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STEROIDS CCXCVII.(1)

SYNTHETIC STUDIES ON INSECT HORMONES. PART III.

AN ALTERNATIVE SYNTHESIS OF ECDYSONE AND 22-ISOECDYSONE.

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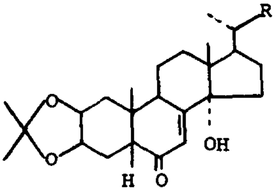
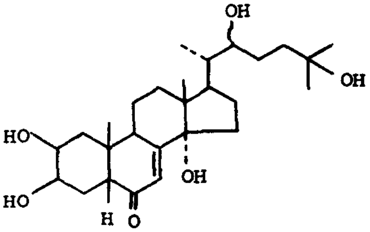
The synthesis of the insect moulting hormone ecdysone (IIa) was reported in a previous communication from this laboratory.(2) In addition, the three C-20 and 22 stereoisomers of ecdysone were obtained,(2) although the method of synthesis used did not allow the assignment of stereochemistry to the latter compounds.

We now wish to record an alternative synthesis from a common tetracyclic intermediate methyl 14α-hydroxy-2β,3β-isopropylidenedioxy-6-oxo-22,23-bisnor-5β-chol-7-enoate(3) (Ia) which proceeds without equilibration at C-20 and affords only ecdysone and 22-isoecdysone.



I

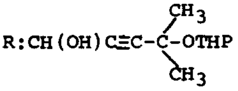


II

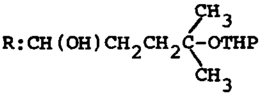
Ia R:COOMe

Ib R:CH_2OH

Ic R:CHO

Id 

$R{:}CH(OH)C{\equiv}C{-}\overset{CH_3}{\underset{CH_3}{C}}{-}OTHP$

Ie 

$R{:}CH(OH)CH_2CH_2\overset{CH_3}{\underset{CH_3}{C}}{-}OTHP$

IIa $22\beta_F$-OH

IIb $22\alpha_F$-OH

Conversion of Ia to the 22-carbinol Ib [m.p. 243-245°; $[\alpha]_D$ +39°; λ_{max}^{MeOH} 241 mμ (ε 10,900). Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.60; H, 8.71]$^{(4)}$ was carried out by sequential$^{(5)}$ tri-t-butoxy aluminum hydride reduction of the 6-ketone and lithium aluminum hydride reduction of the methoxycarbonyl, followed by manganese dioxide$^{(6)}$ oxidation of the resulting allylic 6-hydroxy group. Further oxidation$^{(7)}$ of Ib with dimethyl sulfoxide and dicyclohexylcarbodiimide under trifluoracetic acid catalysis afforded the aldehyde Ic [λ_{max} 241 mμ; n.m.r. 475 (CHO) c.p.s.]. Selective alkylation of Ic with the lithium salt of 3-methylbut-1-yn-3-ol tetrahydropyranyl ether$^{(8)}$ yielded a mixture of the $22\alpha_F$ and $22\beta_F$ epimers of 2β,3β,14α,22,25-pentahydroxy-5β-cholest-7-en-23-yn-6-one 2,3-acetonide-25-tetrahydropyranyl ether, Id. Catalytic hydrogenation (palladium on carbon) of this epimeric mixture afforded the tetrahydro derivatives Ie. The mixture of $22\alpha_F$ and $22\beta_F$ isomers formed during the alkylation step was separated at this stage by thin layer chromatography on Merck silica gel and the individual components were hydrolyzed with $\frac{N}{20}$ hydrochloric acid in aqueous tetrahydrofuran to yield approximately equal amounts of ecdysone IIa [m.p. 170° and 234-236° (from water), mixed m.p. 168° and 235-238°]$^{(9)}$ and 22-isoecdysone IIb [m.p. 251-254° (from acetone);$^{(11)}$ $[\alpha]_D$ -3° (C, 0.2, EtOH); λ_{max}^{EtOH} 244 mμ (ε 11,850); ν_{max}^{KBr} 1655 and 3400 cm^{-1}; n.m.r. (d_5-pyridine) ν 47.5 (18-H), 63.5 (19-H) 84.5 (26 and 27-H) c.p.s. Anal. Calcd. for $C_{27}H_{44}O_6$: C, 69.79; H, 9.55. Found: C, 69.16; H, 9.49].

When assayed$^{(12)}$ in brainless pupae of the silkworm *Samia cynthia*, aqueous solutions of 22-isoecdysone showed activity of 1/4 to 1/8 of ecdysone.

References

1. Steroids CCXCVI, J. Iriarte, P. Crabbe and A. Bowers (publication pending).
2. J. B. Siddall, A. D. Cross and J. H. Fried, J. Am. Chem. Soc., **88**, 862 (1966).
3. J. B. Siddall, J. P. Marshall, A. Bowers, A. D. Cross, J. A. Edwards and J. H. Fried, J. Am. Chem. Soc., **88**, 379 (1966).
4. We wish to thank Dr. L. Throop and his associates for the determination of physical properties herein reported.
5. Direct reduction of Ia with lithium aluminum hydride afforded substantially greater quantities of a product which could not be oxidized to the enone Ib.
6. Obtained from Beacon Chemical Industries, Inc., Cambridge, Massachusetts.
7. J. G. Moffatt, K. E. Pfitzner, J. Am. Chem. Soc., **85**, 3027 (1963).
8. Obtained by the action of dihydropyran in the presence of p-toluenesulfonic acid on 3-methylbut-1-yn-3-ol which has been used independently by U. Kerb, P. Hocks, R. Wiechert, A. Furlenmeier, A. Fürst, A. Langemann and G. Waldvogel, Tetrahedron Letters, 1387 (1966), in a synthesis of ecdysone.
9. Carried out with a sample of ecdysone prepared by the previously reported(2) alternative route. The mass spectrum of this synthetic compound, determined on an Associated Electrical Industries MS-9 spectrometer, was in excellent agreement with the spectrum reported by Karlson, et al.(10) We are indebted to Dr. A. Duffield, Department of Chemistry, Stanford University, for this determination.

10. P. Karlson, H. Hoffmeister, W. Hoppe, R. Huber, Ann., 662, 1 (1963).

11. A mixed melting point analysis (m.m.p. 251-254°) carried out with the previously reported(2) fraction A establishes the identity of the latter compound as 22-isoecdysone.

12. We are indebted to Professor Carroll M. Williams of Harvard University for this determination of biological activity.