Asian Journal of Chemistry Vol. 21, No. 1 (2009), 504-510

Synthesis and Physiological Activities of Some Imines and Their β-Lactams

SOUMYA M. NAIR* and IRA BHATTACHARYA
Department of Chemistry, R.D. National and W.A. Science College
Mumbai-400 050, India
E-mail: soumyanair2000@yahoo.com

The compounds 4-[N-(4-nitro phenyl) methylidinyl] resorcinol (**I**), 4-[N-(4-methyl phenyl)methylidinyl]resorcinol (**II**), 4-[N-(4-methoxy phenyl) methylidinyl]resorcinol (**III**), 4-[N-(4-chloro phenyl)methylidinyl]resorcinol (**IV**) and 4-[N-(4-bromo phenyl) methylidinyl]resorcinol (**V**) have been synthesized by refluxing resorcinol and *p*-chloro aniline with triethylorthoformate. The products formed were further used to prepare their respective β-lactams 3-(chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-nitro phenyl)azetidin-2-one (**VI**), 3-(chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-methyl phenyl)azetidin-2-one (**VII**), 3-(chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-methoxy phenyl)azetidin-2-one (**VIII**), 3-(chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-chloro phenyl)azetidin-2-one (**IX**) and 3-(chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-bromo phenyl)azetidin-2-one (**X**) by using chloroacetylchloride and dry triethylamine. The compounds have been characterized on the basis of elemental and spectral data and screened for their antimicrobial activity.

Key Words: Synthesis, Physiological activities, β-Lactams, Imines.

INTRODUCTION

Several methods of preparing Schiff bases or imines have been reported[1,2]. The Schiff's bases are known for their pharmacological activities[3-5] and hence are widely used. The Schiff's bases are essentially the compounds containing imine (azomethine) functional group (-CH=N-) having carbon-nitrogen double bond. The present work consists of preparation of imines by condensing resorcinol with different amines by using triethylorthoformate[6]. The imines obtained were used to prepare β-lactams by using chloroacetyl-chloride and in the presence of triethylamine. β-lactam consists of a ring system similar to that of penicillin which are widely used as a chemotherapeutic agent in medicine[7]. The β-lactams and imines obtained from the present work were screened for its antimicrobial activity and was found to contain antifungal property and some of the compounds contained antibacterial property.

EXPERIMENTAL

All chemicals used were of LR grade and the melting points reported were determined in open capillary tube and are uncorrected. IR spectra in KBr medium and ^{1}H NMR spectra was recorded.

4-[N-(4-Nitro phenyl)methylidinyl]resorcinol (I): Resorcinol (1.1 g, 0.01 mol) and *p*-nitro aniline (1.38 g, 0.01 mol) were refluxed in the presence of triethylorthoformate (25 mL) for 3 h. Excess of solvent and ethanol formed during the reaction was distilled out. The semisolid mass obtained were triturated with methanol and kept over-night in ice. The solid separated was collected and washed with ethanol. It was dried and crystallized from ethanol.

4-[N-(4-Methyl phenyl) methylidinyl]resorcinol (II): The compound was prepared according to the procedure above by using resorcinol (1.1 g, 0.01 mol), *p*-toluidine (1.02 g, 0.01 mol) and 25 mL of triethylorthoformate and refluxing the reaction mixture for 3 h. After distilling out excess of solvent and ethanol, the semisolid mass obtained was triturated with methanol and kept over-night in ice. The solid separated was collected and washed with ethanol. It was dried and crystallized from ethanol.

4-[N-(4-Methoxy phenyl)methylidinyl]resorcinol (III): The compound was prepared according to the procedure mentioned above by using resorcinol (1.1 g, 0.01 mol), *p*-anisidine (1.23 g, 0.01 mol) and 25 mL of triethylorthoformate.

4-[N-(4-Chloro phenyl)methylidinyl]resorcinol (IV): Resorcinol (1.1 g, 0.01 mol), *p*-chloro aniline (1.27 g, 0.01 mol) and triethylorthoformate (25 mL) were used to prepare the compound according to the procedure mentioned above.

