5α-Cholestano[7,6-*c*]pyrazole Derivatives

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The preparation of 5α-cholestane derivatives containing a fused pyrazole ring from 5α-cholestan-7-ones has been studied. Attempts to prepare the isomeric pyrazoles from 5α-cholestan-6-ones were not successful.

THE preparation of steroid derivatives containing a fused pyrazole ring and their chemical and physiological properties have been the subject of several recent studies.[1-8] Many active compounds have been discovered, *e.g.* androstanes with a fused ring in the 2,3-position [1,2] and various 16,17-fused steroids.[4,5] We have been interested in derivatives containing a pyrazole system fused to ring B of the steroid molecule at the 6,7-position. Two types of parent structure can be envisaged [(3) and (15)]. As a starting material for the former type we chose 3β-hydroxy-5α-cholestan-7-one (1), which was converted into the 6-hydroxymethylene-7-one (2) by treatment with ethyl formate and sodium hydride. The product showed the expected u.v. absorption at 292 nm and on treatment with hydrazine hydrate gave the pyrazole derivative (3), $\lambda_{max.}$ 225 nm,[1] $\nu_{max.}$ 3460 cm^{-1} (OH and NH).

Treatment of the pyrazole (3) with toluene-*p*-sulphonyl chloride (1·3 mol. equiv.) afforded a mixture of monotosylate (72%) and ditosylate (10%). The former showed u.v. absorption at 225 (pyrazole ring) and 251 nm (tosyl group) and i.r. absorption at 3600 cm^{-1} (OH or NH). Since it did not react with collidine under reflux [9,10] structure (6) was proposed, and was confirmed by synthesis. The hydroxy-derivative (3) gave the formate (4) and this was converted into the *N*-tosyl derivative (5). Hydrolysis with potassium carbonate then gave the 3β-hydroxy-compound (6). Treatment of the monotosylate with toluene-*p*-sulphonyl chloride gave the ditosylate (7).

The Δ^2-compound (8) was prepared from the ditosylate (7) by heating under reflux with collidine and characterised by its i.r. absorption at 1652 cm^{-1} (isolated double bond).[11] Hydrolysis with hydrochloric acid in acetone [12] removed the tosyl group, and the product (9) was characterised by its u.v. absorption at 225 nm (with loss of absorption at 251 nm). Hydrogenation of compound (9) over palladium–calcium carbonate gave the saturated derivative (10). This was prepared by another route from the hydroxy-derivative (3), by oxidation to the 3-one (13) followed by Huang-Minlon reduction. Another route to compound (10) involved conversion of 5α-cholestan-7-one (11) into the 6-hydroxymethylene derivative (12) and treatment of this with hydrazine.

Attempts to prepare the isomeric [6,7-*c*]pyrazole derivative (15) from the 6-one (14) were not successful. Reactions of ketone (14) with ethyl formate in pyridine containing sodium ethoxide, or in benzene containing sodium hydride failed, probably for steric reasons.[13]

EXPERIMENTAL

M.p.s were determined on a Kofler micro-hot-stage apparatus. Samples for analysis were dried at 80° and

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and 0·1 Torr. Optical rotations were measured for solutions in chloroform at room temperature.

The microanalyses, spectral analysis, and pharmacological screening were performed in the Laboratories of the Research Institute for Pharmacy and Biochemistry, Prague.

3β-*Hydroxy*-6-*hydroxymethylene*-5α-*cholestan*-7-*one* (2).—Ketone (1) (4·2 g) in benzene (150 ml) was added dropwise to a stirred suspension of sodium hydride (2·7 g) in toluene (15 ml) and ethyl formate (20 ml). The mixture was left overnight, methanol (1 ml) was added, and the product was stirred for another 2 h. Celite (20 g) was added, and the sodium salt was sucked off and washed with benzene and light petroleum. The dry product was suspended in dilute acetic acid (4%; 200 ml) collected by suction. Extraction with chloroform and crystallisation gave the *ketone* (2) (2·17 g) m.p. 187—189° (from methanol), $[\alpha]_D$ +25°, $\lambda_{max.}$ (MeOH) 292 nm (ε 6200) (Found: C, 77·8; H, 10·8. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·8%).

