Asian Journal of Chemistry Vol. 11, No. 4 (1999), 1431–1437

Synthesis of Some Thiazolidinone and Azetidinone Compounds and Their Antmicrobial Activity

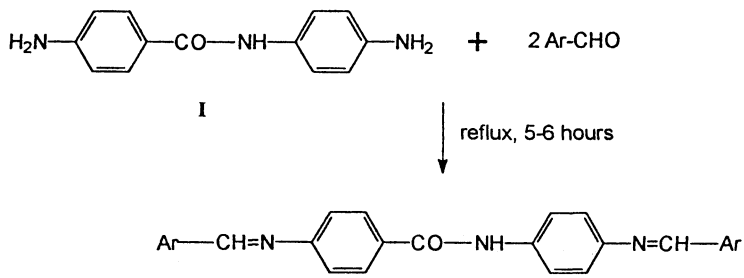
SUNIL B. DESAI, P.B. DESAI and K.R. DESAI*
Department of Chemistry, South Gujarat University
Surat-395 007, India

In the present report we have synthesized various thiazolidinones and azetidinones and screened them for their biological activity.

INTRODUCTION

Diaminobenzaldehyde was found to exhibit insecticidal property[1], growth inhibition of plants[2], tuberculostatic action[3] and herbicidal property[4]. Thiazolidinones are known for their antibacterial[5], antifungal[6,7], anti-convulsant[8,9], antithyroid, amoebicidal[1] and to some extent tuberculostatic activity. A large number of Schiff bases are known to have useful biological activities like tuberculostatic, fungicidal and bactericidal. Biological properties like anaesthetic, anticonvulsant and antitubercular have been shown by thiazolidinone Schiff bases. Azetidinone derivatives are also known as antibiotics, antidepressants, sedatives[11]. The di-imines of diaminobenzanilide **(I)** with different aldehydes were synthesized. These di-imines[12] **(II)** were further reacted with thioglycollic acid and chloroacetyl chloride to give thiazolidinones[13–15] **(III)** and azetidinones[16–19] **(IV)**.

The starting compound, diaminobenzanilide, shows IR absorption peak at 3400–3300 cm^{-1} and 3200–3100 cm^{-1}, 1560 cm^{-1} (C—N stretching for amino group), 1700–1660 cm^{-1} due to (C=O) stretching. The Schiff base of above starting compound shows IR absorption peak at 1630 cm^{-1} due to (C=N) stretching and 1660–1680 cm^{-1} due to (C=O) stretching. The thiazolidinones were characterised by their IR bands at 3330–3300 cm^{-1} (N—H stretching), 720–600 cm^{-1} (C—S stretching), 1750–1680 cm^{-1} (C=O stretching) and 1590–1560 cm^{-1} (C—N sntretching). The azetidinones were characterized by their IR bands at 1730–1680 (C=O stretching), 1715 cm^{-1} and 730 cm^{-1} (C—Cl stretching and bending).



EXPERIMENTAL

All the melting points were in an open capillary tube and all uncorrected IR spectra (KBr) were recorded on Perkin-Elmer spectrometer.

Preparation of di-imine(I)[12]

A mixture of diaminobenzanilide (0.02 mol) and benzaldehyde (0.04 mol) was refluxed in benzene (25 mL) for 4 h. The resulting solid was filtered, dried and crystallised from benzene. Other substituted di-imines were prepared in a similar manner. Analytical data are shown in Table-1.

