TOTAL SYNTHESIS OF HETEROCYCLIC STEROIDS+, PART VII. SYNTHESIS OF (±)-8,13-DIAZA-3-THIA-A-NORGONA-1,5(10)-DIEN-17-ONE*

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ABSTRACT

The total synthesis of (±)-8,13-diaza-3-thia-A-norgona-1,5(10)--dien-17-one (XII) was achieved starting from 2-(2-thienyl) ethylamine (VII) and 3-succinimidopropionyl chloride (IX) as the A and D ring precursors respectively.

In parts I and II of this series, we reported the total synthesis of (±)-3-thia-A-norestra-1,5(10)-dien-17β -ol (I) and (±)-17-thia-3-methoxy-8α,14β-estra-1,3,5(10)-triene-17-dioxide (II) respectively (1,2). Thus in one case the benzenoid A ring of the estrone molecule was replaced by a nearly planar thiophene ring while in the other the electron withdrawing sulfone group was introduced in place of the C_{17}-carbonyl group. In the synthesis of (±)-3,17-dithia-A-nor-14β-estra-1,5(10),6,8-tetraene-17-dioxide (III), presented in part III, the combination of the above mentioned structural modifications were embodied (3). Lastly, the total synthesis of (±)-3-methoxy-6-aza-12-thia-12-dioxo-B-nor-14β-estra--1,3,5(10),8-tetraen-17α-ol (IV) utilising the Fischer indole synthesis was reported in part VI (4).

The azasteroids are the most common among the synthetic heterocyclic steroids. These modified steroids have been shown to possess varied biological activities, such as anti-viral (5), local

anaesthetic (6), analgesic (7,8), anti-inflammatory (8) properties etc. The most important among the azasteroids are the A-benzenoid--8,13-diazasteroids which have been the subject of several syntheses. The benzenoid A ring in these modified steroids could as well be replaced by a thiophene ring leading to (±)-8,13-diaza-3-thia-A--norgona-1,5(10)-dien-17-one (XII), the total synthesis of which is described in the present paper.

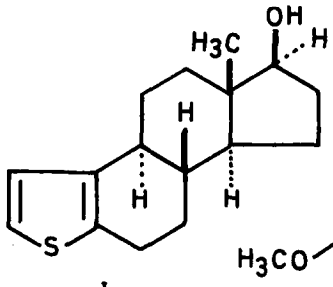
Several synthetic routes have been reported in the literature for the preparation of the A-benzenoid-8,13-diazasteroids. Of these, the route followed by Taylor and Lenard for the synthesis of (±)-2,3--dimethoxy-8,13-diazagona-1,3,5(10)-trien-17-one (V) and (±)-2,3--dimethoxy-8,13-diazagona-1,3,5(10)-triene (VI) (7) was thought to be most suitable for the synthesis of the A-thiopheno-8,13-diazasteroid (XII) as 2-(2-thienyl)ethylamine (VII) (9) and 3-succinimidopropionyl chloride (IX) (10) as the A and D ring precursors respectively are readily accessible.

The amine (VII) was condensed with the acid chloride (IX) in dry tetrahydrofuran in presence of pyridine to give N-(2-thienyl-ethyl)-3-succinimidopropionamide (X) in 46% yield. The IR (KBr) spectrum showed bands at 3390 (amide NH), 1770 and 1692 (succinimido carbonyls) (11) and 1669 cm^{-1} (amide C=O). The NMR ($CDCl_3$) spectrum exhibited a four proton singlet at δ 2.68 for the N-substituted succinimido moiety and multiplets at δ 5.98 (HNC=O) and δ 7.11 (three thiophene protons). The amide (X) when subjected to the Bischler-Napieralski cyclisation yielded a light yellow colored liquid in 76% yield. The TLC analysis of the crude product revealed the presence of a single compound. However the product was difficult

