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Synthesis and antibacterial activity of some new schiff bases and 2-Azetidinones containing iodohyydroxy biphenyl moiety

Subhash B. Junne[1]*, Archana B. Kadam[1], Sainath B. Zangade[1], Saheb L. Shinde[2] and Yeshwant B. Vibhute[1]

[1]Organic Synthesis Laboratory, P. G. Department of studies in Chemistry, Yeshwant Mahavidyalaya, Nanded (MS.) India.
[2]Department of Botany, Yeshwant Mahavidyalaya, Nanded (MS.) India.

Abstract
2-Hydroxy-5-phenylbenzaldehyde on iodination yielded 2-Hydroxy-3-iodo-5-phenylbenzaldehyde. This aldehyde on facile condensation with substituted aromatic amines in presence of catalytic amount of acetic acid to afford new series of Schiff bases. Further these Schiff bases on cyclocondensation reaction with chloroacetyl chloride afforded a biologically active 2-azetidinones derivatives. The structure of newly synthesized compounds characterized on the basis of elemental analysis and spectral data. The compounds prepared were tested against *Xanthomonas citri, Escherichia coli, Erwinia carotovora* and *Bacillus subtilis.* Some of these compounds showed potential antibacterial activity.

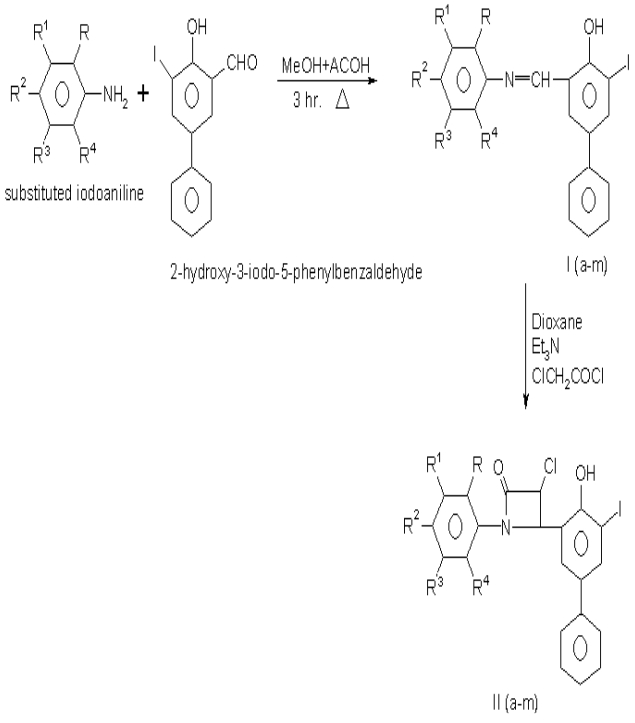
Keywords: 2-Hydroxy-3-iodo-5-phenylbenzaldehyde, Schiff bases, 2-azetidinones, antibacterial activity.

INTRODUCTION

The utility of Schiff bases lay in their usefulness as synthons in the synthesis of bioactive molecules such as 4-thiazolidinines, 2-azetidinones, benzoxazines, formazans, etc. Schiff bases are known to have useful biological activity like insecticidal [1], antibacterial [2], antituberculosis [3], antimicrobial [4] and anticonvulsant [5] activities. They also serve as a back bone for the synthesis of various heterocyclic compounds. The presence of azomethine and sulfonamide functional group is responsible for antimicrobial activity, which can be altered depending upon the type of substituent present on the aromatic rings.

Azetidin-2-one, a four-membered cyclic lactam (β-lactam) skeleton has been recognized a useful building block for the synthesis of a large number of organic molecules by exploiting the strain energy associated with it. Efforts have been made in exploring such new aspects of β-lactam chemistry versatile intermediates for their synthesis of aromatic β-amino acid and their derivatives, peptides, polyamines, polyamino alcohols, amino sugars and polyamino ethers [6]. The cyclic 2-azetidinone skeleton has been extensively used as a template to build the heterocyclic structure fused to the four membered rings. The β-lactam heterocycles are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity [7]. The most widely used antibiotics such as the penicillins, cephalosporins, carumonam, thienamycine, aztreonam and the norcardicins all contain β-lactum rings [8]. The long-term use of β-lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms [9]. Azetidinones are of great biological interest, especially as antitubercular [10], antibacterial [11 and 12], antifungal [13] and as anti-inflammatory, anticonvulsant activity [14]. As part of interest in heterocycles that have been explored for developing pharmaceutically important molecules, 4-thiazolidinones [15] and 2-azetidinones [16] have played an important role in medicinal chemistry, it was thought worthwhile to synthesize some new 2-azetidinones derivatives. All synthesized compounds were assessed for their antibacterial activity against *Xanthomonas citri, Escherichia coli, Erwinia Carotovora* and *Bacillus subtilis* using disc diffusion method [17]. Ampicillin, Stryptomycin was used as standard antibiotics for comparison. Their structures were confirmed by IR, HNMR and elemental analysis.

