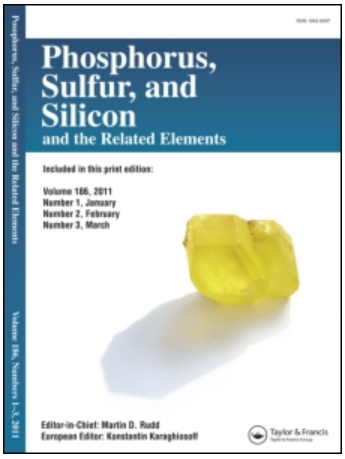

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POLYHETERO POLYCYCLIC RING SYSTEMS: PART XV: SYNTHESES OF STEROID-TYPE COMPOUNDS DERIVED FROM 1-OXO-4,10-DITHIA-1,2,3,4,9,10-HEXAHYDROPHENANTHRENE

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The total syntheses of isoxazolo- and pyrazolo-derivatives (steroid-type compounds) derived from the tricyclic ketone, 1-oxo-4,10-dithia-1,2,3,4,9,10-hexahydrophenanthrene are described.

INTRODUCTION

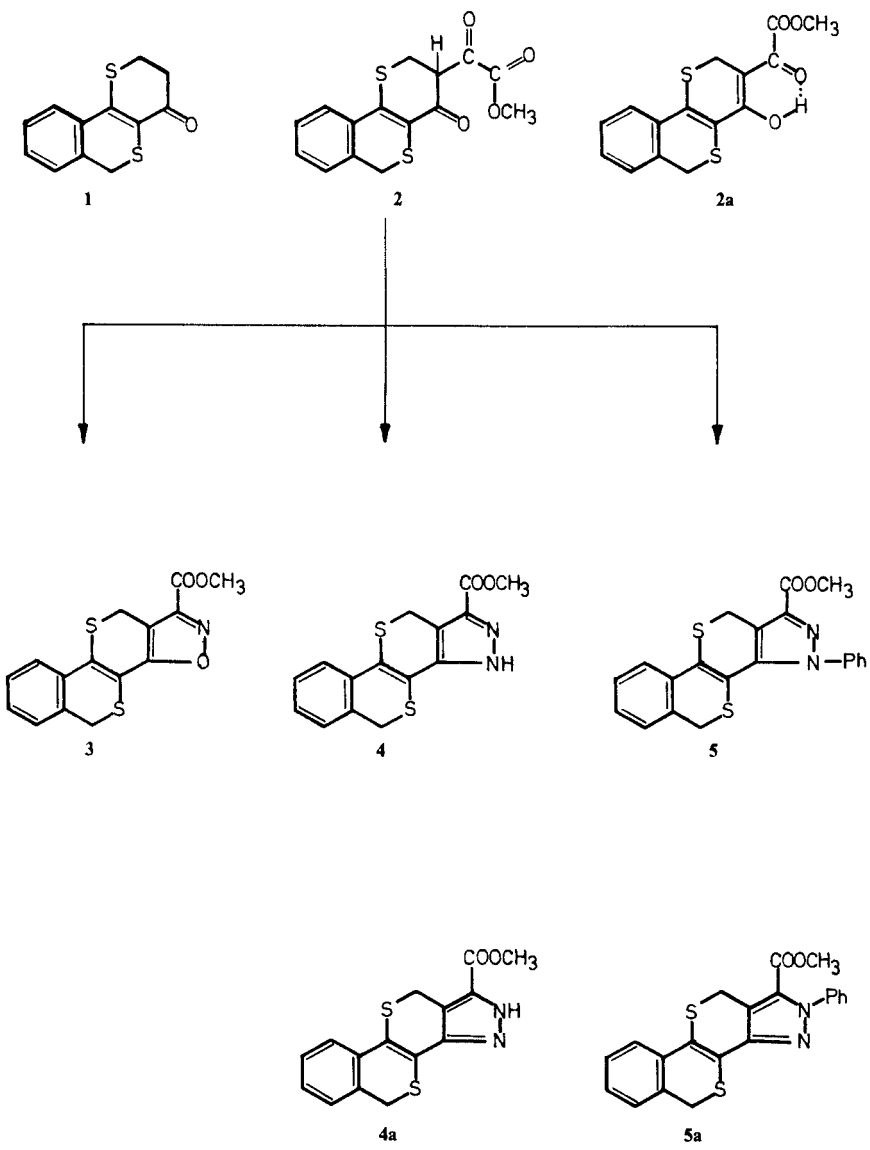
It is well-known[1-7] that the modified steroids obtained by the replacement of D-ring of a natural steroid hormone with an isoxazole or pyrazole ring or by the introduction of hetero atoms such as N, O and S in the steroid nucleus are found to display a wide spectrum of biological activity.[8-12] A careful survey of literature[13-19] on thiasteroids including the most recent compilation of literature on this subject by the authors of this paper[20] reveals interestingly that there has been no report till date on the synthesis of D-ring isoxazole and pyrazole analogues of aromatic steroids with sulfur in 7 and 11 positions of the steroid skeleton. In continuation of our studies on the syntheses of newer types of heterocyclic steroids and elucidation of the structure-activity relationships, we wish to report, herein, the preparation of new steroid-type heterocycles.