to purify as it decomposed to succinimide when distillation under reduced pressure was attempted. It showed a prominent peak at m/e 262 (M^+). The UV (MeOH) spectrum showed absorption maxima at 223, 228 and 258 nm with high ϵ values (conjugated thiophenic system) (12). The absence of bands at 3390 (amide NH) and 1669 (amide C=O) with the concurrent appearance of a band at 1626 cm^{-1} (C=N) in the IR ($CHCl_3$) spectrum suggested that the Bischler-Napieralski product contained 8,13-diaza-3-thia-8,14-seco-A-norgona--1,5(10),8-triene-14,17-dione (XI) as a major constituent. The structure was further supported by the absence of a signal for the NH proton and that for the vinyl proton in the NMR ($CDCl_3$) spectrum of the reaction product. Reductive cyclisation of the secosteroid (XI) to 8,13-diaza-3-thia-A-norgona-1,5(10)-dien-17--one (XII) was achieved in 68% yield by catalytic hydrogenation over platinum oxide. The UV (MeOH) spectrum had an absorption maximum at 233 nm (substituted thiophenic system) indicating the hydrogenation of the C=N bond conjugated to the thiophene ring. The IR (KBr) spectrum showed bands at 2857 and 2778 cm^{-1} (Bohlmann bands) (13). The absence of bands at 1773 and 1709 (succinimido carbonyls) and 1626 (C=N) with the concurrent appearance of band at 1667 cm^{-1} (C=O) confirmed the hydrogenation of the C=N bond and the subsequent involvement of the succinimido ring during reductive cyclisation which was further supported by the absence of a singlet at δ2.62 (N-substituted succinimido protons) in the NMR ($CDCl_3$) spectrum.

The stereochemistry and the overall configuration of the 8,13-diazasteroid (XII) was established by the study of its IR and NMR spectral data and by analogy with the work on the synthesis and the stereochemical determination of A-benzenoid-8,13-diazasteroid (V) by Taylor and Lenard (7), Redeuilh and Viel (14) and Burckhalter and co-workers (15). The Bohlmann bands (13) in the IR spectrum and the upfield shift for the C_9 proton in the NMR spectrum (16) suggested a trans stereochemistry for the B/C ring junction.

A closer look at the NMR spectrum of the 8,13-diazasteroid (XII) revealed two signals at δ 4.05 and δ 4.32. The assignment of the signal at δ 4.05 to the C_{14} proton was in accordance with the reported chemical shift at δ 4.05 for the C_{8a} proton in 2-methyl-2,3,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrimidin-4-one (XIII) (17) as the C_{14} proton in the 8,13-diazasteroid (XII) had the same environment as that of the C_{8a} proton in the amide (XIII). Further, Redeuilh and Viel reported the chemical shift at δ 4.05 for the C_{14} proton in the A-benzenoid-8,13-diazasteroid (V) (14). The other signal at δ 4.32 could be assigned to the C_{12} equatorial proton as Redeuilh and Viel had also reported the signal at δ 4.34 for the C_{12} equatorial proton in the A-benzenoid-8,13-diazasteroid (V) (14). It was observed that any proton that lies in the plane of an amide group and cis to the carbonyl group experiences an anisotropic paramagnetic effect resulting in its deshielding and hence the signal for the C_{12} equatorial proton was observed in the lower field region (13).



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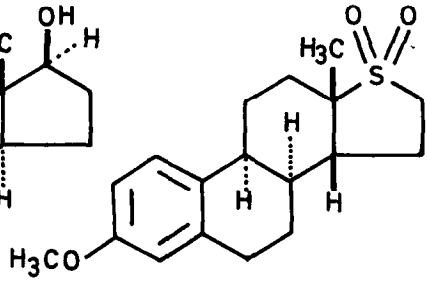

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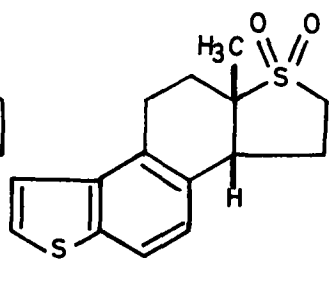

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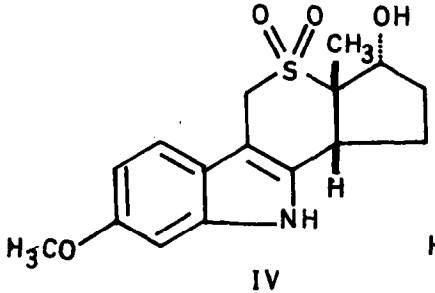

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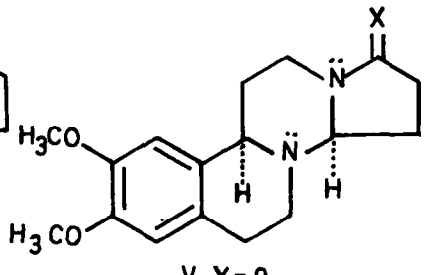
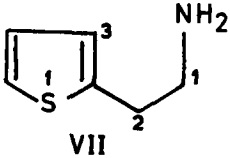


