Synthesis and Characterization a New 1,3-Diazepine Compounds from New Bis 4-Amino-3-Mercpto-1,2,4-Triazole Derivatives

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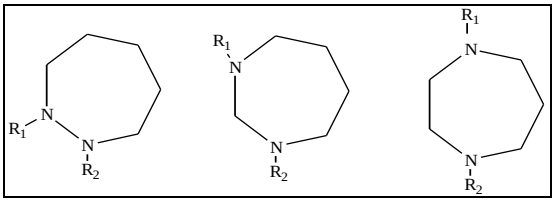
Abstract

Compounds with two triazole rings IVa,b were synthesized through the reaction of diacid hydrazide firstly with CS_2/KOH, and secondly with excess of hydrazine hydrate. The one-step reaction of isatin with benzylidene benzeneamine (S_1–S_{10}) in ethanol gave 2-Ar-3-Ar'[3,4b][1,3]benzodiazepine-4,5-diones (D_1-D_{10}) in good yields. The products were characterized using FTIR, ^{1}HNMR spectroscopy and CHN elemental analyses. [DOI: 10.22401/JNUS.20.2.01]

Keywords: 1,3-Diazepine, 1,2,4-Traiazole, Schiff`s bases.

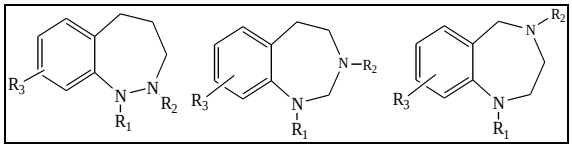
Introduction

Diazepines is a class of seven-membered ring heterocyclic compounds with two nitrogen atoms at 1,2-, 1,3- and 1,4- in the heptane ring instead of carbon atom and these compounds may be saturated and unsaturated with different substituents [1].



[1,2] Diazepine [1,3] Diazepine [1,4] Diazepine

The benzodiazepines are consisting of benzene ring fused with the diazepine ring to give the three analogous [1].



Benzo[1,2]diazepine Benzo[1,3] diazepine Benzo [1,4] diazepine

The biochemistry of diazepines and benzodiazepines has been thoroughly and extensively explored owing to their association with wide spectrum of pharmacological activities, such as, sedatives, anxiolytics, hypnotics, anticonvulsants, antipsychotics, and muscle relaxants [2].

Some 1,3-diazepin-2-ones and other cyclic ureas have received considerable attention recently as potential anti-AIDS drugs [3]. In Fig.(1) for example chlorodiazepoxide (1) known as the first benzodiazepine, was coincidentally available in markets in 1960. It is very important derivative in terms of hypnotic, anxiolytic and muscle relaxant [4]. Diazepam (valium) (2) was also discovered to show better activity in psychotherapy. Then, another derivative of nitrazepam (3) was used against anypnia [5]. Similarly, clonazepam (4) has anxiolytic, anticonvulsant, muscle relaxant and hypnotic properties [6]. Additionally, it was recognized by the Food and Drug Administration (FDA) for treatment of epilepsy [7,8]

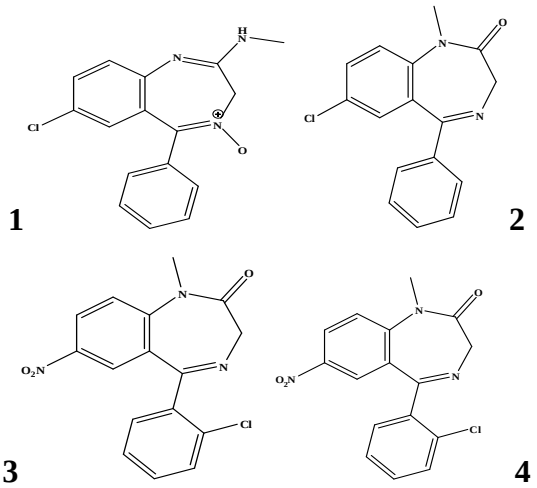


Fig. (1)

Experimental

1- Materials and apparatus

All the chemicals used were supplied form BDH, Merck AND Fluka.

