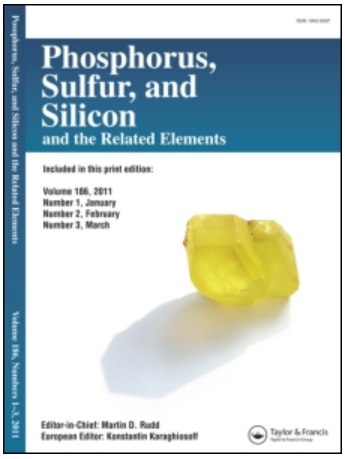

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POLYHETERO POLYCYCLIC RING SYSTEMS: PART XIX: SYNTHESIS OF STEROID-TYPE COMPOUNDS DERIVED FROM 2H-4-OXO-3,4-DIHYDRO-5-METHYL-8-PHENYL-1-THIOPYRANO[2,3-*e*]BENZOFURAN AND 2H,5H-4-OXO-5-METHYL-3,4-DIHYDROINDENO [1,2-*b*]THIOPYRAN

S. R. Ramadas[a]; M. Vijaya Krishna[a]
[a] Department of Chemistry, Indian Institute of Technology, Madras, India

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POLYHETERO POLYCYCLIC RING SYSTEMS: PART XIX: SYNTHESIS OF STEROID-TYPE COMPOUNDS DERIVED FROM 2H-4-OXO-3,4-DIHYDRO-5-METHYL-8-PHENYL-1-THIOPYRANO[2,3-*e*]BENZOFURAN AND 2H,5H-4-OXO-5-METHYL-3,4-DIHYDROINDENO [1,2-*b*]THIOPYRAN

S. R. RAMADAS and M. VIJAYA KRISHNA

Department of Chemistry, Indian Institute of Technology, Madras-600 036, India

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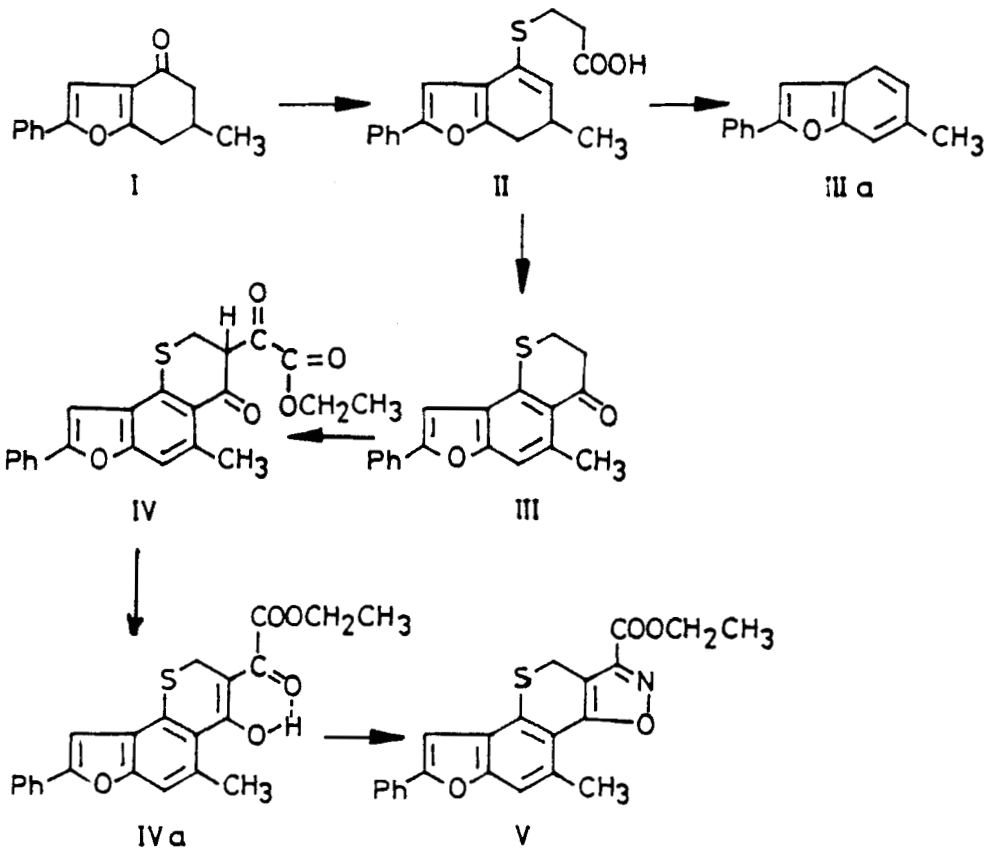
The total syntheses of isoxazolo-derivatives (steroid-type compounds) derived from the tricyclic ketones, 2H-4-oxo-3,4-dihydro-5-methyl-8-phenyl-1-thiopyrano[2,3-*e*]benzofuran and 2H,5H-4-oxo-5-methyl-3,4-dihydroindeno[1,2-*b*]thiopyran are described.

