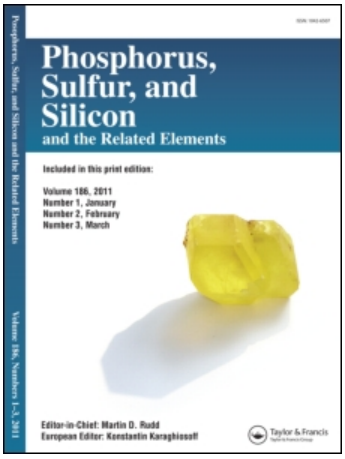

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NEW POLYHETERO POLYCYCLIC RING SYSTEMS: PART-XIII: SYNTHESIS OF STEROID-TYPE COMPOUNDS DERIVED FROM 7-CARBOMETHOXYCARBONYL-5,9-BISTHIA-6-OXO-4,5,6,7,8,9-HEXAHYDRONAPHTHO[2,1-b] THIOPHENE

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NEW POLYHETERO POLYCYCLIC RING SYSTEMS: PART-XIII: SYNTHESIS OF STEROID-TYPE COMPOUNDS DERIVED FROM 7-CARBOMETHOXYCARBONYL-5,9-BISTHIA-6-OXO-4,5,6,7,8,9-HEXAHYDRONAPHTHO [2,1-b] THIOPHENE

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The total syntheses of isoxazolo and pyrazolo-derivatives (steroid-type compounds) derived from the tricyclic ketone, 5,9-dithia-6-oxo-4,5,6,7,8,9-hexahydronaphtho [2,1-b] thiophene are described.

