Int. J. Chem. Sci.: 7(2), 2009, 672-680

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEW (±)-α-AMINO NITRILE DERIVATIVES

N. K. UNDAVIA*, B. S. PATWA[a], H. D. NAVADIYA, A. R. JIVANI and P. N. DAVE

Department of Chemistry, Bhavnagar University, BHAVNAGAR – 364002 (Guj.) INDIA
[a]Department of Industrial Chemistry, Sir P. P. Institute of Science, Bhavnagar University, BHAVNAGAR – 364002 (Guj.) INDIA

ABSTRACT

To explore new therapeutic agents, we have reported the preparation and biological activity of some newly synthesized sydnonimine hydrochloride. m-Phenoxy benzaldehyde cyanohydrin was condensed with different amines leading to formation of (±)-α-amino nitrile. The product was treated with nitrous acid and ethanolic hydrochloric acid to get cyclic sydnonimine hydrochloride. IR spectra and elemental analysis supported the constitution of the product. The products were tested for antibacterial, antifungal and insecticidal activity.

Key words : Sydnonimine hydrochloride, Antibacterial, Antifungal, Insecticidal.

INTRODUCTION

The sydnonimine are mesoionic substance. The meaning of the term mesoionic was applied primarily to compound which cannot be represented even approximately by any one covalent formula or as a hybrid of a number of covalent formula, but which can be depicted as a hybrid of a number of ionic (dipolar, tetrapolar etc.) forms. The revised definition of the word mesoionic and the use of accepted, instead of a special symbolism, were advanced by the reviewer in 1955[1], who realized the advantage of discussing these compounds in term of molecular orbital theory. Almost exactly similar proposals were put forward a few week later and independently by Bieber[2], the difference being a very minor one of symbolism which is mentioned below. These new proposals emphasized the essentially aromatic character of the sydnonimine hydrochloride derivatives[3], which posses biological activities like antibacterial[4], antifungal[5] and insecticidal[6].

* Author for correspondence; E-mail : dr.navadiya@yahoo.com

m-Phenoxy–benzaldehyde reacts with potassium cyanide in ethanol to give hydroxyl-(3-phenoxy-phenyl)-acetonitrile. It reacts with aromatic amine in alcohol and acid at 15^{o}C for 2 hrs at room temperature for 24 hrs to give (3-phenoxy-phenyl)-phenylamino-acetonitrile **(1).** The compound **(1)** reacts with $NaNO_2$ and HCl at 0-5^{o}C to give [(4-chloro-phenyl)-(nitroso)-amino]-(3-phenoxy-phenyl) acetonitrile **(2)**. The compound **(2)** was reacted with dry HCl gas in chloroform at 0-5^{o}C to give (3-(4-chloro-phenyl)-4-(3-phenoxy phenyl) sydnonimine hydrochloride **(3)**. All the compounds synthesized were adequately characterized by their elemental analysis and spectral data.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. The IR spectra were recorded on Bio-Red FTS-40 spectrophotometer using KBr pellets. The purity of all compounds have been checked by thin-layer chromatography[7]. The absorption spectra of all the compounds were recorded on Beckmann DB-GT Grafting Spectrophotometer.

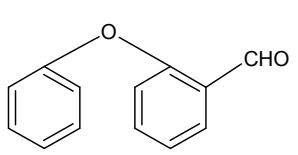
(3-Phenoxy-phenyl)-phenylamino-acetonitrile[8] (1)

Potassium cyanide (1.30 g, 0.02 mole) was dissolved in water (4 mL) and cooled below 5^{o}C. To this, freshly distilled m-phenoxy-benzaldehyde (3.96 g, 0.02 mole) in ethanol (25 mL, 95%) was added. The mixture was stirred maintining temperature below 5^{o}C. To this glacial acetic acid (1.20 g, 0.02 mole) was added with constant stirring below 5^{o}C to obtain hydroxyl-(3-phenoxy-phenyl)-acetonitrile. The compounds were recrystalised with 95% alcohol.

