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A FACILE APPROACH TO RING C MODIFIED STEROIDS

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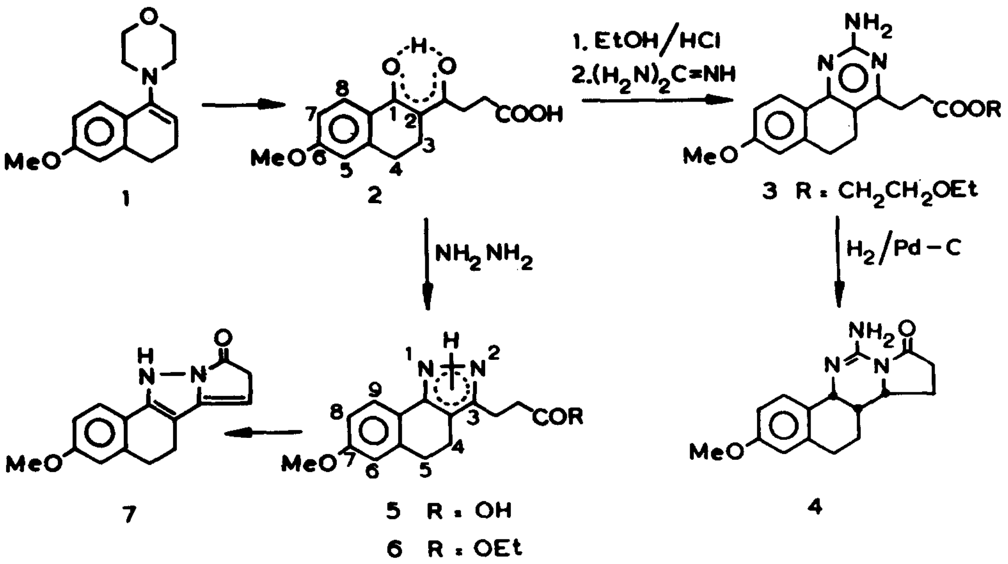
A variety of new approaches for the total synthesis of modified steroids, involving an enamine reaction in the critical step of the synthetic plan, have been recently reported from this laboratory (1a-e). This communication describes a facile transformation of the enamine derived from 6-methoxytetralone-1 to certain ring C modified steroids.

The morpholine enamine of 6-methoxytetralone-1 (1) was conveniently prepared (80%) by the method of White and Weingarten (2); [b.p. 138-140°/2x10^{-5} mm; ν_{max}^{neat} 1620 cm^{-1} (N-C=C); δ^{CDCl_3} 5.12t (1H, C=C-H)]. Acylation of enamine 1 with the acid chloride of monomethyl succinate, using two equivalents of 1, followed by acidic hydrolysis, yielded diketo acid 2; m.p. 165-166°; structure of 2 was attested by its spectral data; ν_{max}^{KBr} 2400-2700 (carboxyl O-H and C=C-OH), 1705 (carboxyl C=O) and 1610, 1600, 1560 cm^{-1}; δ (pentadeuteropyridine) 2.5-2.8 m (4H, C_3 and C_4 methylene protons), 2.95 s (4H, $CO-CH_2CH_2COOH$), 3.72 s (3H, OCH_3), 6.8 d (1H, C_5-H, J=2 c/s), 6.87 2 doublets (1H, C_7-H, J=2 c/s; J=8.5 c/s) and 8.0, d (1H, C_8-H, J=8.5 c/s). 2 was esterified smoothly to the corresponding ethyl ester with ethanol and HCl. When the latter was refluxed (24 h) with one equivalent of guanidine carbonate in 2-ethoxyethanol, the tricyclic system 3 was obtained in good yield: m.p. 104-107°, ν_{max}^{KBr} 3500, 3390 (NH_2), 1722 (ester C=O) and 1630, 1610, 1595, 1555 (pyrimidine). Reduction of 3 in an aqueous acidic solution (pH 3-4) over 10% Pd/C, under pressure (3 atmospheres), gave 11,13-diazasteroid 4, m.p. 205° (dec.), in 70 p.c. yield. Its molecular structure followed from its spectroanalytical data; mol.wt. (MS) Found: 285.14788; Calc. for $C_{16}H_{19}N_3O_2$: 285.14772; ν_{max}^{KBr} 3460 (N-H), 2500-2700 (bonded N-H) and 1710 cm^{-1} (lactam C=O); λ_{max}^{EtOH} 225 (10,000), 276 (1930) and 283 nm (1890). While the presence of a double bond in ring C was implied by mass spectrum and combustion analysis, the UV spectrum indicated that the same was not conjugated with the aromatic ring.