INTRODUCTION

In continuation of our interest[1-4] to synthesise and evaluate the biological activity of new types of polyhetero polycyclic compounds, we wish to report, herein, the total syntheses of new heterocyclic compounds (steroid-type) with the sulphur atom corresponding to position 11 of the steroid nucleus.

DISCUSSION

The starting material, 6-methyl-4-oxo-2-phenyl-4,5,6,7-tetrahydrobenzofuran(I) required for the synthesis of (V) (Scheme 1) was prepared in accordance with the procedure reported by Ramadas and Padmanabhan.[5] Treatment of (I) with β-mercaptopropionic acid in presence of *p*-toluenesulfonic acid (PTS) gave the anticipated β-(6-methyl-2-phenyl-6,7-dihydrobenzofuran-4-ylthio)propionic acid (II) as a thick brown gum in 40% yield. Cyclodehydration of the acid (II) with phosphorus pentoxide in refluxing benzene afforded the tricyclic ketone, 2H-4-oxo-3,4-dihydro-5-methyl-8-phenyl-1-thiopyrano[2,3-*e*]-benzofuran (III) as a yellow solid in 15% yield. The predominant by-product in this reaction was found to be 2-phenyl-6-methylbenzofuran (IIIa) (60% yield). All attempts to improve the yield of the tricyclic ketone (III) were in vain. It is interesting to point out that in the above reaction, simultaneous cyclodehydration and dehydrogenation occurred leading to the formation of benzofuran derivative (III). Such dehydrogenations during



SCHEME 1

cyclodehydration of C-secosteroids have been noticed earlier by several groups of workers.[5-7]

Condensation of the tricyclic ketone (III) with diethyl oxalate in presence of sodium ethoxide gave the corresponding glyoxalate derivative, 2H-4-oxo-3,4-dihydro-5-methyl-8-phenyl-1-thiopyrano[2,3-*e*]benzofuran-3-glyoxalate (IV) as an orange yellow crystalline solid in 60% yield. The IR and NMR spectral data (*vide*—Experimental) indicated clearly that the glyoxalate ester existed entirely in the enolic form (IVa).