FTIR spectra in the range (4000-400) cm^{-1} were recorded using potassium bromide disc on FTIR instrument Model 8300 Shimadzu Spectrophotometer, Japan. ^{1}HNuclear Magnetic Resonance (NMR) spectra were recorded on Brüker ACF 300 spectrometer at 300 MHz, using deutrated chloroform or DMSO as a solvent with TMS was used as an internal standard in University of Ahal Al-Bait, Jordon. Microanalyses were carried out on Euro EA Elemental analyzer A- 3000. Uncorrected melting points were recorded on hot stage Gallenkamp melting point apparatus (U.K.).

2- Procedures

Succinic and Terephthalic dihydrazide

Dimethyl ester of Succinic or Terephthalic (0.025 mol) in 25ml of ethanol was taken in round bottom flask. To that hydrazine hydrate (6ml) was added and refluxed for (4 hours). After cooling the crystals was precipitated out and recrystallized from ethanol to give compounds (II)a yield 89%, m.p.=170-172°C, and (II)b yield 88%, m.p.=132-135°C.

Succinic and Terephthalic dihydrazide [Bis (potassium dithiocarbazinate)]

To a solution of potassium hydroxide (0.04 mol) in ethanol absolute (150 ml), dihydrazides $(II)_{a,b}$ (0.02 mol) and carbon disulfide (3 ml) were added dropwise and the mixture was stirred in ice bath (0-6^{o}C)[6]. The yellow solid was precipitated out and the potassium salt obtained in quantitative yield was directly used without purification.

Bis [(3,3`-thio-4,4`-amino-1,2,4-triazole)-5-yl] ethane [9]

A mixture of potassium salt and Hydrazine hydrate (2 ml) and water (80 ml) was refluxed for 4 hrs., the color of the reaction mixture changed to green, hydrogen sulfide was evolved and a homogenous solution resulted. A white solid was precipitated by dilution with cold water (100 ml) and acidification with concentrated hydrochloric acid. The product was filtered, washed with cold water and recrystallized from ethanol, compound $(IV)_a$ yield 72%, m.p.= 220-222°C.

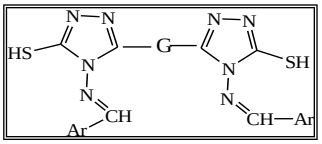
Bis [(3,3`-thio-4,4`-amino-1,2,4-triazole)-5-yl] phenyl

A suspension of potassium salt of terephthalic dihydrazide (2g, 0.005 mol), hydrazine hydrate (2 ml, 0.04 mol) and water (100 ml) was refluxed for (3 hrs). The reaction mixture color was changed to light green, hydrogen sulfide was evolved and a homogenous solution resulted A solid was precipitated by dilution with cold water (100 ml) and acidification with concentrated hydrochloric acid. The product was filtered, washed with cold water dried and recrystallized from ethanol**,** compound $(IV)_b$ yield 82% , m.p.= 198-200°C.

General procedure for preparation of Schiff bases [10]

A mixture of triazole derivative (IVa-b) (0.001 mol) and the corresponding aldehydes (0.002 mol) in ethanol (25 ml) was treated with glacial acetic acid (0.5 ml) and refluxed for (3 hr). The reaction mixture on cooling was filtered and recrystallized from ethanol.

Table (1)
Physical properties of compounds (S_1-S_{10}), [G= $CH_2 – CH_2$ or phenyl, Ar= C_6H_4-CH_3, C_6H_4-OCH_3, C_6H_4-Cl, C_6H_4-Br, C_6H_4-NO_2, C_8H_7].

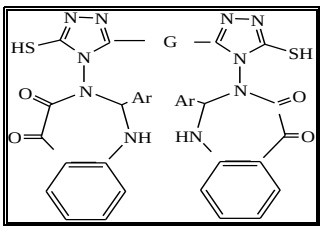


Comp No.	m.p.°C	ν CH = N	Other
S_1	288-290	3100	1554 1345(NO_2)
S_2	212-215	3110	-
S_3	150-153	3114	2987 & 2877 (C-H Aliphatic
S_4	165-170	3100	1100 (C- O)
S_5	211-215	3110	-
S_6	232-235	3102	15564 1353 (NO_2)
S_7	217-220	3098	2997 & 2854 (C-H Aliphatic
S_8	140-143	3097	2965 & 2878 (C-H Aliphatic
S_9	145-147	3112	2987 & 2877 (C-H Aliphatic
S_{10}	142-144	3110	2981& 2876 (C-H Aliphatic

General procedure for synthesis of substituted [1,2,4] triazolo [3,4-b][1,3] diazepine

A mixture of corresponding Schiff bases (S_1-S_{10}) (0.001 mol) and (0.002 mol) of isatine in ethanol (30 ml) was refluxed for (4 hr). The reaction mixture was cooled, filtered and washed with ethanol and recrystallized from ethanol, to give diazepine derivatives (D_1-D_{11}).