Location of the double bond and stereochemical assignment of the C_8, C_9 and C_{14} protons followed from an X-Ray crystal structure determination of the hydrobromide of 4.

While full crystallographic details will be published elsewhere the results of the determination which are relevant to the molecular structure are shown in Figs. 1-3. Fig. 1 gives the various bond angles and bond distances in the molecule. Of particular interest are the Newman projections (Fig. 2) along bonds forming the ring junctions. Conformations along C(9)-C(8) and C(8)-C(14) bonds are skew and the deformation of the dihedral angles in both cases varies between 6°-19°. From the projections it is evident that the B/C junction is cis and the hydrogens on C(8), C(9) and C(14) are all on the same side (cis) of the steroidal plane. It is noteworthy that the atoms of rings C and D excluding C(8) and C(15) lie in one plane (Fig. 3). Combined with the bond length data this suggests, as expected, considerable conjugation in the relevant portion of the protonated system. Although the N(11)-C(12) and C(12)-N bond lengths are very similar in the salt, the assignment of the double bond between N(11) and C(12) in the neutral compound (4) is consistent with the known tautomeric structure of the tetrahydro-2-aminopyrimidines.

Treatment of 2 with hydrazine hydrate resulted in the formation of the hydrazine salt of 5. From a solution of the latter in water, pure 5 could be precipitated as its zwitter ion, by adjusting the pH carefully to 3.5. The overall yield of the tricyclic acid (5), from 2, was 93 p.c. The acid (5) was esterified with HCl and ethanol to give crystalline ester 6; m.p. 105-106°; $\nu_{max}^{CHCl_3}$ 3500 (N-H) and 1720 cm^{-1} (ester C=O); λ_{max}^{EtOH} 272.5 nm (18,900); δ^{CDCl_3} 1.20 t and 4.1 q (5H, OCH_2CH_3), 2.4-3.2 m (8H, C_4, C_5, C_1.C_2, methylene protons), 3.75 s (3H, OCH_3), 6.66, 2 doublets (1H, C_8-H, J=2.5 c/s, J=8.5 c/s), 6.75 s

Fig. 1. Bond length and bond angles. The estimated standard deviations are 0.01 Å and 0.6° respectively.

