Tetrahedron Letters No.37, pp. 3603-3606, 1967. Pergamon Press Ltd. Printed in Great Britain.

A NOVEL TOTAL SYNTHESIS OF 11-OXYGENATED STEROIDS

R.P. Stein, G.C. Buzby Jr., G.H. Douglas and Herchel Smith

Research Division, Wyeth Laboratories Inc.,

Radnor, Pennsylvania

(Received in USA 29 May 1967)

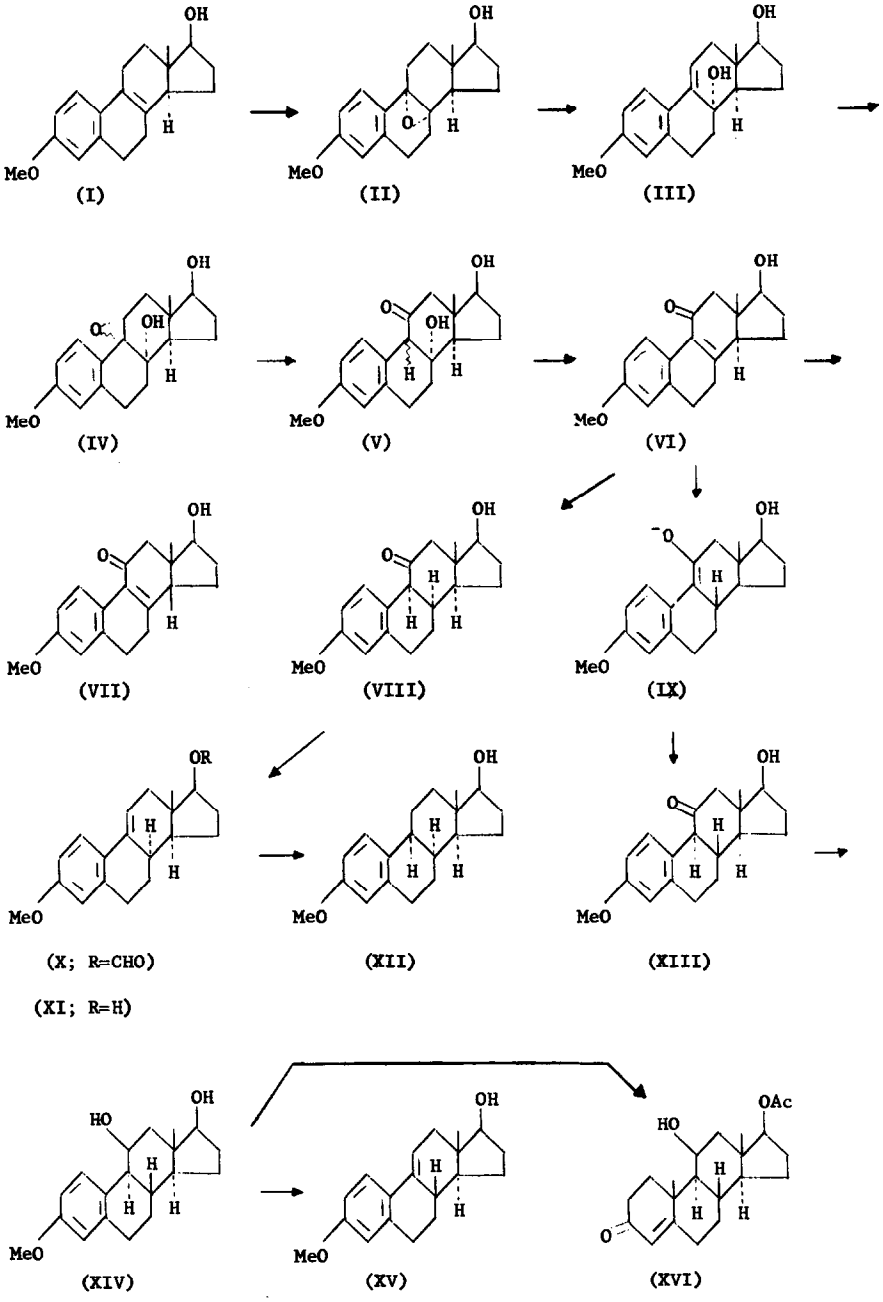
We wish to report various novel reactions and intermediates which permit the development of efficient total syntheses of a wide variety of 11-oxygenated steroids from intermediates which have previously been converted to estrone,[1,2] equilenin,[1,2] equilin,[3] and other steroid hormones.[4]