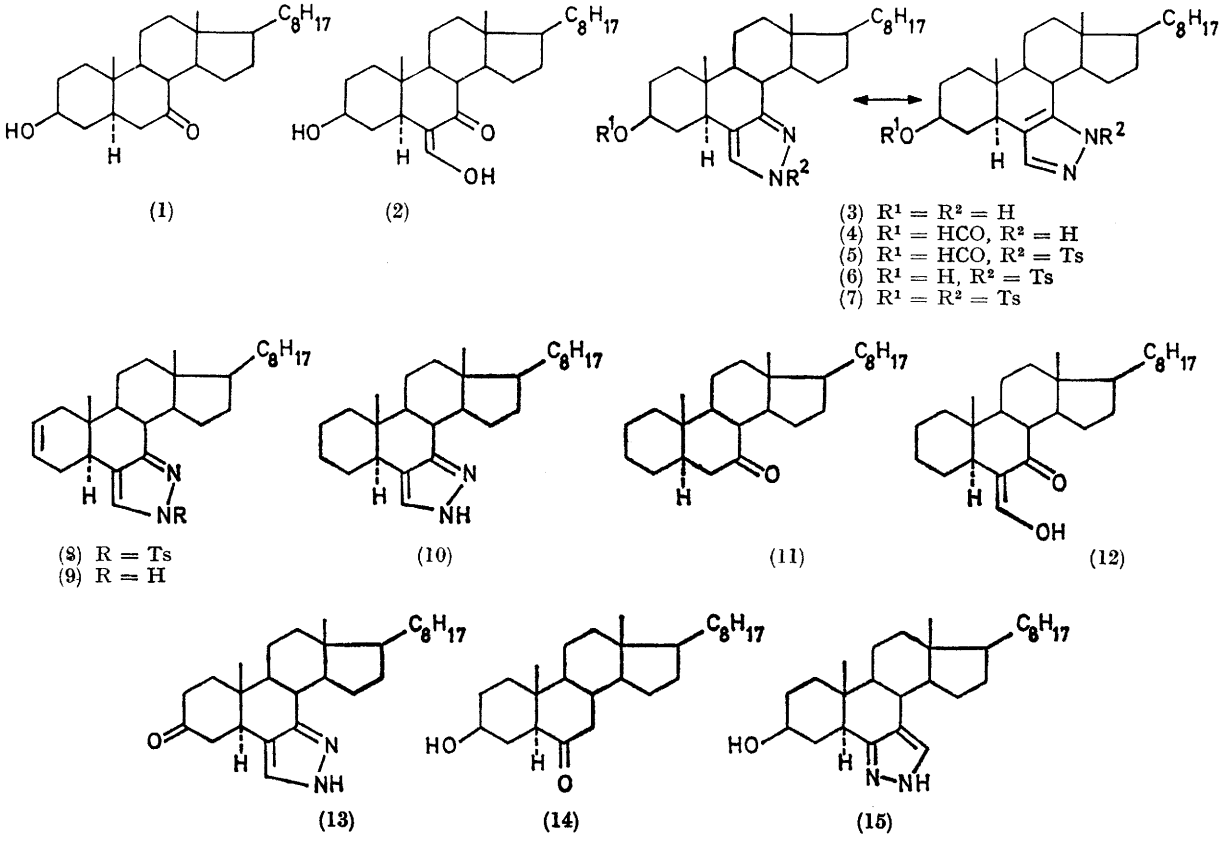
5α-*Cholestano*[7,6-c]*pyrazol*-3β-*ol* (3).—The ketone (2) (5 g) in ethanol (50 ml) and chloroform (10 ml) was refluxed with hydrazine hydrate (5 ml) for 90 min. The solution was concentrated to a small volume, water was added, and the product, collected by suction, gave the *pyrazole* (3), m.p. 274—278° (from ethanol–chloroform), $[\alpha]_D$ +38°, $\lambda_{max.}$ (MeOH) 225 nm (ε 6600) (Found: C, 78·5; H, 11·1; N, 6·8. $C_{28}H_{46}N_2O$ requires C, 78·8; H, 10·9; N, 6·6%).