4-[N-(4-Bromo phenyl) methylidinyl]resorcinol (V): The compound was prepared according to the procedure described by using same amount of resorcinol, triethylorthoformate and *p*-bromoaniline (1.23 g, 0.01 mol).

All the above prepared compounds were further used in the preparation of their respective β-lactams.

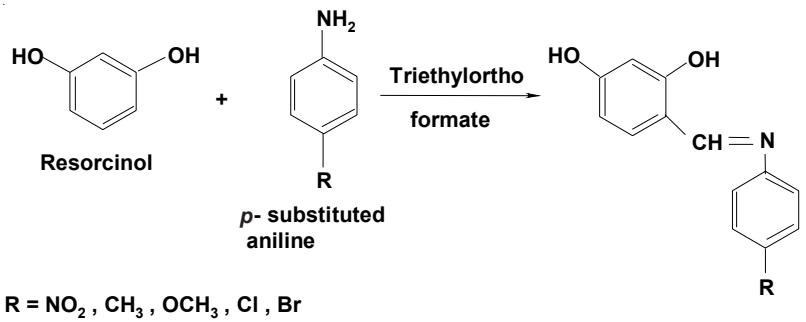
3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-nitro phenyl)azetidin-2-one (VI): 4-[N-(4-nitro phenyl) methylidinyl]resorcinol (4.87 g, 0.01 mol), dry triethylamine (3.03 g, 0.03 mol) and sodium dried benzene (100 mL) were stirred at a temperature of 48-50 °C. Chloroacetyl chloride (3.39 g, 0.03 mol) in 50 mL of benzene were added dropwise over a period of 3 h. After the addition was over the reaction mixture was further stirred for 1 h, cooled and filtered. The filtrate was evaporated to dryness to obtain a dark brown oily mass, which was digested thrice with 20 mL of ether and *n*-hexane (1:1) to remove unreacted Schiff base. The solidified mass was digested with ethanol and filtered. The solid obtained was dried and crystallized from ethanol.

3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-methyl phenyl) azetidin-2-one (VII): 4-[N-(4-Methyl phenyl)methylidinyl]resorcinol (4.56 g, 0.01 mol), dry triethylamine (3.03 g, 0.03mol) and sodium dried benzene (100 mL) were stirred at a temperature of 48-50 °C. Chloroacetyl chloride (3.39 g, 0.03 mol) in 50 mL of benzene were added dropwise over a period of 3 h. After the addition was over the reaction mixture was further stirred for 1 h, cooled and filtered. The filtrate was evaporated to dryness to obtain a dark brown oily mass, which was digested thrice with 20 mL of ether and *n*-hexane (1:1) to remove unreacted Schiff base. The solidified mass was digested with ethanol and filtered. The solid obtained was dried and crystallized from ethanol.

3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-methoxy phenyl) azetidin-2-one (VIII): The compound was prepared by using 4-[N-(4-methoxy phenyl)methylidinyl]resorcinol (4.72 g, 0.01 mol) dry triethylamine (3.03 g, 0.03 mol) and 100 mL of sodium dried benzene. The reaction mixture was stirred at a temperature of 48-50 °C. Chloroacetyl chloride (3.39 g, 0.03 mol) in 50 mL of benzene were added dropwise over a period of 3 h. After the addition was over the reaction mixture was further stirred for 1 h, cooled and filtered. The filtrate was evaporated to dryness to obtain a dark brown oily mass, which was digested thrice with 20 mL of ether and *n*-hexane (1:1) to remove unreacted Schiff base. The solidified mass was digested with ethanol and filtered. The solid obtained was dried and crystallized from ethanol.