DISCUSSION

The key-intermediate, 1-oxo-4,10-dithia-1,2,3,4,9,10-hexahydrophenanthrene (**1**) required for the total syntheses of (**3–5**) (*vide*—Scheme I) was prepared according to the procedure reported earlier by Ramadas and Vijaya Krishna.[21] Condensation of the tricyclic ketone (**1**) with dimethyl oxalate in the presence of dry sodium methoxide gave the corresponding glyoxalate derivative, 1-oxo-4,10-dithia-1,2,3,4,9,10-hexahydrophenanthrene-2-glyoxalate (**2**) as orange red needles, m.p. 93°C, in 60% yield. It was evident from IR and NMR spectral data that the glyoxalate (**2**) existed only in the enolic form (**2a**) (*vide*—Experimental).

Condensation of the aforesaid glyoxalate derivative (**2a**) with hydroxylamine hydrochloride in refluxing glacial acetic acid furnished the corresponding isoxazole analogue, 1-methoxycarbonyl-5H,11H-isoxazolo[4,5-c]thiopyrano[3,2-c][2]benzothiopyran (**3**) as a yellow crystalline solid, m.p. 164°C, in 65% yield.

The glyoxalate (**2a**) on condensation with hydrazine hydrate gave the anticipated pyrazole analogue, 1-methoxycarbonyl-5,11-dihydro-3H-pyrazolo[4,5-c]thiopyrano-[3,2-c][2]benzothiopyran (**4**) as a yellow crystalline solid, m.p. 205–206°C, in 75% yield. Similarly, condensation of (**2a**) with phenylhydrazine hydrochloride gave the



SCHEME 1

expected 1-methoxycarbonyl-3-phenyl-5,11-dihydro-3H-pyrazolo[4,5-c]thiopyrano-[3,2-c][2]benzothiopyran (**5**) as a yellow crystalline solid, m.p. 220–222°C, in 70% yield.

The aforesaid condensation of the glyoxalate ester (**2**) with phenylhydrazine hydrochloride could, in principle, lead to the formation of two isomeric pyrazole derivatives (**5** and **5a**), but, in actual experiment, only one product was obtained. The single crystal X-ray analysis[22] of this product (**5**), m.p. 220–222°C, confirmed the structure as depicted in (**5**) (*vide*—Figure 1). Hence the alternative structure (**5a**) was ruled out. From a knowledge of the above X-ray analysis,[22] the alternative structure

