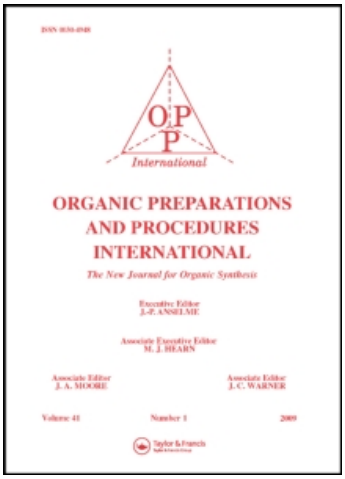

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SYNTHESIS OF STEROIDAL HETEROCYCLIC COMPOUNDS FROM A CLAISEN CONDENSATION PRODUCT OF A 6-KETO STEROL

A. U. Siddiqui[ab]; U. M. Rao[a]; M. Srinivas[a]; A. H. Siddiqui[a]
[a] Department of Chemistry, Nizam College, Osmania universiry, Hyderabad, India [b] Department of Biochemistry, Rice University, Houston, TX, USA

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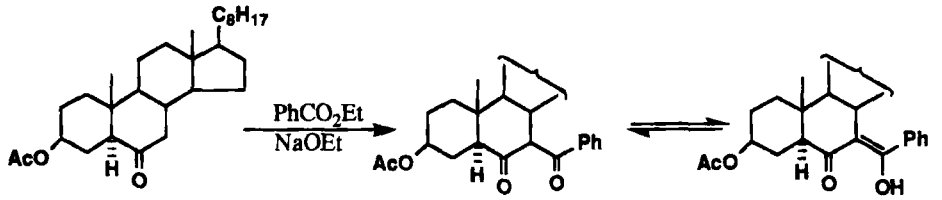
SYNTHESIS OF STEROIDAL HETEROCYCLIC COMPOUNDS FROM A CLAISEN CONDENSATION PRODUCT OF A 6-KETO STEROL

Submitted by (02/03/92)

A. U. Siddiqui,*† U. M. Rao, M. Srinivas and A. H. Siddiqui

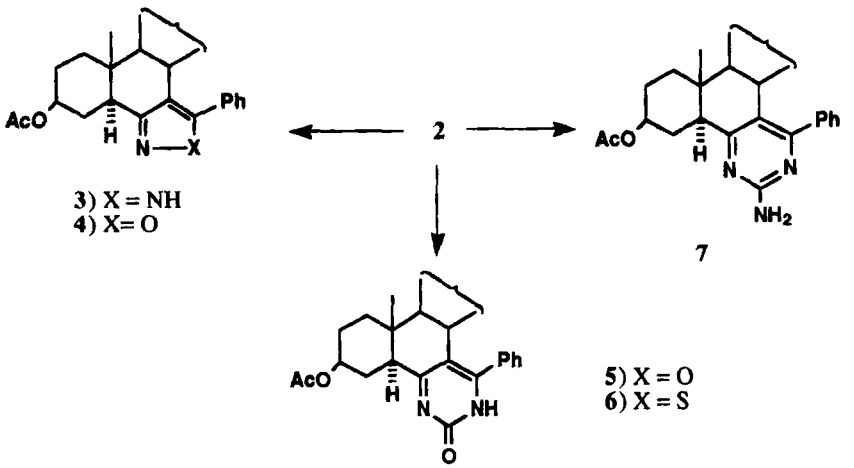
Department of Chemistry, Nizam College, Osmania university Hyderabad-500001, INDIA

Several approaches have been developed for the synthesis of steroidal derivatives with pyrazole, isoxazole and pyrimidine systems.[1] One of the methods involves condensation of a steroidal ketone with ethyl formate to give an α-formyl ketone, followed by reaction with nitrogenous compounds to give pyrazole,[2] isoxazole[3] and pyrimidine[4] systems. This paper describes the condensation of a steroidal ketone with ethyl benzoate to prepare steroidal heterocyclic compounds containing pyrazole, isoxazole and pyrimidine ring systems fused to ring B. The present work was stimulated by reports that steroidal derivatives containing a heterocyclic ring condensed in different positions of the steroidal ring system possess useful biological activities.[5]



1 2 2a

Claisen condensation of 3β-acetoxy-5α-cholestan-6-one (**1**) with ethyl benzoate afforded 3β-acetoxy-7-benzoyl-5α-cholestan-6-one (**2**), which may exist in equilibrium with the more highly conjugated tautomeric form (**2a**). In support of the enol form **2a**, the IR spectrum showed a broad absorption at 3350 (OH) cm^{-1}, and the ^1H NMR showed a singlet at δ 14.1, exchangeable with



3) X = NH
4) X= O

7

5) X = O
6) X = S

deuterium which can be attributed to the enolic OH.

