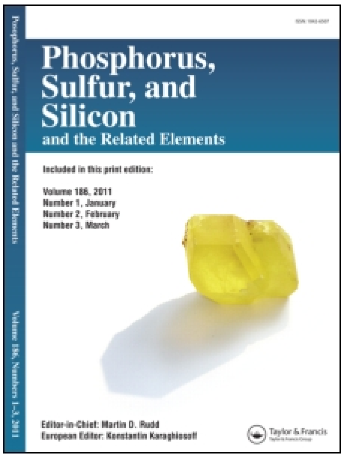

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NEW POLYHETEROPOLYCYCLIC RING SYSTEMS
PART XXV. SYNTHESIS OF STEROID-TYPE COMPOUNDS DERIVED FROM 5,5-DIMETHYL-2,3,5,6-TETRAHYDRO-4H-THIOPYRANO [3,2-g]-BENZTHIADIAZOLE-4-ONE

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The synthesis of the tricyclic ketone, 5,5-dimethyl-2,3,5,6-tetrahydro-4H-thiopyrano[3,2-g][1,2,3]benzthiadiazole-4-one (V) starting with dimedone is described. V served as the key intermediate for the total synthesis of the hitherto unknown 9,10-dihydro-9,9-dimethyl-5H[1,2,3]thiadiazolo-[4′,5′:4,5]thiopyrano[3,2-g][1,2,3]benzothiadiazole (VIII),[1] 9,10-dihydro-9,9-dimethyl-5H-isoxazolo[4′,5′:4,5]thiopyrano[3,2-g][1,2,3]benzothiadiazole (IX) and 9,10-dihydro-9,9-dimethyl-8N-phenyl-5H-pyrazolo-[4′,5′:4,5]thiopyrano[3,2-g]-[1,2,3]benzothiadiazole (X).

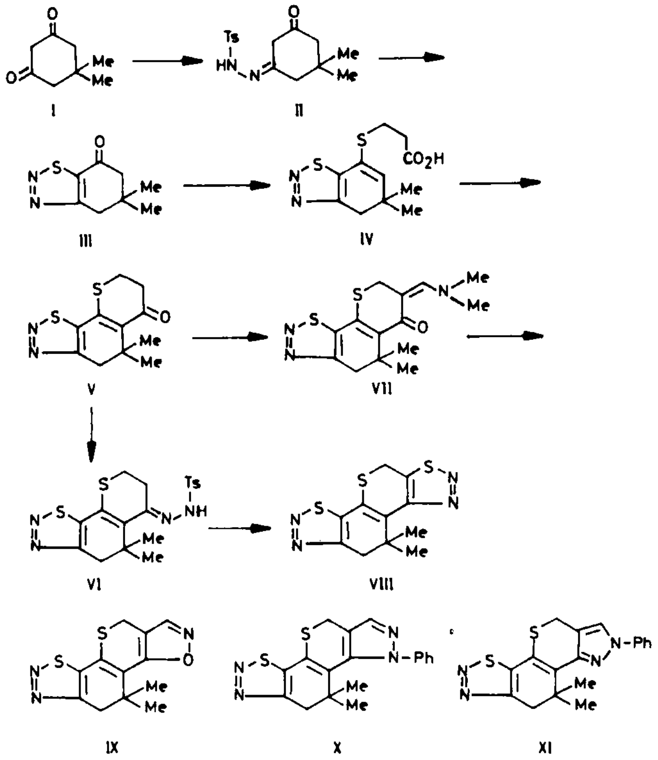
INTRODUCTION

Recent reports[2–7] reveal that several steroidal analogues with the replacement of the D-ring of carbocyclic steroidal ring system by an isoxazole or pyrazole are found to exhibit interesting biological properties. Quite recently Britton and coworkers[8] have claimed that a A-ring fused-steroidal[3,2-d][1,2,3]thiadiazoles are likely to exhibit male contraceptive property. Prompted by the above observation, we undertook the total synthesis of the aforementioned tetracyclic heterocycles with a view to evaluating their antifertility activity more specifically the spermicidal toxicity.