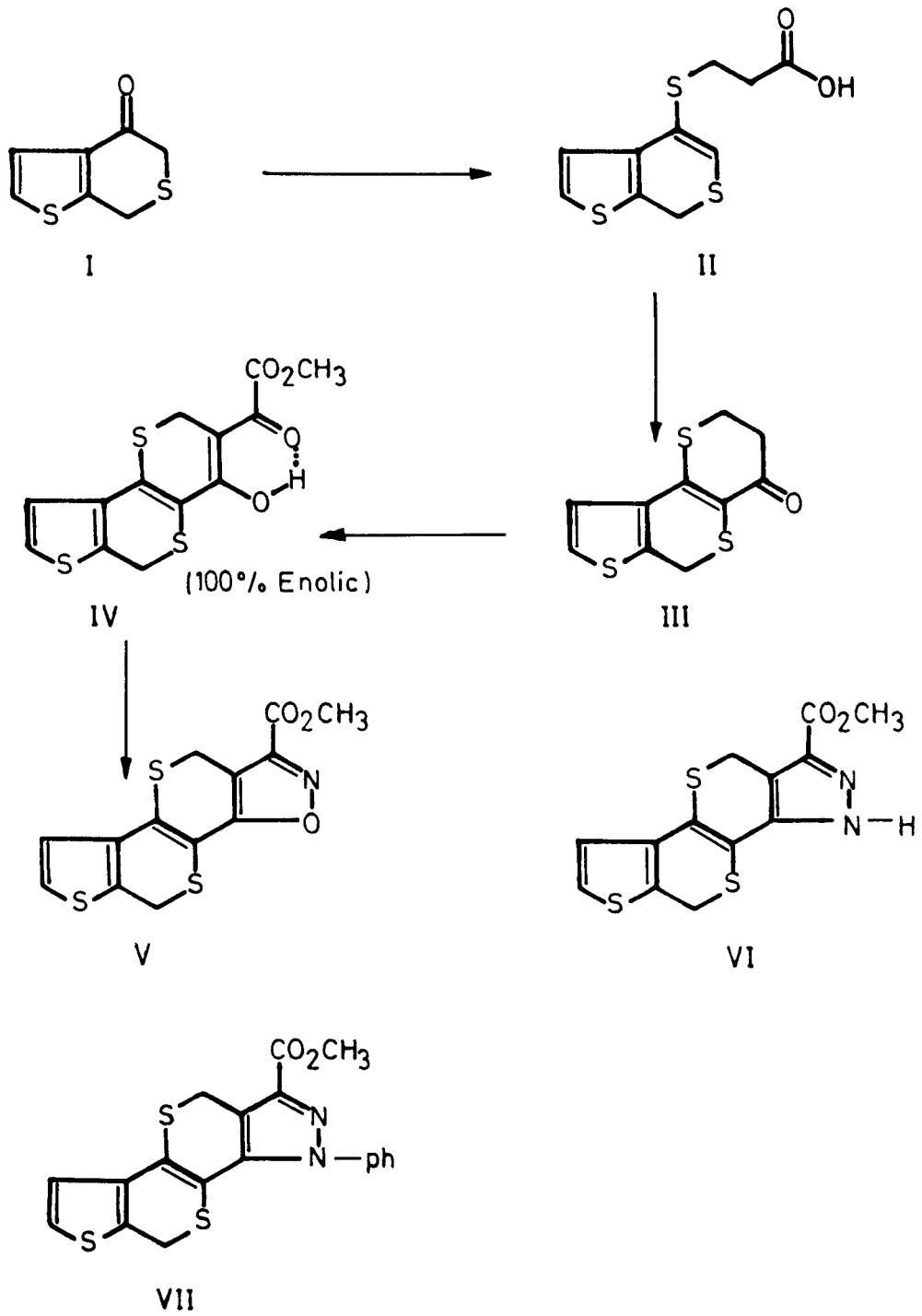
INTRODUCTION

Recent publications[1-6] point out that several steroidal analogues with replacement of D-ring of the normal steroid by an isoxazole or pyrazole ring system and incorporation of heteroatoms such as O.N and S into the steroid skeleton exhibit interesting biological properties[7-10] such as anabolic, anti-tumor, anti-inflammatory, hypotensive etc. A careful survey of literature revealed the fact that there has been no report till date on the synthesis of heterocyclic analogues of the hitherto known A-nor-3-thiaestrone.[11-13] In continuation[14,15] of our interest in the synthesis of newer types of heterocyclic steroids and elucidation of structure-activity correlation of these steroids, we wish to report herein the total synthesis of new steroid type of heterocycles.

DISCUSSION

The starting material 1,6-bisthia-4,5,6,7-tetrahydroinden-4-one (I) (Scheme 1) was prepared according to the procedure described by Alum and Thiagarajan.[16] The heterocyclic ketone (I) on condensation with β-mercaptopropionic acid in refluxing benzene containing trace amount of p-toluenesulphonic acid afforded the bicyclic acid, β-(1,6-bisthia-6,7-dihydroindene-4-ylthio) propionic acid (II), as a dark brown solid in 65% yield. Cyclodehydration of the acid (II) with phosphorus pentoxide in refluxing benzene gave the tricyclic ketone, 5,9-dithia-6-oxo-4,5,6,7,8,9-hexahydronaphtho [2,1-b] thiophene (III) as yellow flakes, m.p. 98°, in 40% yield. Condensation of the tricyclic ketone (III) with dimethyl oxalate in benzene in presence of dry sodium methoxide, gave the corresponding glyoxalate derivative, 7-carbomethoxycarbonyl-5,9-bisthia-6-oxo-4,5,6,7,8,9-hexahydronaphtho [2,1-b] thiophene (IV) ás a red crystalline solid, m.p. 128°, in 80% yield. The spectral data (vide experimental) indicated clearly that it exists only in the enolic form.

The aforementioned glyoxalate derivative (IV) on condensation with hydroxylamine hydrochloride in refluxing glacial acetic acid furnished the corresponding isoxa-



SCHEME 1

zole, A-nor-3,7,11-tristhia-17-methoxycarbonyl-15-oxa-16-azagona-1,5(10),8,13,16-pentaene (V), as yellow crystalline solid, m.p. 155°, in 70% yield.

Condensation of the same glyoxalate derivative (IV) with hydrazine hydrate in refluxing ethanol gave the anticipated pyrazole derivative, A-nor-3,7,11-tristhia-17-methoxycarbonyl-15,16-diazagona-1,5(10),8,13,16-pentaene (VI) as an amorphous solid, m.p. 101–103°, in 55% yield. Similarly condensation of (IV) with phenylhydrazine hydrochloride gave A-nor-3,7,11-tristhia-16-phenyl-17-methoxycarbonyl-15,16-diazagona-1,5(10),8,13,16-pentaene (VII) as an amorphous solid, m.p. 101–103°, in 55% yield. The other possible isomeric structures for compounds (VI and VII) were ruled out based mainly on analogous reactions reported in literature for such pyrazole derivatives[3,4,17] and also from the X-ray diffraction studies carried out in this Laboratory on structurally similar pyrazole derivatives.[18] The structure of 17-methoxycarbonyl-15-phenyl-15,16-bisaza-7,11-bisthiagona-1,3,5(10),8,13,16-hexaene (VIII) was established beyond doubt by its single crystal X-ray analysis. This study indicated that the phenyl group was present at position 15 only. The aforementioned heterocyclic steroid (VIII) was also prepared in an analogous manner as reported for (VII).

