 14-H is spin-coupled to the axial and equatorial protons at 15-C and has an equatorial configuration /7/. The downfield shift of the 18-methyl group proton resonance in (IV) is due to the neighbouring keto-group.

We have no direct experimental proof for the configuration at 9-C, but a tentative conclusion can be drown from Dreiding's models. Inspection of the models shows that the formation of spiroether with a thermodynamically more stable chair conformation of the heterocyclic ring is possible provided that the oxygen is joined in α-region (towards A-B rings).

As with the ketone (IV), the molecular weight, IR and NMR spectra of the carbinol (V) show the presence of an oxygen bridge between C-9 and C-14 and 17-hydroxygroup. The NMR spectrum of (V) in CCl_4 showed an unresolved multiplet at 4,15 ppm with the width 20 cps, that is in good agreement with the axial character of proton at 17a-C. A signal of the equaterial proton on another oxygen-bearing carbon atom was overlapped by the signal of the protons of the methoxy group, but it is revealed in the NMR spectrum of (V) in benzene. The large downfield shift of the multiplet resonance signal (δ = = 1,4 ppm) in spectrum of acetate (VI) from that of the alcohol (V) displays that the 17a-H is axial. The chemical shift of the 14-H resonance signal in alcohol (V) is just the same as in its acetate (VI).

The shift of 18-methyl group proton resonance signal (27 cps) in the ketone (IV) in comparison with that of the carbinol (V) is close to the shift observed for 1-keto- and 1-hydroxy-4,4-dimethyl-cholestanes /8/.

The structures of spiroethers (IV) and (V) confirmed definitely the structures of (II) and (III).

Acknowledgments. The authors are very grateful to Dr. N.T.Zelkova for fermentation, to Dr. V.F.Bistrov and Dr. V.I.Sheichenko for n.m.r. spectra, to Dr. B.Lacoume (University of Nancy) for helpful discussion.

References

1. H.Gibian, K.Kieslish, H.J.Koch, H.Kosmol, C.Rufer, E.Schröder, R.Vössing, *Tetrahedron Letters*, 2321 (1966).
2. H.Kosmol, K.Kieslish, R.Vössing, H.J.Koch, K.Petzoldt und H.Gibian, *Ann. Chem*. **701**, 198 (1967).
3. P.Bellet, G.Nominé, Y.Mathieu, *C.r.Acad.Sc.France*, **263**, 88 (1966).
4. S.N.Ananchenko, V.Ye.Limanov, V.N.Leonov, V.N.Rzheznikov, I.V.Torgov, *Tetrahedron*, **18**, 1355 (1962).
5. Melting points were determined in a Boetius block. Optical rotation values refer to chloroform solution (c=approx.I). The IR spectra were taken on UR-10 (Zeiss) spectrophotometer, and UV spectra in ethanol on an EPS-2 (Hitachi) spectrophotometer. NMR spectra were recorded on a JNM C-60 spectrometer. Chemical shifts are described in ppm downfield from the internal TMS reference. Thin layer chromatography was conducted on silica gel /9/ in benzene-acetone (4:1). The mol. weights were determined on MX-1303 mass spectrometer by Dr. V.L.Sadovskaya.
6. C.Rufer, E.Schröder und H.Gibian, *Ann.Chem.* **701**, 206 (1967).
7. N.S.Bhacca, D.H.Willams, "*Applications of NMR spectroscopy in organic chemistry*", Holden-Day, San Francisco, p.80 (1964).
8. F.Hemmert, A.Lablache-Combier, B.Lacoume, *Bull.Soc.Chim.France*, 982 (1966).
9. I.I.Zaretskaya, L.M.Kogan, O.B.Tikhomirova, I.V.Torgov, *Chimia Prirodnich Soedinenii* (Russian), **5**, 321 (1966).