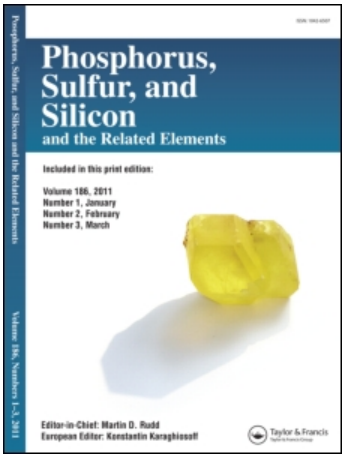

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POLYHETERO POLYCYCLIC RING SYSTEMS: PART XXI: SYNTHESIS OF D-HOMO-6,11,15-TRISTHIA-1,3,5(10),8,13-GONAPENTAEN-17a-ONE

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The synthesis of D-homo-6,11,15-tristhia-1,3,5(10),8,13-gonapentaen-17a-one (V) is described.

INTRODUCTION

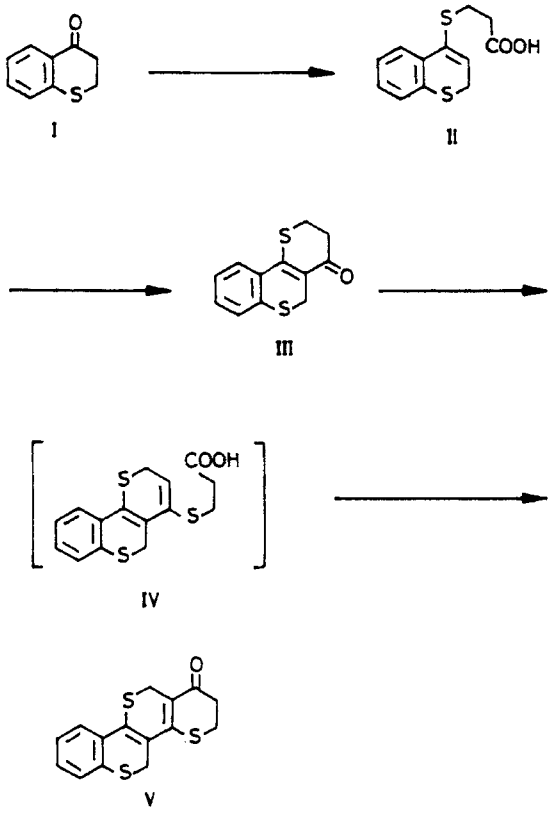
It is well known that heterocyclic steroids display a large spectrum of physiological activity like the anabolic, antitumour and antiinflammatory.[1,2] Thiasteroids such as 6-thia-8,9-dehydroestrones are claimed to possess antifertility activity.[3] Terasawa and Okada[4] have reported that 3-methoxy-16-thia-D-homo-1,3,5(10),8,14-estrapentaen-17aα-ol was found to be an orally potent estrogen with a high antifertility activity as well as lowering serum cholesterol levels. Prompted by these findings and also in continuation of our studies on the synthesis of newer types of thiasteroids, we report herein, the development of a simple approach for the synthesis of the title compound (V).

DISCUSSION

Thiochroman-4-one (I) on condensation with β-mercaptopropionic acid in presence of catalytic amount of *p*-toluenesulfonic acid (PTS) monohydrate gave β-(2H-[1]benzothiopyran-4-ylthio)propionic acid (II) as a colorless crystalline solid in 87% yield.[5]

Cyclodehydration of the acid (II) was effected with phosphorus pentoxide in refluxing benzene to afford 4-oxo-3,4-dihydro-2H,5H-thiopyrano[3,2-c][1]benzothiopyran (III) as shining yellow crystals in 54% yield.

Condensation of the bisthiatricyclic ketone (III) with β-mercaptopropionic acid in presence of catalytic amount of PTS[6] in boiling benzene furnished directly D-homo-6,11,15-tristhia-1,3,5(10),8,13-gonapentaen-17a-one (V) as orange yellow flakes in 12% yield. The isolation of the intermediate acid (IV) was however, found to be unsuccessful. As soon as acid (IV) was formed, it underwent cyclodehydration under the reaction conditions employed affording the tetracyclic ketone (V). Since the tristhiagonane derivative (V) was realised in 12% yield, it is believed that the precursor acid (IV) was formed only to that extent. All attempts to increase the yield of the tetracyclic ketone (V) by increasing the time of the reaction, temperature and the quantity of PTS led to the decomposition of the final product (V) as revealed from a careful thin layer chromatographic study.



The biological screening for this compound (V) is currently in progress and the results will be published elsewhere.

EXPERIMENTAL

The recorded temperatures are uncorrected. Hexane, unless otherwise stated, refers to a petroleum–ether fraction boiling at 60–80°. IR spectra were taken using a Perkin-Elmer-257 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM 390 spectrometer using TMS as internal standard, the chemical shifts being reported in "δ" values. Mass spectra were recorded using a VG Micromass 70–70H spectrometer.