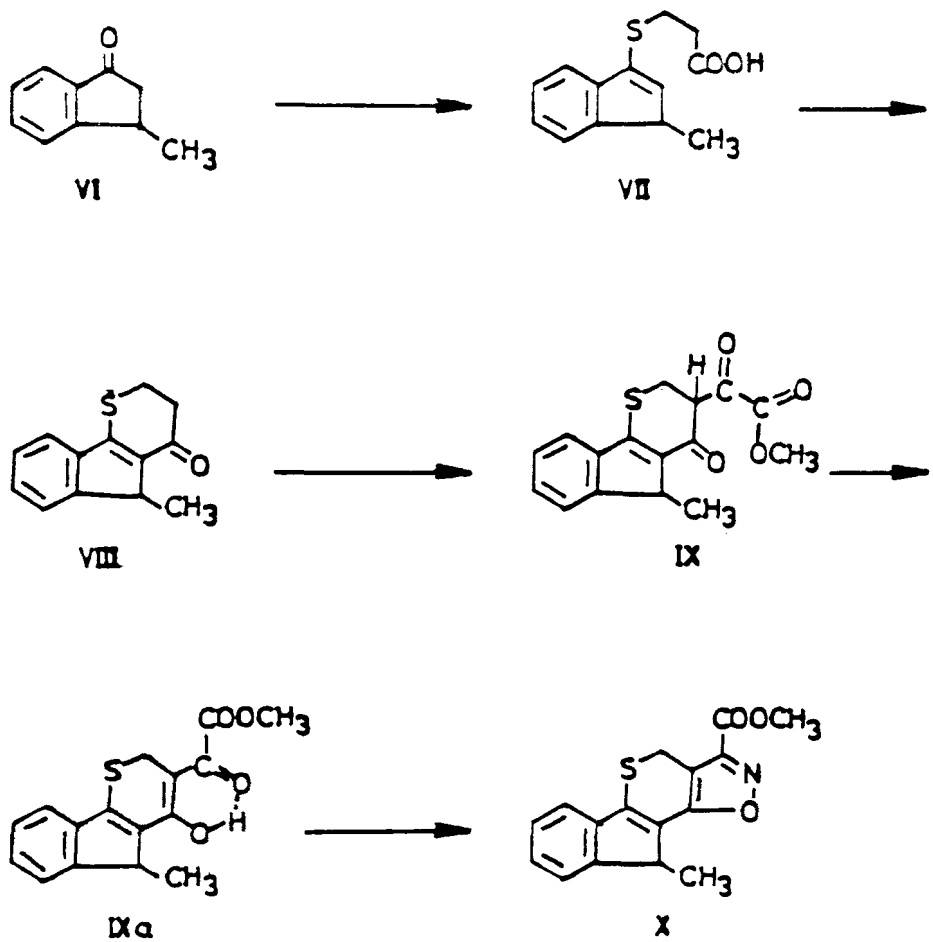
The aforementioned glyoxalate (IVa) on condensation with hydroxylamine hydrochloride in refluxing glacial acetic acid furnished the corresponding tetracycle, 1-ethoxycarbonyl-4-methyl-7-phenyl-10H-isoxazolo[4,5-*c*]thiopyrano[2,3-*e*]benzofuran (V) as a pale yellow solid in 65% yield.

In another series, the tetracyclic derivative (X) was prepared starting with 3-methylindan-1-one (VI) (Scheme 2). The bicyclic ketone (VI), prepared according to the procedure described by Koelsch and coworkers,[8] on treatment with β-mercaptopropionic acid in presence of *p*-toluenesulfonic acid gave the corresponding β-(1-methyl-3-indenylthio)propionic acid (VII) as a dark brown solid in 70% yield.

Cyclodehydration of the acid (VII) with phosphorus pentoxide afforded the tricyclic compound, 2H,5H-4-oxo-5-methyl-3,4-dihydroindeno[1,2-*b*]thiopyran (VIII) as a thick red gum in 25% yield.

Condensation of the tricyclic ketone (VIII) with dimethyl oxalate furnished the corresponding glyoxalate ester, 2H,5H-4-oxo-5-methyl-3,4-dihydroindeno[1,2-*b*]thiopyran-3-glyoxalate (IX) as an orange red crystalline solid in 65% yield. From the spectral data it was evident that the ester (IX) existed only in the enolic form (IXa) (*vide*—Experimental). The glyoxalate derivative (IXa) on condensation with hydroxylamine hydrochloride gave the tetracycle, 1-methoxycarbonyl-4-methyl-4H,10H-indeno[2′,3′ : 5,6]thiopyrano[3,4-*d*]isoxazole (X) as a pale yellow solid in 75% yield. This solid showed extreme instability in solution. The structure assigned to (X) was based on the IR and NMR spectral data obtained by rapid scanning.

The biological evaluation of the compounds (V and X) is in progress at May and Baker Laboratories, England through the courtesy of Prof. B. J. Heywood and the results will be published elsewhere at a later date.



SCHEME 2

EXPERIMENTAL

The recorded temperatures were uncorrected. IR spectra were taken using Perkin Elmer 257 grating spectrophotometer. NMR spectra were recorded on Varian XL 100 spectrometer using TMS as internal standard. Mass spectra were recorded using MAT CH 7 and DS-55 spectrometers.