Freshly distilled aniline (0.02 moles 1.86 g) in 10 mL 95% alcohol and 5 mL of acetic acid (cooled below 5^{o}C) was added with continuous stirring in well ventilated hood to above hydroxyl-(3-phenoxy-phenyl)-acetonitrile. Temperature was maintained at 15^{o}C during addition. The reaction mixture was stirred for further 2 hours and was kept at room temperature (25^{o}C) for 24 hrs to obtain (3-phenoxy-phenyl)-phenylamino-acetonitrile. Long needles were made cyanide and amine free by washing with sufficient diluted hydrochloric acid (0.2 M). The compounds were recrystalised with 95% alcohol. Yield 80%, m. p. 70^{o}C. Anal. Calcd. for $C_{20}H_{16}ON_2$: C, 79.98; O, 5.33; N, 9.33.Found C, 79.78; O, 5.56; N, 9.30%.

Table 1 : Characterization

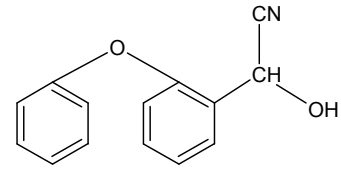
Comp. (3)	R	Molecular formula	Yield (%)	M. P. (^{o}C)	Found (%) (Calcd.)		
					C	N	O
I	(a) Phenyl	$C_{20}H_{17}O_2N_3Cl$	59	>360	65.30 (65.20)	08.70 (08.71)	11.40 (11.40)
II	(b) p-Chlorophenyl	$C_{20}H_{18}O_2N_3Cl_2$	70	>360	59.86 (59.78)	10.47 (10.40)	07.97 (07.94)
III	(c) m-Chlorophenyl	$C_{20}H_{18}O_2N_3Cl_2$	79	>360	59.86 (59.83)	10.47 (10.38)	07.97 (07.89)
IV	(d) o-Chlorophenyl	$C_{20}H_{18}O_2N_3Cl_2$	68	>360	59.86 (59.80)	10.47 (10.39)	07.97 (07.80)
V	(e) o-Tolyl	$C_{21}H_{19}O_2N_3Cl$	64	>360	66.23 (66.20)	11.03 (11.00)	08.40 (08.30)
VI	(f) m-Tolyl	$C_{21}H_{19}O_2N_3Cl$	79	>360	66.23 66.12	11.03 (11.12)	08.40 (08.37)
VII	(g) p-Tolyl	$C_{21}H_{19}O_2N_3Cl$	67	>360	66.23 (66.18)	11.03 (11.09)	08.33 (08.33)
VIII	(h) p-Fluorophenyl	$C_{20}H_{16}O_2N_3FCl$	71	>360	66.42 (66.37)	10.92 (11.01)	08.32 (08.40)



3-Phenoxybenzaldehyde

KCN

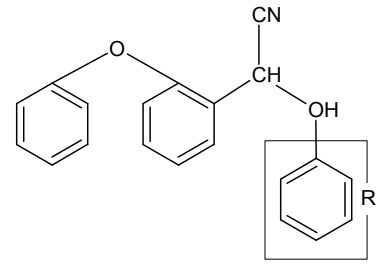
CH_3COOH



Hydroxy (3-Phenoxyphenyl) acetonitrile

Aromatic amine in alcohol and acid

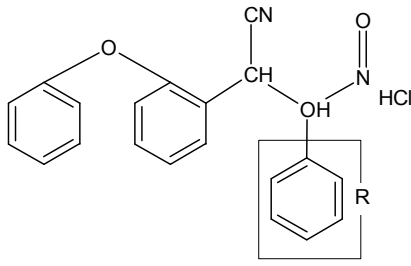
Stirr at 15ºC for 2 hrs and at rom temp. for 24 hrs.



(3-Phenoxy-phenyl)-phenylamino-acetonitrile
(1)

$NaNO_2$/HCl

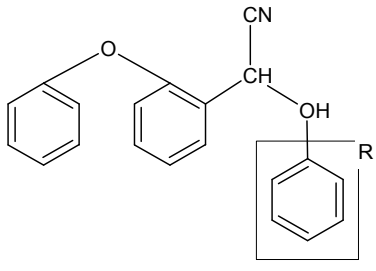
0-5ºC



4-Phenyl-(nitroso)-amino]-(3-Phenoxy-phenyl) acetonitrile hydrochloride
(2)

$CHCl_3$ Extraction

Ethanolic HCl 0ºC for 24 hrs



3-(4-Phenyl)-4-(3-phenyl) sydnonimine hydrochloride
(3)

Where R = Phenyl, o-Chloro phenyl, m-Chloro phenyl, p-Chloro phenyl, o-Tolyl, m-Tolyl, p-Tolyl, p-Fluorophenyl (I to VIII)