Table (2)
Physical properties of compounds (D1 – D_{11}) [G= $CH_2 – CH_2$ or phenyl, Ar= C_6H_4-CH_3, C_6H_4-OCH_3, C_6H_4-Cl, C_6H_4-Br, C_6H_4-NO_2, C_8H_7].

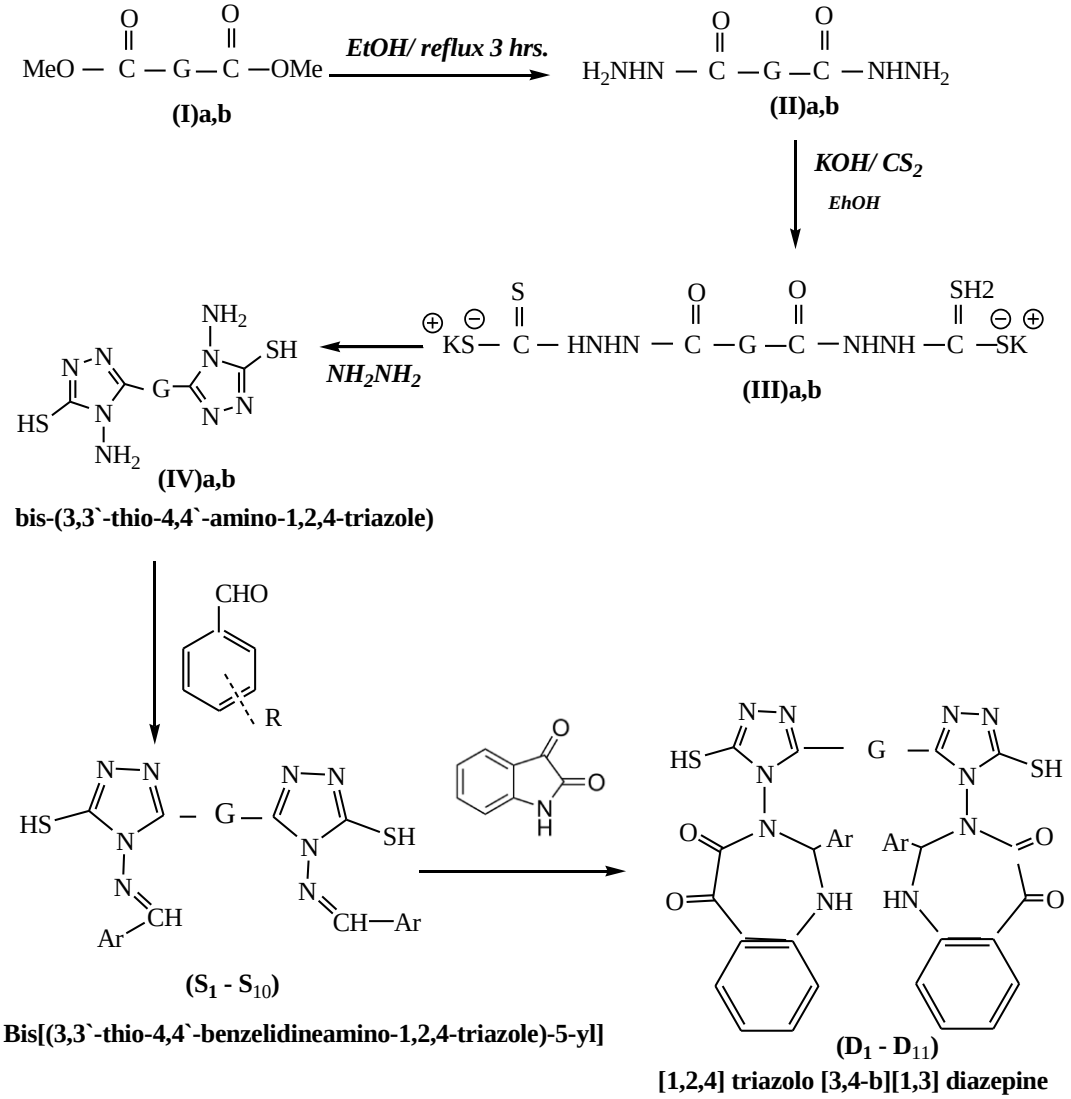


Comp. No.	mp.	ν (N – H)	ν (C = O) ketone	ν (C = O) lactome	Others
D_1	280-283	3280	1724	1693	-
D_2	+280	3282	1726	1693	-
D_3	182-185	3398	1714	1672	628 ν (C – Cl)
D_4	123-125	3219	1721	1686	3078 ν (C – H) Arom.
D_5	140-142	3268	1732	1685	1089 ν (C – O)
D_6		3307	1729	1643	1083 ν (C – O)
D_7	+280	3310	1722	1658	3082 ν (C – H) Arom.
D_8	261-264	3263	1726	1660	1552&1325ν (NO_2)
D_9	275-277	3238	1739	1700	1558& 1339 ν (NO_2)
D_{10}	248-250	3196	1719	1649	931 ν (C – Br)
D_{11}	265-268	3129	1721	1659	985 ν (C – Br)

Results and Discussion

Synthesis of substituted [1,2,4] triazolo [3,4-b] [1,3] diazepine (D_1 - D_{11}):

The title compounds were synthesized according to the following scheme:



G = —Ph or — CH_2CH_2 —

Ar- : - C_6H_4-CH_3, C_6H_4-OCH_3, C_6H_4-Cl, C_6H_4-Br, C_6H_4-NO_2, C_8H_7

Scheme (1): The synthetic pathway for [3,4-b][1,3] diazepine compounds (D_1 - D_{11}).

Compounds $(I)_{a,b}$ were prepared from direct esterfication of succinic acid and terphthalic acid with methanol in acidic media[11]. Compounds $(II)_{a,b}$ were prepared from the reaction of esters $(I)_{a,b}$ with hydrazine hydrate [12].