V, X = O
VI, X = H, H



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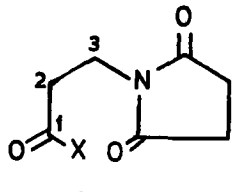
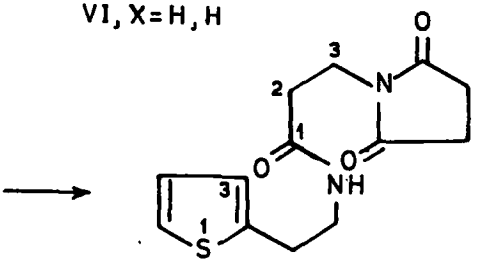
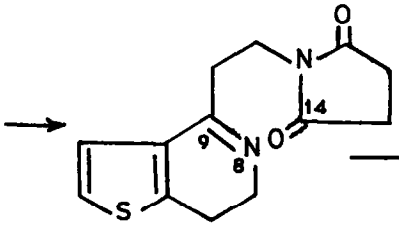


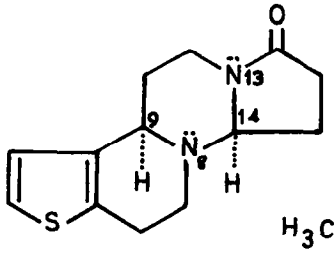
VIII, X = OH
IX, X = Cl



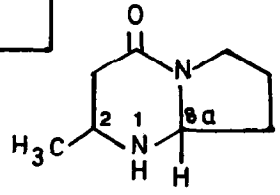
X



XI



XII



XIII

The stereochemistry of the C/D ring junction in the 8,13--diazasteroid (XII) was assigned as trans by analogy with the work of Redeuilh and Viel on the synthesis of the A-benzenoid-8,13--diazasteroid (V) (14).

The A-thiopheno-8,13-diazasteroid (XII) and the A-benzenoid--8,13-diazasteroid (V) are structurally similar except for the A rings. An identical sequence of reactions has been employed in the synthesis of both the modified steroids. Therefore it might reasonably be assumed that the same mechanistic pathways have been followed in the formation of these two compounds. Further, their IR and NMR spectral data were comparable. The trans-anti-trans configuration was assigned to the A-benzenoid-8,13-diazasteroid (V) on the basis of X-ray crystallographic studies (15). Hence, it could be concluded that the 8,13-diazasteroid (XII) has the trans--anti-trans configuration.

EXPERIMENTAL (19)

N-(2-Thienylethyl)-3-succinimidopropionamide (X)

A solution of 3-succinimidopropionyl chloride (IX) /prepared from 3-succinimidopropionic acid (VIII) (10.26 g, 0.06 mole) and thionyl chloride (44 ml, 0.82 mole)/ in dry tetrahydrofuran (distilled over lithium aluminium hydride, 50 ml) was added dropwise to a solution of 2-(2-thienyl)ethylamine (VII) (7.68 g, 0.06 mole) in dry tetrahydrofuran (50 ml) in presence of pyridine (dried over potassium hydroxide pellets, 6.5 ml) at 0° under nitrogen atmosphere with stirring. After the addition was over, the solution was stirred overnight. It was then decomposed by pouring on ice-cold water and extracted with chloroform (3 x 50 ml). The combined organic layers were washed with hydrochloric acid (10%, 3 x 20 ml) followed by brine and dried over anhydrous sodium sulfate. The solvent was removed on a water--bath to give a crude dark colored product (10.3 g), which was chromatographed over silica gel (170 g, eluent: 3% methanol in

chloroform). Fractions showing a single spot on the TLC were mixed and the solvent was removed to afford pure amide (X) which was further purified by crystallisation from ethyl acetate, mp 128°; yield: 7.75 g (45.8%). The analytical sample was prepared by recrystallisation from ethyl acetate; mp 128°. IR: (KBr) 3390 (amide NH), 1770, 1692 (succinimido carbonyls), 1669 (amide C=O), 1546, 1408, 1342, 1242, 1160 cm^{-1}. UV: (MeOH) 232 nm, log ϵ 3.96 (substituted thiophenic system). NMR: ($CDCl_3$) δ 2.68 (4H, singlet) O=C-CH_2-CH_2-C=O; δ 5.98 (1H, multiplet) secondary amide proton; δ 7.11 (3H, multiplet) thiophene protons. Mass spectrum: m/e 280 (M^+), 184, 182, 155, 154, 126, 112, 111, 110, 97.