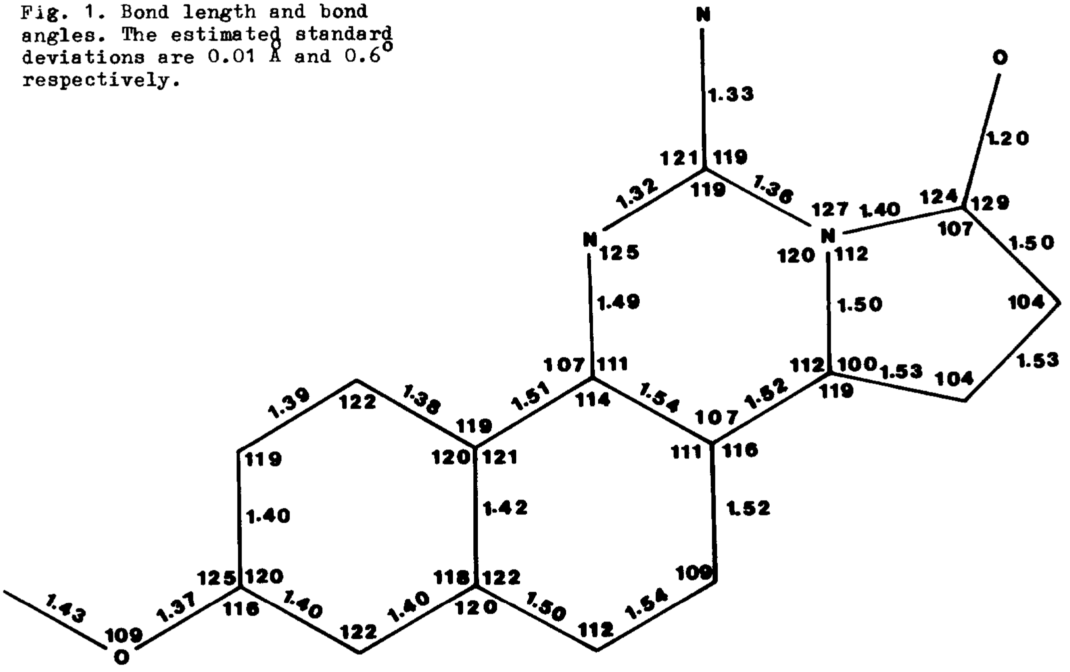


Fig. 2. Newman projections

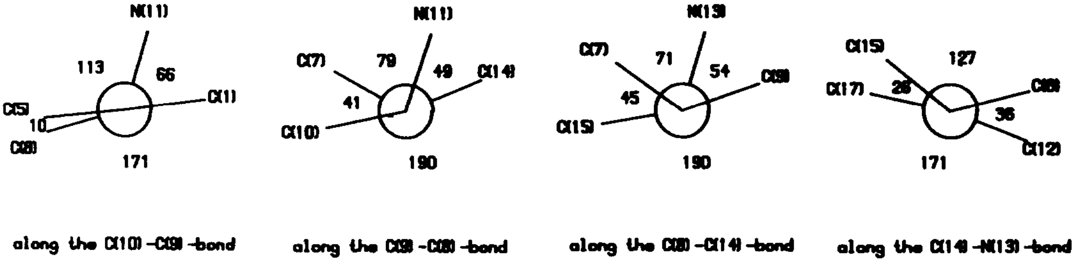
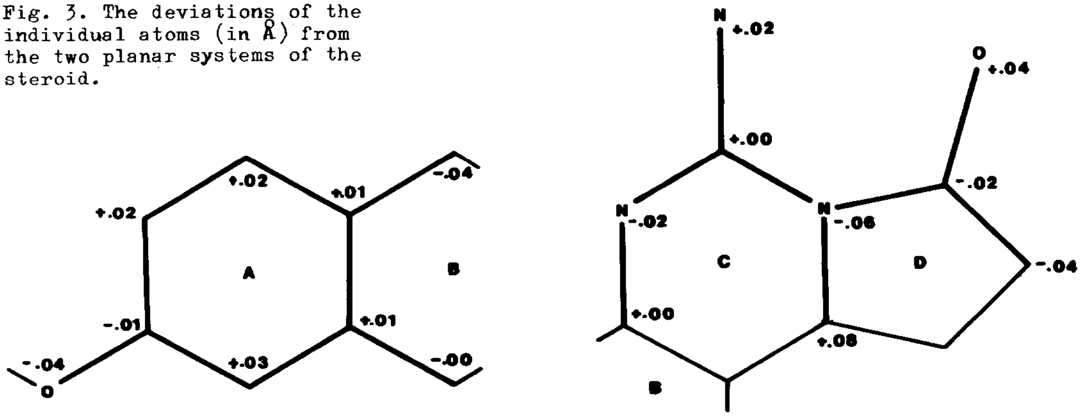


Fig. 3. The deviations of the individual atoms (in Å) from the two planar systems of the steroid.



(1H, C_6-H) and 7.6 d (1H, C_9-H, J=8.5 c/s). mol.wt. (MS) Found: 300.14856, $C_{17}H_{20}N_2O_3$ requires: 300.14738. Refluxing a solution of ester 6 in dioxane, with sodium hydride, gave a crystalline product. The latter is assigned C-norsteroidal structure 7 on the basis of the following spectral data: mol.wt. (MS) Found: 254.10496, $C_{15}H_{14}N_2O_2$ requires: 254.10552, ν_{max}^{KBr} 3400 (N-H) and 1665 cm^{-1} (bonded lactam C=O): λ_{max}^{EtOH} 274 (11,400) and 337 nm (15,200). The long wavelength band in the UV spectrum strongly supports the extended chromophore present in 7.

The preparation of hetero-steroids 4 and 7 illustrates the principle via which diketo ester 2 can be utilized in the synthesis of ring C modified steroids. Further applications of this versatile intermediate are currently under investigation.

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