Reaction of 3β-acetoxy-7-benzoyl-5α-cholestan-6-one (**2**) with hydrazine hydrate gave the pyrazole derivative **3**. The structure of **3** is supported by ^{1}H NMR downfield signals for the NH proton at δ 8.1, exchangeable with deuterium and IR absorptions at 3360 (NH) and 1640 (C=N) cm^{-1}. The reaction of benzoyl derivative **2** with hydroxylamine hydrochloride afforded the isoxazole derivative **4** which showed IR absorptions at 1625 (C=N) and 690 (N-O) cm^{-1} and ^{1}H NMR signals for the aromatic protons at δ 7.3-7.8. Reaction of **2** with urea gave the pyrimidine derivative **5** whose ^{1}H NMR showed an exchangeable singlet for the NH proton at δ 7.9. The IR spectrum showed absorptions at 3410 (NH), 1685 (C=O of pyrimidine) and 1630 (C=N) cm^{-1}. Similarly, condensation of **2** with thiourea gave the pyrimidine derivative **6.** The ^{1}H NMR spectrum of **6** gave a broad exchangeable singlet for the NH proton at δ 7.8, and the IR spectrum showed absorptions at 3420 (NH), 1630 (C=N) and 1350 (C=S) cm^{-1}. Reaction of **2** with guanidine hydrochloride gave the pyrimidine derivative (**7**) whose ^{1}H NMR gave a broad singlet for NH_2 protons at δ 5.7, exchangeable with deuterium, and the IR spectrum showed absorptions at 3410, 3220 (NH_2) and 1630 cm^{-1} (C=N) cm^{-1}.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 137 spectrophotometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian A-60 instrument with TMS as internal standard. Chemical shifts are given in ppm (δ). 3β-Acetoxy-5α-cholestan-6-one **1** was prepared by a known procedure.[6]

3β-Acetoxy-7-benzoyl-5α-cholestan-6-one (2).- A mixture of 3β-acetoxy-5α-cholestan-6-one (**1**) (2 g, 4.5 mmol) and ethyl benzoate (1.35 g, 9 mmol) in dry pyridine (50 mL) was added dropwise to sodium ethoxide (0.5 g sodium metal in 15 mL of absolute ethanol) at room temperature, and the mixture was stirred under nitrogen for 6 hrs. The mixture was concentrated under reduced pressure, and the residue was diluted with ice water (50 mL). The aqueous solution was neutralized with 1M HCl, and the precipitate was collected and recrystallized from methanol to give 1.48 g (60%) of **2** as a colorless solid, mp. 151-153°. IR: 3350 (OH), 1720 (acetate C=O), 1700 (C=O), 1560-1520 (C=C), 1240 (C-O) cm^{-1}; ^{1}H NMR: δ 14.1 (s, 1H, OH exchangeable), 7.4-7.9 (m, 5H, aromatic), 4.60 (m, 1H, $W_{1/2}$ = 14 Hz, H-3α),[7] 3.0 (m, 1H, 8-H), 1.15 (s, 3H, C_{19}-H_3), 0.91 (d, 3H, J = 6.5 Hz, C_{21}-H_3), 0.73 (s, 3H, C_{18}-H_3).
Anal. Calcd. for $C_{36}H_{52}O_4$: C, 78.83; H, 9.49. Found: C, 78.78; H, 9.40

5'-Phenyl-3β-acetoxy-5α-cholestano[6,7-c]pyrazole (3).- A mixture of 3β-acetoxy-7-benzoyl-5α-cholestan-6-one (**2**) (0.5 g, 0.91 mmol), methanol (25 mL), acetic acid (2-3 drops) and 99% hydrazine hydrate (0.186 g, 3.64 mmol) was refluxed for 2 hrs. The mixture was concentrated and poured onto ice. The precipitate was collected and recrystallized from ethanol to give 0.31 g (62%) of **3** as a colorless solid, mp. 168-170°. IR: 3360 (NH), 1725 (C=O), 1640 (C=N), 1560-1510 (C=C), 1240 (C-O) cm^{-1}; ^{1}H NMR: δ 8.1 (br s, 1H, NH exchangeable), 7.3-7.8 (m, 5H, aromatic), 4.55 (m, 1H, $W_{1/2}$ = 14 Hz, H-3α), 3.1 (m, 1H, 8-H), 1.18 (s, 3H, C_{19}-H_3), 0.90 (d, 3H, J = 6.5 Hz, C_{21}-H_3), 0.76 (s, 3H, C_{18}-H_3).
Anal. Calcd. for $C_{36}H_{52}N_2O_2$: C, 79.41; H, 9.56; N, 5.14. Found: C, 79.35; H, 9.64; N, 5.06

5′-Phenyl-3β-acetoxy-5α-cholestano[6,7-c]isoxazole (4).- To a solution of **2** (1.0 g, 1.82 mmol) in methanol (30 mL), hydroxylamine hydrochloride (0.5 g, 7.2 mmol) and sodium acetate (0.75 g, 9 mmol) were added, and the mixture was refluxed for 4 hrs. The mixture was concentrated and poured onto ice. The precipitate was collected and recrystallized from methanol to give 0.52 g (52%) of **4** as a colorless solid, mp. 183-184°. IR: 1720 (C=O), 1625 (C=N), 1550-1520 (C=C), 690 (N-O) cm^{-1}; ^1H NMR: δ 7.3-7.8 (m, 5H, aromatic), 4.58 (m, 1H, $W_{1/2}$ = 14 Hz, H-3α), 3.15 (m, 1H, 8-H), 1.16 (s, 3H, C_{19}-H_3), 0.93 (d, 3H, J = 6.0 Hz, C_{21}-H_3), 0.75 (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{36}H_{51}NO_3$: C, 79.20; H, 9.35; N, 2.57. Found: C, 79.28; H, 9.40; N, 2.50