TABLE-1
ANALYTICAL DATA OF THE SCHIFF'S BASE

Compound number	SubstituentAr- (m.f.)	m.w.	m.p. (°C)	Yield (%)	Elemental analysis, % Theoretical (Practical)		
					C	H	N
1	C_6H_5— ($C_{27}H_{21}N_3O$)	403	192	91	80.39 (80.41)	5.21 (5.24)	10.42 (10.44)
2	4-$OCH_3C_6H_4$— ($C_{29}H_{25}N_3O_3$)	463	176	88	69.97 (69.95)	5.39 (5.36)	9.07 (9.09)
3	2-OHC_6H_4— ($C_{27}H_{21}N_3O_3$)	435	210	95	74.48 (74.44)	4.82 (4.84)	9.65 (9.67)
4	C_6H_5—CH=CH— ($C_{31}H_{25}N_3O$)	455	188	93	81.75 (81.77)	5.49 (5.47)	9.23 (9.21)
5	C_4H_3S— ($C_{23}H_{17}N_3OS_2$)	415	132	89	66.50 (66.51)	4.09 (4.11)	10.12 (10.14)
6	3,4,5-$(OCH_3)_3C_6H_2$— ($C_{33}H_{33}N_3O_7$)	583	183	95	67.92 (67.94)	5.66 (5.65)	7.20 (7.22)
7	2-$NO_2C_6H_4$— ($C_{27}H_{19}N_5O_5$)	493	175	75	65.72 (65.75)	3.85 (3.86)	14.19 (14.18)
8	3-$OC_6H_5C_6H_4$— ($C_{39}H_{29}N_3O_3$)	587	169	92	79.72 (79.69)	4.94 (4.98)	7.15 (7.17)
9	3-$OC_2H_5$4-OHC_6H_3— ($C_{31}H_{29}N_3O_5$)	523	164	78	71.12 (71.13)	5.54 (5.57)	8.03 (8.05)
10	N,N-$(CH_3)_2C_6H_4$— ($C_{29}H_{25}N_5O$)	459	180	93	75.81 (75.83)	5.54 (5.53)	15.25 (15.22)
11	3-BrC_6H_4— ($C_{27}H_{19}N_3OBr_2$)	561	178	80	57.75 (57.78)	3.38 (3.36)	7.48 (7.50)
12	2-$OCH_3C_6H_4$— ($C_{29}H_{25}N_3O_3$)	463	191	76	69.97 (69.98)	5.39 (5.37)	9.07 (9.06)

Preparation of thiazolidinone (II)[13–15]

Thiogllycollic acid (0.015 mol) was added dropwise to the dimine (0.0075 mol) in benzene. The reaction mixture was then refluxed in water bath at 80°C

for 15 h. The product was separated, dried and crystallzed from benzene. Other substituted thiazolidinones were prepared in a similar manner. Analytical data for different substituted thiazolidinones are shown in Table-2.

TABLE-2
ANALYTICAL DATA OF THE THIAZOLIDINONES

Compound number	Substituent Ar- (m.f.)	m.w.	m.p. (°C)	Yield (%)	Elemental Analysis, %, Theoretical (Practical)		
					C	H	N
13	C_6H_5— ($C_{33}H_{25}N_3O_3S_2$)	551	118	74	67.51 (67.48)	4.53 (4.50)	7.62 (7.65)
14	4-OCH_3—C_6H_4— ($C_{33}H_{29}N_3O_5S_2$)	611	141	78	64.81 (64.76)	4.74 (4.69)	6.87 (6.84)
15	2-OH—C_6H_4— ($C_{31}H_{25}N_3O_5S_2$)	583	159	85	63.80 (63.84)	4.28 (4.33)	7.20 (7.22)
16	C_6H_5—CH=CH— ($C_{35}H_{29}N_3O_3S_2$)	603	123	69	69.65 (69.62)	4.80 (4.83)	6.97 (6.99)
17	C_4H_3S— ($C_{27}H_{21}N_3O_3S_4$)	563	89	71	57.54 (57.55)	3.73 (3.76)	7.46 (7.44)
18	3,4,5-$(OCH_3)_3C_6H_2$— ($C_{37}H_{37}N_3O_9S_2$)	731	112	85	60.73 (60.75)	5.06 (5.04)	5.74 (5.70)
19	2-$NO_2C_6H_4$— ($C_{31}H_{23}N_5O_7S_2$)	641	131	73	58.03 (58.07)	3.58 (3.57)	10.72 (10.68)
20	3-OC_6H_5—C_6H_4— ($C_{43}H_{33}N_3O_5S_2$)	735	127	82	70.20 (70.22)	4.49 (4.52)	5.71 (5.73)
21	3-OC_2H_5-4-OHC_6H_3— ($C_{35}H_{33}N_3O_7S_2$)	671	114	78	62.59 (62.57)	4.91 (4.92)	6.25 (6.27)
22	N,N-$(CH_3)_2$—C_6H_4— ($C_{33}H_{29}N_5O_3S_2$)	607	105	63	65.23 (65.20)	4.77 (4.74)	11.53 (11.55)
23	3-Br—C_6H_4— ($C_{31}H_{23}N_3O_3S_2Br_2$)	709	118	78	52.46 (59.48)	3.24 (3.26)	5.92 (5.95)
24	2-OCH_3—C_6H_4— ($C_{33}H_{29}N_3O_5S_2$)	611	121	67	64.81 (64.82)	4.74 (4.77)	6.87 (6.89)