Anal. Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.71; H, 5.75; N, 10.00; S, 11.42. Found : C, 55.94; H, 5.65; N, 9.72; S, 11.20%.

The Bischler-Napieralski cyclisation of N-(2-thienylethyl)--3-succinimidopropionamide (X) to 8,13-diaza-3-thia-8,14--seco-A-norgona-1,5(10),8-triene-14,17-dione (XI)

To a solution of N-(2-thienylethyl)-3-succinimidopropionamide (X) (1.4 g, 5 m mole) in toluene (dried over sodium, 100 ml) was added freshly distilled phosphorus oxychloride (4.6 ml, 0.05 mole) and the reaction mixture was refluxed under nitrogen atmosphere for 2 hrs. It was cooled and then decomposed by slow addition of ice-cold water. The dark colored residue dissolved slowly in water on keeping for some time. The toluene layer was separated from the aqueous solution and extracted with hydrochloric acid (10%, 2 x 10 ml). The acidic extracts and the original aqueous portion were mixed and extracted with chloroform (2 x 50 ml) to remove the starting amide (X). The acidic portion was basified with sodium carbonate and extracted with chloroform (3 x 50 ml) and dried over anhydrous sodium sulfate. Removal of the solvent left the residue of the secosteroid (XI); yield: 1 g (76.3%). The TLC analysis of the crude product revealed that it consisted of a single compound. However it was difficult to purify as it decomposed to succinimide when distillation under reduced pressure was attempted and was therefore used for the next reaction without further purification. IR: ($CHCl_3$) 2985, 1778, 1709 (succinimido carbonyls), 1626 (C=N), 1527, 1399, 1250, 1163 cm^{-1}. UV: (MeOH) 223 nm, log ϵ 4.19; 228 nm, log ϵ 4.18; 258 nm, log ϵ 3.64 (conjugated thiophenic system). NMR: ($CDCl_3$) δ 2.62 (4H, singlet) O=C-CH_2-CH_2-C=O; δ 7.17 (2H, singlet) thiophene protons. Mass spectrum: m/e 262 (M^+), 261, 164, 163, 162, 135, 99.

8,13-Diaza-3-thia-A-norgona-1,5(10)-dien-17-one (XII)

To a solution of 8,13-diaza-3-thia-8,14-seco-A-norgona--1,5(10),8-triene-14,17-dione (XI) (1.05 g, 4 m mole) in ethanol (30 ml) was added platinum oxide catalyst (100 mg) and the mixture was hydrogenated at 53 psi for 17-18 hrs. The catalyst was

filtered and the solvent was removed on a water-bath to afford a crude product (1 g), which was chromatographed over alumina (neutral, gr II, 150 g eluent : chloroform). Fractions showing a single spot on the TLC were mixed and the solvent was removed. The product was crystallised from benzene-pet. ether 60-80° affording a white crystalline product, mp 138°; yield: 0.68 g (68.4%). The analytical sample was prepared by recrystallisation from benzene-pet. ether 60-80°; mp 139°. IR: (KBr) 2941, 2857, 2778 (Bohlmann bands), 1667 (C=O), 1439; 1357, 1299, 1266, 1190, 1099, 1056, 717 cm^{-1}. UV: (MeOH) 233 nm, log ϵ 3.91 (substituted thiophenic system). NMR: ($CDCl_3$) δ 4.05 (1H, multiplet) C_{14} proton; δ 4.32 (1H, multiplet) C_{12} equatorial proton; δ 6.84 (1H, doublet J = 6.0 Hz) and δ 7.17 (1H, doublet J = 6.0 Hz) thiophene protons. Mass spectrum: m/e 248 (M^+), 191, 164, 138, 112, 111.

Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.89; H, 6.50; N, 11.28; S, 12.90. Found: C, 63.16; H, 6.69; N, 11.08; S, 13.18%.

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NOTES AND REFERENCES

\+ This paper forms a part of the Ph.D. thesis of S.H.T. submitted to the University of Bombay in 1982.

* All the compounds in the synthetic sequence are racemic. To clarify the stereochemical presentation, only one enantiomer is depicted.

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19. Recorded temperatures are uncorrected. IR spectra were taken on a Perkin-Elmer Infracord spectrophotometer model 137 B as films or as chloroform solution in case of liquids and as KBr discs for solid samples. UV spectra were determined on a Carl-Zeiss spectrophotometer RPQ-20 A as solution in methanol, NMR spectra were obtained on a Varian A-60-A spectrometer, using TMS as internal standard. Mass spectra were recorded on VG Micromass model 7070F spectrometer.