Synthetic Studies on Antheridiol

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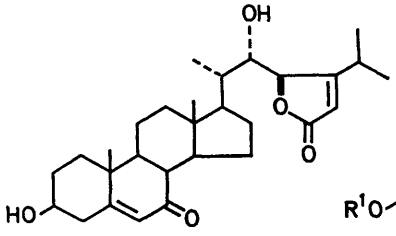
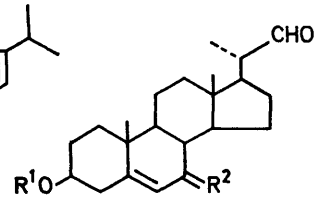
Summary Antheridiol (mixture of $C_{22}C_{23}$ epimers) has been obtained in 40% yield by aldol condensation of 3-tetrahydropyranyloxy-Δ^5-7-oxo-bisnorcholenaldehyde and β-isopropylbut-2-enolide with subsequent removal of the tetrahydropyranyl protecting group.

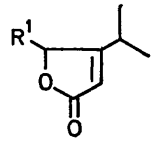
THE fungal sex hormone, antheridiol, is obtained only in *minute* amounts from the fungus *Achlya bisexualis*;[1] the reported yield of synthetic material was very low.[2] We describe here a novel synthesis which affords in moderate yield an epimeric mixture ($C_{22}C_{23}$) of antheridiol (**1**).



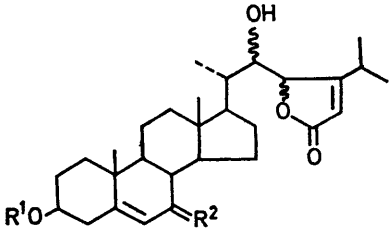
(1)



(2) $R^1 = O\cdot[CH_2]_4\cdot CH$, $R^2 = O$
(7) $R^1 = Ac$, $R^2 = H_2$



(3) $R^1 = Br$
(4) $R^1 = H$



(5) $R^1 = O\cdot[CH_2]_4\cdot CH$, $R^2 = O$
(6) $R^1 = H$, $R^2 = O$
(8) $R^1 = H$, $R^2 = H_2$
(9) $R^1 = Ac$, $R^2 = H_2$

We planned to use a Reformatsky reaction for condensation of the aldehyde (**2**)[3] and the bromobutenolide (**3**). Treatment of γ-bromobut-2-enolide[4] with ethereal 2-diazopropane[5] gave an unstable pyrazoline which when heated in xylene gave the bromobutenolide (**3**) (35% yield). Reaction of (**2**) and (**3**) yielded a product which exhibited biological activity *ca.* 1% that of antheridiol; no pure antheridiol tetrahydropyranyl ether (or any of its epimers) was isolable by chromatography.

Other ways of linking the C_{22} aldehyde and C_7 lactone were therefore investigated. The isopropylbutenolide (**4**) was prepared by condensation of the acetate of 1-hydroxy-3-methylbutan2-one[6] and ethyl bromoacetate.[7] The carbanion of (**4**), which is the intermediate in the Reformatsky reaction described above, could also be generated by treatment of (**4**) with trityl-lithium in tetrahydrofuran. When the carbanion was allowed to react with (**2**) at −70°† a 40% yield of crystalline product (**5**) was obtained, m.p. 210—223°. The product moved as a single spot in several t.l.c. solvent systems.

Treatment of (**5**) with dilute HCl–MeOH gave, in quantitative yield, a crystalline product (**6**), m.p. 250—255° (decomp.), which moved as a single spot in several solvent systems and had the same R_F as that of authentic antheridiol. However, the i.r. spectrum was slightly different from that of antheridiol. The product (**6**), as well as (**5**), is presumably a mixture of $C_{22}C_{23}$ epimers. Both (**5**) and (**6**) showed biological activity *ca.* 10% that of authentic antheridiol.

Reaction of the carbanion of (**4**) with the aldehyde (**7**)[3] in tetrahydrofuran at −70° yielded 7-deoxyantheridiol (**8**; epimeric mixture) (50%), m.p. 198—200°. A substantial amount of the corresponding acetate (**9**), m.p. 207—212°, was also obtained from the reaction, so that the combined yield of condensation product was *ca.* 70%. The compound (**8**) was readily converted into (**6**), m.p. 245—255° (decomp.) by photo-oxygenation and oxidative rearrangement.[2] Both (**8**) and (**9**) showed biological activity *ca.* 1% that of antheridiol.

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† A similar method was used by the Syntex workers for preparation of an intermediate in their synthesis of antheridiol. It was determined that no epimerisation occurred at C_{20} during the condensation.[2]

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