A FACILE SYNTHESIS OF P-BIS(4-THIAZOLIDINON-3-YL)PHENYLENES AND RELATED SYSTEMS AND RELATED SYSTEMS

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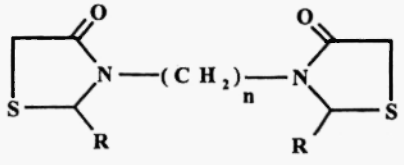
Abstract: p-Bis(4-thiazolidinon-3-yl)phenylenes were synthesized from cycloaddition of thioglycollic acid with schiff bases of p-phenylenediamine or by treatment of p-bis(thiouredo)phenylenes with ethyl chloroacetate .The effect of hydrazines, hydroxylamine, acetamidine and N-phenylthiourea on p-bis(arylidenethiazo- arylidenethiazolidinon-3-yl)phenylenes **IIb** and **IV** have been reported .Some of the newely compounds were subjected under biological tests .

Introducation

Recently,an enormous amount of research in studying the synthesis and biologiccl activity of thiazolidinone has been reported . Among these , thiazolidinones showed antiinflammatory [1], anticonvulsants [2], antimicrobial [3] and fungcidial activity [4] as well as antiplatelet activity factor [5] . In this communication we have been previously studied the synthesis and biological activity of 4-thiazolidinones [6] . The present investigation deals with the use of p–phenylenediamine in the sythesis of some interest bis thiazolidinones of expected pharmacological action and study their effect on cellobiase activity .

Results and Discussion

A few examples of bis thiazolidines were reported in the literature ,among these compounds , bis thiazolidines (A) showed positive fungicidal and bactericidal activity [7] . This fact aroused our interest to synthesize some interesting bis thiazolidinones and their fused systems to evaluate their cellobiase activity .



n = 0 , 2 , 3 , 4

(A)

For this purpose we use p–phenylenediamine as a suitable starting material thus , when p-phenylenediamine was allow to react with some aromatic aldehydes , namely o-chloro, p-chloro and p-methoxybenzaldehyde yielded the respective p-bis(arylideneamino)phenylenes, which underwent cycloaddition with mercaptoacetic acid in dry solvent to afford p-bis(2-aryl-4-oxo-thiazolidlin-3-yl) phenylenes (**Ia-c**)the mass spectrum of compound **Ib** gave molecular ion with low abundance at m/e 500 , which loss two HCN and C_6H_4 radical giving peak at m/e 325 and its base peak appear at m/e 136 [$C_6H_8NCl^+$]. Presence of active CH_2 group in

compounds **Ia-c** was confirmed from condensation of **Ia-c** with p-nitrobenzaldehydes in boiling acetic acid containing fused sodium acetate to afford the corresponding5-(m-nitrobenzylidene)derivatives **IIa–c.**

Structure of compounds **IIa–c** was established by good elemental analysis and established by good elemental analysis and spectroscopic data. On the otherhand, addition of phenylisothiocyanate to compound **Ib** afforded the non –isolable intermediate **III** [8,9] , which on treatment with an equimolar amount ethyl chloroacetate in DMF containing KOH yielded a novel tetrathiazolidinone derivative **IV** (Scheme 1) .

It has been reported in our previous work [10] that thiourea derivative reacts with ethyl chloroacetate to produce thiazolidinones thus , reaction of p-phenylenediamine with phenyl isothiocyanate and p-chlorobenzoylisothiocyanate afforded p-bis(thiouredo)-phenylene and p-bis(p-chlorobenzoylthiouredo)phenylene respectively .When bis thioureas were allowed to react with equimolar amount of ethy- lchloroacetate,p-bis(5-phenylimino-thiazolidinone)phenylene(**V**) and bis(pchlor-obenzoyliminothiazolidinone)phenylene(**VI**)were obtained and their elemental analysis and spectral data were compatible with the assigned structures (Scheme1) . p-Bis [2-(m-nitrobenzylidene)–5-phenylimino-4-oxo-thiazolin-3-yl] Pheylene (**VII**) was produced on condensation of **V** with m-nitrobenzaldehyde in acetic acid fused sodium acetate mixture , while tetra thiazolidinone derivative **IX** was formed from intraction between compound **VI** with phenylisothiocyanate followed by addition of ethyl chloroacetate .The formation of compound **IX** propably formed through the non- isolable intermediate **VIII** (Scheme 1) .

