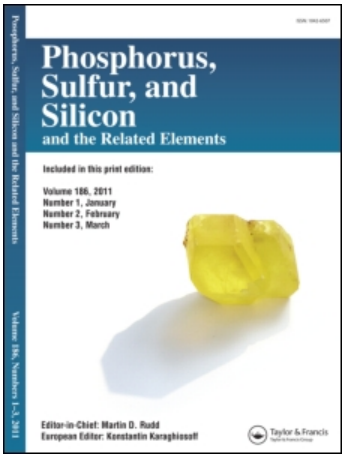

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NEW POLYHETERO POLYCYCLIC RING SYSTEMS: PART XIV: SYNTHESES OF 15-OXA-16-AZA AND 15,16-BISAZA ANALOGUES OF 3-DEOXY-12-THIAEQUILENIN

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NEW POLYHETERO POLYCYCLIC RING SYSTEMS: PART XIV: SYNTHESES OF 15-OXA-16-AZA AND 15,16-BISAZA ANALOGUES OF 3-DEOXY-12-THIAEQUILENIN

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

INTRODUCTION

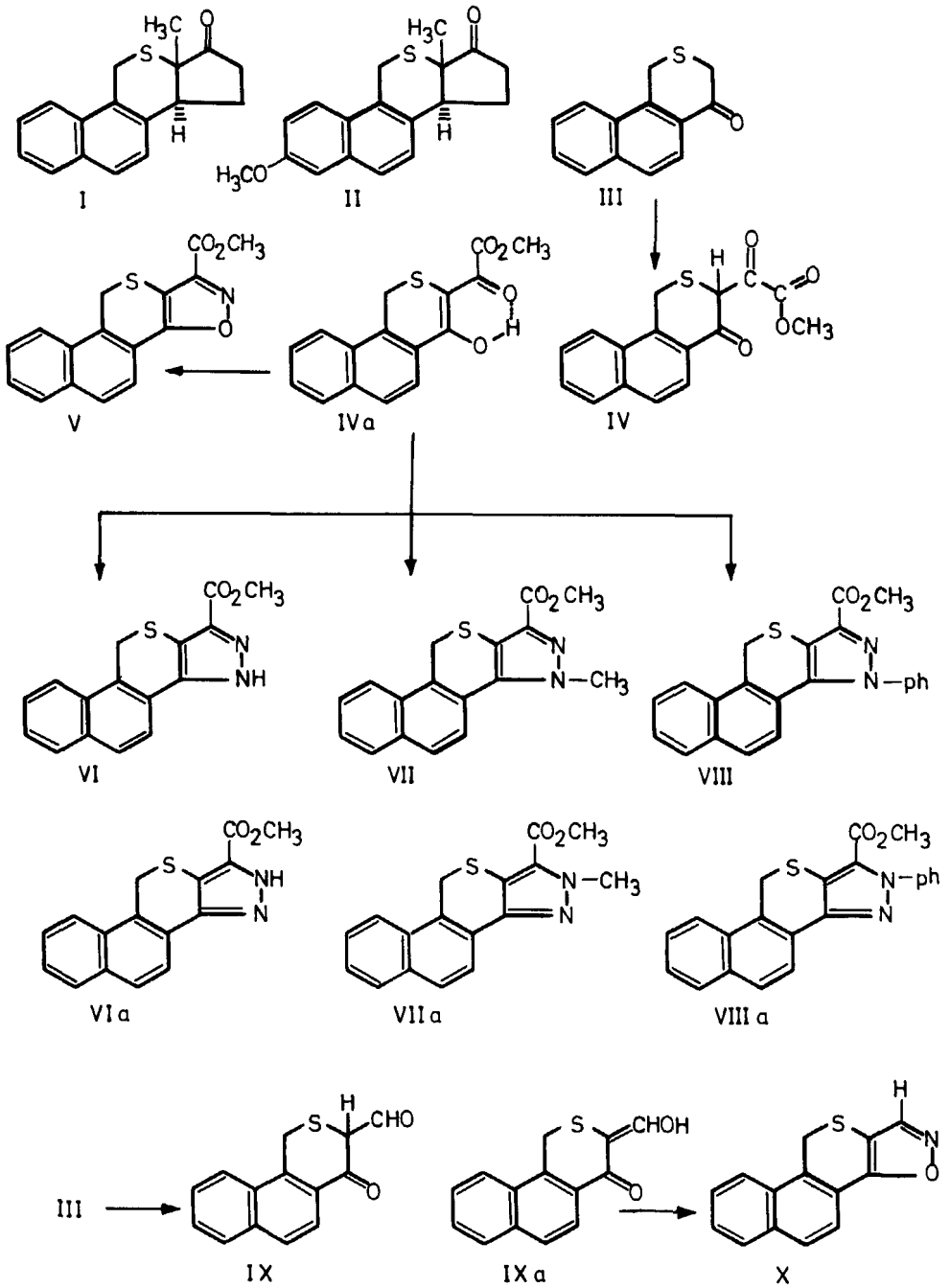
Recent reports[1-3] indicate that the steroids wherein the carbocyclic D-ring is replaced by a heterocycle such as pyrazole or isoxazole and also incorporation of a hetero atom such as N, O and S in the steroid nucleus exhibit unusual and interesting biological properties.[4] A careful study of literature[5] on thiasteroids and its analogues points out the fact that there has been no report till date on the total synthesis of 12-thiaequilenin, 12-thiaestrone and their isoxazole and pyrazole analogues. In a broad programme to study the influence of a sulphur atom in 12-position of the steroid skeleton on chemical, spectroscopic and biological activity of 12-thiasteroid in comparison with that of the corresponding carbocyclic steroid (lacking the sulphur atom), the investigations concerning the total syntheses of 3-deoxy-12-thiaequilenin (I) and its methyl ether (II) were communicated recently.[6]

