Synthesis and study of the biological activity of some new Thiohydantoin Derivatives

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Abstract: 1-acetyl-3-[(5-bromo-2-acetoxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (2) and 5-acetyl-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione(3)prepared by Acylation of 3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione(1) by different method. The reaction of 3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (1) with bromine in presence of glacial acetic acid result the 5-bromo- 3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo -imidazolidin-2-thione (4). The Acylation of compound (4) with acetic anhydride led to formation 5-bromo-1,5-diacetyl-3-[(5-bromo-2-acetoxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (5). The hydrazinolysis of compound (1) with hydrazine hydrated led to formation of 2, 4-dihydrazino-3-[(5-bromo-2-hydroxy-phenylmethyl)-amino]-imidazolidine (6). The condensation of compound (1) with different aldehyde led to formation of (7a-c). The action of acetic anhydride on compounds (7a-c) under reflux led to formation of (8a-c).

Keywords: Thiohydantoin, imidazolidin-2-thione, Acylation, bromination, hydrozonolysis, condensation.

Introduction:

The chemistry and properties of hydantoins and their derivatives have been investigated for more than 140 years. The hydantoin moiety which is present in various biologically active compounds represents a pharmaceutical importance.

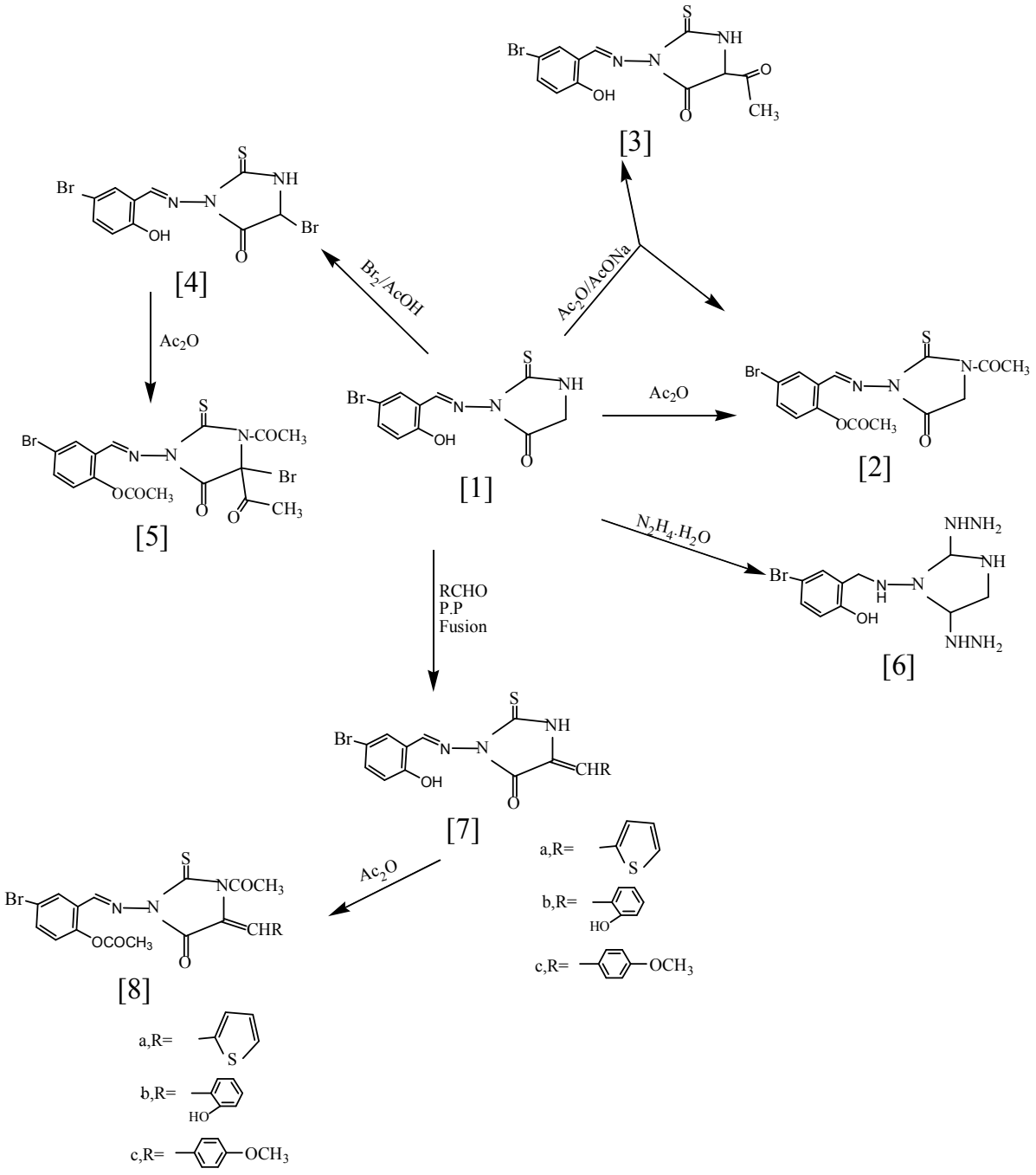
The 1-aminohydantion[1-2] is an antimicrobial drug for the treatment of urinary tract infections, while its analog Dantrolene represents a well known skeletal muscle relaxant.Another 1-aminohydantoin, azmilide, is a promising drug candidate for the treatment of cardiac arrhythmia. Phenylhydantoin[3], a 5,5– diphenyl-imidazolidin-2,4–dione is an anticonvulasant used for the treatment of epilepsy. Sulfahydantoin[4] acts as a serine protease inhibitor.