[(4-Phenyl)-(nitroso)-amino]-(3-phenoxy-phenyl) acetonitrile hydrochloride (2)

To a solution of [(4-phenyl) amino] (phenoxy-phenyl) acetonitrile (0.02 mole, 6.70 g) in ethanolic hydrochloride solution (25 mL), a solution of saturated sodium nitrite (4 g in 10 mL water) was added, maintaining temperature at 0ºC. The content was kept at 0-5^{o}C with constant stirring for an hour to form [(4-phenyl)-(nitroso)-amino]-(3-phenoxy-phenyl) acetonitrile hydrochloride. Yield 63%, m. p. 197ºC Anal. Calcd. for $C_{20}H_{16}O_2N_3Cl$: C, 65.66; O, 08.75; N, 11.49.Found C, 65.60; O, 08.72; N, 11.45%.

3-(4-Phenyl)-4-(3-phenoxy-phenyl) sydnonimine hydrochloride (3) (I)

[(4-Phenyl)-(nitroso)-amino]-(3-phenoxy-phenyl) acetonitrile was extracted in chilled chloroform. 20 mL ethanolic hydrochloride solution was added to chloroform extract and dry hydrogen chloride gas was passed for an hour through it, maintaining temperature below 5^{o}C. The reaction mass was kept at 0-5ºC for 24 hrs. to obtain crude sydnonimine hydrochloride. The product was recrystalised from methyl ethyl ketone. Yield 59%, m. p. >360^{o}C Anal. Calcd. for $C_{20}H_{18}O_2N_3Cl$: C, 65.30; O, 08.70; N, 11.42.Found C, 65.20; O, 08.71; N, 11.40%. IR : 1612 cm^{-1} due to –N-H and at 3333 cm^{-1} due to –N-H secondary amine. The absorption at 296 cm^{-1} is due to C – Cl aromatic. The aromatic and aliphatic C-H appear at 3050 cm^{-1} and 2920 cm^{-1}, respectively. The absorption at 752 cm^{-1} is due to one adjacent –C-H aromatic. The absorption at 1690 cm^{-1} is due to amide carbonyl stretch. The absorption at 1248 cm^{-1} is due to C-O-C ether stretching.

Other compoundss (**II-VIII**) were synthesized similar to **(3) (I).** Characterization data are present in Table 1.

RESULTS AND DISCUSSION

The synthesized sydnonimine hydrochloride derivatives deals with the biological evaluation. The tests are performed to evaluate biological activity against various microorganisms like bacteria, fungus and insects by different methods[9-12].

Table 2 indicates minimum concentration required for inhibiting the growth of *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pyogenes* and *Pseudomonas aeruginosa*. It can be seen that sydnonimine hydrochlorides **(I-VIII)** synthesized using aniline, o/p-chloroaniline, o/m-tolylamine and p-fluoroaniline, as aromatic amine show good activity against some test species. They required 50 ppm or less concentration for inhibition of bacteria. Compounds synthesized using aniline, o/m/p-chloroaniline, o/m/p-tolylamine and aniline as aromatic amines show moderate activity against some test

species. They required 50 to 100 ppm concentration of the compound while compounds synthesized using o/m/p-chloro aniline, o/p-tolylamine and p-fluoroaniline, as aromatic amine show poor activity or no activity up to 1000 ppm concentration of compound.

Table 2 : Bactericidal evaluation concentration compounds in μg/mL. (Standard drugs Gentamycin)

Comp.	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. pyogenus*
I	50	100	50	50
II	100	200	100	25
III	100	500	100	100
IV	200	500	100	25
V	100	1000	200	12.5
VI	50	100	50	50
VII	100	500	200	100
VIII	200	100	50	50
Gentamycin	0.05	1	0.25	0.5

Table 3 indicates minimum concentration required for inhibiting the growth of *Candida albicans*, *Aspergillus niger*, *Aspergillus clavatus*, *Aspergillus flavus*, *Sclerotium sclera*, *Sclerotium rolfsi*, *Collectotrichum logenarium*, *Rhizoctonia solani*, *Fusarium oxysporum. Alternaria burnsil* and *Alternaria solani.* It can be seen that sydnonimine hydrochloride **(I-VIII)** synthesized using aniline, o/m/p-chloroaniline, m/p-tolylamine and p-fluoroaniline, as aromatic amine show good activity against some fungi. They required 100 ppm or less concentration for inhibition of fungi. Compounds synthesized using aniline, o/m/p-chloroaniline, o/m/p-tolylamine and p-fluoro aniline, as aromatic amine show poor activity or no activity up to 500 to 1000 ppm or more concentration of compound.