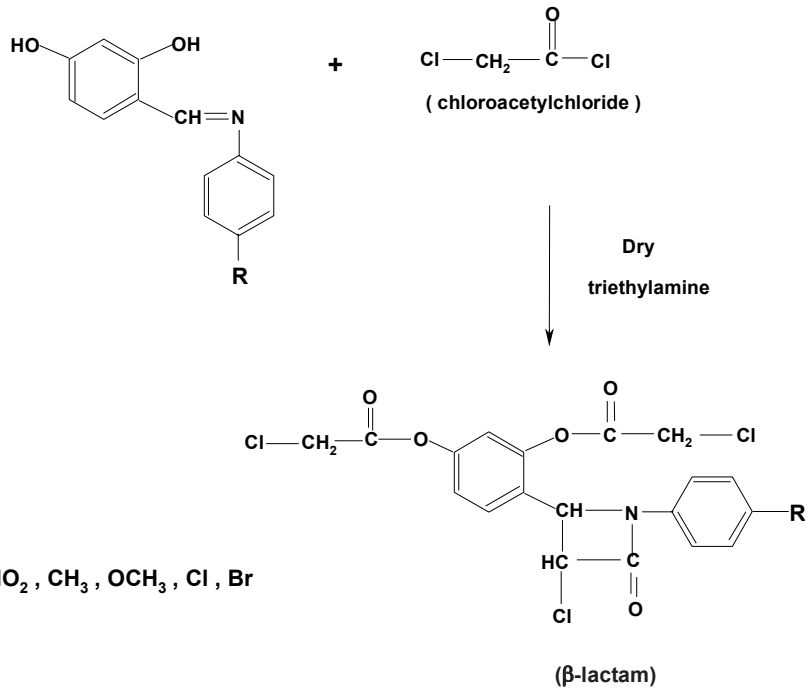
3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-chloro phenyl) azetidin-2-one (IX): The compound was prepared according to the procedure above by using 4-[N-(4-chloro phenyl) methylidinyl]resorcinol (4.77 g, 0.01 mol) dry triethylamine (3.03 g) and 100 mL of sodium dried benzene. The reaction mixture was stirred and chloroacetyl chloride (3.39 g, 0.03 mol) in 50 mL of benzene were added dropwise over a period of 3 h. After the addition the mixture was again stirred for 1 h cooled and filtered. The filtrate was evaporated to dryness to obtain a dark brown oily mass, which was digested thrice with 20 mL of ether and *n*-hexane (1:1) to remove unreacted Schiff base. The solidified mass was digested with ethanol and filtered. The solid obtained was dried and crystallized from ethanol.

3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-bromo phenyl) azetidin-2-one (X): The compound was prepared according to the procedure above by using 4-[N-(4-bromo phenyl)methylidinyl]resorcinol (5.21 g, 0.01 mol) dry triethylamine (3.03 g), 100 mL of sodium dried benzene chloroacetyl chloride (3.39 g, 0.03 mol) in 50 mL of benzene and 20 mL of (1:1) ether and *n*-hexane.



R = NO_2 , CH_3 , OCH_3 , Cl , Br

For structure (I) : R = NO_2
For structure (II) : R = CH_3
For structure (III) : R = OCH_3
For structure (IV) : R = Cl
For structure (V) : R = Br



R = NO_2 , CH_3 , OCH_3 , Cl , Br

(β-lactam)

For structure (VI) : R = NO_2
For structure (VII) : R = CH_3
For structure (VIII) : R = OCH_3
For structure (IX) : R = Cl
For structure (X) : R = Br

Scheme

RESULTS AND DISCUSSION

All the imines formed were stable yellow coloured solids. 4-[N-(4-nitro phenyl)methylidinyl]resorcinol (**I**) had a melting point of 159 °C and yield of 1.9 g. The colour of the compound was dark yellow. [Found (%): C 60.15, H 3.45, N 10.35. $C_{13}H_{10}O_4N_2$ requires (%): C 60.46, H 3.87, N 10.85]. The IR spectrum showed peaks at 3483 cm^{-1} (phenolic O-H *str.*), 1303 cm^{-1} (Ar-NO_2), 1655 cm^{-1} (-CH=N- *str.*).