EXPERIMENTAL

NMR spectra were recorded on Varian XL 100 spectrometer using TMS as internal standard. IR spectra were measured using Perkin–Elmer 257 Grating spectrophotometer. Mass spectra were determined with *MATCH 7* spectrometer. Melting points are uncorrected.

1,6-Bisthia-4,5,6,7-tetrahydroindene-4-one[16] *(I)*:

2-Chloromethylthiophene (26 g) on condensation with thioglycollic acid (19 g) in presence of 2N sodium hydroxide (123 ml) afforded 1-(2′-thienyl)-2-thiabutyric acid (27 g) as a colorless liquid, b.p. 180°C/10 mm (reported,[16] b.p. 206°C/15 mm). 1-(2′-Thienyl)-2-thiabutyric acid (25 g) on cyclodehydration with phosphorus pentoxide in refluxing benzene gave the desired 1,6-bisthia-4,5,6,7-tetrahydroindene-4-one (8.7 g) as a reddish yellow liquid, b.p. 150–155°C/15 mm (reported,[16] b.p. 168°C/16 mm).

β-(1,6-Bisthia-6,7-dihydroindene-4-ylthio)propionic acid (II):

A solution of the bicyclic ketone (I) (12 g), β-mercapto-propionic acid (7.5 g) and p-toluenesulphonic acid (600 mg), in dry benzene (125 ml) was refluxed for 16 hours using a Dean–Stark water separator. The benzene solution was cooled and extracted with 2N sodium carbonate solution (3 × 40 ml). The combined alkaline extracts was cooled, acidified with ice cold dilute hydrochloric acid (1 : 1) and extracted with benzene (3 × 60 ml). The combined benzene extract was washed with water (2 × 40 ml) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the acid (II) as a dark brown liquid (11.5 g, 65%) which on preparative chromatography employing methylene chloride and ethyl acetate (8 : 2) afforded the analytical sample. IR(KBr)ν_{max} 3040 (broad), 1700, 1415 cm^{-1}; NMR (acetone-d_6); δ, 2.85 (t, 2H), 3.15 (t, 2H), 4.30 (s, 2H), 6.70 (s, 1H) and 7.50 (s, 2H).

Anal: Calcd for $C_{10}H_{10}O_3S_3$:	C, 46.51;	H, 3.88
Found:	C, 46.93;	H, 3.98

5,9-Bisthia-6-oxo-4,5,6,7,8,9-hexahydronaphtho [2,1-b] thiophene (III):

A mixture of the acid (II) (10.1 g) and P_2O_5 (40 g) in dry, thiophene-free benzene (150 ml) was refluxed for 2½ hours. The reaction mixture was cooled and the benzene solution decanted. The solid residue was decomposed with ice-cold water and extracted with benzene (5 × 30 ml). The combined benzene extract was washed with saturated sodium bicarbonate solution (2 × 40 ml) and then with water (2 × 30 ml). The benzene extract was dried (Na_2SO_4). Evaporation of the solvent gave a thick dark yellow liquid which on chromatography over silicagel (200 g) (60–120 mesh) furnished from benzene eluates the analytically

pure tricyclic ketone (III) as a yellow solid, m.p. 98°C (3.75 g, 40%), IR ($CHCl_3$)ν_{max} 1635 cm^{-1}; NMR ($CDCl_3$); δ 2.85 (t, 2H), 3.25 (t, 2H), 3.9 (s, 2H) and 7.1 (s, 2H). MS showed mass peaks at m/z 240 (M^+; 100%), 239 (54%), 212 (95%), 184 (36%), 140 (40%).

Anal: Calcd for $C_{10}H_8OS_3$; C, 50.00; H, 3.33
Found: C, 50.35; H, 3.85

7-Carbomethoxycarbonyl-5,9-bisthia-6-oxo-4,5,6,7,8,9-hexahydronaphtho [2,1-b] thiophene (IV):

To a suspension of sodium methoxide (prepared from 0.6 g of sodium and dry methanol) in dry benzene (25 ml) was added under dry nitrogen atmosphere, a solution of dimethyl oxalate (3.2 g) in dry benzene (25 ml), followed by a solution of the tricyclic ketone (III) (3.25 g) in dry benzene (40 ml). The temperature of the reaction mixture was maintained at 10–15°C. The mixture was stirred for 6 hours and then decomposed with ice-cold water (25 ml). The benzene layer was washed with 10% sodium hydroxide (2 × 15 ml). The combined alkaline extracts were cooled and acidified with dilute hydrochloric acid (1 : 1) and extracted with ether (3 × 75 ml). The ethereal layer was washed with saturated sodium chloride solution (2 × 50 ml) and dried (Na_2SO_4). Removal of the solvent left a reddish-brown gum which on crystallization form methanol yielded the analytical sample of (IV) as a red crystalline solid, m.p. 128°C, (3.53 g, 80%). IR ($CHCl_3$)ν_{max} 3300 (sharp intense band, intramolecularly hydrogen bonded-OH), 1720 (ester carbonyl), 1600 cm^{-1} (chelated carbonyl). NMR ($CDCl_3$); δ 3.95 (s, 3H), 4.05 (s, 2H, methylene at C_8), 4.4 (s, 2H, methylene at C_4) and 7.2 (s, 2H). MS gave ions at m/z 326 (M^+; 10%), 298 (8%), 267 (44%), 238 (88%), 212 (45%) and 184 (85%), 152 (42%), 140 (100%).