The activating influence of the carbonyl group on the exocyclic double bond in both **II** and **VII** render them susceptible to the addition of several amino compounds thus , reaction of **IIb** with phenylhydrazine [12] in dioxan containing catalytic amount of pipiredine afforded p-bis(pyrazolo [3,4-d] thiazolin-3-yl) phenylene derivative **X** ,while treatment of **IIb** and or **VII** with hydroxylamine hdrochloride afforded the respective p-bis(isoxazolo[3,4-d]thiazolidine) pheny- lene drivatives **XI a,b** (Scheme 2) .

Taking in consideration the biological activity of pyrimidines[13-15] , it of interest to prepare some bis –thiazolidines fused with pyrimidine moiety . Thus , treatment of **IIb** and or **IV** with acetamidine or N- phenylthiourea in DMF yielded the respective p-bis(2,5,7-trisubstitutedpyrimido[4,5-d]thiazolin-3-yl) phenylenes **XIIa,b** and p-bis(2,7,8-trisubstituted-4-thioxo-pyrimido [3,4-d] thiazolin-3-yl] phenylenes **XIIa,b** respectively (Scheme 2) .The structure of the isolated products were assigned on the basis of elemental analysisand spectral data . On the other hand, p-bis(thiazino[4,5-d]thiazolin-3-yl)phenylenes **XIVa-b** were produced when **IIb** and or **IV** reacted with N-phenylthiourea in ethanol contai-ning few drops of HCl [6] (Scheme2) .

Biological Activity

In continuation to our research program directed to investigation of some newely heterocycles as a potential activity on the enzyme cellobiase [16,17] produced by thermophilic fungi .Thus,the effect of some selected bis thiazolidinones on the activity of enzyme cellobiase produced by thermotolerant fungns, *Absidia corymbifera* , was reported .The tested compound (10:g) was dissolved in DMF (1ml) and added to the assay mixture consisting of 0.5 ml of the enzymatic solution and 4.5 ml of citrate phosphate buffer (pH=5.0) containing cellobiase (1%) .

i) ArCHO
ii) SHCH2COOH
i) PhNCS
ii) ClCH2COOEt
PhNCS
DMF/ KOH
ClCH2COOEt
I
a , Ar = C6H4Cl-2
b , Ar = C6H4-Cl-4
c , Ar = C6H4-OCH3-4
II
a , Ar = C6H4Cl-2
b , Ar = C6H4-Cl-4
c , Ar = C6H4-OCH3-4
III
IV
Ar = C6H4-Cl-4
V
VI
VII
VIII
IX
i) ClCH2COOEt

Scheme 1

X
PhNHNH2
NH2OH.HCl
(II b) Or (IV)
NH
CH3-C-NH2
PhNHCSNH2
DMF
HCl
XI
a , Ar = C6H4Cl-4
b , Ar = C6H5N =
XII
a , Ar = C6H4Cl-4
b , Ar = C6H5N =
XIII
a , Ar = C6H4Cl-4
b , Ar = C6H5N =
XIV
a , Ar = C6H4Cl-4
b , Ar = C6H5N =

Scheme 2

Table 1: Physical Characterization and Spectroscopic data of the new Compounds * .