Scheme



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*Corresponding Author

Subhash B. Junne
Organic Synthesis Laboratory, P. G. Department of studies in Chemistry,
Yeshwant Mahavidyalaya, Nanded (MS.) India.

Email: sbjunne@gmail.com

R	R^1	R^2	R^3	R^4
H	H	NO_2	H	I
H	H	I	H	NO_2
H	H	I	H	Cl
H	H	Cl	H	I
I	H	CH_3	H	I
I	H	NO_2	H	I
CH_3	I	H	NO_2	H
H	H	COOH	H	I
I	H	COOH	H	I
I	H	H	NO_2	H
H	H	H	Cl	I
H	H	I	H	COOH
Cl	H	I	H	Cl

MATERIALS AND METHODS

All melting points were taken in open capillaries and are uncorrected. FT-IR spectra were recorded on perkin-Elmer-157 spectrophotometer instrument using KBr discs. ^{1}HNMR were taken on a Bruker WN-400 FTMHz NMR instrument using DMSO/$CdCl_3$ solvent and TMS as a internal standard (chemical shift in δ ppm). The purity of the compounds was monitored by thin layer chromatography.

Typical Procedure for Preparation of Schiff Bases

Equimolar quantity of 2-hydroxy -3- iodo -5-phenyl benzaldehyde (0.01 mmol) and substituted aromatic amines(0.01mmol) in requisite methanol (15-20 ml) containing few drops of acetic acid was refluxed for 3 hr. The resultant solution was cooled and poured in cold water. The separated solid was filtered, recrystallized from ethyl alcohol. Physical and analytical data is given in table 1.

Spectroscopic data of selected compounds

N-(4-nitro-6-iodo phenyl)-2-iodo-4-hydroxy biphenyl,5-yl azomethine (Ia)

Yield: 80%; Melting point: 155 ^{0}C. IR (KBr, cm^{-1}): 3015 (-OH), 1620, (C=N), 1500, 1470, 1400(C=C) 1420, 1560 (-NO_2). ^{1}H NMR (DMSO-d_6): 7.10-8.0 (m, 10H, Ar-H), 8.2 (s, 1H, N=CH), 13.2 (s, 1H, Ar-OH). MS (m/z): 570(M^+). Anald. Calcd. for $C_{19}H_{12}N_2O_3I_2$: C, 40.00, H, 2.01, N, 4.91 Found C, 40.05, H,2.18, N, 4.98.

N-(4-chloro-6-iodophenyl)-2-iodo-4-hydroxy biphenyl,5-yl Azomethine (Id)

Yield: 80%; Melting point: 110 ^{0}C. IR (KBr,cm^{-1}): 3019 (-0H), 1612 (C=N), 1466, 144, 1384, 1354 (C=C), ^{1}H NMR (DMSO-d_6): 7.23-7.90 (m, 10H, Ar-H), 8.15 (s, 1H=CH), 13.01 (s,1H.-OH), MS (m/z): 559, (M^+100), 432 (50), 305 (04), 277 (03), 241 (03), 139 (07), 86 (04). Anald. Calcd. for $C_{19}H_{12}NOCII_2$: C, 40.78, H, 2.14, N, 2.50 Found C, 40.70, H, 2.10, N, 2.54.

N-(2,6-di-iodo-4-methyl phenyl)-2-iodo-4-hydroxy biphenyl,5-yl azomethine (Ie)

Yield: 75%; Melting point: 120^{o}C; IR (KBr cm^{-1},): 3050 (-OH), 2910 (-CH_3), 1650 (C=N) 1490, 1410, 1390(C=C).^{1}HNMR (DMSO-d_6):; 2.1 (s, 3H,CH_3), 6.9-8.0 (m, 9H, Ar-H), 8.1 (s, 1H, N=CH). 13.2 (s, 1H, OH). MS (m/z): 665(M^+). Anald. Calcd. for $C_{20}H_{14}NOI_3$: C, 36.09, H, 2.10, N, 2.10 Found C, 36.14, H, 2.15, N, 2.16.

N-(3-iodo-5-nitro-2-methyl phenyl)-2-iodo-4-hydroxy biphenyl, 5-yl azomethine (Ig)

Yield: 72%; Melting point: 160^{0}C. IR(KBr,cm^{-1}): 3019(-OH), 1610(C=N), 1462, 1440, 1390, 1390, 1365(C=C), ^{1}HNMR (DMSO-d_6): 2.5 (s, 3H, CH_3),7.23-7.85 (m, 10H, Ar-H), 8.15 (s, 1H, =CH), 13.02 (s, 1H, OH), MS (m/z): 584(M^+). Anald. Calcd. for $C_{20}H_{14}N_2O_3I_2$: C, 18.39, H, 1.58,, N, 4.01 Found C, 18.42, H, 1.49,N, 4.06.