β-(2H-[1]Benzothiopyran-4-ylthio)propionic acid (II). A solution of thiochroman-4-one (16.4 g, 0.1 m), β-mercaptopropionic acid (13.8 g, 0.13 m) and PTS monohydrate (1 g, 0.0058 m) in dry benzene (175 ml) was refluxed for 12 hours using a Dean-Stark water trap.[5] The benzene solution was washed with water (3 × 60 ml) and extracted with 5% sodium bicarbonate solution (3 × 100 ml). The combined aqueous extracts were cooled and neutralised with hydrochloric acid (1 : 1) at 0–5° to afford a dark brown solid. This solid was filtered, washed with water and dried (22 g, 87% yield). Repeated recrystallisation of the crude solid from benzene after treatment with norite furnished the analytical sample of β-(2H-[1]benzothiopyran-4-ylthio)propionic acid (II) as colorless crystalline solid, m.p. 132–134°C; IR(KBr) ν_{max} 3260–2800 (broad, bonded carboxylic OH), 1700 cm^{-1} (acid dimer); ^{1}H-NMR ($CDCl_3$) δ 2.3–2.9 (m, 4 H, S—CH_2—CH_2—COOH), 3.2 (d, 2H, S—CH_2—CH=), 6.0 (t, 1H, S—CH_2—CH=), 6.8–7.6 (m, 4 H, aromatic protons) and 8.5–9.3 (broad, 1 H, acid proton, disappeared on D_2O exchange). MS gave ions at m/z 252 ($M^{+\cdot}$, 17%), 180 (12%), 179 (100%) and 147 (46%). Anal. Calcd. for: $C_{12}H_{12}O_2S_2$; C, 57.14; H, 4.76%. Found: C, 56.96; H, 4.65%.

4-Oxo-3,4-dihydro-2H,5H-thiopyrano[3-2-c][1]benzothiopyran (III). A mixture of the bicyclic acid (II) (5.04 g, 0.02 m) and phosphorus pentoxide (20 g) in dry, thiophene-free, benzene (150 ml) was refluxed for 2 hours. The reaction mixture was cooled and the benzene solution decanted. The solid red mass was decomposed with ice-cold water (100 ml) and extracted with benzene (3 × 50 ml). The combined benzene extracts were washed with water (2 × 50 ml), saturated sodium bicarbonate solution (2 × 50 ml) and again with water (3 × 50 ml). The benzene layer was dried (Na_2SO_4). Evaporation of the dried solvent gave the tricyclic ketone (III) as a reddish brown solid (2.9 g). Chromatography of this material over silica gel furnished from benzene–hexane (1 : 1) eluates, analytically pure sample of compound (III) (2.52 g, 54% yield) as lustrous yellow crystals, m.p. 120–122°C; IR($CHCl_3$) ν_{max} 1650 (conjugated carbonyl), 1600–1400 cm^{-1} (aromatic skeletal vibrations); ^{1}H-NMR ($CDCl_3$) δ 2.6–3.2 (m, 4 H, S—$\underline{CH_2}$—$\underline{CH_2}$—CO), 3.6 (s, 2 H, Ar—S—$\underline{CH_2}$), 6.8–7.6 (m, 4 H, aromatic protons); MS showed ions at m/z 234 ($M^{+\cdot}$, 100%), 201 (51%), 178 (90%). Anal. Calcd. for: $C_{12}H_{10}OS_2$: C, 61.54; H, 4.27%. Found: C, 61.42; H, 4.13%.

D-Homo-6,11,15-tristhia-1,3,5(10),8,13-gonapentaen-17a-one (V). A solution of the tricyclic ketone (III) (1.17 g, 0.005 m), β-mercaptopropionic acid (0.59 g, 0.0056 m) and PTS monohydrate (500 mg) in dry, thiophene-free, benzene (60 ml) was refluxed for 16 hours using a Dean-Stark water separator.[6] The benzene solution was washed with water (3 × 25 ml) and 10% sodium bicarbonate solution (2 × 40 ml). The aqueous alkaline layer was chilled and acidified with ice-cold dilute hydrochloric acid (1 : 1). No traces of the expected acid (IV) were isolated. The organic layer after washing with water (2 × 25 ml) and drying (Na_2SO_4), was evaporated to afford a dark brown solid which on chromatography over silica gel gave from benzene–hexane (1 : 1) eluates the title compound (V) as orange yellow flakes (0.18 g, 12% yield), m.p. 174–175°C; IR(KBr) ν_{max} 1630 (CO with extended conjugation), 1590–1480 cm^{-1} (aromatic skeletal vibrations); ^{1}H-NMR ($CDCl_3$) δ 2.5–3.2 (m, 4 H, S—$\underline{CH_2}$—$\underline{CH_2}$—CO), 3.6 (s, 4 H, Ar—S—$\underline{CH_2}$, S—$\underline{CH_2}$—C=), 6.8–7.5 (m, 4 H, aromatic protons); MS m/z 304 ($M^{+\cdot}$, 73%) Anal: Calcd. for: $C_{15}H_{12}OS_3$: C, 59.21; H, 3.95%. Found: C, 59.1; H, 3.81%.

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