The reaction of hydrazide compounds $(II)_{a,b}$ with carbon disulfide in basic media leads to the formation of dithio carbazinate salts $(III)_{a,b}$ which undergo cyclization in excess of hydrazine hydrate to give 3,3`-thio-4,4`-amino-1,2,4-triazole $(IV)_{a,b}$.

The structures of compounds $(IV)_a$ and $(IV)_b$ were characterized using FTIR, ^{1}H-NMR spectroscopic technique. The purity of final compounds were confirmed by using an elemental analysis. The elemental analysis of compounds $(IV)_{a,b}$ are listed in Table (3).

Table (3)
Elemental analysis (CHNS-O) for compounds $(IV)_{a,b}$.

Comp. No.	Formula	%C		% H		%N		%S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
$(IV)_a$	$C_{10}H_{10}N_8S_2$	39.21	39.98	3.26	4.17	36.60	36.84	20.91	18.93
$(IV)_b$	$C_6H_{10}N_8S_2$	27.90	29.05	3.87	4.12	43.41	42.09	24.80	23.07

The FTIR spectrum of compound $(IV)_a$, (KBr disc cm^{-1}), show the appearance of bands at 3450, 3272, 3165, 3055, 1625, 1598 and 825 which could be assigned to ν N – H (asymm. and symm.), ν C – H (aromatic), ν C = N, ν C = C and out of plane bending of *para*- disustituted benzene ring.

Compounds (S_1 – S_{10}) were synthesized by the reaction of terephthalic or succinic dihydrazide [Bis(potassium dithiocarbazinate)] $III_{a,b}$ with hydrazine hydrate to achieve Bis [(3,3`-thio-4,4`-amino-1,2,4-triazole)-5-yl] ethane or phenyl IVa,b followed by condensation reaction with different aromatic aldehyde to achieve Bis[(3,3`-thio-4,4`-benzelidineamino-1,2,4-triazole)-5-yl]ethane or phenyl (S_1 – S_{10}).