The dl-diol III,[3,5] with m-chloroperbenzoic acid in benzene-hexane, gave the epoxydiol IV,[6] m.p. 176-178°, λ_{max} 235 mμ (ε 12,900).[7] The same product was more conveniently obtained directly from the dl-estratetraene I[2] by treatment with 2 equivalents of the peracid in benzene-hexane, the formation of IV presumably involving the acid-catalyzed rearrangement of the initially produced epoxide II[3] and epoxidation of the resulting III. Methanolic HCl at or below room temperature transformed IV to the 11-oxo-estratetraene VI, m.p. 210-213°, λ_{max} 247 mμ (ε 17,300), probably through formation and dehydration of the ketol V. The overall yield for the five stage sequence I - VI was 52%. Refluxing methanolic HCl or methanolic NaOH epimerized VI to VII, m.p. 108-112°, λ_{max} 243 mμ (ε 16,150), evidently through the corresponding 8(14), 9(11)-dienol or dienolate anion. Catalytic hydrogenation over palladized charcoal in dimethylformamide converted VI to an estratriene m.p. 175-177° (ethanol solvate) formulated as VIII. Sodium borohydride reduction of VIII followed by treatment of the resulting 11,17-diol with methanesulfonyl chloride in pyridine-dimethylformamide[8] gave the formate X, m.p. 117-119°, λ_{max} 259 mμ (ε 18,400), which was converted with methanolic sodium hydroxide to the estratetraenol XI, m.p. 142-145° (propan-2-ol solvate), λ_{max} 258 mμ (ε 19,800). Lithium in aniline-liquid ammonia converted X to dl-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol XII, m.p. 102-104°, identical with an authentic sample,[9] thereby confirming the structures of VI and XI. Notably, had the metal-ammonia reduction given a trans-BC ring junction, the resulting trans-syn-trans-stereochemistry would have required ring C in the 9-epimer of XII to assume a boat conformation.

VI was converted by lithium-ammonia reduction in 60% yield to the 11-oxo-estratriene XIII m.p. 177-180° and transformed thence with sodium borohydride in methanol to the diol XIV. After treatment with methanesulfonyl chloride in dimethylformamide and saponification of the resulting 17-formate, XIV gave the previously prepared dl-steroid XV,[2] m.p. 128-130°, thereby confirming the 8β-stereochemistry of XIII. The 9α-stereochemistry of XIII is consistent with its proton NMR spectrum, which is closely similar in the aromatic region to that reported for d-3-methoxyestra-1,3,5(10)-triene-11,17-dione,[10] and is confirmed by its conversion with ethanolic KOH to a gummy 9-epimer displaying similar aromatic proton resonances to d-3-methoxy-9β-estra-1,3,5(10)-triene-11,17-dione.[10] Various 11-oxo-9α-estra-1,3,5(10)-trienes and related substances are known to undergo base catalyzed epimerization at the 9-position.[11-13] The formation of what is apparently the less stable 9α-epimer by lithium-ammonia reduction of VI is to be attributed to a kinetically-controlled protonation of the enolate anion IX formed by the addition of two electrons and a proton to the substrate (cf.[14]). A related kinetically controlled protonation of a 17(20)-en-20-olate anion has recently been elucidated in the dl-18-methylpregna-1,3,5(10)-triene series.[15]