The melting point recorded for 4-[N-(4-methyl phenyl)methylidinyl] resorcinol (**II**) formed was 201 °C and yielded 2.3 g. The colour of the compound was yellow. [Found (%): C 73.69, H 5.13, N 13.89. $C_{14}H_{13}O_2N$ requires (%): C 74, H 5.72, N 14.09]. The IR spectrum showed peaks at 3471 cm^{-1} (phenolic O-H *str.*), 1649 cm^{-1} (-CH=N- *str.*).

4-[N-(4-Methoxy phenyl)methylidinyl]resorcinol (**III**) obtained were dark yellow coloured compound with a melting point 211 °C and the yield was 2 g. [Found (%): C 68.83, H 5.19, N 5.32 and $C_{14}H_{13}O_3N$ requires (%): C 69.13, H 5.34, N 5.76]. The IR spectra recorded showed absorption at 3745 cm^{-1} (phenolic O-H *str.*), 1651 cm^{-1} (-CH=N- *str.*).

4-[N-(4-Chloro phenyl)methylidinyl]resorcinol (**IV**) obtained were dark yellow coloured compound with a melting point 189 °C and the yield was 2.3 g. [Found (%): C 62.87, H 3.89, N 5.35, $C_{13}H_{10}O_2NCl$ requires (%) C 63.03, H 4.04, N 5.65]. The IR spectra recorded showed absorption at 3745 cm^{-1} (phenolic O-H *str.*), 1658 cm^{-1} (-CH=N- *str.*).

4-[N-(4-Bromo phenyl)methylidinyl]resorcinol (**V**) that was prepared had melting point 139 °C and a yield of 1.9 g. [Found (%): C 51.89, H 2.8, N 3.76. $C_{13}H_{10}O_2NBr$ requires (%) C 53.42, H 3.42, N 4.79].

The β-lactams prepared from their respective imines were all crystallized from ethanol to form crystalline solids. The spectral analysis showed that the phenolic OH groups were acetylated. The NMR spectra of all the β-lactams prepared showed peaks at 5 ppm which proved the presence of acetyl group, 7.60 and 7.45 ppm showed absorption of aromatic rings, N-C=O at 3.3 ppm.

3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-nitro phenyl)azetidin-2-one (**VI**) prepared was light yellow crystalline solids. It had a melting point 169 °C, Yield: 2.39 g. [Found (%): C 46.98, H 2.24, N 5.23, $C_{19}H_{13}O_7N_2Cl_3$ requires (%): C 46.76, H 2.66, N 5.74]. IR 1786 cm^{-1} (β-lactam C=O *str.*), 1813 cm^{-1} (ester C=O *str.*).

3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-methyl phenyl) azetidin-2-one (**VII**) prepared was light yellow crystalline solids. It had a melting point 140 °C, Yield: 2.02 g. [Found (%): C 52.13, H 3.1, N 2.9, $C_{20}H_{16}O_5NCl_3$ requires (%) C 52.57, H 3.5, N 3.06] IR: 1793 cm^{-1} (β-lactam C=O *str.*), 1894 cm^{-1} (ester C=O *str.*).

3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-methoxy phenyl) azetidin-2-one (**VIII**): Melting point 124 °C, Yield 2.45 g. [Found (%): C 50.48, H 3.01, N 2.43, $C_{20}H_{16}O_6NCl_3$ requires (%): C 50.79, H 3.38, N 2.96].

3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-chloro phenyl) azetidin-2-one (**IX**) prepared was a white crystalline solid with a melting point of 161 °C. Yield was 3.13 g [Found (%): C 47.36, H 2.34, N 2.54, $C_{19}H_{13}O_5NCl_4$ requires (%): C 47.79, H 2.72, N 2.93]. IR: 1793 cm^{-1} (β-lactam C=O *str.*) 1886 cm^{-1} (ester C=O *str.*).