β-(6-methyl-2-Phenyl-6,7-dihydrobenzofuran-4-ylthio)propionic acid (II). A solution of 6-methyl-4-oxo-2-phenyl-4,5,6,7-tetrahydrobenzofuran[5] (I) (29.3 g), β-mercaptopropionic acid (13.8 g) and *p*-toluenesulfonic acid (1.72 g) in dry benzene (250 ml) was refluxed for 16 hours using a Dean-Stark water separator. The benzene solution was cooled and extracted with 2N potassium carbonate solution (4 × 40 ml). The combined aqueous alkaline extracts were chilled and acidified with dilute hydrochloric acid (1 : 1) at 0–5°C to afford a thick black gum, which on chromatographic purification over silica gel (350 g) from methylene chloride eluates (7500 ml) gave a fairly pure sample of the acid (II) as a thick brown gum (16 g; 40%). This material defied all attempts towards solidification. IR ($CHCl_3$) ν_{max} 3040–2950 (bonded OH), 1700 (acid dimer), 1650 (olefinic stretch), 1600, 1490, 1460 and 1420 cm^{-1}; NMR ($CDCl_3$): δ 1.1 (d, 3 H, J = 7 Hz), 1.9–3.4 (m, 7 H, methylene at C_7, S—CH_2—CH_2—CO and methine proton at C_6), 6.6 (d, 1 H, J = 11 Hz, olefinic proton) and 7.0–7.8 (m, 6 H, aromatic).

2H-4-Oxo-3,4-dihydro-5-methyl-8-phenyl-1-thiopyrano[2,3-e]-benzofuran (III). A mixture of the bicyclic acid (II) (12.5 g) and phosphorus pentoxide (50 g) in dry, thiophene-free, benzene (250 ml) was refluxed for 4 hours. The reaction mixture was cooled and the benzene solution was decanted. The solid red mass was decomposed with ice-cold water (200 ml) and extracted with benzene (3 × 100 ml). The combined benzene extracts were washed with saturated sodium bicarbonate solution (2 × 40 ml) and water (2 × 30 ml). Evaporation of the dried solvent gave a thick yellow gum (5.4 g). Chromatography of this material over neutral alumina (150 g) gave from benzene–hexane (1 : 1) eluates (5000 ml) the tricyclic ketone (III) (1.77 g; 15%) as a yellow solid. An analytical sample was obtained on recrystallisation from methylene chloride–hexane (1 : 1) mixture, m.p. 132°C. IR ($CHCl_3$) ν_{max} 1665 (C=O), 1590, 1565, 1490 and 1440 cm^{-1}; NMR ($CDCl_3$): δ 2.7 (s, 3 H, methyl group at position 5) 2.9–3.5 (m, 4 H, S—CH_2—CH_2—CO), 6.9 (s, 1 H, proton at position 9) and 7.0–8.0 (m, 6 H, aromatic); MS gave ions at m/z 294 ($M^{+\cdot}$, 72%), 266 (100%), 238 (10%), 237 (8%), 209 (11%), 165 (11%) and 133 (12%). Anal: Calcd. for $C_{18}H_{14}O_2S$: C, 73.47; H, 4.76. Found: C, 73.21; H, 4.52.

The benzene–hexane (1 : 3) eluates (1000 ml) obtained in the above chromatography afforded a side product (IIIa) (4.6 g; 50–60%) as a white crystalline solid, m.p. 135–137°C (reported,[9] m.p. 140°C). All attempts to improve the yield of the required product (III) in the above cyclodehydration reaction, employing phosphorus pentoxide in benzene at room temperature or polyphosphoric acid (PPA) at room temperature and 100°C were met with little success.