XIV was also prepared[16] from dl-XV by a previously established 4 stage sequence[17] involving hydroboration of the 9(11)-bond, and its 11β-hydroxy configuration was confirmed by its transformation, by the method[17] used for d-XIV, to the dl-androstenol XVI, m.p. 212-215°, λ_{max} 241 mμ (ε 15,850), which was identical in UV, IR, and NMR spectra to the corresponding d-enantiomorph, prepared from d-adrenosterone by reduction with lithium aluminum hydride, oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone, and selective acetylation. The presently described route from I to XIV via VI (overall yield ca. 24%) appears more efficient than the alternate one involving the acid catalyzed transformation of an estra-1,3,5(10),8-tetraene to the 9(11)-isomer,[2,18] followed by the hydroboration-oxidation-reduction sequence,[17] chiefly because of low yields and the formation of difficultly separable mixtures at the hydroboration stage[16] (cf.[19]).

Acknowledgement. We thank Messrs. R.C. Smith and C.R. Walk for skilled technical assistance.


OH
MeO
H
O
(I)
(II)
(III)
(IV)
(V)
(VI)
(VII)
(VIII)
(IX)
OR
(X; R=CHO)
(XI; R=H)
(XII)
(XIII)
HO
OAc
(XIV)
(XV)
(XVI)

REFERENCES

1. G.A. Hughes and H. Smith, Chem. and Ind., 1022 (1960).
2. G.H. Douglas, J.M.H. Graves, D. Hartley, G.A. Hughes, and H. Smith, J. Chem. Soc., 5072 (1963).
3. R.P. Stein, G.C. Buzby, Jr., and H. Smith, Tetrahedron Letters, 5015 (1966).
4. H. Smith, G.A. Hughes, G.H. Douglas, G.R. Wendt, G.C. Buzby, jun., R.A. Edgren, J. Fisher, T. Foell, B. Gadsby, D. Hartley, D. Herbst, A.B.A. Jansen, K. Ledig, B.J. McLoughlin, J. McMenamin, T.W. Pattison, P.C. Phillips, R. Rees, J. Siddall, J. Siuda, L.L. Smith, J. Tokolics, and D.H.P. Watson, J. Chem. Soc., 4472-92 (1964).
5. Unless specifically noted otherwise, all steroids described herein are racemates and, where special emphasis of this is required, are denoted by the prefix dl-. The prefix d- is used to denote steroids corresponding in absolute configuration at C_{13} with estrone.
6. All of the new substances characterized here gave satisfactory elemental analyses, and showed infra-red, ultra-violet, and proton nuclear magnetic resonance absorption spectra consistent with the assigned structures.
7. This ultra-violet absorption is closely similar to that observed for 8α,9α-epoxy-estra-1,3,5(10)-trienes (ref. 3).
8. R.P. Stein, G.C. Buzby, Jr., and H. Smith (manuscript in preparation) will describe other applications of this reagent.
9. G.C. Buzby, Jr., E. Capaldi, G.H. Douglas, D. Hartley, D. Herbst, G.A. Hughes, K. Ledig, J. McMenamin, T. Pattison, H. Smith, C.R. Walk, G.R. Wendt, J. Med. Chem., 9, 338 (1966).
10. H. Hasegawa and K. Tsuda, Chem. Pharm. Bull (Japan) 12, 473 (1964).
11. E.J. Bailey, J. Elks, J.F. Oughton, and L.S. Stephenson, J. Chem. Soc., 4535 (1961).
12. E. Caspi, E. Cullen, and P.K. Grover, J. Chem. Soc., 212 (1963).
13. J.A. Edwards, P. Crabbe, and A. Bowers, J. Am. Chem. Soc., 85, 3313 (1963).
14. H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, New York, 1963, p. 234 and references there cited.
15. G.A. Hughes, T.Y. Jen, and H. Smith, Steroids, 8, 947 (1966).
16. T.Y. Jen, G.A. Hughes, and H. Smith, unpublished work.
17. P. Turnbull, K. Syhora, and J.H. Fried, J. Am. Chem. Soc., 88, 4764 (1966).
18. G.A. Hughes and H. Smith, British Patent 1,024,912 (priority from 22 June 1961).
19. A. Bowers, J.S. Mills, C. Casas-Campillo and C. Djerassi, J. Org. Chem. 27, 361 (1962).