Preparation of azetidinone (III)[16–19]

Chloroacetyl chloride (0.015 mol) was added slowly to a mixture of di-imine (0.0075 mol) and triethylamine (0.015 mol) in benzene. The reaction mixture was refluxed at 80°C for 15–16 h. The resulting solid was obtained by distilling off benzene. The product was recrystallized from benzene. Other substituted azetidinones were prepared in a similar manner. The analytical data for different substituted azetidinones are shown in Table-3.

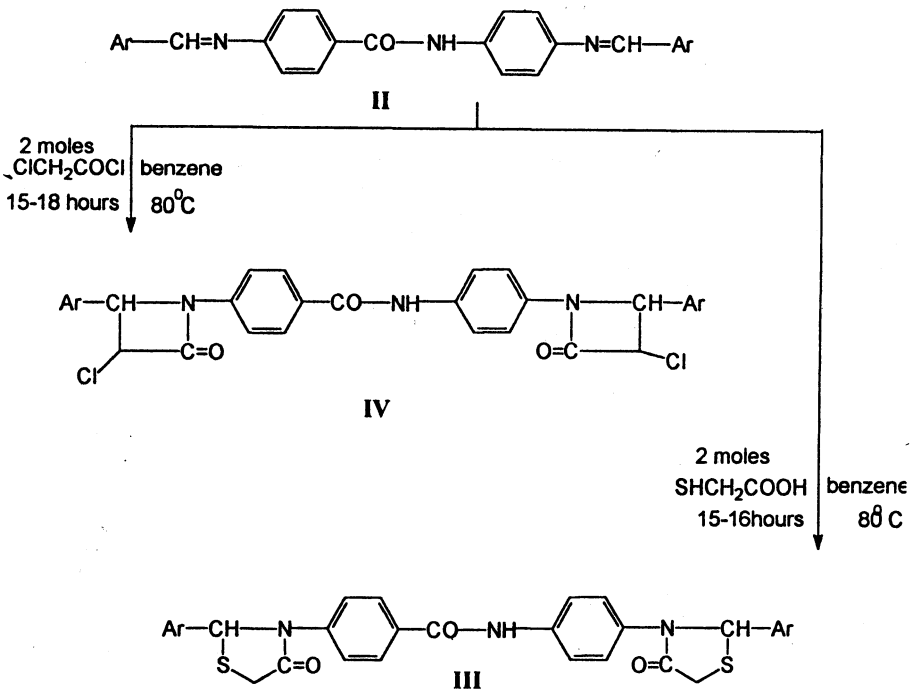


TABLE-3
ANALYTICAL DATA OF THE AZETIDINONES

Compound number	Substituent Ar- (m.f.)	m.w.	m.p. (°C)	Yield (%)	Elemental Analysis, % Theoretical (Practical)		
					C	H	N
25	C_6H_5— ($C_{31}H_{23}N_3O_3Cl_2$)	556	>250	92	66.90 (66.87)	4.13 (4.11)	7.55 (7.51)
26	4-OCH_3—C_6H_4— ($C_{33}H_{27}N_3O_5Cl_2$)	616	>250	78	64.28 (64.26)	4.38 (4.34)	6.81 (6.79)
27	2-OH—C_6H_4— ($C_{31}H_{23}N_3O_5Cl_2$)	588	>250	89	63.26 (63.28)	3.91 (3.94)	7.14 (7.18)
28	C_6H_5—CH=CH— ($C_{35}H_{27}N_3O_3Cl_2$)	608	>250	95	69.07 (69.05)	4.40 (4.43)	6.90 (6.88)
29	C_4H_3S— ($C_{27}H_{19}N_3O_3S_2Cl_2$)	568	>250	86	57.04 (57.06)	3.34 (3.37)	7.39 (7.41)
30	3,4,5-$(OCH_3)_3$—C_6H_2— ($C_{37}H_{35}N_3O_9Cl_2$)	736	>250	91	60.32 (60.29)	4.75 (4.73)	5.70 (5.71)