2H-4-Oxo-3,4-dihydro-5-methyl-8-phenyl-1-thiopyrano[2,3-e]-benzofuran-3-glyoxalate (IV). To a stirred suspension of sodium ethoxide (prepared from 0.21 g of sodium) in dry benzene (20 ml) under dry nitrogen atmosphere was added a solution of diethyl oxalate (1.31 g) in dry benzene (15 ml), followed by a solution of the ketone (III) (1.32 g) in dry benzene (20 ml) and the temperature was maintained at 0–5°C. After stirring the mixture for 6 hours at this temperature, ice-cold water (35 ml) followed by ether (50 ml) were added. The organic layer was separated and washed with 5% aqueous sodium hydroxide solution (3 × 25 ml). The combined alkali extracts were chilled and acidified with ice-cold dilute hydrochloric acid (1 : 1) to afford an orange solid, which on recrystallisation from acetone-ethanol furnished the analytical sample of the glyoxalate (IV) (1.06 g; 60%) as an orange yellow solid, m.p. 118–120°C. IR ($CHCl_3$) ν_{max} 1735 (ester carbonyl), 1610 (chelated carbonyl), 1580 and 1450 cm^{-1}; NMR ($CDCl_3$): δ 1.45 (t, 3 H, J = 7 Hz), 2.7 (s, 3 H, Ar—CH_3), 4.15 (s, 2 H, S—CH_2—), 4.4 (q, 2 H, J = 7 Hz) and 7.0–8.0 (m, 7 H, aromatic); MS showed mass peaks at m/z 394 ($M^{+\cdot}$, 4%), 366 (25%), 321 (47%), 293 (44%), 292 (83%), 266 (100%), 238 (17%), 209 (7%) and 165 (23%). Anal: Calcd. for $C_{22}H_{18}O_5S$; C, 67.0; H, 4.57. Found: C, 66.82; H, 4.21.

1-Ethoxycarbonyl-4-methyl-7-phenyl-10H-isoxazolo[4,5-c]-thiopyrano[2,3-e]benzofuran (V). A mixture of the glyoxalate derivative (IVa) (0.79g) and thoroughly dried hydroxylamine hydrochloride (0.14 g) in 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 pale yellow solid was filtered, dried and purified by chromatography through silica gel (50 g). The solid obtained from chloroform eluates (1500 ml) was recrystallised from methylene chloride to afford the analytical sample of (V) as a very pale yellow crystalline solid, m.p. 140°C (0.51 g; 65%); IR ($CHCl_3$) ν_{max} 1720 (ester carbonyl), 1660, 1480, 1445, 1435 and 1145 cm^{-1} (trisubstituted isoxazole[10] ring breathing vibrations); NMR ($CDCl_3$): δ 1.5 (t, 3 H, J = 7 Hz), 2.8 (s, 3 H, Ar—CH_3), 4.3 (s, 2 H, S—CH_2), 4.55 (q, 2 H, J = 7 Hz), 7.0 (s, 1 H, proton at position 8) and 7.0–8.0 (m, 6 H, aromatic); MS showed mass peaks at m/z 391 ($M^{+\cdot}$, 52%), 362 (5%), 318 (100%), 301 (11%), 292 (17%), 266 (36%) and 238 (7%). Anal: Calcd. for $C_{22}H_{17}NO_4S$; C, 67.82; H, 4.35; N, 3.58. Found: C, 68.3; H, 4.73; N, 3.40.

β-(1-Methyl-3-indenylthio)propionic acid (VII). Reaction of the bicyclic ketone (VI) (7.3 g) with β-mercaptopropionic acid (5.3 g) was carried out in the same manner as described for compound (II) to afford a solid which on recrystallisation from benzene–hexane mixture (1 : 1) furnished the analytical sample of (VII) as a dark brown crystalline solid, m.p. 99–100°C (8.2 g; 70%); IR ($CHCl_3$) ν_{max} 3050–2900 (bonded OH), 1705 (acid dimer), 1595, 1510, 1460 and 1420 cm^{-1}; NMR ($CDCl_3$): δ 1.3 (d, 3 H, J = 7 Hz), 2.4–3.8 (m, 5 H, S—CH_2—CH_2—CO and methine proton), 7.0–7.5 (m, 5 H, olefinic and aromatic protons) and 11.2 (s, 1 H, acid proton, disappeared on D_2O exchange); MS gave ions at m/z 234 ($M^{+\cdot}$, 37%), 161 (48%), 129 (100%), 128 (44%), 115 (12%) and 106 (17%). Anal: Calcd. for $C_{13}H_{14}O_2S$; C, 66.67; H, 5.98. Found: C, 66.58; H, 5.8.

