HETEROCYCLIC STEROIDS-PART X: TOTAL SYNTHESIS OF 12,15-BISTHIA-1,3,5(10),6,8,13(14)-GONAHEXAEN-17-ONE

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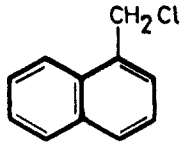
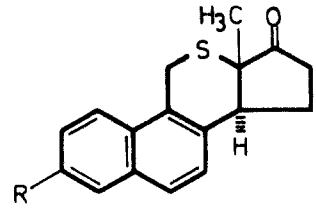
ABSTRACT

The total synthesis of 12,15-bisthia-1,3,5(10),6,8,13(14)-gonahexaen-17-one(III) from 1-chloromethylnaphthalene(IV) is herewith described.

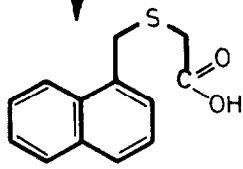
Recent publications on heterocyclic steroidal systems (1 to 5) indicate that there has been no report on the total synthesis of 12-thiasteroids in the equilenin series. In a broad programme to study the influence of sulphur in position '12' of the steroid nucleus on the biological activity, the total syntheses of 3-deoxy-12-thiaequilenin(I) and 12-thiaequilenin methyl ether (II) were undertaken as early as in 1975 based on a new approach (6). In continuation of our studies on structure-activity relationships, the synthesis of the title compound (III) was achieved adopting a short and simple synthetic approach. 1-Chloromethylnaphthalene(IV), upon treatment with thioglycollic acid in 2N sodium hydroxide, furnished a product which upon recrystallization from carbon tetrachloride gave the analytically pure sample of 1-naphthylmethylthioacetic acid (V) as a pale yellow crystalline solid in 80% yield. It may be pointed out here that Luma and Berchtold (7) have also reported the synthesis of acid (V)



IV



I R = H
II R = OMe



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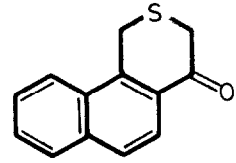

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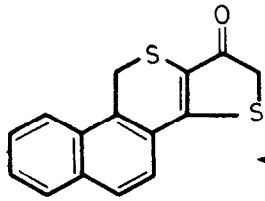
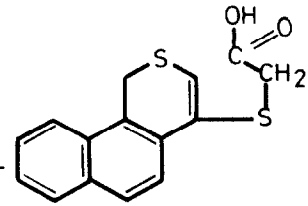


III



VII

almost in comparable yield to the present one by condensing 1-mercaptomethylnaphthalene with chloroacetic acid. The thioacetic acid derivative (V) on cyclodehydration with phosphorous pentoxide in refluxing benzene afforded a brownish thick gum which on chromatography afforded from benzene-hexane (1:1) eluates a fairly pure sample of the ketone (VI) which on recrystallization from carbon tetrachloride yielded the analytically pure sample of 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene (VI) as an yellow crystalline solid in 25-30% yield. Luma and Berchtold (7) have also reported the cyclodehydration of the thioacetic acid derivative (V) essentially under conditions similar to what we employed but the authors (7) reported the resulting tricyclic ketone (VI) in lower yields. The tricyclic ketone (VI) upon reaction with thioglycollic acid in presence of p-toluenesulphonic acid (PTS) in benzene at reflux temperature, afforded a product which upon recrystallization from benzene gave the analytically pure sample of (3-thia-3,4-dihydrophenanthren-1-yl) thioacetic acid (VII) as a dark brown crystalline solid in 50% yield. The thioacetic acid derivative (VII) on further cyclodehydration with PTS in refluxing benzene gave a brown gummy solid. Chromatography of this product through silica gel and recrystallization from methanol gave a pure sample of 12,15-bisthia-1,3,5(10),6,8,13(14)-gonahexaen-17-one (III) as an orange

crystalline solid in 15% yield. The structure assigned to it was supported by its spectral data (see Experimental).

All attempts to hydrogenate the 13,14-olefinic bond in (III) employing the conventional catalysts were unsuccessful thereby preventing the desired methylation at C_{13}. In view of these limitations, further transformation of (III) into the desired 3-deoxy-12,15-bisthiaequilenin could not be achieved.

EXPERIMENTAL (8)

1-Naphthylmethylthioacetic acid (V): To a well-stirred solution of thioglycollic acid (7g) in 2N sodium hydroxide solution (55 ml) maintained at 0-5°C, was added dropwise a solution of 1-chloromethylnapthalene (IV) (11.25g) in 50 ml of acetone for about one hour and stirring was continued for about fifteen hours. Water (50 ml) was added to the reaction mixture and the aqueous layer was washed with ether (2x25 ml) and then neutralized with aqueous dilute hydrochloric acid (1:1) at 0°C to afford a solid, which was filtered, washed with water and dried. Recrystallization of the crude solid from carbon tetrachloride gave the analytical sample of (V) (13g, 80% yield) as a pale yellow crystalline solid, m.p. 111-112° reported (7) m.p. 110-111° ; IR(KBr) ν_{max} 3200-2800 (bonded OH stretching and CH_2-stretch), 1680 (CO acid dimer), 1590 and 1500 cm^{-1} (aromatic C=C stretch). ^{1}H-NMR($CDCl_3$) δ 3.2(s,2H,-S-CH_2-COOH), 4.4(s,2H,Ar-CH_2-S), 7.4-8.4(m,7H,aromatic protons) and 11.0(s,acid proton) and the last signal disappeared on shaking with D_2O; mass peaks at m/z 232 ($M^{+\cdot}$,18%), m/z 173(3%), m/z 171 (4.3%), m/z 141(100%), m/z 139(63%) and m/z 115(12%).

