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RESEARCH ARTICLE

Chemical and Biological Studies on Some Pregnane Derivatives

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Abstract: Reaction of the pregnane derivatives **(1), (2), (3)**, and (**4)** with hydrazines, afforded the pyrazoline derivatives, **(5a,b), (6a,b), (7a, b),** and (**8a,b)** respectively, compound (**1)** and (**3)** reacted with urea and thiourea and give pyrimidine and pyrimidinethione derivatives **(9a,b)** and (**10a,b)** respectively. Also, compound **(1)** reacted with hydroxylamine hydrochloride and guanidine carbonate in refluxing ethanol and yield the isoxazole derivative **(11),** and the aminopyrimidine (**12)**. Evaluation of the biological activity of the synthesized compounds, were carried and they had a significant effects as antibiotics and gram positive bacteria, and gram negative bacteria.

Keywords: Pyrimidine, Pyrazoline, Isoxazoline

Introduction

The present work is an extension to our studies on the preparation of some derivatives of α, β-unsaturated ketone pregnane by introducing of an extra heterocyclic ring into the pregnane nucleus and the observation of their biological activities[1,2] due to the important position of pregnane series in the field of biochemistry as a natural steroidal hormones, so many trials were done for the preparation of this series[3,4], condensation of pegnane and it's epoxide with hydrazines[5,6] to give steroidal pyrazol were also studied by Kamernits[7] Synthesis of multideutrated sterols is highly needed to achieve the most accurate gas chromatography mass spectra (GC-MS) analysis of biologically relevant steroids. This can be useful, for example in the bile acids biosynthesis for metabolites such as 24-, 25- or 27-hydroxycholesterol[8].

Experimental

All melting points (m.p °C) are not corrected. Infrared spectra (IR) were measured on: IR spectrum (KBr/pye unicum SP-1100) and the nuclear magnetic resonance (NMR) measured on: Jeol Ex. 270 F.T. spectrometer.

*Reaction of compound **(1)**, **(2)**, **(3)** and **(4)** with hydrazines; formation of **(5a,b)**, **(6a,b)**, **(7a,b)** and **(8a,b)***

A solution of hydrazinehydrate, and/or phenylhydrazine (0.01 mole) in *n*-butanol (30 mL) and the appropriate pregnane derivative (0.01 mole) was heated under reflux for 6 h. The yellow solid obtained after cooling was collected and crystallized from the proper solvent to give compounds(**5a,b), (6a,b), (7a,b) and (8a,b)** (Table 1).

*Reaction of compounds **(1)** and **(3)** with urea and thiourea; formation of compounds **(9a b)** and **(10a ,b)***

A mixture of compound **(1)** and/or **(3)** (0.01 mole), urea,and /or thiourea (0.01 mole) and potassium hydroxide (1 g) in 30 mL absolute ethanol was refluxed for 5 h. The product was collected and crystallized from the proper solvent into compounds **(9a,b)** and **(10a,b)** (Table 1).

*Reaction of **(1)** with hydroxylaminehydrochloride, formation of the isoxazole derivative **(11)***

A mixture of **(1)** (0.01 mol0 and hydroxylaminehydrochloride (0.01 mole) in ethanol (30 mL) was refluxed for 6 h. The reaction mixture was concentrated and left to cool. The solid precipitated was collected and crystallized from acetic acid into **(11)** (Table 1).

*Reaction of compound **(1)** with guanidine carbonate; formation of **(12)***

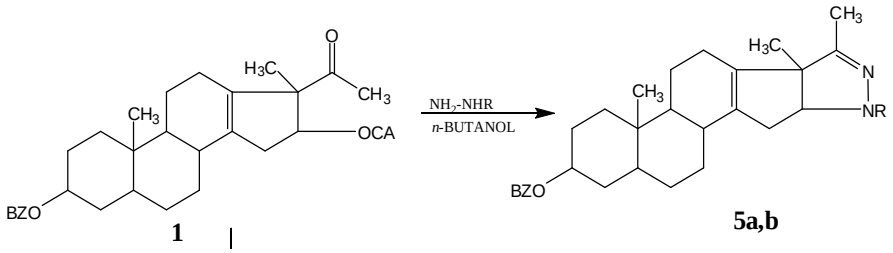
A mixture of **(1)** (0.01 mole) and guanidine carbonate (0.01 mole) in ethanol (30 mL) was refluxed for 8 h. The solid formed after concentration and cooling was collected and crystallized from ethanol (Table 1).

