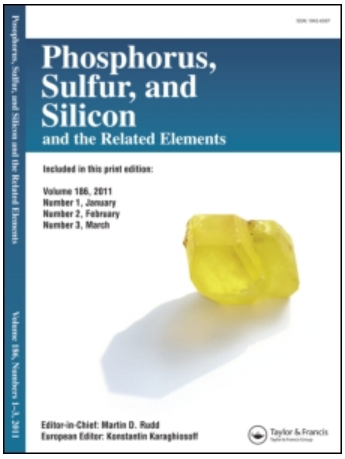

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POLYHETERO POLYCYCLIC RING SYSTEMS: PART XXVI: SYNTHESES OF HETEROCYCLIC STEROIDAL ANALOGUES DERIVED FROM 4-OXO-3, 4-DIHYDRO-2H,5H-THIOPYRANO [3,2-c][1]BENZOTHIOPYRAN

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POLYHETERO POLYCYCLIC RING SYSTEMS: PART XXVI: SYNTHESES OF HETEROCYCLIC STEROIDAL ANALOGUES DERIVED FROM 4-OXO-3,4-DIHYDRO-2H,5H-THIOPYRANO [3,2-c][1]BENZOTHIOPYRAN

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The total syntheses of the isoxazolo- and the pyrazolo-derivatives (steroidal analogues) derived from the tricyclic ketone, 4-oxo-3,4-dihydro-2H,5H-thiopyrano-[3,2-c][1]benzothiopyran[1] are described.

INTRODUCTION

Synthetic modifications of the steroidal nucleus and steroidal functional groups have been carried out to get modified steroids and steroidal analogues[2–7] which display unusual but interesting biological properties. In continuation of our studies on the syntheses of newer types of heterocyclic steroids[8–16] in a programme to undertake the biological screening of these compounds,[17] we wish to report, herein, the preparation of a few new steriod-type heterocycles.

DISCUSSION

The key-intermediate, 4-oxo-3,4-dihydro-2H,5H-thiopyrano-[3,2-c][1]benzothiopyran (I) required for the total syntheses of (III–V) was prepared according to the procedure developed earlier by Ramadas and Kumaresan.[1] Condensation of the tricyclic ketone (I) with dimethyl oxalate in the presence of dry sodium methoxide, in dry, thiophene-free, benzene afforded the corresponding glyoxalate derivative, 1-Hydrox-4,9-bisthia-1,2,3,4,9,10-hexahydrophenanthrene-2-glyoxalate (II), as a dark red solid, m.p. 105–107°C, in 88% yield. It is strongly evident from the spectral data (IR and ^{1}H-NMR) that the glyoxalate ester exists only in the enol form (vide-experimental).

Condensation of the glyoxalate ester (II) with hydroxylamine hydrochloride furnished the isoxazole derivative, 17-methoxycarbonyl-15-oxa-16-aza-6,11-bisthiagona-1,3,5(10),8,13,16-hexaene (III) as yellow needles, m.p. 147–148°C, in 69% yield.

The aforesaid glyoxalate derivative (II) on condensation with (i) methylhydrazine and (ii) phenylhydrazine hydrochloride gave the corresponding pyrazole derivatives (IV & V) respectively. Based on the X-ray diffraction studies[18] carried

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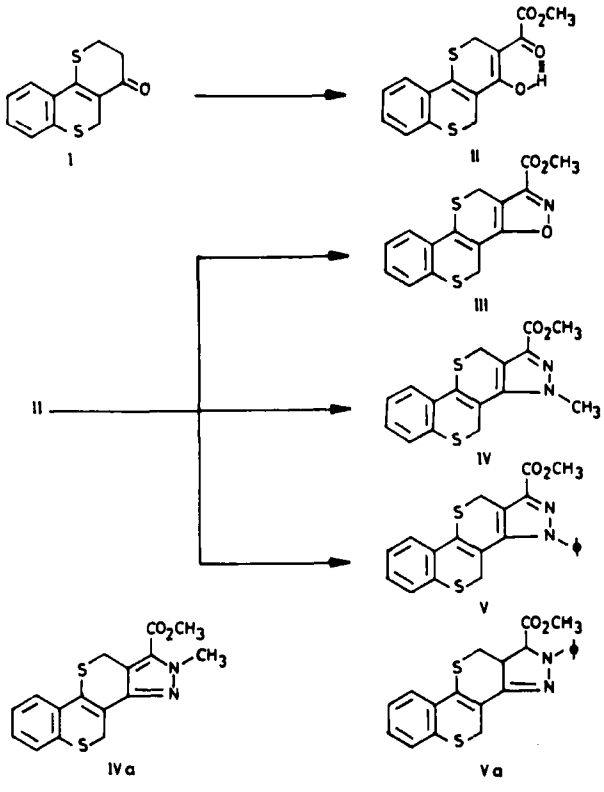

out in these Laboratories on structurally similar pyrazole derivatives, the alternative structures (IVa and Va) were ruled out.

EXPERIMENTAL

Melting points reported herein are uncorrected. Hexane, unless otherwise stated, refers to a petroleum ether fraction boiling at 60–80°C. IR spectra were recorded using Perkin–Elmer-1310 spectrophotometers. ^{1}H-NMR spectra were recorded on EM-390 spectrometer using TMS as the internal standard. Mass spectra were recorded on Varian MAT CH-7 spectrometer.