In continuation of our studies on structure-activity relationships, the total syntheses of 15-oxa-16-aza as well as 15,16-bisaza analogues corresponding to the hitherto unknown 3-deoxy-12-thiaequilenin are described in this paper.

DISCUSSION

The tricyclic ketone, the key-intermediate (III) required for the total syntheses of (V–VIII and X) was prepared according to the procedure described earlier by these authors.[7]

Condensation of the tricyclic ketone (III) with dimethyl oxalate in the presence of dry sodium methoxide gave the anticipated glyoxalate derivative, 2-carbomethoxycarbonyl-1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene (IV) as a red solid, m.p. 93–94°C, in 60% yield. That the glyoxalate (IV) existed only in the enolic form (IVa) was evident from its IR and NMR spectral data (*vide*—experimental).



SCHEME 1

The aforementioned glyoxalate derivative (IVa) on condensation with (i) hydroxylamine hydrochloride (ii) hydrazine hydrate (iii) methylhydrazine and (iv) phenylhydrazine hydrochloride gave the corresponding isaxazole (V) and pyrazole derivatives (VI–VIII) respectively. The structures assigned to the pyrazole derivatives (VI–VIII) were based on their spectral data (*vide*—Experimental). The alternative structures (VIa, VIIa and VIIIa) for the pyrazole derivatives were ruled out based on the x-ray diffraction studies carried out in our Laboratories on structurally analogous pyrazole derivatives.[8]

Condensation of the tricyclic ketone (III) with ethyl formate in presence of dry sodium methoxide gave the expected formyl derivative, 1-oxo-2-formyl-3-thia-1,2,3,4-tetrahydrophenanthrene (IX) as a yellow amorphous solid, m.p. 112–113°C, in 45% yield. The formyl derivative (IX) on further condensation with hydroxylamine hydrochloride afforded the isoxazole derivative (X) as an orange solid, m.p. 132–133°C, in 60% yield.

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 recorded on *MAT CH7* spectrometer. Melting points reported herein are uncorrected.