Compound number	Substituent Ar- (m.f.)	m.w.	m.p. (°C)	Yield (%)	Elemental Analysis, % Theoretical (Practical)		
					C	H	N
31	2-NO_2—C_6H_4— ($C_{31}H_{21}N_5O_7Cl_2$)	646	>250	78	57.58 (57.55)	3.25 (3.27)	10.83 (10.86)
32	3-OC_6H_5—C_6H_4— ($C_{43}H_{31}N_3O_5Cl_2$)	740	>250	92	69.72 (69.69)	4.18 (4.19)	5.67 (5.70)
33	3-OC_2H_5-4-OH, C_6H_3— ($C_{35}H_{31}N_3O_7Cl_2$)	676	>250	84	61.58 (61.56)	5.42 (5.39)	6.15 (6.11)
34	N,N-$(CH_3)_2$—C_6H_4— ($C_{33}H_{27}N_5O_3Cl_2$)	612	>250	87	64.70 (64.73)	4.41 (4.44)	11.43 (11.45)
35	3-Br—C_6H_4— ($C_{31}H_{21}N_3O_3Cl_2Br_2$)	714	>250	68	52.10 (52.09)	2.94 (2.96)	5.88 (5.87)
36	2-OCH_3—C_6H_4— ($C_{33}H_{27}N_3O_5Cl_2$)	616	>250	85	64.28 (64.25)	4.38 (4.40)	6.81 (6.80)

RESULTS AND DISCUSSION

The compounds were screened in *vitro* for their antibacterial activity by Kirby-Bauer[20] technique. The compounds were solubilised in dimethylformamide (DMF) and tested at 5μ g/mL against gram-positive bacteria, *viz.*, *Staphylococcus aureus* and *Bacillus subtilis* and gram-negative bacteria, *viz.*, *Escherichia coli* and *Salmonella paratyphi-B*. These bacterial species are known human pathogens. Two of them, *Staphylococcus aureus* and *Escherichia coli*, are normal inhabitants of the upper respiratory tract, skin, intestine and vagina. The same bacterial species were pathogenic causing endocarditis, nephritis, respiratory infections and intestinal infections, whereas *Salmonella paratyphi*-B and *Bacillus subtilis* cause food poisoning[21].

Table-4 shows the *in vitro* antibacterial activity of different substituted di-imines, thiazolidinones and azetidinones, compounds derived from diaminobenzanilide. All of them were found nearly non-inhibitory for gram-negative bacteria while in case of gram-positive bacteria except 4,4′bis[2″-methoxybenzylidene] diaminobenzanilide all were ineffective for *Staphylococcus aureus*. But all compounds are effective against *Bacillus subtilis* except 4,4′-bis-[cinnamylidene] diaminobenzanilide, 4,4′-bis[3″,4″5″-trimethoxy-benzylidene]-diaminobenzanilide, 4,4′-bis[2″-oxo-5″-(2‴-hydroxyphenyl)thiazolidine] benzanilide, 4,4′-bis[2″-oxo-5″-(3‴-bromophenyl) thiazolidine]benzanilide, and 4,4′-bis[2″-oxo-5″-((4‴-N,N-dimethyl)-phenyl)-thiazolidine]benzanilide. Among all of them screened in this study the most effective compounds are 4,4′-bis[2‴-methoxybenzylidene] diaminobenzanilide, 4,4′-bis[2″-oxo-5″-(3‴-phenoxyphenyl)-thiazolidine]benzanilide, 4,4′-bis[2″-oxo-5″2‴-nitrophenyl)-thiazo- lidine] benzanilide showing greater than 12.0 mm zone size.