Anal: Calcd for $C_{13}H_{10}O_4S_3$; C, 47.86; H, 3.07
Found: C, 47.96; H, 3.15

A-Nor-3,7,11-tristhia-17-methoxycarbonyl-15-oxa-16-azagona-1,5(10),8,13,16-pentaene (V):

A mixture of the glyoxalate derivative (IV) (720 mg) and hydroxylamine hydrochloride (70 mg) in acetic acid (15 ml) was quickly heated in oil bath preheated to 180°C and continued refluxing for 7–8 minutes under anhydrous conditions. The brown solution was cooled and added to ice-cold water (50 ml). The precipitated solid was filtered and dried. A benzene solution (60 ml) of the above crude solid was quickly filtered through a short column of silicagel (60–120 mesh) (40 g). The resulting benzene eluate (50 ml) on evaporation furnished the isoxazole derivative (V) as a yellow solid which on recrystallization from methanol afforded the analytical sample, m.p. 155°C (0.5 g, 70%). IR(KBr)ν_{max} 1720 cm^{-1}; NMR (acetone-d_6); δ, 4.18 (s, 3H), 4.48 (s, 2H), 4.58 (s, 2H) and 7.55 (q, 2H). MS gave mass peaks at m/z 323 (M^+; 100%), 264 (70%), 236 (16%), 203 (16%), 184 (17%), 152 (11%), 140 (50%) and 108 (46%).

Anal: Calcd for $C_{13}H_9NO_3S_3$: C, 48.3; H, 2.79; N, 4.33
Found: C, 48.52; H, 2.91; N, 3.97

A-Nor-3,7,11-tristhia-17-methoxycarbonyl-15,16-diazagona-1,5(10),8,13,16-pentaene (VI):

A solution of the glyoxalate (IV) (0.7 g) and hydrazine hydrate (0.19 g) in ethanol (75 ml) and acetic acid (10 ml) was refluxed for 3 hours. The reaction mixture was concentrated and poured into ice-cold water (50 ml). The greenish-yellow solid precipitated was filtered and recrystallized from chloroform-methanol (1 : 1) to furnish the analytical sample of (VI) as an amorphous yellow solid, m.p. 181°C (0.42 g; 60%): IR (KBr)ν_{max} 3250 and 1700 cm^{-1}. NMR (DMSO-d_6): δ, 3.9 (s, 3H), 4.28 (s, 2H), 4.4 (s, 2H) and 7.28 (q, 2H); MS showed mass peaks at m/z 322 (M^+; 100%), 321 (99%), 308 (22%), 288 (41%), 262 (27%), 234 (24%), 184 (10%) and 152 (9%).

Anal: Calcd for $C_{13}H_{10}N_2O_2S_3$; C, 48.45; H, 3.11; N, 8.70
Found: C, 48.31; H, 3.32; N, 8.31

A-Nor-3,7,11-tristhia-16-phenyl-17-methoxycarbonyl-15,16-diazagona-1,5(10),8,13,16-pentaene (VII):

Treatment of the glyoxalate (IV) (0.5 g) with phenyl-hydrazine hydrochloride (0.3 g), adopting the procedure indicated above, gave a greenish yellow gummy solid which on recrystallization from ethanol-chloroform (1 : 1) afforded the analytical sample of (VII) as an amorphous solid, m.p. 101–103°C (0.34 g; 55%); IR (KBr)ν_{max} 1710, 1640, 1590 and 700 cm^{-1}; NMR (DMSO-d_6); δ, 3.9 (s, 3H, $COOCH_3$), 4.28 (s, 2H, methylene at C_{12}), 4.35 (s, 2H, methylene at C_6) and 7.15 to 7.5 (AB-quartet, J = 10 Hz)

Anal: Calcd for $C_{19}H_{14}N_2O_2S_3$; C, 57.27; H, 3.52; N, 7.03
Found: C, 57.32; H, 3.82; N, 7.53

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