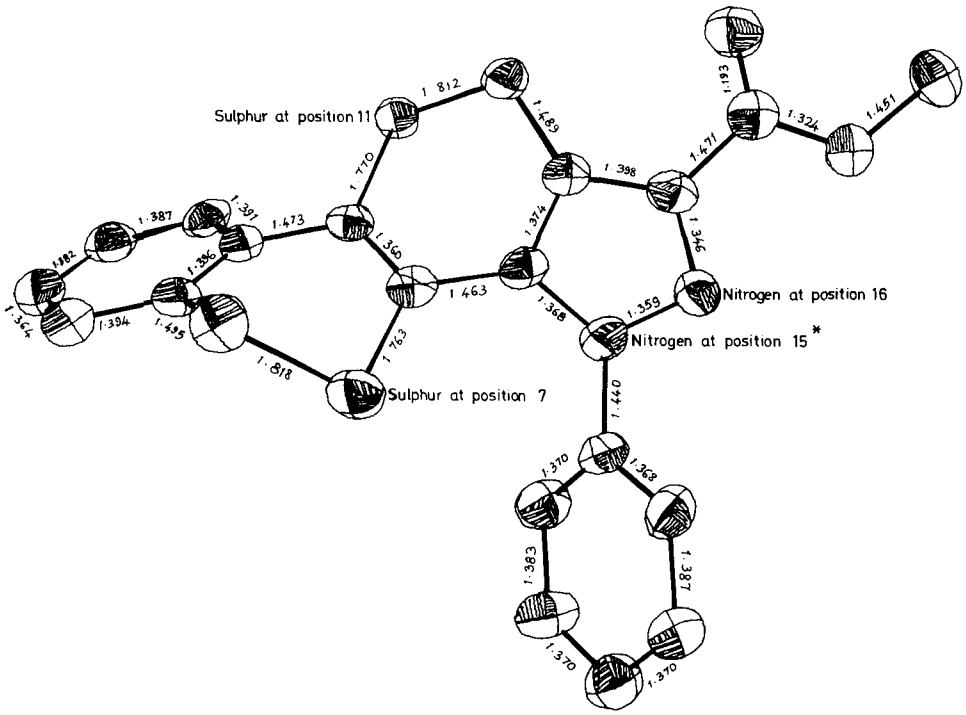


FIGURE 1 Ortep plot of (**5**). *Steroid numbering. Bond distances are given in Å.

(**4a**) was also ruled out for the product obtained on condensation of (**1a**) with hydrazine hydrate under identical experimental conditions.

The biological evaluation of the compounds (**1–5**) is in progress at May and Baker Laboratories, England through the courtesy of Prof. B. J. Heywood. Compound (**1**) was, however, found to be inactive when tested for herbicidal, insecticidal, antibacterial and antiprotozoal activity. The biological activity of the rest of the compounds will be published at a later date.

EXPERIMENTAL

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

1-Oxo-4,10-dithia-1,2,3,4,9,10-hexahydrophenanthrene-2-glyoxalate (2). A solution of 1-oxo-4,10-dithia-1,2,3,4,9,10-hexahydrophenanthrene (**1**) (4.68 g) in dry benzene (40 ml) was added dropwise to a cooled (0–5°C) and well-stirred mixture of dry sodium methoxide (prepared from 0.92 g of sodium) and dimethyl oxalate (4.8 g) in dry benzene (25 ml) under dry nitrogen atmosphere. As the condensation proceeded, a brownish solid gradually appeared. After stirring the mixture for 5 hours at 0–5°C, ice-cold water (100 ml) followed by ether (100 ml) was added. The organic layer was separated and washed with 5% aqueous sodium hydroxide solution. The combined alkali extracts were chilled and acidified with dilute hydrochloric acid (1 : 1) at 0–5°C to give a brownish red precipitate, which was filtered and dried. Very rapid chromatography of this solid over silicagel (70 g) gave from benzene-methylene chloride (1 : 1) eluates (3500 ml), an orange red solid. Recrystallization of this red solid from methylene chloride-petroleum ether (40–60°C) (1 : 1) yielded the analytical sample of the glyoxalate (**2**) as orange red needles, m.p. 93°C (2.83 g; 60%); IR ($CHCl_3$) ν_{max} 3650 (chelated OH stretch), 1725 (ester carbonyl), 1610 (chelated carbonyl), 1490, 1430

and 1260 cm^{-1}; NMR ($CDCl_3$); δ 3.8 (s, 2H, methylene at C_3), 3.95 (s, 3H, ester methyl), 4.4 (s, 2H, benzylic methylene); 7.1–7.9 (m, 4H, aromatic) and 10.5 (s, broad, 1H, enolic proton); MS gave the mass peaks at m/z 320 (M^+; 44%), 232 (100%), 289 (23%), 261 (50%), 233 (76%), 206 (23%); 180 (20%), 178 (27%) and 134 (45%). Anal: Calcd for $C_{15}H_{12}O_4S_2$; C, 56.25; H, 3.75. Found: C, 55.98; H, 4.21.