TABLE-4
ANTIBACTERIAL ACTIVITY REPORT OF THE SCHIFF BASES SYNTHESISED FROM DIAMINOBENZANILIDE

Compound number	Zone of inhibition (mm)			
	Escherichia coli	*Salmonella paratyphi-B*	*Staphylococcus aureus*	*Bacillus subtilis*
1	6.00	6.00	6.00	7.00
2	6.00	6.00	6.00	7.00
3	6.00	6.00	6.00	9.00
4	6.00	9.00	6.00	6.00
5	6.00	6.00	6.00	8.00
6	6.00	7.00	8.00	6.00
7	6.00	6.00	8.00	7.00
8	6.00	6.00	6.00	8.00
9	6.00	6.00	6.00	7.00
10	9.00	6.00	8.00	7.00
11	6.00	8.00	8.00	8.00
12	6.00	9.00	10.00	12.00
13	6.00	6.00	6.00	8.00
14	6.00	6.00	6.00	8.00
15	6.00	6.00	6.00	6.00
16	6.00	6.00	6.00	9.00
17	8.00	7.00	7.00	10.00
18	6.00	6.00	7.00	8.00
19	6.00	6.00	9.00	11.00
20	7.00	7.00	7.00	18.00
21	7.00	6.00	6.00	8.00
22	6.00	6.00	6.00	6.00
23	6.00	6.00	7.00	9.00
24	6.00	7.00	7.00	9.00
25	6.00	6.00	6.00	8.00
26	6.00	6.00	6.00	8.00
27	8.00	7.00	7.00	8.00
28	6.00	6.00	6.00	10.00
29	6.00	6.00	6.00	8.00
30	6.00	6.00	6.00	7.00
31	6.00	6.00	6.00	7.00
32	6.00	7.00	6.00	9.00
33	6.00	6.00	6.00	7.00
34	6.00	6.00	6.00	9.00
35	6.00	6.00	6.00	8.00
36	6.00	6.00	6.00	8.00

ACKNOWLEDGEMENT

The authors are grateful to the South Gujarat University, Surat for providing research facilities.

REFERENCES

1. F. Beran, V. Prey and Helen Bohm, *Mitt. Chem. Forschunge Inst. Ind. Osters*, **5**, 43 (1951).
2. H.E. Thompson, Carl P. Swanson and A.G. Norman, *Botan. Gaz*, **107**, 476 (1946).
3. Y. Takeo, G.R. Pscheidt and H.E. Himwich, *Life Sci.*, **5**, 1503 (1966) (Eng.).
4. H. Schwartz and J.B. Skaptason, *Chem .Abstr.*, **65**, 15282h (1966).
5. K.J. Mehta and A.R. Parikh, *Indian J. Chem.*, **16B**, 836 (1978).
6. T. Haken and P. Webb, Eur. Pat. Appl. EP. 91, 148 (1982); *Chem. Abstr.*,**100**, 139089n (1984).
7. M.M. Shah and P.C. Joshi, *Asian J. Chem.*, **1**, 141 (1989).
8. R. Kumar, T.K. Gupta and S.C. Parmar, *J. Pract. Chem.*, **312**, 201 (1970).
9. C. Dwivedi, T.K. Gupta and S.C. Parmar, *J. Med. Chem*, **15**, 553 (1972).
10. K.K. Thaker, B.R. Parekh and N.C. Desai, *J. Indian Chem. Soc.*, **64**, 491 (1987).
11. P.G. Summer, *Chem. Rev.* **76**, 113 (1976).
12. K. Von Auwers and H. Stuhlmann, *Ber.*, **59**, 1043 (1926).
13. F.C. Brown, *Chem. Revs.*, **61**, 463 (1961).
14. A. Mustafa, W. Asker, A.F.A. Shallaby and M.E.E. Shobby, *J.Org. Chem.*, **23**, 1992 (1958).
15. G.R. Newkome and A. Nayak, *Advances of Heterocyclic Chemistry*, **25**, 83 (1979).
16. K. Shanker, V. Shrivastava and A. Gulati, *Indian J. Chem.*, **26B**, 652 (1987).
17. S.D. Sharma, V. Kaur and A. Saluja, *Indian J. Chem.*, **33B**, 624 (1994).
18. J.M. Vanderveen, S. Bari, I. Krishnan, M.S. Manhas and A.K. Bose, *J. Org. Chem.*, **54**, 5758 (1989).
19. Y.H. Talia and K.R. Desai, *M. Phil Thesis*, South Gujarat University, Surat (1997).
20. M.M. Kirby, A.W. Bauer, J.C. Sherris and M. Truck, *Am. J. Clin. Pathol.*, **45**, 493–496 (1966).
21. L.M. Prescott, J.P. Harley and D.A. Klein, *Microbiology*, 3rd Edn., Wm. C. Brown, London (1966).

(*Received*: 3 May 1999; *Accepted*: 28 July 1999) AJC–1810