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A NEW APPROACH TO THE TOTAL SYNTHESIS OF B-NORSTEROIDS

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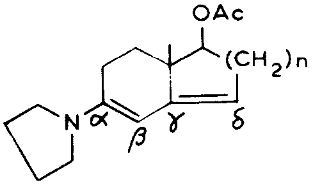
Recent communications on the synthesis of racemic (1) and optically active (2) B-norestrone prompt us to report a new approach for the total synthesis of B-norsteroids. The latter approach emerged from our broader studies in the field of enamine and dienamine chemistry. Other cases of utilization of enamines, in the synthesis of modified steroids, have been previously reported from this laboratory (3-5).

The pyrrolidine dienamine 1a was readily obtained from the corresponding α,β-unsaturated ketone in a conventional manner. The freshly distilled product is a light orange liquid which solidifies to a green crystalline mass upon standing at -20° for a few days; $\nu_{max}^{CHCl_3}$ cm^{-1} 1720 (ester C=O), 1620 (N-C=C). Alkylation of 1a with m-methoxybenzyl bromide, in refluxing DMF, exclusively gave the β-substitution product 2a (6) in excellent yield (85%). The structure of 2a was attested by its spectral data; $\nu_{max}^{CHCl_3}$ cm^{-1} 1725 (ester C=O), 1650 (unsaturated C=O); δ^{CDCl_3} 3.75 s (3H, Ar-OCH_3), 2.08 δ (3H, $OCOCH_3$), 1.17 s (3H, C_{13}-CH_3), 4.65-4.98 m (1H, H-COAc); the vinyl-proton region showed no bands. Attempted cyclization of 2a under influence of a wide assortment of acid catalysts gave poor yields of both 3a and the corresponding C_{17}-alcohol. 2a was subsequently converted to ketone 4a via two standard - hydrolytic and oxidative - transformations. Ring closure of 4a could be smoothly affected with H_3PO_4 and P_2O_5, to afford B-norsteroid 5a in practical yield (35%) (7). The ketone 5a, m.p. 158-159°, gave analytical and spectral data consistent with the assigned structure. [Found: C, 80.98; H, 6.80; O, 12.22; $C_{18}H_{18}O_2$ requires: C, 81.17; H, 6.81; O, 12.02; λ_{max}^{EtOH} 308 (27,200); ν_{max}^{KBr} cm^{-1} 1736 (C=O), 1620 (C=C), 1600, 1580. δ^{CDCl_3} 7.25-6.7 m (3H, Ar-H), 5.74 m (1H, C=C-H), 3.80 s (3H, OCH_3), 1.15 s (C_{13}-CH_3)]. The spectral characteristics are in complete agreement with those reported for 5a by Burckhalter and Sciavolino (1). In a parallel sequence of reactions, D-homo-B-norsteroid 5b, m.p. 145.5-147.5°, was obtained. [Found: C, 81.30; H, 7.17: $C_{19}H_{20}O_2$ requires: C, 81.39; C, 81.39; H, 7.19: ν_{max}^{KBr} cm^{-1} 1695 (C=O), 1630, 1600, 1570;

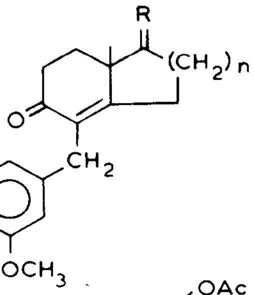
λ_{max}^{EtOH} 308 (25,600); δ^{CDCl_3} 7.24-6.71 m (3H, Ar-H); 5.82 t (1H, =C-H), 3.79 s (3H, OCH_3), 1.25 s (3H, C_{13}-CH_3). Formation of acetate 3b, in variable yield, was observed during attempts at direct cyclization of 2b.

The principle embodied in the enamine-approach is potentially capable of wide application in steroid synthesis. With the choice of the appropriate electrophilic reagent the scheme can be extended to the synthesis of natural hormones or to steroids modified in rings A and/or B. Investigations in this direction are currently underway in this laboratory.



1a n = 1

1b n = 2

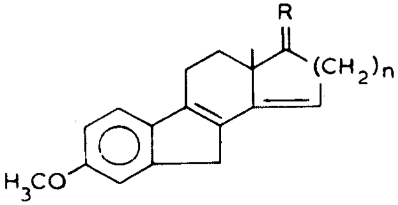


2a n = 1 , R = $\begin{smallmatrix}\text{OAc}\\ \text{H}\end{smallmatrix}$

2b n = 2 , R = $\begin{smallmatrix}\text{OAc}\\ \text{H}\end{smallmatrix}$

4a n = 1 , R = =O

4b n = 2 , R = =O



3a n = 1 , R = $\begin{smallmatrix}\text{OAc}\\ \text{H}\end{smallmatrix}$

3b n = 2 , R = $\begin{smallmatrix}\text{OAc}\\ \text{H}\end{smallmatrix}$

5a n = 1 , R = =O

5b n = 2 , R = =O

References

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6. (a) The substitution pattern of the dienamine is dependent upon the nature of the electrophilic reagent and the conditions of the reaction. Diazonium salts, e.g., in CH_2Cl_2 or $CHCl_3$, give both the β- and δ-substitution products. (b) The presence of small amounts of 3a is consistently observed in the reaction mixture. Both these points will be the subject of a forthcoming communication.
7. No attempts have been made to optimize the conditions for the cyclization step.