1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene-2-glyoxalate (IV). A solution of 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene (III)[7] (4.3 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 (4.7 g) in dry benzene (20 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 (2 × 30 ml). The combined alkaline extracts were chilled and acidified with dilute hydrochloric acid (1 : 1) at ice temperature to give a red precipitate which was filtered and dried. Recrystallisation from ethanol gave the analytical sample of the glyoxalate (IV) as a red crystalline, solid, m.p. 93°C (3.6 g; 60%); IR (KBr)ν_{max} 3590, 1720 (ester carbonyl), 1610 (chelated carbonyl), 1590, 1560, 1450 and 1250 cm^{-1}; NMR ($CDCl_3$); δ 3.95 (s, 3H, ester methyl), 4.25 (s, 2H, methylene at C_4) and 7.5–8.2 (m, 7H, enolic and aromatic protons): MS gave ions at m/z 300 (M^+; 44%), 268 (20%), 241 (63%), 213 (42%), 212 (41%), 185 (26%), 184 (41%), 168 (63%), 140 (55%). Anal: Calcd for $C_{16}H_{12}O_4S$; C, 64.0; H, 4.0. Found: C, 64.15; H, 4.28.

17-Methoxycarbonyl-12-thia-15-oxa-16-azagona-1,3,5(10),6,8,13,16-heptaene (V). A mixture of the glyoxalate derivative (IV) (0.9 g) and thoroughly dried hydroxylamine hydrochloride (0.2 g) in glacial acetic acid (25 ml) was quickly heated in an oil bath preheated to 170°C and further refluxing continued for 7 minutes. The resulting brown solution was poured into ice-cold water. The separated solid was filtered, dried and was purified by passing through a short column of silicagel (15 g). The solid obtained from benzene eluates was recrystallised from chloroform-hexane (1 : 1) to give the analytical sample of (V) as a light brown crystalline solid, m.p. 149–150°C (0.52 g; 60%); IR ($CHCl_3$)ν_{max} 1730, 1660, 1650, 1580, 1450, 1230 and 1200 cm^{-1}; NMR ($CDCl_3$); δ 4.03 (s, 3H, ester methyl), 4.5 (s, 2H, methylene at C_{11}), 7.5–8.1 (m, 6H, aromatic protons); MS showed mass peaks at m/z 297 (M^+; 80%), 266 (3%), 253 (7%), 238 (7%), 212 (11%), 209 (100%), 184 (15%) and 168 (23%). Anal: Calcd for $C_{16}H_{11}NO_3S$; C, 64.65; H, 3.70; N, 4.71. Found: C, 64.96; H, 3.58; N, 4.52.

17-Methoxycarbonyl-12-thia-15,16-bisazagona-1,3,5(10),6,8,13,16-heptaene (VI). A solution of the glyoxalate derivative (IV) (0.9 g) in glacial acetic acid containing hydrazine-hydrate (0.4 ml) was refluxed for 3 hours and then poured into ice-cold water. The separated solid was filtered, dried and its solution in chloroform (40 ml) was passed through a short column of silicagel (15 g). Evaporation of the chloroform eluates yielded a purified product which was recrystallised from chloroform-hexane to afford the analytical sample of (VI) as a pale yellow crystalline solid, m.p. 212–213°C (0.44 g; 50%); IR (KBr)ν_{max}

3200 (NH stretch), 1710, 1550, 1490, 1270 and 1210 cm^{-1}; NMR (DMSO—d_6); δ 3.1 (s, broad, NH), 4.02 (s, 3H), 4.5 (s, 2H) and 7.45–8.2 (m, 6H); MS showed mass peaks at m/z 296 (M^+; 100%), 295 (19%), 281 (10%), 264 (24%), 236 (5%) and 208 (14%). Anal: Calcd for $C_{16}H_{12}N_2O_2S$; C, 64.86; H, 4.05; N, 9.46. Found: C, 64.39; H, 4.05; N, 9.38.