DISCUSSION

In order to achieve the synthesis of the hitherto unknown tricyclic ketone viz. the key intermediate (V)[1] needed for the total synthesis of (VIII, IX and X) (Scheme I), we developed a new synthetic strategy adopting the general observation made by Hurd and Mori[9] to obtain [1,2,3]thiadiazole. Treatment of monotosylhydrazone of dimedone[10] with excess of thionyl chloride (freshly distilled) in methylene chloride at room temperature gave the hithero unknown bicyclic ketone, 5,5-dimethyl-4,5,6,7-tetrahydro-7-oxo[1,2,3]benzothiadiazole (III) as a pale yellow crystalline solid, m.p. 45–46°, in 61% yield.

Condensation of the bicyclic ketone (III) with 3-mercaptopropionic acid[11] in the presence of catalytic amount of p-toluenesulfonic acid (PTS) in refluxing benzene gave the bicyclic acid (IV) as a thick dark liquid in 67% yield. The crude



Scheme I

acid (IV), without further purification, was directly subjected to cyclodehydration with phosphorus pentoxide to furnish the expected tricyclic ketone,5,5-dimethyl-2,3,5,6-tetrahydro-4H-thiopyrano[3,2-g][1,2,3]benzthiadiazole-4-one (V) as pale yellow crystals, m.p. 148–9° in 40% yield.

Condensation of the tricyclic ketone (V) with p-toluenesulfonylhydrazide in absolute methanol containing a few drops of conc. hydrochloric acid furnished the corresponding tosylhydrazone (VI) as golden yellow crystals, m.p. 181–2°, in 98% yielded. The tosylhydrazone (VI) on treatment with excess of thionyl chloride in methylene chloride at room temperature gave the anticipated [1,2,3]thiadiazole derivative (VIII) as a orange yellow solid, m.p. 179–80°, in 27% yield.

The common intermediate, required for the synthesis of isoxazole (IX) and pyrazole (X), was obtained by condensing the tricyclic ketone (V) with N,N-dimethylformamide dimethylacetal at 80°. The expected 3-dimethylamino-methylene-5,5-dimethyl-2,3,5,6-tetrahydro(3H, 4H)-thiopyrano[3,2-g][1,2,3]thia-diazole-4-one (VII) was isolated as a red orange solid, m.p. 163–4°, in 86% yield. When the condensation of (VII) with hydroxylamine hydrochloride was carried out in refluxing absolute methanol, it gave the expected isoxazole derivative (IX) as orange yellow crystals, m.p. 145–6°, in 87% yield.

Also when the condensation of (VII) with phenylhydrazine hydrochloride in the presence of a few drops of glacial acetic acid was carried out in refluxing absolute ethanol, it furnished the pyrazole derivative (X) as a red orange solid, m.p. 207–8°, in 87% yield. Based on our earlier findings[12] in such condensations employing phenylhydrazine (including the X-ray confirmation of the results), we proposed the structure (X) for the condensation product (X). Thus the alternative structure (XI) was ruled out for this product. Assignment of structure (X) for this product finds further support from the recent publication of Schenone and coworkers.[13]

EXPERIMENTAL

NMR spectra were recorded on Varian EM 390 90 MHz spectrometer using TMS as internal standard. IR spectra were measured using Perkin Elmer 781 Grating spectrophotometer. Mass spectra recorded on Fennigan Mat 8230 spectrometer. Melting points reported herein are uncorrected.

5,5-Dimethyl-4,5,6,7-tetrahydro-7-oxo[1,2,3]benzothiadiazole (III)

A suspension of monotosylhydrazone of dimedone (II) (9.24 g) in 100 ml of dry methylene chloride was added dropwise 10 ml of thionly chloride at room temperature with stirring and continued for 36 hours, during which the reaction mixture became dark red in colour. The solvent and excess of thionyl chloride were removed under reduced pressure. The residual dark thick liquid was chromatographed over silica gel (150 g) (60–120 mesh), initially hexane eluates (1000 ml) gave expected p-toluenesulfonyl chloride. Ethyl acetate-hexane (1:9) eluates furnished the expected bicyclic ketone (III), as a yellow crystalline solid. Recrystallisation from hexane-ethyl acetate gave pale yellow crystals (3.3 g, 61%) of analytical purity, m.p. 45–46°. IR(KB$_r$): ν_{max} 1685 cm^{-1} (carbonyl); ^{1}H-NMR(CDCl$_3$): δ 1.1(s, 6H, $2C\underline{H_3}$ at C_5), 2.4(s, 2H, $C\underline{H_2}$ at C_6), and 3.1(s, 2H, $C\underline{H_2}$ at C_4); MS: m/z 182($M^{+\cdot}$, 40%) Anal: calcd. for $C_8H_{10}N_2OS$; C, 52.75; H, 5.49. Found: C, 52.53; H, 5.30.