2H,5H-4-Oxo-5-methyl-3,4-dihydroindeno[1,2-b]thiopyran (VIII). Cyclodehydration of the bicyclic acid (VII) (7 g) was carried out following the procedure described for (III) with phosphorus pentoxide (30 g) to yield the tricyclic ketone (VIII) as a thick red gum (1.62 g; 25%). All attempts to solidify this gum were in vain. IR (film) ν_{max} 1660 (C=O), 1520, 1460 and 1420 cm^{-1}; NMR ($CDCl_3$): δ 1.45 (d, 3 H, J = 7 Hz), 2.5–3.5 (m, 4 H, S—CH_2—CH_2—CO), 3.8 (q, 1 H, J = 7 Hz, methine proton) and 7.3–7.5 (m, 4 H, aromatic). Anal: Calcd. for $C_{13}H_{12}OS$; C, 72.22; H, 5.55. Found: C, 71.74; H, 5.95.

2H,5H-4-Oxo-5-methyl-3-4-dihydroindeno[1,2-b]thiopyran-3-glyoxalate (IX). Reaction of the ketone (VIII) (1.08 g) with dimethyl oxalate (1.2 g) in presence of dry sodium methoxide (prepared from 0.23 g of sodium) adopting the procedure described for (IV) afforded a dark orange red solid (1.5 g). This solid on very rapid chromatography over silica gel (25 g) gave from methylene chloride eluates (1000 ml) an orange red solid which on recrystallisation from methylene chloride–hexane mixture (3 : 2) furnished the analytical sample of (IX) as an orange red crystalline solid, m.p. 104°C (0.98 g; 65%); IR ($CHCl_3$) ν_{max} 3060–2900 (chelated enolic OH), 1725 (ester carbonyl), 1600 (chelated carbonyl), 1500, 1460 and 1420 cm^{-1}; NMR ($CDCl_3$): δ 1.55 (d, 3 H, J = 7 Hz), 4.0 (s, 3 H, —O—CH_3), 4.03 (q, 1 H, J = 7 Hz, methine proton), 4.5 (AB-quartet, 2 H, J_{AB} = 14 Hz, S—CH_2—), 7.3–7.5 (m, 4 H, aromatic) and 11.1 (s, 1 H, enolic proton, exchanged with D_2O); MS showed mass peaks at m/z 302 ($M^{+\cdot}$, 41%), 243 (62%), 242 (22%), 214 (100%), 200 (14%), 188 (16%), 173 (16%), 160 (35%), 145 (14%), 128 (16%) and 115 (19%). Anal: Calcd. for $C_{16}H_{14}O_4S$; C, 63.57; H, 4.64. Found: C, 63.40; H, 5.07.

1-Methoxycarbonyl-4-methyl-4H,10H-indeno[2',3': 5,6]thiopyrano[3,4-d]-isoxazole (X). Condensation of the glyoxalate derivative (IX) (0.9 g) with hydroxylamine hydrochloride (0.2 g) following the procedure described for (V) afforded a yellow solid which on chromatography over silica gel (20 g) on rapid evaporation of the benzene eluates (1500 ml) using a rotary-evaporator under reduced pressure gave a sticky solid. This material on trituration with hexane at ice temperature afforded a fairly pure sample of (X) as a yellow solid, m.p. 124°C (0.67 g; 75%). Attempted recrystallisation of the above solid from methylene chloride-hexane revealed the decomposition of the material. IR ($CHCl_3$) ν_{max} 1725 (ester carbonyl), 1635, 1525, 1460, 1440, 1150 and 1120 cm^{-1} (trisubstituted isoxazole[10] ring breathing vibrations); NMR ($CDCl_3$): δ 1.55 (d, 3 H, J = 7 Hz), 3.85 (m, 4 H, O—CH_3 and methine proton), 4.3 (s, 2 H, S—CH_2) and 7.0–7.5 (m, 4 H, aromatic).

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