15-Methyl-17-methoxycarbonyl-12-thia-15,16-bisazagona-1,3,5(10),6,8,13,16-heptaene (*VII*). The glyoxalate (IV) (0.9 g) on treatment with methylhydrazine (0.4 ml) in acetic acid following the procedure indicated above, gave a yellow solid, which was recrystallised from chloroform-hexane to furnish (VII) as a pale yellow crystalline solid, m.p. 190–191°C (0.44; 50%), IR ($CHCl_3$)ν_{max} 1720, 1610, 1580 and 1200 cm^{-1}; NMR ($CDCl_3$); δ 3.9 (s, 3H), 4.15 (toothed 's', 5H, N—CH_3 and methylene at C_{11}) and 7.2–8.1 (m, 6H); MS gave ions at m/z 310 (M^+, 100%), 295 (14%), 279 (9%), 263 (12%), 251 (25%), 249 (34%), 235 (20%), 222 (18%), 209 (4%), 195 (13%), 181 (31%) and 168 (18%). Anal: Calcd for $C_{17}H_{14}O_2N_2S$; C, 65.81; H, 4.52; N, 9.03. Found: C, 65.42; H, 4.81; N, 9.54.

15-Phenyl-17-methoxycarbonyl-12-thia-15,16-bisazagona-1,3,5(10),6,8,13,16-heptaene (*VIII*). Reaction of the glyoxalate (IV) (0.9 g) with phenylhydrazine hydrochloride (0.5 g) was carried out in the same manner as described for compound (VII). The solid obtained after usual work-up was recrystallised from chloroform-hexane to give the analytical sample of (VIII) as a pale yellow crystalline solid, m.p. 212–213°C (0.55 g; 50%); IR ($CHCl_3$)ν_{max} 1720, 1600, 1480, 1300 and 1220 cm^{-1}; NMR ($CDCl_3$); δ 4.0 (s, 3H), 4.2 (s, 2H) and 7.2–8.1 (m, 11H); MS showed mass peaks at m/z 372 (M^+; 100%), 314 (21%), 311 (32%), 286 (13%), 243 (12%) and 209 (25%). Anal: Calcd for $C_{22}H_{16}N_2O_2S$; C, 70.97; H, 4.30; N, 7.53. Found: C, 70.5; H, 4.5; N, 7.51.

1-Oxo-2-hydroxymethylene-3-thia-1,2,3,4-tetrahydro-phenanthrene (*IX*). This was prepared adopting the procedure described earlier for (IV). Thus formylation of (III) (1.07 g) with ethyl formate (1.5 g) in the presence of dry sodium methoxide (prepared from 0.47 g of sodium) furnished a crude solid which on recrystallisation from ethanol afforded the analytical sample of (IX) as a yellow amorphous solid, m.p. 112–113°C (0.54 g; 45%); IR ($CHCl_3$)ν_{max} 1640, 1590 and 1550 cm^{-1}; NMR ($CDCl_3$); δ 4.15 (s, 2H), 7.2–8.05 (m, 7H, enolic and aromatic protons); MS indicated mass peaks at m/z 242 (M^+; 90%), 213 (20%), 185 (27%), 181 (24%), 152 (49%), 141 (50%) and 139 (100%). Anal: Calcd for $C_{14}H_{10}O_2S$; C, 69.42; H, 4.13. Found: C, 69.81; H, 4.31.

12-Thia-15-oxa-16-azagona-1,3,5(10),6,8,13,16-heptaene (*X*). Condensation of the formyl derivative (IX) (0.4 g) with dried hydroxylamine hydrochloride (0.14 g) was carried out exactly following the procedure described earlier for (V). Thus the solid obtained after the usual work-up was passed through a short column of silicagel (15 g). The product obtained from benzene eluates was recrystallised from chloroform-hexane to give the analytical sample of (X) as an orange red solid, m.p. 132–133°C (0.28 g; 60%); IR (KBr)ν_{max} 1600, 1470, 1450, 1280 and 1190 cm^{-1}; NMR ($CDCl_3$); δ 4.4 (s, 2H), 7.3–8.0 (m, 6H) and 8.2 (s, 1H, proton at C_{17}); MS gave ions at m/z 239 (M^+; 60%), 238 (38%), 210 (12%), 184 (24%), 168 (25%), 140 (95%) and 139 (100%). Anal: Calcd for $C_{14}H_9NOS$; C, 70.29; H, 3.77; N, 5.86. Found: C, 70.40; H, 4.10; N, 5.93.

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