Comp. No.	M.p.°C	Yield (%)	Solvent	M.Formula (Mol.wt.)	IR ν cm⁻¹ Selected peaks	¹HNMR (DMSO – d_6) δ (ppm)
Ia	280	79	DMF-H_2O	$C_{14}H_{18}N_2S_2O_2Cl_2$ (501)	2950(aliphaticC-H),1660(CO),820(p-disubstituted benzene, 750(cyclicC-S-C)	———
Ib	240	65	DMF-H_2O	$C_{24}H_{18}N_2S_2O_4Cl_2$ (501)	2950(aliphaticC-H),1660(CO),830(p-disubstituted benzene, 750(cyclicC-S-C)	4.2(s,2H,CH_2),6.1(s,1H,C_5-H),7.1–7.4(m,12H,Ar-H)
Ic	250	72	EtOH	$C_{26}H_{22}N_2S_2O_4$ (492)	2950(aliphaticC-H),1665(CO),820(p-disubstituted benzene, 750(cyclicC-S-C)	3.7(s,3H,OCH_3),4.1(s,2H,CH_2),6.1(s,1H,C_5-H),7.1–7.5 (m,12H,Ar-H)
IIa	265	69	Ethanol	$C_{38}H_{24}N_4S_2C_6Cl_2$ (752)	3050(=C-H),1650(CO),830(p-disubstituted benzene 750(cyclic C-S-C)	2.2(s,1H,=C-H),6.1(s,1H,C_5-H),7.0-7.4(m,20H,Ar-H)
IIb	200	71	Methanol	$C_{38}H_{24}N_4S_2C_6Cl_2$ (752)	3050(=C-H),1660(CO),820(p-disubstituted benzene, 760(cyclic C-S-C)	———
IIc	210	80	DMF-H_2O	$C_{40}H_{30}N_4S_2O_8$ (744)	3050(=C-H),1660(CO),840(p-disubstituted benzene 750(cyclic C-S-C)	———
IV	>300	72	AcOH	$C_{42}H_{28}N_4S_4O_4Cl$ (787)	2970(CH),1680,1660(CO),820(p-disubstituted benzene,745(cyclic C-S-C)	4.1(s,2H,CH,CH_2),6.1(s,1H,C_5-H),6.9-7.4(m,22H,Ar-H)
V	180	78	AcOH	$C_{16}H_{10}N_4S_2O_4$ (512)	2950(CH),1680,1660(CO),840(p-disubstituted benzene),760(cyclic C-S-C)	4.1(s,1H, CH_2),6.9-8.2(m,14H,Ar-H)
VI	155	55	DMF-H_2O	$C_{16}H_{14}N_4S_2O_4Cl_2$ (581)	2955(CH),1675,1660(CO),840(p-disubstituted benzene),760(cyclic C-S-C)	———
VII	140	80	DMF-H_2O	$C_{40}H_{24}N_6S_2O_8$ (752)	3010(=C-H),1675,1665(CO),820(p-disubstituted benzene),755(cyclic C-S-C)	2.1(s,1H,=C-H), 7.1-8.2(m,22H,Ar-H)
IX	210	67	Acetic acid	$C_{42}H_{36}N_4S_2C_6Cl_2$ (845)	2950(CH),1680,1660(CO),820(p-disubstituted benzene),750(cyclic C-S-C)	———
X	260	68	DMF-H_2O	$C_{10}H_{16}S_2O_4Cl_2$ (947)	2950(CH),1630(C=N), 830(p-disubstituted benzene), 745 (cyclic C-S-C)	3.3(d,1H,CH-S),3.6(d,1H CH-N),6.2(s,1H,C_2-H),6.9-7.2 (m,30H,Ar-H)
XIa	250	82	AcOH-H_2O	$C_{44}H_{36}N_6S_2O_6Cl_2$ (785)	2940(CH),1640(C=N),840(p-disubstituted benzene),750(C-S-C)	3.3(d,1H,H-C-S),3.7 (d,1H,H-C-O),6.2(s,1H,C_2-H),7.0-7.4 (m,20H,Ar-H)
XIb	160	58	Ethanol	$C_{38}H_{28}N_8S_2O_6$ (756)	2920(CH),1615(C=N),830(p-disubstituted benzene),750(C-S-C)	———
XIIa	150	65	AcOH	$C_{42}H_{32}N_8S_2O_4Cl_2$ (847) *	2930(CH),1640(C=N),820(p-disubstituted benzene),740(C-S-C)	2.6(s,3H,CH_3),2.8(s,3H,CH_3),3.4(d,H,H-C-S-),3.7(d,1H H-C-N),6.3(s,1H,C_2-H),6.9-8.1(m,20H,Ar-H)
XIIb	120	69	DMF-H_2O	$C_{42}H_{30}N_{10}S_2O_4$ (812)	2930(CH),1640(C=N),820(p-disubstituted benzene),745(C-S-C)	———
XIIIa	238	71	DMF-H_2O	$C_{10}H_{36}N_4S_2O_4Cl_2$ (947)	2930(CH),1640(C=N),1190(C=S),840(p-disubstituted benzene),740(cyclic C-S-C)	2.8(d,1H,H-C-S)3.6(d,1H,H-C-N)6.2(s,1H,C_2-H),6.9-7.3 (m,20H,Ar-H)
XIIIb	123	55	Ethanol	$C_{52}H_{38}N_{10}S_2O_4$ (930)	2930(CH),1640(C=N),1190(C=S),840(p-disubstituted benzene) 750(cyclic C-S-C)	———
XIVa	245	75	AcOH	$C_{10}H_{36}N_4S_2O_4Cl_2$ (947)	2920(CH),1645(C=N), ,810(p-disubstituted benzene),745(cyclic C-S-C)	3.4(d,1H,H-C-S),6.1(s,1H,C_2-H),7.1-7.6 (m,30H,Ar-H)
XIVb	175	62	Ethanol	$C_{52}H_{38}N_{10}S_2O_4$ (930)	2930(CH),1640(C=N), ,810(p-disubstituted benzene),740(cyclic C-S-C)	———