1-Hydroxy-4,9-bisthia-1,2,3,4,9,10-hexahydrophenanthrene-2-methylglyoxalate (II)

To a cooled (0–5°C) and stirred mixture of sodium methoxide (prepared from 0.46 g of sodium) and dimethyl oxalate (2.4 g) in dry benzene (15 ml) under nitrogen atmosphere was added a solution of the tricyclic ketone[1] (I) (2.34 g) in

dry benzene (40 ml). The resultant mixture was stirred for 8 hours at 0–5°C. Ice-cold water (50 ml) followed by ether (50 ml) was added. The organic layer was separated and washed with 5% aqueous solution of sodium hydroxide. The combined alkali extracts was chilled and acidified with cold, dilute HCl to give a dark red solid which was filtered and dried (3.0 g). The above compound crystallizes as orange red needles from methylene chloride-petroleum ether (40–60°) (2.8 g, yield 88%), m.p. 105–107°C; IR($CHCl_3$) ν_{max} 3400 (chelated —OH stretch), 1730 (ester carbonyl), 1590 (chelated carbonyl), 1520 and 1430 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.65 (s, 2H, methylene at C_3), 3.75 (s, 3H, —$COOCH_3$), 4.10 (s, 2H, Ar-S-CH_2), 6.8–7.6 (m, 4H, aromatic) and 15.0 (s, broad, 1H, enolic —OH, disappeared on D_2O exchange); MS showed peaks at m/z 320 ($M^{+\cdot}$, 43%), 260(26%), 233(100%), 232(89%), 205(15%), 203(20%), 177(23%). Anal. Calcd. for $C_{15}H_{12}O_4S_2$; C, 56.25: H, 3.75. Found C, 56.58; H, 3.61%.

17-Methoxycarbonyl-15-oxa-16-aza-6,11-bisthiagona-1,3,5(10), 8,13,16-hexaene (III)

A mixture of the glyoxalate ester (II) (0.48 g) and thoroughly dried hydroxylamine hydrochloride (0.11 g) in freshly distilled glacial acetic acid (10 ml) was quickly heated to reflux in an oil bath preheated to 170°C and further refluxing continued for 7 minutes. The resultant brown solution was poured into ice-cold water. The crude yellow solid obtained was purified by passing through a short column of silica gel (20 g). Evaporation of the benzene eluates (200 ml) followed by recrystallization from hexane-chloroform (1:1) yielded the isoxazole derivative (III) (0.33 g) as yellow needles, m.p. 147–148°C, in 69% yield. IR($CHCl_3$) ν_{max} 1725 (conjugated carbonyl), 1680, 1450, 1435, 1250, 1210 and 1155 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.65 (s, 2H, methylene at C_{12}), 3.8 (s, 3H, —$COOCH_3$), 4.10(s, 2H, Ar—S—CH_2) and 6.8–7.6 (m, 4H, aromatic); MS gave ions at m/z 317($M^{+\cdot}$, 64%), 286(3%), 258(100%), 230(11%), 178(33%), 177(37%), 134(22%). Anal: Calcd. for $C_{15}H_{11}NO_3S_2$; C, 56.78; H, 3.47. Found C, 57.03; H, 3.80%.

17-Methoxycarbonyl-15,16-bisaza-15-methyl-6,11-bisthiagona-1,3,5(10),8,13,16-hexaene (IV):

Condensation of the glyoxalate (II) (0.64 g) with methylhydrazine (0.092 g) was carried out in glacial acetic acid (10 ml) for 3 hours in a similar way as described in the preparation of (III). Chromatographic purification of the crude solid over silica gel (30 g) gave from benzene eluates (300 ml), a yellow solid which recrystallized from hexane-methylene chloride affording the N-methylpyrazole analogue (IV) as yellow crystals (0.34 g), m.p. 140–141°C, in 52% yield. IR($CHCl_3$) ν_{max} 1715 (conjugated carbonyl), 1590, 1460 and 1370 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.65 (s, 2H, methylene at C_{12}), 3.80 (s, 3H, —$COOCH_3$), 3.95 (s, 2H, Ar—S—CH_2), 4.00 (s, 3H, N—CH_3) and 6.8–7.6 (m, 4H, aromatic); MS gave ions at m/z 330 ($M^{+\cdot}$, 100%), 315(52%), 271(38%), 270(18%), 238(25%), Anal. Calcd. for $C_{16}H_{14}N_2O_2S_2$, C, 58.18; H, 4.24. Found C, 58.10; H, 4.33%.

17-Methoxycarbonyl-15,16-bisaza-15-phenyl-6,11-bisthiagona-1,3,5(10),8,13,16-hexaene (V):

The glyoxalate (II) (0.64 g) on treatment with phenylhydrazine hydrochloride (0.29 g) in glacial acetic acid (10 ml) in the same manner described for the preparation of (III) furnished a crude yellow solid which on recrystallization from hexane-methylene chloride yielded the N-phenylpyrazole derivative as yellow needles (0.62 g), m.p. 176–178°C, in 79% yield. IR($CHCl_3$) ν_{max} 1715 (conjugated carbonyl), 1580, 1480, 1360 and 1200 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.05 (s, 2H, methylene at C_{12}), 3.80 (s, 3H, —$COOC\underline{H}_3$), 4.05 (s, 2H, Ar-S-$C\underline{H}_2$) and 6.8–7.7 (m, 9H, aromatic); MS indicated peaks at m/z 392 ($M^{+\cdot}$, 17%), 377(3%), 333(20%), 315(3%), 284(51%), 283(100%), 282(88%). Anal. Calcd. for $C_{21}H_{16}N_2O_2S_2$; C, 64.29; H, 4.08. Found C, 63.98; H, 4.27%.

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