The structures of all products were identified using FT-IR and ^{1}H-NMR for some of theme. All resultant spectral data were in correspondence with expected values. The purity of compounds were confirmed by using an elemental analysis. The elemental analysis of compounds (S_1 – S_{10}) are listed in Table (4). The observed values are in well agreement with theoretical values indicating structure of respective compounds.

Table (4)
Elemental analysis (CHNS-O) for compounds (S_1 – S_{10}).

Comp. No.	Formula	%C		% H		% N		% S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
S_1	$C_{24}H_{16}N_{10}O_4S_2$	50.34	49.88	5.55	4.99	24.47	25.02	11.18	10.96
S_2	$C_{24}H_{16}N_8S_2Br_2$	45.01	45.34	2.50	2.61	17.50	18.01	10.00	9.78
S_3	$C_{26}H_{22}N_8S_2$	61.17	61.67	4.31	4.66	21.96	22.21	12.54	12.87
S_4	$C_{26}H_{22}N_8O_2S_2$	57.56	56.89	4.05	4.21	20.66	19.88	11.80	11.75
S_5	$C_{32}H_{22}N_8S_2$	65.97	65.11	3.78	4.34	19.24	20.23	10.99	11.09
S_6	$C_{20}H_{16}N_{10}O_4S_2$	45.80	46.08	3.05	2.99	26.71	26.05	12.21	12.45
S_7	$C_{20}H_{16}N_8S_2Br_2$	40.55	39.43	2.70	2.45	18.92	19.12	10.81	11.12
S_8	$C_{22}H_{22}N_8S_2$	57.14	56.98	4.76	4.35	24.24	24.66	13.85	13.99
S_9	$C_{22}H_{22}N_8O_2S_2$	53.44	52.96	4.45	4.51	22.67	23.08	12.95	13.04
S_{10}	$C_{28}H_{22}N_8S_2$	62.92	60.01	4.11	4.58	20.97	21.54	11.98	10.77

The spectroscopic observation of $(S)_2$ is given show the disappearance of NH_2 bands and the appearance of bands at 3110, 2724, 1621, 1602 and 841.1 which could be assigned to ν C – H of azomethane group[11], ν S – H, ν CH = N, ν C = C and out of plane bending of *para*- disustituted benzene ring.

^{1}H-NMR (DMSO-d_6), δ in ppm) for compouns $(S)_2$: 7.61-7.50 (d-d, 12H, arom. H), 9.2 (s, 2H, CH = N), 12.6(s, 2 H, SH). Table (5) shows the FT-IR absorption bands for synthesized compounds.

Compounds (D_1 - D_{11}) were synthesized by the reaction of Schiff base compounds (S_1-S_{10}) with isatin in ethanol is turn collapses to the 7-membered heterocyclic system to give substituted [1,2,4] triazolo [3,4-b][1,3] diazepine derivatives compounds.

The elemental analysis of compounds (D_1-D_{11}) are listed in Table (5).

Table (5)
Elemental analysis (CHNS-O) for compounds (D_1 - D_{11}).

Comp. No.	Formula	%C		% H		% N		% S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
D_1	$C_{42}H_{30}N_{10}O_4S_2$	62.84	64.11	3.74	3.25	17.45	19.96	7.98	7.22
D_2	$C_{38}H_{30}N_{10}O_4S_2$	60.47	58.88	3.97	4.98	18.56	17.87	8.48	7.05
D_8	$C_{40}H_{24}N_{12}O_8S_2$	55.55	56.25	2.77	2.94	19.44	19.94	7.40	5.86
D_9	$C_{36}H_{24}N_{12}O_8S_2$	52.94	53.32	2.94	3.19	20.58	21.23	7.84	6.68
D_{10}	$C_{40}H_{24}N_{10}O_4S_2Br_2$	51.51	52.37	2.57	3.10	15.02	17.65	6.86	8.03
D_{11}	$C_{36}H_{24}N_{10}O_4S_2Br_2$	48.87	50.06	2.71	3.31	15.84	16.25	7.24	6.95

The transformation is confirmed by shows the appearance of new bands at 1724, 1693 which could be attributed to (C = O of ketone stretching) and (C = O of lactam stretching) as well as the appearance of N – H stretching band at 3280.

6.95-8.31 (d-d, 16H, arom. H), 3.91(s, 4H, CH_2 – CH_2), 10.91(s, 2H, SH), 3.78 (s, 6 H, OCH_3).

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