1-Methoxycarbonyl-5H,11H-isoxazolo[4,5-c]thiopyrano[3,2-c][2]benzothiopyran (3). A mixture of the glyoxalate derivative (**2**) (0.64 g) and thoroughly dried hydroxylamine hydrochloride (0.14 g) in freshly distilled glacial acetic acid (15 ml) was quickly heated on an oil bath preheated to 170°C and further refluxing continued for 7 minutes. The resulting reddish brown solution was poured into ice-cold water. The separated yellow solid was filtered and dried (0.6 g) and was purified by passing through a short column of silicagel (20 g). The solid obtained on evaporation of the benzene eluates (1200 ml) was recrystallized from chloroform-hexane (1 : 3) to yield the analytically pure sample of (**3**) as a yellow crystalline solid, m.p. 164°C (0.41 g; 65%); IR ($CHCl_3$) ν_{max} 1730 (ester carbonyl), 1685, 1490, 1550, 1435, 1150 (ring breathing vibrations of the trisubstituted[23] isoxazole moiety), 1230 and 1200 cm^{-1}; NMR ($CDCl_3$); δ 3.9 (s, 2H), 4.01 (s, 3H, ester methyl), 4.3 (s, 2H, benzylic methylene) and 7.0–8.0 (m, 4H, aromatic); MS gave ions at m/z 317 (M^+; 77%), 258 (100%), 230 (10%), 197 (23%), 178 (16%), 146 (6%) and 134 (36%). Anal: Calcd for $C_{15}H_{11}NO_3S_2$; C, 56.78; H, 3.47; N, 4.42. Found: C, 56.99; H, 3.99; N, 4.77.

1-Methoxycarbonyl-5,11-dihydro-3H-pyrazolo[4,5-c]thiopyrano[3,2-c][2]benzothiopyran (4). A solution of the glyoxalate (**2**) (0.64 g) in glacial acetic acid (12 ml) containing hydrazine hydrate (0.1 g) was refluxed for 3 hours and then poured into ice-cold water. The separated solid was filtered, dried (0.7 g) and its solution in methylene chloride (500 ml) was passed through a short column of silicagel (25 g). Evaporation of the methylene chloride eluates yielded a yellow solid, which on recrystallization from methylene chloride furnished the analytical sample of (**4**) as a yellow crystalline solid, m.p. 205–206°C (0.47 g; 75%); IR ($CHCl_3$) ν_{max} 3400 (NH stretch), 1720 (ester carbonyl), 1590, 1460, 1440, 1390 (ring breathing vibrations of trisubstituted[23] pyrazole moiety) and 1200 cm^{-1}; NMR ($CDCl_3$); δ 3.85 (s, 2H), 3.95 (s, 3H, ester methyl), 4.3 (s, 2H, benzylic methylene), 5.0 (s, broad, 1H, NH proton, disappeared on D_2O exchange) and 7.0–8.0 (m, 4H, aromatic); MS gave ions at m/z 316 (M^+; 100%), 301 (32%), 283 (39%), 257 (30%), 228 (23%) and 134 (20%). Anal: Calcd for $C_{15}H_{12}N_2O_2S_2$; C, 56.96; H, 3.79; N, 8.86. Found: C, 57.42; H, 3.85; N, 8.57.

1-Methoxycarbonyl-3-phenyl-5,11-dihydro-3H-pyrazolo[4,5-c]thiopyrano[3,2-c][2]benzothiopyran (5). Reaction of the glyoxalate (**2a**) (0.64 g) with pyenylhydrazine hydrochloride (0.29 g) was carried out in the same manner as described for (**4**). Chromatography of the solid (0.8 g) obtained from the above reaction over silicagel (25 g) furnished from benzene-methylene chloride eluates (1 : 1) (1800 ml) a yellow solid which on recrystallization from hexane-chloroform gave the analytical sample of (**5**) as a yellow crystalline solid, m.p. 220–222°C (0.55 g; 70%); IR ($CHCl_3$) ν_{max} 1715 (ester carbonyl), 1590, 1475, 1360 (ring breathing vibrations of tetrasubstituted[23] pyrazole moiety) and 1200 cm^{-1}; NMR ($CDCl_3$) δ 3.65 (s, 2H), 3.97 (s, 3H, ester methyl), 4.34 (s, 2H, benzylic methylene) and 7.0–8.0 (m, 4H, aromatic); MS showed mass peaks at m/z 392 (M^+; 45%), 377 (12%), 333 (100%), 300 (13%) and 77 (72%). Anal: Calcd for $C_{21}H_{16}N_2O_2S_2$; C, 64.29; H, 4.08; N, 7.14. Found: C, 64.70; H, 4.15; N, 7.37.

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