Among the known thiohydantoins, 2-thiohydantoins are most notably known due to their wide applications as hypolipidemic, anticarcinogenic, antimutagenic, antithyroidal, antiviral (e.g., against herpes simplex virus, HSV), human immunodeficiency virus (HIV) and tuberculosis), antimicrobial (antifungal and antibacterial), antiulcer and anti-inflammatory agents, as well as pesticides. Additionally, 2-thiohydantoins have been used as reference standards for the development of C-terminal protein sequencing, as reagents for the development of dyes and in textile printing, metal cation complexation and polymerization catalysis[5]. Also, 2-Thiohydantoin derivatives have been identified as molecules which may interact with a wide range of applications as theropeutics[6-8] as well as fungicides and herbicides[9].

It is therefore not surprising that various different synthetic methods have been developed to prepare 2-thiohydantoin and its derivatives.

Result and Discussion:

Acylation of 3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione(1) with acetic anhydride give1-acetyl-3-[(5-bromo-2-acetoxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (2) while 5-acetyl-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione(3)prepared by Acylation of (1) by acetic anhydride in presence of fused sodium acetate. The reaction of (1) with bromine in presence of glacial acetic acid under stirrer result the 5-bromo- 3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo -imidazolidin-2-thione (4). The Acylation of compound (4) with acetic anhydride led to formation 5-bromo-1,5-diacetyl-3-[(5-bromo-2-acetoxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (5) Show in scheme (1).



Scheme [1]

The hydrazinolysis of compound (1) with hydrazine hydrated in presence of ethanol led to formation of 2, 4-dihydrazino-3-[(5-bromo-2-hydroxy-phenylmethyl)-amino]-imidazolidine (6) scheme (1).

The condensation of compound (1) with different aldehyde such as(Thiophen-carboxyl-aldehyde, Salicyldehyde and Anizaldehyde) in presence of piperdine under fusion condition led to formation of the following compounds 5-thiophenlidene-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7a),5-(2-hydroxy-benzylidene)-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7b) and 5-(p-methoxy-benzylidene)-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7c) respectively.

The action of acetic anhydride on compounds (7a-c) under reflux led to formation 1- acetyl-5-thiophenlidene-3-[(5-bromo-2-acetoxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (8a),1-acetyl-5-(2-hydroxy-benzylidene)-3-[(5-bromo-2- acetoxy -phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (8b) and 1-acetyl5-(p-methoxy-benzylidene)-3-[(5-bromo-2- acetoxy -phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (8c).

Antimicrobial studies

Applying the agar plate diffusion technique[10] for some of the newly synthesized compounds was screened in Vitro for antimicrobial activity against:

I)- Gram positive bacteria such as:

1-Bacillus Subtilis.

2-Staphylococcus Aureas.