5α-*Cholestano*[7,6-c]*pyrazol*-3β-*yl Formate* (4).—The hydroxy-derivative (3) (300 mg) in formic acid (95%; 3 ml) was heated on a steam-bath for 1 h. Water was added and the product was extracted into benzene and washed three times with water. The solvent was evaporated off and the residue gave the *formate* (4) (215 mg), m.p. 254—256° (from acetone), $[\alpha]_D$ +15°, $\lambda_{max.}$ (MeOH) 225 nm (ε 6100) (Found: C, 76·5; H, 10·5; N, 6·3. $C_{29}H_{46}N_2O_2$ requires C, 76·6; H, 10·2; N, 6·3%).

N-*Tosyl*-5α-*cholestano*[7,6-c]*pyrazol*-3β-*yl Formate* (5).—The formate (4) (1 g) and toluene-*p*-sulphonyl chloride (500 mg) were dissolved in pyridine (5 ml) and left overnight. Water was added and the product was extracted into benzene. The extract was washed with water, dilute hydrochloric acid, sodium hydrogen carbonate solution, and water. Crystallisation gave the *tosyl derivative* (5) (1·1 g), m.p. 205—207° (from acetone–methanol), $[\alpha]_D$ +12°, $\lambda_{max.}$ (MeOH) 225 and 250 nm (ε 6100 and 8000) (Found: C, 71·1; H, 8·7; N, 4·7; S, 5·6. $C_{36}H_{52}N_2O_4S$ requires C, 71·0; H, 8·6; N, 4·6; S, 5·3%).

N-*Tosyl*-5α-*cholestano*[7,6-c]*pyrazole*-3β-*ol* (6).—(*a*) The formate (5) (650 mg) in ethanol (10 ml) and benzene (10 ml) was stirred with a solution of potassium carbonate (150 mg) in water (0·3 ml) and left overnight. Crystallisation afforded the *tosyl derivative* (6) (520 mg), m.p. 189—191° (from acetone–methanol), $[\alpha]_D$ +55°, $\lambda_{max.}$ (MeOH) 225 and 251 nm (ε 12,000 and 14,000) (Found: C, 72·4; H, 9·0; N, 4·6; S, 5·3. $C_{35}H_{52}N_2O_3S$ requires C, 72·4; H, 9·0; N, 4·8; S, 5·5%).

(*b*) The hydroxy-derivative (3) (500 mg) and toluene-*p*-sulphonyl chloride (300 mg) in pyridine (5 ml) were left overnight. Water was added, the product was extracted into benzene, and after the usual work-up the residue (720 mg) was purified on a silica gel column (10 g).



Fractions eluted with benzene contained the *ditosyl derivative* (7) (75 mg), m.p. 200—202° (from ether), $[\alpha]_D$ +13°, $\lambda_{max.}$ (MeOH) 225 and 251 nm (ε 24,600 and 12,900) (Found: C, 68·9; H, 7·2; N, 3·7; S, 8·7. $C_{42}H_{58}N_2O_5S_2$ requires C, 69·2; H, 7·2; N, 3·8; S, 8·8%). Fractions eluted with chloroform contained the tosyl derivative (6) (490 mg), m.p. 185—188°, identical with the product prepared in (*a*).

N-*Tosyl*-5α-*cholestano*[7,6-c]*pyrazol*-3β-*yl Tosylate* (7).—The hydroxy-derivative (3) (1·1 g) and toluene-*p*-sulphonyl chloride (1 g) in pyridine (5 ml) were left overnight. The usual work-up and crystallisation gave the ditosyl derivative (7), m.p. 195—200° (from methanol).

A sample of monotosylate (6) gave the ditosylate in a similar way, m.p. 193—197°.

N-*Tosyl*-5α-*cholest*-2-*eno*[7,6-c]*pyrazole* (8).—The ditosyl derivative (7) (2·5 g) in collidine (15 ml) was refluxed for 1 h. Water was added and the product was extracted into benzene. The extract was washed with dilute hydrochloric acid, water, sodium hydrogen carbonate solution, and water. The residue (1·8 g) in light petroleum–benzene (1 : 1) was filtered through a silica gel column (6 g) to give the *unsaturated derivative* (8) (1·7 g), m.p. 149—151° (from hexane), $[\alpha]_D$ +92°, $\lambda_{max.}$ (MeOH) 225 and 252 nm (ε 11,200 and 14,100) (Found: C, 74·3; H, 9·1; N, 4·9; S, 5·7. $C_{35}H_{50}N_2O_2S$ requires C, 74·7; H, 9·0; N, 5·0; S, 5·7%).