5,5-Dimethyl-2,3,5,6-tetrahydro-4H-thiopyrano[3,2-g][1,2,3]-thiadiazole-4-one (V)

A solution of (III) (3.64 g) in 100 ml dry benzene was treated with 3-mercaptopropionic acid (3 ml) in the presence of PTS and the resulting mixture was refluxed employing a Dean–Stark water-separator for 48–50 hours. The reaction flask was cooled and the benzene solution was washed with water (2 × 30 ml) and extracted with 5% aqueous sodium bicarbonate (3 × 75 ml). The combined sodium bicarbonate extracts was acidified and extracted with ethyl acetate (3 × 100 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent furnished thick dark liquid (3.62 g, 67%). This crude acid was directly subjected to cyclodehydration with phosphorus pentoxide (20 g) in refluxing dry benzene (100 ml) for 4–6 hours. The reaction mixture was cooled and poured onto broken ice (150 g) and extracted with benzene (100 ml). The benzene layer was washed with 5% aqueous sodium bicarbonate (3 × 75 ml) and finally with water (75 ml), dried over anhydrous sodium sulfate. Removal of benzene gave a dark yellow liquid which was chromatographed over silica gel (100 g) (60–120 mesh). Ethyl acetate-hexane (2:8) eluates gave a yellow solid which was recrystallised from ethyl acetate-hexane to furnish yellow crystals (V) (1.4 g, 40%) of analytical purity, m.p. 148–9°. IR(KBr): ν_{max} 1660 cm^{-1} (conjugated carbonyl); ^{1}H-NMR ($CDCl_3$): δ 1.3(s, 6H, $2C\underline{H}_3$ at C_5), 2.8(t, 2H, $C\underline{H}_2$ at C_3), 3.01(s, 2H, $C\underline{H}_2$ at C_6) and 3.3(t, 2H, $C\underline{H}_2$ at C_2); MS: m/z 252 ($M^{+\cdot}$, 32%). Anal: Calcd. for $C_{11}H_{12}N_2OS_2$; C, 52.48; H, 4.76 Found: C 52.52; H, 4.80.

9,10-Dihydro-9,9-dimethyl-5H-[1,2,3]thiadiazolo[4′,5′:4,5]-thiopyrano[3,2-g][1,2,3]benzothiadiazole (VIII)

To a solution of tricyclic ketone (V) (0.252 g) in 15 ml of absolute methanol containing a drop of conc. hydrochloric acid was added *p*-toluenesulfonylhydrazide (0.186 g) at room temperature. The resulting reaction mixture was allowed to stand overnight and then methanol was evaporated under diminished pressure. The solid thus obtained was recrystallised from methanol to furnish golden yellow crystals (VI), m.p. 181–2°, 98% yield. IR(KBr): ν_{max} 1590 cm^{-1} (aromatic —C═C), 1180 cm^{-1} (—SO_2); ^{1}H-NMR(DMSO-d_6): δ 1.1(s, 6H, $2C\underline{H}_3$ at C_5), 2.2(s, 2H, $C\underline{H}_2$ at C_3), 2.4(s, 3H, aromatic $C\underline{H}_3$), 2.8(s, 2H, $C\underline{H}_2$ at C_6), 3.3(s, 2H, $C\underline{H}_2$ at C_2) and 7.1–7.4 (AB pattern, 4H, aromatic $\underline{H}$); MS: m/z 265 [(M—$CH_3C_6H_4SO_2$—; 40%)]. Anal: Calcd. for $C_{18}H_{20}N_4O_2S_3$; C, 51.42; H, 4.76; Found: C, 51.25; H, 4.85. The tosylhydrazone (VII) (0.415 g) obtained earlier was suspended in 10 ml of methylene chloride and treated with thionyl chloride (2 ml) and resulting mixture was stirred at room temperature for a period of 12 hours. The solvent and the excess of thionyl chloride were removed in a rotary evaporator at room temperature to furnish a thick red liquid. Purification by preparative TLC over silica gel gave (VIII) as orange yellow solid of analytical purity, m.p. 179–80°, in 27% yield. ^{1}H-NMR($CDCl_3$): δ 1.3(s, 6H, $2C\underline{H}_3$ at C_9), 3.03(s, 2H, $C\underline{H}_2$ at C_{10}) and 4.0(s, 2H, $C\underline{H}_2$ at C_5); m/z 294($M^{+\cdot}$, 80%). Calcd for $C_{11}H_{10}N_4S_3$; C, 44.89; H, 3.4 Found: C, 44.98 H, 3.32.