Results and Discussion

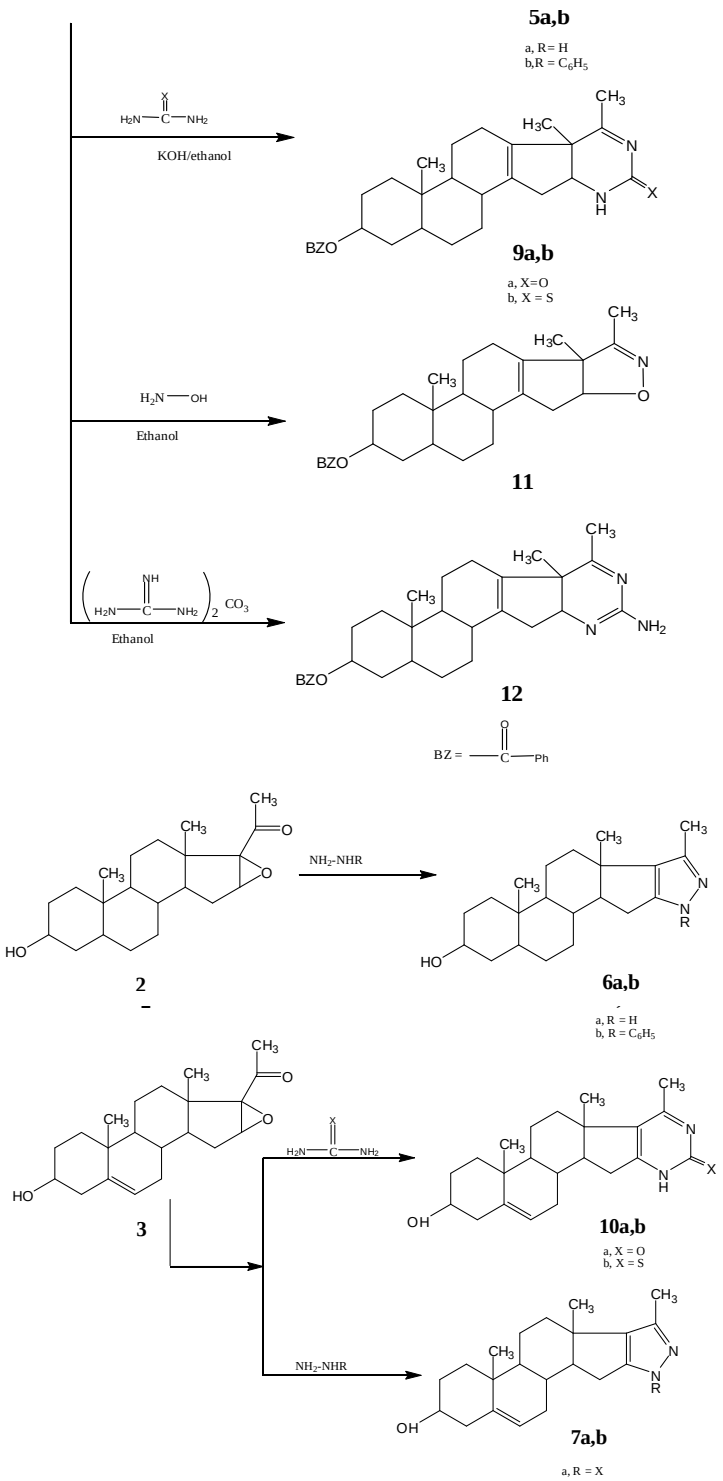
It has been found that, when compounds **(1)**, **(2)**, **(3)** and **(4)** was allowed to react with hydrazines, namely (hydrazinehydrate and phenylhydrazine) in refluxing *n*-butanol it yield the hydrazones, which rearranged immediately into the isomeric pyrazoline derivatives **(5a,b), (6a,b)**, **(7a,b)**, and **(8a,b)**, respectively (Scheme 1). The structure of the synthesized compounds **(5a,b)**, **(6a,b)**, **(7a,b)**, and **(8a,b)** was confirmed from their correct spectral data (Table 1).

