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A PRACTICAL SYNTHESIS OF ANTHERIDIOL

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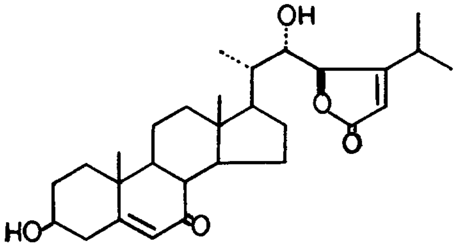
We wish to report the synthesis of stereochemically pure antheridiol (1), the sex hormone of the fungus Achlya, in an overall yield of approximately 20% from a readily accessible C_{22} aldehyde. An earlier communication[1] described the preparation of the 3-acetate of 7-deoxy-7-dihydroantheridiol (2) and the corresponding diol (3). Repetition of the aldol condensation under slightly different conditions gave a 70% yield of (2) and a 5% yield of (3).[2] The product (2) was resolved by chromatography on silica gel and fractional crystallisation into (in order of decreasing rf on tlc with ethyl acetate/petroleum ether) the 22S, 23R isomer [mp 164-166°; ir (KBr) 1760 (shoulder) 1733 cm^{-1}; nmr δ ($CDCl_3$) .70 (18-H), 1.02 (19-H), 1.17, 1.22 (pair of d, J 6.5 Hz, 26- and 27-H), 2.03 (acetate) 3.61 (d, J 9 Hz, 22-H), 4.94 (d, J 9 Hz, 23-H), 5.4 (m, 6-H), 5.78 (t, J 1 Hz, 28-H)] the 22R, 23S isomer [mp 219-223°; ir 1818 (w), 1767 (s), 1739 (w), 1715 (s) cm^{-1}; nmr δ .72 (18-H) 1.03 (19-H), 1.05 (d, J 6.5 Hz, 21-H), 1.18, 1.23 (pair of d, J 7 Hz, 26- and 27-H), 2.03 (acetate) 3.6 (d, J 8.5 Hz, 22-H), 4.91 (d, J 8.5 Hz, 23-H), 5.4 (m, 6-H) and 5.77 (t, J 1 Hz, 28-H] the 22R, 23R isomer [mp 202-208°; ir 1760, 1733 cm^{-1}; nmr δ .73 (18-H), 1.03 (19-H), 1.13 (d, J 6 Hz, 21-H), 1.17, 1.25 (pair of d, J 7 Hz, 26- and 27-H), 2.03 (acetate), 3.9 (broad peak, 22-H), 4.91 (broad singlet, 23-H), 5.4 (m, 6-H), 5.82 (28-H)] and the 22S, 23S isomer [mp 175-180°, 195-198°; ir; 1736 cm^{-1}; nmr δ .75 (18-H, 1.03 (19-H), 2.03 (acetate), 3.89 (d, J 4.5 Hz, 22-H), 5.07 (broad singlet, 23-H), 5.4 (m, 6-H) 5.82 (28-H).[3]

The isomers were present in a ratio of approximately 2:10:2:1. It is worth noting that the coupling constant between 22-H and 23-H in the erythro isomers (RS and SR) is much greater than that in the threo isomers. This agrees nicely with the prediction from Newman projections.[7]

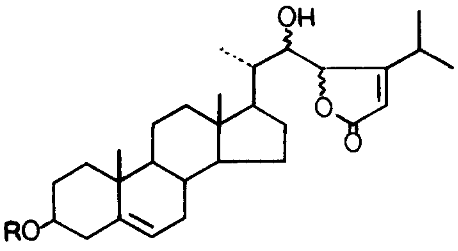
The isomer with the correct stereochemistry, i.e. 22S, 23R, was deacetylated in quantitative yield by acid hydrolysis to give 7-deoxy-7-dihydroantheridiol; mp 230-234°; ir 1740 cm^{-1} and the

latter on photooxygenation and rearrangement afforded antheridiol (1) in 35% yield. A somewhat better yield was obtained by converting 7-deoxy-7-dihydroantheridiol to the bis-tetrahydropyranyl ether followed by oxidation with Collins reagent to give the 7-ketone.[8] Careful acid hydrolysis then furnished (1).