***(C,H N) analyses of the reported compounds are within ± 0.4% of the theoretical values.**

The assay mixture was incubated at 40 °C for 30 min. and the released glucose was estimated colourimetery using Speakol – K at 505 nm as indicated for cellobiase activity using glucose oxidase methods [18,19]. the obtained results were recorded in table 2 .

Table 2 : cellobiase activity .

Compds	IIb	VII	X	XIa	XIb	XIIa	XIIb	XIVb	XIIIa	XIIIb
Amount of glucose (g)	0.0	2.66	0.42	1.02	3.60	3.34	2.53	5.04	2.82	3.80

- Blank [1 ml of distilled water] = 0.592 :g / ml.
- Control [1 ml of DMF only] = 1.8 :g / ml .

From the above results we showed that the maximum activity of cellobiase was appeared for compound **XIVb** due to the presence of bis thiazinothiazolidinone moiety . Also , the introduction of pyrimidine moiety to thiazolidine in one molecular framwork enhanced the cellobiase activity as shown for compounds **XIIa,b** and **XIIIa,b** . On the other hand , bis thiazolidinone **II** showed no effect on the cellobiase activity .

Experimental

M.p's reported are uncorrected . IR spectra obtained (KBr) on perkin–Elmer 598 spectrophotometer (; cm^{-1}), ^{1} H NMR are measured on Bruker 200 M Hz – 152 MM spectrophotometer using DMSO – d_6 as a solvent and TMS as internal standard (chemical shift δ , ppm) and mass spectra recorded on a MS 5988 spectrometer (70 eV)

p-Bis(arylideneamino) phenylene (schiff bases)

A mixture of p-phenylenediamine (0.01 mol) and apporpiate aromatic aldehyde (0.025) in ethanol (25 ml) containing few drops of acetic acid was refluxed for 1hr . The solid obtained was filtered off and recrystallized from the proper solvent to give the corresponding arylidineamino derivative .

Yellow crystals from ethanol , m.p.140 ° (yield 80 %) and yellow crystals from Methanol , m.p.200 ° (yield 78%) .

p-Bis(o-chlorobenzylidenamino)phenylene,yellow crystals,m.p.140° (yield 80%)

p-Bis(p-chlorobenzylidenamino)phenylene,yellow crystals,m.p. 200 °(yield 75%)

p-Bis(p-methoxybenzylidenamino)phenylene,yellowcrystals,m.p. 205°(yield78%)

p-Bis(2-aryl-4-thiazolidinon-3-yl) phenylenes (Ia-c)

A mixture of the appropiate schiff base (0.01 mol) and thioglycollic acid (0.03 mol) in dry benzene (30 ml) was refluxed for 8 h., then the excess solvent was removed under reduced pressure .The obtained solid was washed several times with sodium carbonate solution and recrystallized from proper solvent to give **Ia-c** (Table 1) .

p-Bis(2-substituted-5-arylidene-4-oxo-thiazolin-3-yl) phenylenes (IIa-c) and VII

A mixture of **Ia** or **Ib** or **Ic** or **V** (0.01 mol) and p-nitrobenzaldehyde (0.025 mol) in a acetic acid (30 ml) containing fused sodium acetate (1g) was refluxed for 6 h., cooled and

pour onto cold water . The solid obtained was filtered off and recrystallized from the proper solvent to give **IIa-c** or **VII** (Table1) .

p-Bis[5-substituted-2-(3-phenyl-4-oxo-thiazolin-2-ylmethylidene)-4-oxo-thiazolin-3-yl] phenylenesIV and IX

To a solution of potassium hydroxide (0.02 mol) in DMF (20 ml) , compound **Ib** or **VI** (0.01 mol) was added and the reaction mixture was stirred for 30 min., then phenyl isothiocyanate (0.02 mol) was added to the resulting mixture and stirring was continued for 8h., ethyl chloroacetate (0.02 mol) was added to the above miture dropwise . After complete the addition the reaction mixture was stirred for 24 h.. The solid obtained was collected and recrystallized from proper solvent to give **IV** or **IX** (Table 1) .

