Tetrahedron Letters No.39, pp. 3505-3512, 1965. Pergamon Press Ltd.
Printed in Great Britain.

PERHYDROFLUORENE DERIVATIVES BY STEPWISE BIRCH REDUCTION OF THE FLUORENE NUCLEUS[1]

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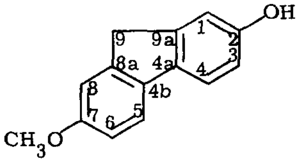
(Received 12 July 1965; in revised form 9 August 1965)

The perhydrofluorene nucleus is a characteristic feature of a number of important natural products. Among these are the steroid alkaloids of the jerveratrum and ceveratrum type,[2] which possess the C-nor-D-homosystem, and the plant growth hormone giberellic acid and its many structural variants produced by the fungus Giberella fujikuroi[3] and other fungi. This ring system is also present in the B-norsteroids[4,5,6] obtained by ring contraction of conventional steroids. More recently, growing interest in the biological properties of steroid hormones, in which the basic ring skeleton has been altered, has prompted the synthesis of hormone analogs possessing the C-nor-D-homosystem from natural precursors, in which that system is either preformed (as in jervine),[7] or in which it can be generated by Wendler-Hirschmann rearrangement (as from hecogenin).[8,9] Total synthetic approaches to the C-nor-D-homosystem of the jerveratrum alkaloids by Johnson et al.[10] and to the giberellins by House et al.[11] further attest to the interest in the perhydrofluorene system.

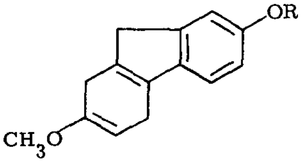
It occurred to us that if the necessary asymmetric centers could be introduced stereospecifically into readily available fluorene derivatives such tricyclic intermediates could serve for a variety of synthetic objectives.

Fluorene is subject to stepwise electrophilic substitution in positions 2 and 7. Derivatives substituted both symmetrically and unsymmetrically in these positions are therefore readily available. We chose to explore the Birch reduction[12] of 2-hydroxy-7-methoxyfluorene (Ia)[13] guided by the following considerations. It was to be expected that by maintaining one of the oxygen functions in the free phenolic form the conjugate anion formed under the conditions of the reaction would effectively prevent reduction of the phenolic ring. It was anticipated, moreover, that the styrene system most likely to arise by reduction of the methoxyl-containing ring (e. g. IIa) could be preserved at this stage as well, due to delocalization of the negative charge over the whole conjugated system. Reduction of the styrene double bond, hopefully with complete stereochemical control, could then be undertaken to be followed by reduction, after methylation, of the phenolic ring. The above objectives have been fully realized.

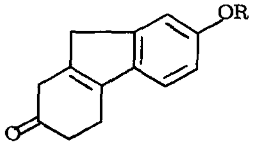
Reduction of Ia with 6 atoms of lithium in ammonia in the presence of *t*-butanol gave after partial neutralization to pH 9 in 73% yield the 5,8-dihydrofluorene IIa,[14] m.p. 143-4°; λ_{max}^{alc} 264 mμ (13,000), 272 mμ (10,300) sh. (styrene system); λ_{max}^{KOH}[15] 284 mμ (14,000); λ_{max}^{KBr} 2.90 μ (OH) 5.96, sh. 6.10 μ (enol ether), 6.18, 6.29 μ (aromatic ring). Its n. m. r. spectrum showed 3 aromatic protons at 2.94τ, J_{ortho} = 8.5, J_{para} = 1 (4-H), 3.27τ, J_{ortho} = 8.5, J_{meta} = 2 (3-H) and 3.03τ (1-H), a phenolic proton at 5.05τ, a vinyl proton at 5.14τ(6-H),[16] three methoxyl protons at 6.35τ and 6 methylene protons at 6.79 and 6.85τ(5,8 and 9-CH_2). Acetylation with pyridine-acetic anhydride furnished a monoacetate (IIb) m.p. 158-9°; λ_{max}^{alc} 261 mμ (12,900); λ_{max}^{KBr} 5.69 μ (CH_3CO), 5.98, 6.11 μ (enol ether), 6.32 μ (arom.); n. m. r. 5.15τ (6-H),