Anal. Calcd. for $C_{13}H_{12}O_2S$: C,67.24; H,5.17%.

Found: C,66.89; H,5.29%.

1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene (VI):

A mixture of the acid (V) (8.7g), phosphorous pentoxide (36g) and thiophene-free dry benzene (125 ml) was refluxed under anhydrous conditions for five hours. The

benzene layer was separated and the residue was decomposed with ice-cold water. The aqueous layer was extracted with benzene (2x25 ml); the combined benzene extracts were washed with saturated solution of sodium bicarbonate (3x20 ml) and then with water (2x20 ml). The brownish thick gum, obtained on evaporation of the dried benzene extract, was chromatographed through silica gel (130g). The benzene-hexane (1:1) eluates upon evaporation gave the pure product, which on recrystallization from carbon tetrachloride yielded the analytically pure sample of the tricyclic ketone (VI) (2.2g, 25-30% yield) as a yellow crystalline solid, m.p. 123-124° reported (7), m.p. 125-126° ; IR(KBr) ν_{max} 1670 (CO stretch), 1600, 1570 (aromatic skeletal vibrations) 1260 cm^{-1} (C-S stretch); ^{1}H-NMR($CDCl_3$) δ 3.5(s,2H,-S-CH_2-CO-), 4.2(s,2H,Ar-CH_2-S) and 7.3-8.3 (m,6H,aromatic protons); ^{13}C-NMR($CDCl_3$) 28.47 (t,-S-CH_2-CO), 37.47 (t,Ar-CH_2-S), 125.76-142.55 (aromatic carbons) and, 193.44(s,CO); mass peaks at m/z 214 ($M^{+\cdot}$,72%), m/z 184(2%), m/z 172(2%), m/z 171(5%), m/z 168(100%), m/z 141(30%), m/z 140(64%) and m/z 139(28.3%).

Anal. Calcd. for $C_{13}H_{10}OS$: C,72.90; H,4.67%.

Found: C,73.10; H,4.67%.

(3-Thia-3,4-dihydrophenanthren-1-yl)thioacetic acid (VII):

A mixture of the tricyclic ketone (VI) (1.07g), thioglycollic acid (0.5g) and PTS (0.1g) was refluxed in dry benzene for 16 hours under anhydrous conditions. The benzene layer was extracted with 10% sodium hydroxide solution (2x20 ml) and the alkaline extract cooled to 0° was acidified with hydrochloric acid (1:1) to give the corresponding VII as a solid, which was filtered and dried in vacuum. Recrystallization from benzene gave the analytical sample of VII (0.73g, 50% yield) as a dark brown crystalline solid, m.p. 174-175°; IR(KBr) ν_{max} 3200-2800 (bonded OH and CH_2 stretching), 1700 (CO stretch acid dimer), 1600-1400 (aromatic skeletal vibrations). The olefinic stretching appears to have merged with the aromatic skeletal vibrations because of its conjugation with sulphur atom. ^{1}H-NMR($CDCl_3$) δ 3.7(s,2H,-S-CH_2-COOH), 4.52 (s,2H,Ar-CH_2-S), 7.4(s,1H,-S-CH-C) and 7.6-8.4 (m,6H, aromatic protons); mass peaks at m/z 288 ($M^{+\cdot}$,100%), m/z 287(12%), m/z 229(65%), m/z 228(24%), m/z 197(18%), m/z 185(59%), m/z 184(38%), m/z 165(18%) and m/z 152(18%).

Anal. Calcd. for $C_{15}H_{12}O_2S_2$:C,62.50; H,4.17%.

Found: C,62.72; H,4.31%.

12,15-Bisthia-1,3,5(10),6,8,13(14)-gonahexaen-17-one(III):

A mixture of tricyclic acid (VII) (0.28g) and PTS (20 mg) was refluxed in dry benzene (20 ml) for 3 hours using a Dean-Stark apparatus. The benzene layer was washed thoroughly with saturated sodium bicarbonate solution (2x10 ml) and then with water (10 ml). Evaporation of the dried solvent yielded a gummy solid which was dissolved in benzene and quickly passed through a short column of silica gel (15g). The product obtained from benzene eluates was recrystallized from methanol to give (III) (40 mg, 15% yield) as a crystalline solid, m.p. 141-142°; IR(KBr) ν_{max} 1680 (conjugated carbonyl stretch), 1600-1480 cm^{-1} (aromatic skeletal vibrations) and 1620 cm^{-1} (sh) (olefinic stretch). ^{1}H-NMR($CDCl_3$)δ 3.50(s,2H,-S-CH_2-C=O), 4.25(s,2H,Ar-CH_2-S) and 7.4-8.1 (m,6H, aromatic protons), mass peaks at m/z 270 ($M^{+\cdot}$,2%), m/z 212(50%), m/z 168(90%), m/z 140(100%),and m/z 139 (60%).

Anal. Calcd. for $C_{15}H_{10}OS_2$: C,66.66; H,3.70%.

Found: C,67.01; H,3.83%.

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8. The recorded temperatures are uncorrected. IR spectra were taken using a Perkin-Elmer grating infrared spectrophotometer, model 257. NMR spectra were recorded on Varian XL 100 spectrometer using tetramethylsilane (TMS) as the internal standard, the chemical shifts being reported in 'δ' values. Mass spectra were taken using A MAT-CH 7 spectrometer.