Reaction of p-phenylenediamine with phenyl isothiocyanate or p-chloro-benzoyl isothiocyanate

A mixture of p-phenylenediamine (0.01 mol) and phenyl isothiocyanate or p-chlorobenzoyl isothiocyanate (0.03 mol) in absolute ethanol (30 ml) was refluxed for 6 h.,cooled and poured onto cold water the solid obtained was filtered and recrystallized from the proper solvent to give p-bis(N-substitutedthiourea) phenylenes .

p-Bis(thiouredo)phenylene:pale yellow crystals from DMF/H_2O , m.p.280 ° (yield 80 %) .

p-Bis(p-chlorobenzylthiouredo)phenylene:orange crystals from acetic acid , m.p.205 ° (yield 66 %) .

p-Bis(5-phenylamino-4-oxo-thiazolidin-3-yl)phenylene (V) and p-Bis[5-(-p-chlorobenzoylimino)-4-oxo-thiazolin-3-yl] phenylene (VI)

A mixture of p-bis(thiouredo) phenylene or p-bis[(p-chlorobenzoyl) thiouredo]phenylene (0.01 mol) and ethyl chloroacetate (0.025 mol) in ethanol (30 ml) containing fused sodium acetate (1g) was refluxed for 6 h., cooled and pour onto crushed ice. The solid obtained was collected and recrystallized from the proper solvent to give **V** or **VI** (Table1) .

p-Bis(pyrazolo[3,4-d] thiozolin-3-yl)phenylene derivative X

A mixture of **IIb** (0.001 mol) and phenyl hydrazine (6 ml) in dioxan (30 ml) containing a few drops piperidine was refluxed for 3h. The solid obtained after cooling was filtered off and recrystallized fromDMF/H_2O to give **X** as yellow crystals m.p.260 °, yield 68 % .

p-Bis{2-(substituted)-6-(3-nitrophenyl) isoxazolo[3,4-d]thiazolin-3-yl} phenylenes(XIa,b)

A mixture of **IIb** or **IV** (0.01 mol) and hydroxylamine hydrochloride (0.025 mol) in DMF (30 ml) was refluxed for 4h., cooled and pour onto cold water . The solid produced was filtered off and recrystallized from the proper solvent .to give **XIa,b** (Table1) .

p-Bis{2-substituted)-5-methyl-7-(m-nitrophenyl)pyrimido[4,5-d]thiazolin-3-yl}phenylenes(XIIa,b)

A mixture of **IIb** or **IV** (0.01 mol) and acetamidine hyrochloride (0.025 mol) in DMF / sodium ethoxide mixture was refluxed for 6h., cooled and pour onto crushed ice and treated with few drops of hydrochloric acid .The solid obtained was filtered off and recrystallized from the proper solvent to give **XIIa,b** (Table1) .

p-Bis(2,7,8-trisubstituted-4-thioxopyrimido[4,5-d]thiazolin-3-yl)phenylenes (XIIIa,b)

A mixture of **IIb** or **IV** (0.01mol) and N-phenyl thiourea (0.025 mol) in DMF was refluxed for 8h., cooled and pour onto cold water . The solid obtained was collected and recrystallized from the proper solvent to give **XIIIa,b**(Table 1) .

p-Bis(2,5,7-trisubstituted-thiazino[4,5-d]thiazolin-3-yl)phenylenes (XIVa,b)

A mixture of **IIb** or **IV** (0.01 mol) and N-phenyl thiourea (0.025 mol) methanol containing few drops of conc. HCl was refluxed for 6hrs., cooled and poured onto crushed ice . The solid obtained was filtered off and recrystallized from the proper solvent

XIVa:orange crystals from acetic acid , m.p.245 ° (yield 75 %) .

XIVb:pall brown crystals from ethanol , m.p.172 ° (yield 62 %) .

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