3-Dimethylaminomethylene-5,5-dimethyl-2,3,5,6-tetrahydro-thiopyrano[3,2-q][1,2,3]benzthiadiazole-4-one (VII)

To a solution of N,N-dimethylformamide dimethylacetal (1 ml) was added (V) (0.4 g) and stirred at 80° for a period of 15 h. Excess of dimethylformamide dimethylacetal was removed under vacuo and the residue was treated with dry ether (3 ml) and the solid separated was filtered and recrystallised from ethyl acetate to furnish red orange solid, m.p. 163–4°, in 86% yield. IR(KBr): ν_{max} 1660 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 1.1(s, 6H, $2C\underline{H}_3$ at C_5), 3.01(s, 8H, $N(C\underline{H}_3)_2$ and $C\underline{H}_2$ at C_6), and 3.9(s, 2H, $C\underline{H}_2$ at C_2); MS: m/z 307($M^{+\cdot}$ 20%). Anal: Calcd. for $C_{14}H_{17}N_3OS_2$, C, 54.72; H, 5.53 Found: C, 54.58: H, 5.30.

9,10-Dihydro-9,9-dimethyl-5H-isoxazolo[4′,5′:4,5]thio-pyrano[3,2-g][1,2,3]benzthiadiazole (IX)

A mixture of (VII) (0.307 g) and hydroxylamine hydrochloride (freshly dried under vacuum) (0.07 g) in absolute methanol was refluxed for 3 h. Methanol was evaporated and the residue was diluted with water, extracted with ether (3 × 10 ml), dried over anhydrous sodium sulfate. Evaporation of ether gave a solid which on recrystallisation from methanol afforded (IX) as orange yellow crystals of analytical purity, m.p. 145–6°, in 87% yield. ^{1}H-NMR($CDCl_3$): δ 1.4(s, 6H, 2 $\underline{CH_3}$ at C_9), 3.2(s, 2H, $\underline{CH_2}$ at C_{10}), 3.8(s, 2H, $\underline{CH_2}$ at C_5) and 7.8 (s, 1H, —C$\underline{H}$ at C_3); MS: m/z 277 ($M^{+\cdot}$, 18%). Anal: Calcd. for $C_{12}H_{11}N_3OS_2$; C, 51.98; H, 3.97 Found: C, 52.03; H, 3.90.

9,10-Dihydro-9,9-dimethyl-8N-phenyl-5$\underline{H}$-pyrazolo[4′,5′:4,5]-thiopyrano[3,2-g][1,2,3]benzothiadiazole (X)

To a solution of (VII) (0.307 g) in absolute ethanol (25 ml) containing a few drops of glacial acetic acid was treated with phenylhydrazine hydrochloride and refluxed for 6 h. Ethanol was evaporated under vacuo and the residue was diluted with water, extracted with ether (3 × 10 ml),dried over anhydrous sodium sulfate. Evaporation of dried ether extract afforded a solid which on recrystallisation from methanol furnished red orange solid of analytical purity, m.p. 207–8°, in 87% yield. ^{1}H-NMR ($CDCl_3$): δ 0.95(s, 6H, 2$\underline{CH_3}$ at C_9), 3.01(s, 2H, $\underline{CH_2}$ at C_{10}), 3.68(s, 2H, $\underline{CH_2}$ at C_5), 7.2(s, 5H, aromatic $\underline{H}$) and 7.4(s, 1H, —C$\underline{H}$ at C_3), MS: m/z 352 ($M^{+\cdot}$, 15%). Anal: Calcd. for $C_{18}H_{16}N_4S_2$; C, 61.38; H, 4.54 Found: C, 61.42; H, 4.65.

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