The stereochemistry at $C_{22}C_{23}$ in (2) was changed from RS (or RR) to SR in the following way. Jones oxidation of (2), (22R, 23S), gave the 22-ketone (4), (23S), in almost quantitative yield;

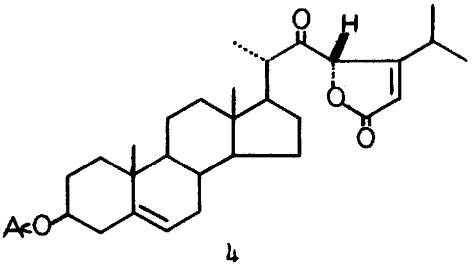


1



2 R = Ac

3 R = H



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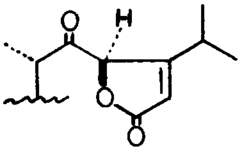

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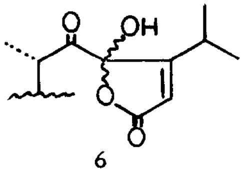

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mp (crude product) 152-158°; ir 1802, 1770, 1733, 1724 (shoulder) cm^{-1}; nmr δ .67 (18-H), 1.02 (19-H), 1.18 (d, J 7 Hz, 21-H), 1.21, 1.23 (pair of d, J 7 Hz, 26- and 27-H), 2.03 (acetate), 5.33 (d, J 2 Hz, 23-H, the signal partly overlapped that at 5.4 due to 6-H), 5.92 (t, J 1 Hz, 28-H); MS m/e 436 (M -60). Similarly, Jones oxidation of (2), (22R, 23R), gave the 22-ketone (5), (23R); mp 156-160°; nmr δ .73 (18-H), .98 (d, J 7 Hz, 21-H), 1.03 (19-H), 1.21, 1.23 (pair of d, J 7 Hz, 26- and 27-H), 2.03 (acetate), 5.23 (d, J 2 Hz, 23-H), 5.4 (m, 6-H), 5.88 (28-H). The ketones (4) and (5) were stable in chloroform solution, but in methanol they existed partly as the enol (λ_{max} 321 nm) and enolate (λ_{max} 363 nm). Addition of alkali caused a sharp increase in the intensity of the 363 nm peak. It disappeared entirely on acidification with restoration of the 321 nm peak. When allowed to stand at room temperature overnight in tetrahydrofuran-methanol in the presence of silica gel, the compounds were autoxidised to the 23-hydroxy-ketone (6) in quantitative yield; mp 214-217°; ir 1779, 1730, 1709 cm^{-1}; nmr δ .67 (18-H), 1.01 (19-H), 2.02 (acetate), 5.4 (m, 6-H), 6.11 (d, J 1.5 Hz, 28-H); MS m/e 452 (M -60).[9]

Reduction of (6) with sodium borohydride in tetrahydrofuran-methanol (3:1) gave an almost quantitative yield of (2) which contained about 30% of the 22S, 23R isomer. (Other conditions, e.g. sodium borohydride in methanol or isopropanol gave a smaller proportion of the 22S, 23R isomer). This isomer could be separated as described above and the remaining material put through the oxidation-reduction sequence again so as to produce more 22S, 23R isomer.

ACKNOWLEDGEMENT.-- This investigation was supported by grants GM-12150 from the National Institute of General Medical Sciences and 5-S01 RR05621 from the General Research Support Branch, National Institutes of Health.

NOTES AND REFERENCES

1. T. C. McMorris and R. Seshadri, <u>Chem. Comm.</u>, 1646 (1971).

2. In previous condensations a commercial sample of butyl lithium (90% in hydrocarbon) several months old, was used. It contained solid, presumably lithium hydroxide, and caused appreciable deacetylation of the steroid. In the experiment reported here a new sample of butyl lithium was used. Treatment with excess of triphenyl methane in tetrahydrofuran at -20° gave trityl lithium which reacted rapidly with β-isopropylbut-2-enolide at -30°. The resulting pale yellow solution was then cooled to -70° for condensation with the aldehyde. All manipulations involving butyl lithium were carried out in an atmosphere of pure argon.

3. The configuration at $C_{22}C_{23}$ in antheridiol was tentatively assigned as SR[4] and this has now been confirmed.[5] The configuration at $C_{22}C_{23}$ in the acetate, mp 219-223° is RS since on hydrolysis it gave a diol with the same properties as those reported for the erythro isomer of 7-deoxy-7-dihydroantheridiol.[6] The third acetate, mp 202-208°, must be RR since on oxidation it yields a different 22-ketone than that yielded by the RS isomer (see text) and the remaining acetate, mp 175-180°, 195-199° is SS.

4. D. M. Green, J. A. Edwards, A. W. Barksdale and T. C. McMorris, Tetrahedron, **27**, 1199 (1971).

5. J. A. Edwards, J. Sundeen, W. Salmond, T. Iwadare and J. H. Fried, Tetrahedron Letters, 791 (1972).

6. J. A. Edwards, J. S. Mills, J. Sundeen and J. H. Fried, J. Amer. Chem. Soc., **91**, 1248 (1969).

7. L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969. p. 291.

8. W. G. Dauben, M. Lorber and D. S. Fullerton, J. Org. Chem., **34**, 3587 (1969)

9. Without silica gel the autoxidation was much slower and a competing reaction, namely shift of the double bond out of conjugation with the lactone carbonyl and also opening of the lactone ring, resulted in a lower yield of (6).