Tetrahedron Letters No. 21, pp. 975-977, 1962. Pergamon Press Ltd. Printed in Great Britain.

A NOVEL SYNTHESIS OF STEROIDAL INDOXYLS AND INDOLES

Alfred Hassner and Makhluf J. Haddadin

Department of Chemistry, University of Colorado, Boulder, Colorado

(Received 29 June 1962, in revised form 30 July 1962)

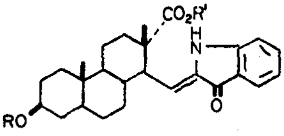
IN attempts towards the synthesis of steroidal alkaloids[1] we treated 5-androstene-3β-ol-17-one with o-nitrobenzaldehyde in basic solution and obtained instead of the expected 16-(o-nitrobenzal) compound a yellow acidic product, m.p. 267-269° (dec.), in 75 per cent yield, to which structure Ia is attributed on the following grounds.[2] Ia gives a red-brown 2,4-dinitrophenylhydrazone. It shows ultraviolet absorption (238, 262, 455 mμ; ε 16,500, 25,000 and 5000 respectively) characteristic of indoxyls[3] but indicating further conjugation. Diazomethane or Fischer esterification converts acid Ia into a methyl ester IIa which is acetylated to IIIa or converted by Oppenauer oxidation into IV. Compounds I-IV clearly indicate the presence of N-H in the infrared and N.M.R. thus excluding a structure such as V. IIb obtained analogously from androstane-17-one via Ib had strong infrared bands at 3350 (N-H), 1725 (CO_2CH_3), 1690 (conj. C=O), 1640 (conj. C=C), 1610 (indole type phenyl),[3] 750 and 705 cm^{-1} (1,2-disubstituted phenyl) and N.M.R. doublet at τ 4.2 (olefinic H split by one adjacent H). Chromic acid oxidation of III yields isatin and a steroidal acid. Reaction of II with bromine takes place with bromine addition to the double bond

---

[1] A. Hassner and M.J. Haddadin, J. Org. Chem. 27, 1911 (1962).

[2] Satisfactory analyses for all compounds reported were obtained by Pascher Laboratories, Bonn, Germany. Ultraviolet spectra were run in methanol solution, infrared spectra in potassium bromide.

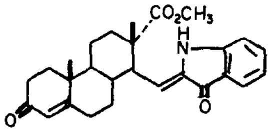
[3] B. Witkop and J.B. Patrick, J. Amer. Chem. Soc. 73, 2188 (1951).



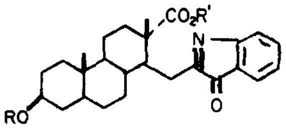
I R=H, R'=H

II R=H, R'=CH_3

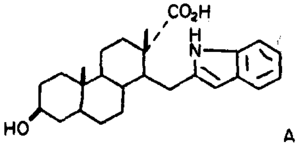
III R=Ac, R'=CH_3



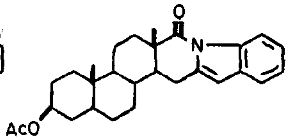
IV



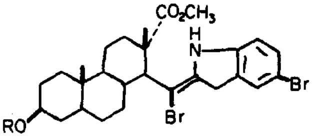
V



VI

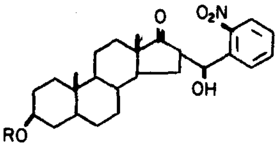


VII



VIII R=H

IX R=Ac



X

series "a" refers to 5,6-dehydro compounds

series "b" refers to 3-desoxy compounds

followed by loss of HBr, as well as with substitution[4] leading to VIII, which can be acetylated to IX.

Indoxyl I is reduced only slowly and not cleanly by catalytic hydrogenation but is converted in good yield to indole VI upon treatment with sodium borohydride followed by acidification. VI gives a positive Ehrlich test for indoles and shows ultraviolet absorption nearly identical with that of 2-methylindole. Heating with acetic anhydride transforms VI into lactam VII. The latter shows ultraviolet absorption characteristics of N-acylated indoles and is hydrolyzed to VI by heating with alkali. We find

---

[4] Isatins and related compounds are known to be substituted by halogen <u>para</u> to the nitrogen, <u>cf</u>. E. Kambli, <u>Helv. Chim. Acta</u> **24**, 93E (1941); furthermore the N.M.R. spectra of VIII and IX are indicative of 5-substituted indoxyls.

the reaction with o-nitrobenzaldehyde to be general for 17-ketosteroids; reaction with simpler ketones leads to complex products that are still under study. We were able to show that the 16-(α-hydroxy-o-nitrobenzyl)-17-ketosteroid (X), but not a 16-(o-nitrobenzal)-17-ketosteroid, is an intermediate in the reaction.[5] Condensation of m- and p-nitrobenzaldehyde with 17-ketosteroids proceeds normally to yield the corresponding 16-nitrobenzal derivatives.

Acknowledgement - We are indebted to the National Institutes of Health, National Cancer Institute for financial support of this work (Grant CY-4474).

---

[5] Details on the mechanism of this reaction and the analogous reaction of acetone with o-nitrobenzaldehyde to yield indigo [A. Baeyer and V. Drewsen, Chem. Ber. **15**, 2856 (1882)] will be reported later.