II)- Gram negative bacteria such as:

1-Escherichia Coli species.

2-Pseudomonas species.

III)- Fungi such as:

1-Candida albicans.

Procedure:

Nutrient agar medium had been utilized for growing test organisms. This medium was of the following composition (g/L) peptone (5.0 gm), beef extract (3.0 gm), sodium chloride (5.0 gm); agar (18.00 gm) and water (100 CC). Each compound was tested at the prementioned concentration dissolved in dimethyl formamide, while dimethyl formamide itself was used as control for comparison.

Bacterial suspensions from activity growing cultures were prepared using sterile distilled water. The media was prepared, poured into 9 cm diameter plates, allowed to solidify and then one mL/ plate of bacterial suspension was transferred aseptically to these plates incubated at 27 °C for 24 hours. The compounds were tested at 100 µg/mL concentration and the activity was determined by measuring the zone of inhibition.

The screening results given in the following tables indicated that all the compounds exhibited antimicrobial activities against one or the other type of bacteria and fungi.

Table (1): Antimicrobial Activities of some synthesized compounds [1 to 8c]

Compound	*Pseudomona Sp.*	*Escherchia coli*	*Bacillus Subtilis*	*Staphylococcus Aureus*	*Candida albicans*
[1]	_	_	_	++++	_
[2]	+++	+	_	_	+++++
[3]	+++	+	_	_	++++
[4]	_	_	_	_	_
[5]	+++	_	+	+++++	_
[6]	_	_	_	+++++	+++++
[7a]	_	_	_	_	+++
[7b]	_	_	_	_	_
[7c]	_	_	_	_	_
[8a]	++	++++	_	_	+++++
[8b]	++	+	_	_	_
[8c]	++	++++	_	_	_

Experimental Section

Melting points were measured on a MEL-TEMP II apparatus and uncorrected. Infrared spectra were measured with Perkin-Elmer FT IR 410 spectrometer in KBr pellets in the Micro-analytical Unit at the Faculty of Science, Cairo University, Egypt. The ^{1}H-NMR spectra were performed on a VARIAN MERCURY 300 MHz spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard in the Micro-analytical Unit at the Faculty of Science, Cairo University, Egypt. Mass spectra were obtained on a Joel JMSD-300 spectrometer operating at 70 eV in the Micro-analytical Unit at the Faculty of Science, Cairo University, Egypt. The elemental analyses were conducted using an elemental analyzer Heneaas CHN-OSRAPID 1106 in the Elemental-analysis Unit at the Faculty of Science, Cairo University, Egypt.

1-acetyl -3-[(5-bromo-2-acetoxy-phenylmethylene) -amino]-4-oxo-imidazolidin-2-thione (2).

This reaction carried by two methods:

1) **By acetic anhydride:**

A solution of (1) in acetic anhydride (25 ml) was heated under reflux for 2-3 hr, then cooled and poured into ice-water. The resulting product was filtered off, washed with water, dried and purified by re-crystallization with ethanol to give (2).

2) **By acetic anhydride in presence of fused sodium acetate:**

A solution of (1) in acetic anhydride (25 ml) in presence of fused sodium acetate (0.03 mol) was heated under reflux for 4 hr, then cooled and poured into ice-water. The resulting product was filtered off, washed with water, dried and purified by re-crystallization with ethanol to give (2).Compound (2) has white crystals, yield 57% and m.p 220 ^{o}C.
^{1}H-NMR (DMSO-d_6): δ, 2 (S, 3H, $COCH_3$), 2.3 (S, 3H, $COCH_3$), 4.4(S, 2H, NCH_2CO), 7.1-7.7 (m,3H, ArH), 7.9 (S, 1H, CH=N) ppm.

5-acetyl-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (3).

A solution of (1) (0.01 mol) in acetic anhydride (25 ml) in presence of fused sodium acetate (0.03 mol) was heated under reflux for 4 hr, then cooled and poured into ice-water. The resulting product was filtered off to give (9).The mother liquor was concentrated give (3).The solid producte was filtered, dried and recryslalization from methanol to give (100 as pale brown crystals, yield 50% and m.p 285 ^{o}C.
^{1}H-NMR (DMSO-d_6): δ, 2.5 (S, 3H, $COCH_3$), 4 (S, 2H, NCHCO), 7-8 (m,3H, ArH), 8.6 (S, 1H, CH=N), 11 (S, 1H, NH), 12.1(br.-S, 1H, OH) ppm

5-bromo- 3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo -imidazolidin-2-thione (4).