Table 3 : Fungicidal evaluation concentration compounds in µg/mL. (Standard drug Nystatin)

Comp. (3)	Candida albican	*Aapergillus*			*Sclerotium*		*Collectotrichum logenarium*	*Rhizoctonia solani*	*Fusarium oxysporum*	*Alternaria*	
		niger	*clavatus*	*flavus*	*sclera*	*rolsfii*				*burnsil*	*solani*
I	500	200	200	1000	500	500	500	500	250	500	200
II	200	500	100	500	500	1000	1000	500	1000	>1000	1000
III	100	500	1000	500	500	500	500	500	1000	>1000	500
IV	50	200	500	200	200	500	500	1000	500	500	500
V	100	100	100	100	1000	1000	1000	100	500	250	1000
VI	100	500	1000	1000	500	500	500	500	250	500	500
VII	100	500	200	1000	500	200	200	1000	1000	>1000	1000
VIII	100	500	500	200	1000	1000	1000	500	200	500	500
Nyst.	100	100	100	100	100	100	100	100	100	100	100

Table 4 indicates minimum concentration required for inhibiting the growth of *Heliothus armygera*. It can be seen that sydnonimine hydrochlorides **(I-VIII)** synthesized using aromatic amines like, aniline, o/m/p-chloroaniline, o/m/p-tolylamine and p-fluoro aniline. Aniline shows good response on test species; o-chloroaniline shows good response on test species. m-chloroaniline shows good response on test species; p-chloroaniline shows good response on test species; o-tolylamine shows good response on test species; m-tolylamine shows moderate response on test species; p-tolylamine shows good response on test species and p-fluoroaniline shows good response on test species. Compound requiring 100 ppm or less concentration for inhibition of *Heliothus armygera* is said to have good response on test species. Compounds requiring 100 to 150 ppm concentration for inhibition of *Heliothus armygera* is said to give moderate response on test species. Compounds requiring 150 to 250 ppm or less concentration for inhibition of *Heliothus armygera* is said to have poor response on test species. Compounds requiring more than 250 ppm concentration is said to have no response to test species *Heliothus armygera*.

Table 4 : Insecticidal evaluation concentration compounds in μg/mL. (Standard drugs Cypermethrine)

Comp.	*Heliothus armygera*
I	075
II	050
III	050
IV	075
V	100
VI	125
VII	100
VIII	025
Cypermethrine	025

ACKNOWLEDGEMENT

The authors are grateful to Dr. D. R. Korat, Principal, Sir P. P. Institute of Science, Bhavnagar University, Bhavnagar for providing necessary research facilities. Authors are also thankful to Professor Dr. S. B. Mehta, Head, Dept. of Chemistry, Bhavnagar University, Bhavnagar.

REFERENCES

1. Belgium Patent, 518222, Dec., 12 (1962).
2. Bieber, ibid, 1055.
3. Bakar and Oils, Nature, **150**, 703 (1946).
4. A. A. F. Wasfy, Indian J. Chem., **42B**, 3102 (2003).
5. A. Robert and H. E. Russdt, J. Med. Chem., **15**, 335 (1972).
6. A. Topozada and R. D. O'brien, J. Insect Physiol., **13**, 691 (1967).
7. Bemard Fried and Joseph Sherma, Thin Layer Chromatography: Technique and Applications, Marcel Dekkar, Inc., New York and Basel (1982).
8. D. Nekvason, Zh. Org. Khim., **31 (4),** 591 (1995).
9. K. A. Thakar, J. Inst. Chemist, **49**, 1147 (1973).
10. S. A. Walksman, Microbial Antagonism and Antobiotic Substances, Commonwealth Fund, New York, 2nd Edition, **72** (1947).
11. R. N. Trigiano, Plant Pathology Concepts and Laboratory Exercise, CRC Press.
12. H. Meyer, Arch. Exptl. Pathol. Pharmacol. Sci., **57**, 895 (1982).

Accepted : 21.03.2009