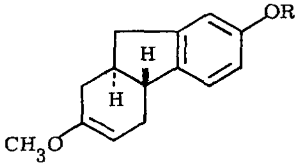
Ia
Ib CH_3 = H
Ic H = CH_3



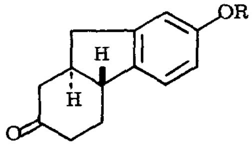
IIa R = H
IIb R = Ac
IIc R = CH_3



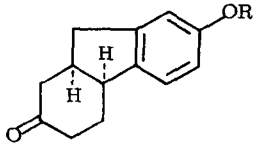
IIIa R = H
IIIb R = Ac
IIIc R = CH_3



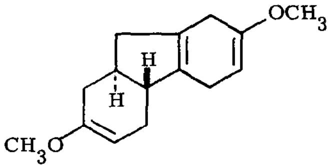
IVa R = H
IVb R = Ac
IVc R = CH_3



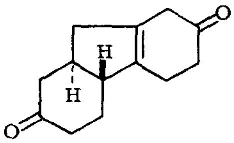
Va R = H
Vb R = Ac
Vc R = CH_3



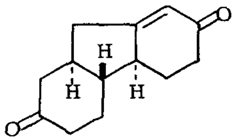
VIa R = H
VIb R = Ac



VII



VIII



IX

6.38τ (CH_3O), 7.72τ (CH_3CO), and methylation with diazomethane or with dimethylsulfate and excess base yielded the dimethyl ether IIc, m.p. 121-2°; λ_{max}^{alc} 264 mμ (14,600); λ_{max}^{KBr} 5.98, 6.11 μ (enol ether) 6.22, 6.34 μ (arom.); n.m.r. 5.18τ (tr. J ~1.5) (6-H), 6.20τ (2-OCH_3), 6.39τ (7-OCH_3). Since IIa, IIb and IIc possess only a single non-aromatic vinyl proton the second double bond shown by UV to be conjugated with the aromatic ring must be in the 4b,8a-position. This establishes structure IIa for the reduction product.[17] Hydrolysis of the enol ether grouping in IIa, IIb and IIc with 95% acetic acid at room temperature gave the corresponding 2-ketones IIIa, m.p. 227-31°; λ_{max}^{alc} 267 mμ (12,000); λ_{max}^{KOH} 299 mμ (19,000); λ_{max}^{KBr} 3.04, 5.82, 6.18 μ; IIIb,[18] m.p. 112-3°; λ_{max}^{KBr} 5.70, 5.81, 6.10, 6.31 μ; and IIIc, m.p. 89-91°; λ_{max}^{alc} 266.5 mμ (15,000); λ_{max}^{KBr} 5.84, 6.22, 6.33 μ, none of which showed vinyl proton absorption in the n.m.r. An attempt to cause equilibration of the conjugated double bond in IIIa between the 4b,8a- and 4b,5-positions by treatment with 0.5N HCl in dioxane at 40° for 24 hours produced 2,7-dihydroxyfluorene (Ib) in 20% yield, m.p. 270-72°,[19] λ_{max}^{alc} 276 mμ (26,100), 288 mμ (20,800) sh, 321 mμ (5,000).

Catalytic reduction of IIIa with Pd/C in ethyl acetate or, more significantly, with PtO_2 in acetic acid[20,21] gave as the sole product the dihydro-derivative VIa, m.p. 144-6°; λ_{max}^{alc} 283 mμ (2,600); λ_{max}^{KOH} 241.5 mμ (8,500), 302 mμ (3,300); λ_{max}^{KBr} 5.90, 6.20 μ, to which the 4b,8a-cis structure must be assigned because of its mode of formation.[22] Its acetate VIb had m.p. 71-72°; λ_{max}^{alc} 262 mμ (1,000) sh., 269.5 mμ (1,500), 276 mμ (1,400); λ_{max}^{KBr} 5.69, 5.85, 6.22, 6.30 μ.

More drastic reduction of Ia with 90 atoms of Li in ammonia in the presence of ethanol afforded in 50% yield the tetrahydro enol ether IVa,[23] m.p. 132-3°. Its UV spectrum, λ_{max}^{alc} 282 mμ (2,900); λ_{max}^{KOH} 241 mμ (7,800), 298 mμ (2,400); indicates that the styrene double bond has been reduced. λ_{max}^{KBr} 2.96, 6.04, 6.17, 6.31 μ; n.m.r. 5.10 τ (phenolic proton), 5.25 τ, J = 5 (6-H),[16] 6.44 τ (OCH_3); acetate (IVb) m.p. 110-11°; λ_{max}^{alc} 262.5 mμ (1,420) sh., 268.5 mμ (1,750), 275 mμ (1,530); λ_{max}^{KBr} 5.69, 5.98, 6.11, 6.31 μ; n.m.r. 5.26 τ, J = 5.5 (6-H), 6.45 τ (OCH_3), 7.74 τ (CH_3CO). Hydrolysis of the enol ether IVa with 95% acetic acid gave the ketone Va, m.p. 240-43°; λ_{max}^{alc} 282.5 mμ (2,800); λ_{max}^{KOH} 242 mμ (10,000), 301 mμ (3,400); λ_{max}^{KBr} 3.03, 5.96, 6.19 μ; acetate (Vb) m.p. 142-4°; λ_{max}^{alc} 262 (990) sh., 269 mμ (1,400), 275 mμ (1,360); λ_{max}^{KBr} 5.70, 5.85, 6.22, 6.31 μ; methyl ether (Vc), m.p. 94-96°; λ_{max}^{alc} 278 mμ (3,140), 287.5 mμ (2,600); λ_{max}^{KBr} 5.87, 6.14, 6.29 μ; n.m.r. 6.21 τ (2-OCH_3). Since Va and Vb were not identical with the products obtained by catalytic hydrogenation (VIa and VIb) the former as well as IV must possess the two rings in <u>trans</u>-fusion.