5α-*Cholest*-2-*eno*[7,6-c]*pyrazole* (9).—The tosylate (8) (1·43 g) in acetone (30 ml) and concentrated hydrochloric acid (4 ml) were refluxed for 5 h. Water was added and the product, collected by suction and washed with water, gave the *pyrazole* (9) (670 mg), m.p. 197—200° (from acetone), $[\alpha]_D$ +170°, $\lambda_{max.}$ (MeOH) 225 nm (ε 4900) (Found: C, 80·9; H, 10·9; N, 6·7. $C_{28}H_{44}N_2,0{\cdot}5H_2O$ requires C, 80·5; H, 10·9; N, 6·7%). Chromatography of the mother liquor on silica gel gave more pyrazole (9) (100 mg).

5α-*Cholestano*[7,6-c]*pyrazole* (10).—(*a*) The unsaturated derivative (9) (170 mg) in ethanol (5 ml) was hydrogenated over palladium–calcium carbonate (5%; 50 mg). After 30 min, absorption of hydrogen ceased; the catalyst was filtered off, the solvent was evaporated, and the residue was crystallised from acetone to give *compound* (10) (130 mg), m.p. 195—197°, $[\alpha]_D$ +93°, $\lambda_{max.}$ (MeOH) 225 nm (ε 7100) (Found: C, 81·5; H, 11·5; N, 7·0. $C_{28}H_{46}N_2$ requires C, 81·9; H, 11·3; N, 6·8%).

(*b*) The 3-ketone (13) (440 mg), potassium hydroxide (300 mg), and hydrazine hydrate (0·5 ml) in triethylene glycol (5 ml) were heated at 190—200° for 90 min. Water was added and the product was collected by suction and washed with water. Crystallisation gave derivative (10) (315 mg), m.p. 193—196° (from methanol), identical with the compound prepared in (*a*).

(*c*) The hydroxymethylene derivative (12) (200 mg) in ethanol (5 ml), chloroform (2 ml), and hydrazine hydrate (0·5 ml) was refluxed for 90 min. After the usual work-up the product was crystallised from acetone; m.p. 193—195° (75 mg).

5α-*Cholestan*[7,6-c]*pyrazol*-3-*one* (13).—The pyrazole (3) (2 g) in acetic acid (30 ml) and chromium trioxide (480 mg) in acetic acid (4 ml) were left overnight. Water was added and the product was extracted into chloroform. The extract was washed with dilute sodium hydroxide solution and water and evaporated. A solution of the product in methylene chloride was filtered through a silica gel column (10 g); the product gave *ketone* (13) (1·20 g), m.p. 219—220° (from acetone), $[\alpha]_D$ +45°, $\lambda_{max.}$ (MeOH) 224 nm (ε 5500) (Found: C, 78·9; H, 10·4; N, 6·7. $C_{28}H_{44}N_2O$ requires C, 79·2; H, 10·4; N, 6·6%).

6-*Hydroxymethylene*-5α-*cholestan*-7-*one* (12).—A solution of the ketone (11) (3·78 g) in pyridine (40 ml) was added dropwise to a suspension of sodium methoxide [from sodium (600 mg)] in pyridine (15 ml) and ethyl formate (15 ml). The mixture was stirred for 60 h, poured into water, and acidified with hydrochloric acid (5 ml); the product was collected by suction and washed with water. Chromatography on silica gel (40 g) gave 5α-cholestane (eluted with light petroleum) (405 mg), m.p. 76—80° (lit.,[14] 79—80°), followed by *ketone* (12) (325 mg), m.p. 104—106° (from acetone), $[\alpha]_D$ +33°, $\lambda_{max.}$ (MeOH) 294 nm (ε 2700) (Found: C, 80·8; H, 11·2. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%). Further elution, with light petroleum–benzene (9 : 1) and benzene gave starting material (11) (1·61 g).

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