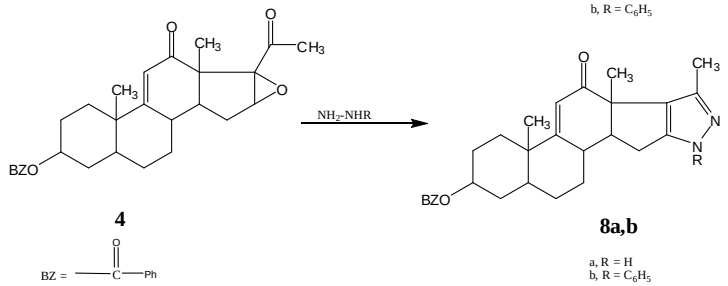
When compounds **(1)** and (**3)** was reacted with urea, thiourea in refluxing absolute ethanol in the presence of potassium hydroxide it afforded the compounds **(9a,b)** and (**10**a,b), respectively (scheme 1).

On the other hand, reaction of compound **(1)** with hydroxylaminehydrochloride, and guanidine carbonate gave the isoxazol derivative (**11)** and the aminopyrimidine **(12),** respectively (Scheme 1). Chemical structure of the compounds **(9a,b)**, **(10a,b)**, **(11)**, and **(12)** was elucidated from their correct spectral data (Table 1).



1 **5a,b**


5a,b
a, R= H
b,R = C6H5
KOH/ethanol
9a,b
a, X=O
b, X = S
Ethanol
11
Ethanol
12
BZ =
2
NH2-NHR
6a,b
a, R = H
b, R = C6H5
3
10a,b
a, X = O
b, X = S
NH2-NHR
7a,b
a, R = X



Scheme 1

Table 1. Physical and Spectral Data of Compounds **(5-12)**

Compd.	M.P.°C/% Solvent of crystallization	Yield %	IR cm^{-1}	^1H NMR ppm
5a	278 Ethanol	37	1610 (υ C=N) 1680 (υ C=O)	1.6-2.4 (9H, $3CH_3$) 6.3 (s, NH proton)
5b	296 Ethanol	42	1590 (υ C=N) 1670 (υ C=O) 3350 (υ NH)	1.5 – 2.6 (9H, $3CH_3$) 7.4 – 8 (m, 10H, Ar H'S)
6a	186 Methanol	38	1600 (υ C=N) 3360 (υ NH) 3460 (υ OH)	6.5 (s, 1H,NH) 1.5 – 2.3 (9H, 3 CH_3)
6b	211 Methanol	52	1580 (υ C=N) 3470 (υ OH)	1.3 – 2.4 (9H, $3CH_3$) 7.3 – 7.8 (m, 5H, Ar H'S)
7a	247 Ethanol	61	1580 (υ C=N) 3356 (υ NH) 3470 (υ OH)	1.2-2.3 (9H, $3CH_3$) 6.4 (s, 1H,NH)
7b	268 Ethanol	49	1610 (υ C=N) 3450 (υ OH)	1.3 – 2.5 (9H, $3CH_3$) 7.4 – 8.0 (m, 5H, Ar H'S)
8a	189 Ethanol	56	1560 (υ C=N) 3360 (υ NH) 1660 (υ C=O),1710 (_C=O)	1.2 – 2.4 (9H, 3 CH_3) 6.5 (s, NH) 7.1-8 (5H , ArH'S)
8b	205 Ethanol	63	1580 (υ C=N) 1650 (υ C=O) 1670 (υ C=O)	1.3 – 2.3 (9H, $3CH_3$) 7.2 – 8.3 (m, 10, Ar H'S)
9a	243 Ethanol	68	1630 (υ C=H) 1680 (υ C=O) 3350 (υ NH)	7.6 (s, NH) 1.3 – 2.4 (9H, 3 CH_3 7.8 – 8.3 (m, 5H Ar H'S)
9b	197 Ethanol	54	1610 (υ C=N) 1690 (υ C=O) 3340 (υ NH)	1.2 – 2.4 (9H, 3 CH_3) 5.7 (s, NH proton) 7.6 – 8.1 (m, 5H, Ar H'S)
10a	211 Ethanol	51	1600 (υ C=N) 3320 (υ NH) 3460 (υ OH)	1.3 – 2.5 (9H, 3 CH_3) 7.5 (s, 1H, NH)