Methylation of IVa gave the dimethyl ether IVc, m.p. 71-2°; λ_{max}^{alc} 277 mμ (3,200), 287 mμ (2,500); λ_{max}^{KBr} 6.08, 6.19, 6.32, 12.74 μ; n.m.r. 5.25 τ, J = 5.5 (6-H), 6.21 τ (2-OCH_3) 6.44 τ (7-OCH_3), which on reduction with 80 atoms of Li in ammonia in the presence of ethanol furnished in 83% yield the dienol ether VII, m.p. 71-72°; UV: end absorption; λ_{max}^{KBr} 5.95, 6.06, 12.79 μ. n.m.r. 5.30 τ (3-H), 5.33 τ, J = 5.5 (6-H), 6.42 and 6.48 τ (2 and 7-OCH_3), 7.25 τ (1 and 4-CH_2). Hydrolysis of VII with 95% acetic acid afforded the $\beta\gamma$-unsaturated ketone VIII, m.p. 100-101°; UV: only low intensity absorption; λ_{max}^{KBr} 5.85 μ; no vinyl protons in the n.m.r., which was converted with 0.02N KOH at room temperature into the $\alpha\beta$-unsaturated ketone IX, m.p. 103-4°;

λ_{max}^{alc} 237 mμ (14,000); λ_{max}^{KBr} 5.87, 6.05 μ; n.m.r. 4.05 τ (1-H). The conditions employed in the reactions leading from IVc to IX would not be expected to cause epimerization at C-4b. Accordingly, VII, VIII and IX are assigned the 4b,8a-*trans*-stereochemistry. Confirmation of this assignment was obtained by Pd-dehydrogenation[24] of IX., This reaction furnished the *trans*-ketone Va under conditions, which did not cause epimerization of the *cis*-ketone VIa, but, instead, caused dehydrogenation of the latter to 2,7-dihydroxyfluorene (Ib). These findings are compatible only with the intervention of zero or an even number of inversions at C-4b during the reaction sequence IVc to IX. The latter possibility can be safely excluded. The *trans*-*anti*-structure was assigned to IX in analogy to the formation of 10β-H-steroids from $\Delta^{5(10)}$-3-ketones under similar conditions. Direct reduction of 2,7-dimethoxyfluorene (Ic) with 30 atoms of Li in ammonia and *t*-butanol furnished the crystalline dienol ether VII in 20% yield.

The phenolic ketones IIIa, Va and VIa were tested for their ability to induce vaginal cornification in immature rats and found to be inactive at doses of 100μg/rat/day over a 7 day period; 0.1μg of estrone is estrogenic under similar conditions.

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15. 1% KOH in methanol.

16. This signal appears as a broad singlet in IIa and IIb but is sufficiently resolved in IIc to reveal its triplet nature (J ~ 1.5). This is to be expected of a system oscillating rapidly between two identical conformations, in which the mean dihedral angle between the planes described by the 6H-6C-5C and 6C-5C-5H bonds is 60°. In contrast, the signal for the 6-proton in the enol ethers IVa, IVb, IVc and VII consists of two broad doublets (J = 5.5). Dreiding models indicate that the dihedral angles between the 6H-6C-5C plane on the one hand and the 6C-5C-5βH and 6C-5C-5αH planes on the other are 36° and 84°, respectively, from which J-values of ~ 6.5 and < 1 may be calculated. If allylic coupling with the 8β-proton (~ 1-3 cps) is also considered the observed pattern for the 6-proton is in excellent agreement with the assigned structure, but not with the isomeric Δ^7-structure. (Cf. N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964, pages 49, 108).

17. Reduction of fluorene to 1, 2, 3, 4-tetrahydrofluorene with retention of the styrene double bond by the use of Li in methylamine was reported by R. A. Benkeser in "Advances in Chemistry Series", Reinhold Publishing Co., New York, Vol. 23, 1957, page 58.

18. Direct acetylation of IIIa gave colored products from which IIIb could not be isolated in crystalline form.

19. Taken in sealed capillary. 2,7-Dihydroxyfluorene sublimes at 237-240°. C. D. Nenitzescu and M. Avram (Acad. rep. populare Romîne, Studii cercetâri chim, 4, No. 1-2, 57 (1956); C. A. 51, 3534 (1957)) report m.p. 233°; R. A. Barnes and R. W. Faessinger (J. Org. Chem., 26, 4544 (1961)) report 249-250°.

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23. Reduction of Ia with amounts of lithium intermediate between 6 and 90 atoms led to mixtures of the dihydro and tetrahydro enol ethers IIa and IVa. Attempted further reduction of the presumed intermediate IIa under conditions which smoothly produced IVa from Ia likewise led to mixtures of IIa and IVa, in which the former predominated. Complete resistance towards reduction by Li in ammonia was shown by the alcohol, m.p. 216-17°, obtained by reaction of IIIa with $NaBH_4$ in methanol, probably as a result of further suppression of electron addition by the second anionic site. These findings are in full accord with our prediction regarding the resistance to reduction of the styrene double bond in the presence of phenolic hydroxyl, and suggest that in the reduction of Ia to IVa, IIa is not a major intermediate.

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