A solution of (1) (0.01 mol) in acetic acid (30 ml) was heated at 25-35 ^{o}C**,**a solution of bromine (0.1 mol) in acetic acid (10 ml) was added drop wise with stirrer during 30 min, after addition the mixture was stirred for 2 hr. The reaction mixture poured into ice-water. The resulting product was filtered off, washed with water, dried and purified by re-crystallization from methanol to give (4) as pale yellow crystals, yield 52% and m.p 295 ^{o}C.
^{1}H-NMR (DMSO-d_6): δ, 4 (m, 2H, CH and NH), 7-8 (m, 3H, ArH), 8.7 (S, 1H, =CH), 12(br.-S, 1H, OH) ppm.

5-bromo-1, 5-diacetyl-3-[(5-bromo-2-acetoxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (5).

A solution of (4) (0.01 mol) in acetic anhydride (30 ml) was heated under reflux for 2-3 hr, then cooled and poured into ice-water. The resulting product was filtered off, washed with water, dried and purified by re-crystallization from ethanol to give (5) as pale brown crystals, yield 58% and m.p 185 ^{o}C.
^{1}H-NMR (DMSO-d_6): δ, 2 (S, 3H, $COCH_3$), 2.5 (S, 3H, $COCH_3$), 7.2-8 (m, 3H, ArH), 8.3 (S, 1H, CH=N) ppm.

2, 4-dihydrazino-3-[(5-bromo-2-hydroxy-phenylmethyl)-amino]-imidazolidine (6).

A mixture of (1) (0.01 mol) and Hydrazine hydrated (0.04 mol) in (25 ml) of methanol was heated under reflux for 3 hr.The reaction mixture was cooled and poured into ice-water. The resulting solid was filtered off, washed with water, dried and recrystalization from ethanol to give (6) as pale yellow crystals, yield 70% and m.p 150 ^{o}C (Element test –ve (S)).
^{1}H-NMR (DMSO-d_6): δ,1-1.4 (m,1H, CH), 4 (S, 8H,2 CH_2 and 2NH_2), 7.2-7.9 (m, 3H, ArH), 9 (S, 2H, 2NH), 12.5(S, 1H, OH) ppm.

5-Arylidene-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7a-c).

A mixture of compound (1) (0.01 mol) with different aldehyde such as (Thiophen-carboxyl-aldehyde, Salicyldehyde and Anizaldehyde) (0.01 mol) in

presence of piperdine (1 ml) was fused on hot plate at 120-125 ^{o}C for 1 hr. The reaction mixture was cooled and acidified with Hydrochloric acid (2%). The crude product was filtered off, washed with water, dried and recryslalization from ethanol to give (7a-c) respectively.

5-thiophenlidene-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7a):

Compound (7a) precipitated as yellow crystals, yield 73% and m.p 255 ^{o}C. . ^{1}H-NMR (DMSO-d_6): δ, 6-8 (m, 8H, ArH and =CH)), 10 (S, 1H, NH), 12 (S, 1H, OH) ppm.

5-(2-hydroxy-benzylidene)-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7b):

Compound (7b) precipitated as yellow crystals, yield 76% and m.p 260 ^{o}C. ^{1}H-NMR (DMSO-d_6): δ, 7-8 (m, 7H, ArH)), 8.8 (S, 2H, 2=CH), 10.5 (S, 1H, NH), 12.5 (S, 2H, 2 OH) ppm.

5-(p-methoxy-benzylidene)-3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7c):

Compound (7c) precipitated as yellow crystals, yield 73% and m.p 240 ^{o}C. ^{1}H-NMR (DMSO-d_6): δ, 2.7 (S, 3H, CH_3), 6.9-8 (m, 7H, ArH)), 8.7 (S, 2H, 2=CH), 10.9 (S, 1H, NH), 12.5 (S, 1H, OH) ppm.

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