6′-Phenyl-3β-acetoxy-5α-cholestano[6,7-d]pyrimidin-2′-one (5).- To a solution of **2** (0.5 g, 0.91 mmol) in methanol (20 mL) was added urea (0.22 g, 3.64 mmol) and 2 drops of piperidine. The mixture was refluxed for 6 hrs and then concentrated and poured onto ice. The precipitate was collected and recrystallized from methanol to give 0.3 g (57%) of **5** as a colorless solid, mp. 190-192°. IR: 3410 (NH), 1720 (acetate C=O), 1685 (C=O of pyrimidine), 1625 (C=N), 1545-1510 (C=C) cm^{-1}; ^1H NMR: δ 7.9 (br s, 1H, NH exchangeable), 7.2-7.6 (m, 5H, aromatic), 4.65 (m, 1H, $W_{1/2}$ = 14 Hz, H-3α), 3.1 (m, 1H, 8-H), 1.20 (s, 3H, C_{19}-H_3), 0.90 (d, 3H, J = 6.5 Hz, C_{21}-H_3), 0.76 (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{37}H_{52}N_2O_3$: C, 77.62; H, 9.09; N, 4.90. Found: C, 77.58; H, 9.18; N, 5.0

6′-Phenyl-3β-acetoxy-5α-cholestano[6,7-d]pyrimidin-2′-thione (6).-A mixture of **2** (0.5 g, 0.91 mmol), methanol (20 mL), thiourea (0.275 g, 3.64 mmol) and 2 drops of piperidine were refluxed for 6 hrs. The mixture was concentrated and poured onto ice. The precipitate was collected and recrystallized from methanol to give 0.27 g (50%) of **6** as a colorless solid, mp. 184-186°. IR: 3420 (NH), 1730 (C=O), 1630 (C=N), 1550-1520 (C=C), 1350 (C=S) cm^{-1}; ^1H NMR: δ 7.8 (br s, 1H, NH exchangeable), 7.3-7.6 (m, 5H, aromatic), 4.65 (m, 1H, $W_{1/2}$ = 14 Hz, H-3α), 3.1 (m, 1H, 8-H), 1.20 (s, 3H, C_{19}-H_3), 0.91 (d, 3H, J = 6.0 Hz, C_{21}-H_3), 0.76 (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{37}H_{52}N_2O_2S$: C, 75.51; H, 8.84; N, 4.76. Found: C, 75.60; H, 8.76; N, 4.70

2′-Amino-6′-Phenyl-3β-acetoxy-5α-cholestano[6,7-d]pyrimidine (7).- A mixture of **2** (0.5 g, 0.91 mmol), methanol (30 mL), guanidine hydrochloride (0.35 g, 3.64 mmol) and sodium acetate (0.75 g; 9 mmol) was refluxed for 8 hrs. The mixture was concentrated and poured onto ice. The precipitate was collected and recrystallized from ethanol to give 0.320 g (61%) of **7** as a colorless solid, mp. 196-198°. IR: 3420, 3210 (NH_2), 1725 (C=O), 1630 (C=N), 1540-1510 (C=C), 1240 (C-O) cm^{-1}; ^1H NMR: δ 7.3-7.7 (m, 5H, aromatic), 5.7 (br s, 2H, NH_2 exchangeable), 4.55 (m, 1H, $W_{1/2}$ = 14 Hz, H-3α), 3.2 (m, 1H, 8-H), 1.17 (s, 3H, C_{19}-H_3), 0.90 (d, 3H, J = 6.5 Hz, C_{21}-H_3), 0.78 (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{37}H_{53}N_3O_2$: C, 77.75; H, 9.28; N, 7.35. Found: C, 77.60; H, 9.36; N, 7.28

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† Present address: Department of Biochemistry, Rice University, P. O. Box 1892, Houston, TX 77251, USA.

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NEW HETEROCYCLES FORMING REACTIONS OF ACYL THIOFORMANILIDES

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Zhong E Lu*, Da Qing Sun, Tian Lin Xu, Jun Wan, Le Cun Xu and Ke Qian Chen

Department of Chemistry
Suzhou University
Suzhou 215006, PEOPLE'S REPUBLIC OF CHINA

Acyl thioformanilides (**1**)[1,2] have two possible sites for nucleophilic attack. The present communication describes new reactions of **1** with *o*-phenylenediamine, semicarbazide and aminoguanidine (Scheme 1). The acyl thioformanilides (**1**) were synthesized by the method of Adiwidjaja.[2]