3-(Chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-bromo phenyl) azetidin-2-one (**X**). The compound prepared was yellow coloured crystalline compounds. It had a melting point of 170 °C, Yield: 3.05 g. [Found (%): C 43.58, H 2.3, N 2.47. $C_{19}H_{13}O_5NBrCl_3$ requires (%) C 43.72, H 2.49, N 2.68]. IR: 1798 cm^{-1} (β-lactam C=O *str.*), 1884 cm^{-1} (ester C=O *str.*).

Antimicrobial activity: The compounds were tested for their antimicrobial activity by using ditch plate method[8] against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus cereus, Klebsiella pneumonia, Candida albicans, C. krusei, Aspergillus fumigatus, A. flavis*. The solutions of the compounds were prepared using Nutrient agar plate at a concentration of 1 mg/mL The powdered drug is then mixed with nutrient agar butt and poured in the center of the plate and kept to harden. The listed organisms are then streaked across the plates. The plates were incubated at 37 °C for 24 h. It was found that both the imines and the β-lactams prepared were active against antifungal organisms and some of the compounds were found active against antibacterial organisms.

TABLE-1
ACTIVITY AGAINST ANTIFUNGAL ORGANISMS

Name of compound	CA	CK	AF	AF1
4-[N-(4-chloro phenyl)methylidinyl]resorcinol	A	A	A	A
3-(Chloro)-4-[(2,4-di-chloroacetoxy)phenyl]-1-(4-methyl phenyl)azetidin-2-one	A	A	A	A
3-(Chloro)-4-[(2,4-di-chloroacetoxy)phenyl]-1-(4-chloro phenyl)azetidin-2-one	A	A	A	A
3-(Chloro)-4-[(2,4-di-chloroacetoxy)phenyl]-1-(4-bromo phenyl)azetidin-2-one	A	A	A	A

CA = *Candida albicans*; CK = *Candida krusei*; AF = *Aspergillus fumigatus*; AF1 = *A. flavis*; A = Active

The compounds 3-(chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-methyl phenyl) azetidin-2-one, 3-(chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-chloro phenyl)azetidin-2-one and 3-(chloro)-4-[(2,4-dichloroacetoxy)phenyl]-1-(4-bromo phenyl) azetidin-2-one were found to be inactive against antibacterial organisms.

TABLE-2
ACTIVITY AGAINST ANTIBACTERIAL ORGANISMS

Name of compd.	EC	PA	BC	SA	KP
4-[N-(4-chloro phenyl) methylidinyl]resorcinol	A	A	A	NA	A

EC = *Escherichia coli*, PA = *Pseudomonas aeruginosa*, BC = *Bacillus cereus*, SA = *Staphylococcus aureus*, KP = *Klebsiella pneumonia*.
A = Active; NA = Not active.

ACKNOWLEDGEMENTS

The authors are thankful to Mr. M.R. Mulwani, Head, Department of Chemistry and the authorities of R.D. National and W.A. Science College for providing us with the necessary facilities to carry out the work. Thanks are also due to Dr. M.A. Dave, Ex. Principal, K.J. Somaya College, Mumbai for his constant support and encouragement.

REFERENCES

1. W.F. Smith, *Org. Chem. Bull.*, **35**, 6 (1963).
2. E.H. Cordes and W.P. Jencks, *J. Am. Chem. Soc*., **85**, 2843 (1963).
3. E.M. Hodnett and W. Willie, *Proc. Okla Akad. Sci.*, **46**, 107 (1966).
4. J.H. Billman, F. Kochler and R. Hay, *J. Pharm. Sci.*, **58**, 767 (1969).
5. E.M. Hodnett and W.J. Dunn, *J. Med. Chem.*, **13**, 768 (1970).
6. Nina Pippalia, M.Sc. Thesis, University of Mumbai (1993).
7. H.T. Clarke, J.R. Johnson and R. Robinson, Chemistry of Penicillines, Princeton University Press (1949).
8. C. Robert, Medical Microbiology ELBS and E and S, Livingstone, Britten, edn. 11, pp. 895, 901 (1970).

(*Received*: 4 January 2008; *Accepted*: 30 August 2008) AJC-6795