Contd…

10b	178 Ethanol	39	1580 (υ C=N) 3350 (υ NH) 3480 (υ OH)	1.4 – 2.6 (9H, 3 CH_3) 5.8 (s, 1H,NH)
11	256 Acetic acid	44	1630 (υ C=N) 1690 (υ C=H)	1.4 – 2.3 (9H, 3 CH_3) 7.5 – 8.2 (m, 5H, Ar H'S)
12	271 Ethanol	58	1590 (υ C=N) 1690 (υ C=O) 3350,3220 (υ NH_2)	1.2 – 2.4 (9H, 3 CH_3) 7.2 – 8.0 (m, 5H, Ar H'S) 6.3 (s, 2H,NH_2)

Assay of antimicrobial activity of some pergnane derivatives

The biological activity of the tested compounds (Table 2) have evaluated (estimated) using filter paper disc methods[9,10] discovering the substances (**5a), (6b), (7b), (9a), (9b), (10a), (10b), (11), and (12**) in the appropriate solvent indicated in table applied. The inhibition zones of microbial growth surrounding the paper disc (5 mmφ) were measured in mm (millimeter) at the end of incubation period (18-24 h at 37°C).

The biological effect of the mentioned compounds is studied as antibiotics and against Gram positive bacteria (*Staphylococcus aureus*) and Gram negative bacteria (*Echerichia coli, Pseudomonas aerugonosa, Klebsiella spp, Proteus vulgaris*).
From this study it was found that:

1. The compounds **(5a), (7b), (9b), (10a), (10b), (11), and (12)** have high effect on *proteus vulgaris* bacteria.
2. The sulfur heterocyclic compound is the highest biological effect.
3. Comparison between the compounds **(9a), (9b), (10a), and (10b)** indicate compounds **(9b) and (10b)** has high effect against most types of bacteria, because it contains sulfur in its ring.

Table 2. Antimicrobial activity of the test compounds

Compound	Solvent	Diameter of Inhibition Zone				
		S. aureus	*E. coli*	*p. aer*	*K. spp*	*Pr. Vulg*
5a	EtOH	++ ve	++ ve	++ ve	++ ve	+++ ve
6b	EtOH	-ve	- ve	+ ve	++ ve	++ ve
7b	EtOH	++ ve	++ ve	++ ve	++ ve	+++ ve
8a	EtOH	++ ve	++ ve	++ ve	++ ve	++ ve
9a	Acetone	+ ve	+ ve	++ ve	++ ve	++ ve
9b	Acetone	+++ ve	++ ve	++ ve	+++ ve	+++ ve
10a	Acetone	+ ve	- ve	++ ve	++ ve	+++ ve
10b	Acetone	+++ ve	+++ ve	+++ ve	+++ ve	+++ ve
11	EtOH	++ ve	++ ve	++ ve	+++ ve	++ ve
12	EtOH	- ve	- ve	+ ve	++ ve	++ ve

+ve = 8 mm, ++ ve = 12 mm, +++ ve = 18 mm, S. aureus = Staphylococcus aureus, E. coli = Echerichia coli, p. aer = Pseudomonas aerugonosa, K. spp = Klebsiella spp, Pr. Vulg = Proteus vulgaris

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