N-(4-carboxylic-6-iodo phenyl)-2-iodo-4-hydroxy biphenyl, 5-yl azomethine (Ih)

Yield: 78%; Melting point: 130 ^{0}C. IR (KBr,cm^{-1}): 3010-3215 (-OH), 1650 (C=N), 1740 C=O),1490, 1450, 1400, (C=C), ^{1}H NMR(DMSO-d_6): 7.0-1.1 (m, 10H, Ar-H), 8.3 (s, 1H, N=CH), 11.1 (s, 1H, OH), 13.2 (s, 1H, Ar-OH). MS (m/z): 559(M^+). Anald. Calcd. for $C_{20}H_{13}NO_3I_2$: C, 42.17, H, 2.28, N, 2.46 Found C, 42.22, H, 2.21, N, 2.41.

N-(2,6dichloro-4-iodo phenyl)-2-iodo-4-hydroxy biphenyl,5-yl Azomethine (Im)

Yield: 80%; Melting point: 75 ^{0}C; IR (KBr, cm^{-1}): 3015 (-OH), 1635 (C=N), 1520, 1475, 1400. ^{1}H NMR (DMSO-d_6), 7.-8.1 (m, 9H, Ar-H), 8.3 (s, 1H, N=CH), 13.2 (s, 1H, Ar-OH). MS (m/z): 594(M^+). Anald. Calcd. for $C_{19}H_{11}NOCl_2I_2$: C, 33.38, H, 1.85, N, 2.35 Found C, 38.32, H, 1.90, N, 2.41.

Typical Procedure for Preparation of 2-Azetidinones

A solution of Shciff base (0.01 mmole) in dry dioxane (50 ml) was added to a well stirred mixture of chloroacetyl chloride (0.012 mmole) and triethylamine (0.03 mmole) in dry dioxane at 0^{0}C. The reaction mixture was stirred further for 6 hr. Excess of dioxane was removed by evaporation and then residue poured into cold water. The separated solid thus obtain was filtered, washed with water and recrystallized from ethyl alcohol: 1-4 dioxane. Physical and analytical data is given in Table 1.

3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1-(2-iodo-4-nitrophenyl)azetidin-2-one (IIa):

Yield: 72%; Melting point: 234^{0}C; IR (KBr, cm^{-1}): 3325 (OH), 1730 (C=O), 1610, 1550, 1490 (C=C), 1510, 1370, (NO_2). ^{1}H NMR (DMSO-d_6): 2.5 (s, 1H, -CH), 4.2 (s, 1H, -CHCl), 7.3-8.5 (m, 10H, Ar-H), 13.1 (s, 1H, Ar-OH). MS (m/z): 646(M^+). Anald. Calcd for $C_{21}H_{13}N_2O_4CII_2$: C, 39.00, H, 2.01, N, 4.33 Found C, 39.08, H, 2.08, N, 4.36

3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1-(4-chloro-6-iodophenyl)azetidin-2-one (IId):

Yield: 68%; Melting point: 232^{o}C. IR (KBr,cm^{-1}): 3348 (OH), 1726 (C=O), 1600, 1579, 1577, 1490 (C=C). ^{1}H NMR (DMSO-d_6). 2.6 (s, 1H, -CH), 4.25 (s, 1H, -CHCl), 7.22-8.25 (m, 10H, Ar-H), 13.2 (s, 1H, ArH). MS (m/z): 636(M^+). Anal. Calcd for $C_{21}H_{13}NO_2Cl_2I_2$: C,39.62; H, 2.04, N, 2.20, Found C, 39.68; H, 2.09; N,2.12.

3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1-(2,6-di-iodo-4-mehthylphenyl)azetidin-2-one (IIe):

Yield: 65%; Melting point: 240^{o}C. IR (KBr, cm^{-1}): 3350 (OH), 2920 (-CH_3), 1725 (C=O), 1610, 1580, 1515(C=C). ^{1}H NMR (DMSO-d_6): 2.1 (d, 3H, CH_3), 2.4 (s, 1H, CH), 4.4 (s, 1H, CH), 7.0-8.2 (m, 9H, ArH), 13.3 (s, 1H, ArOH). MS (m/z): 741(M^+). Anal. Calcd for

$C_{22}H_{15}NO_2ClI_3$: C, 35.62, H, 2.02, N, 1.88. Found C, 35.67, H, 2.10, N,1.93.

3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1-(3-iodo-5-nitro-2-methylphenyl) azetidin-2-one (IIg):

Yield 68%; mp 246°C; IR (KBr,cm^{-1}): 3342 (-OH), 1728(C=O),1600, 1578, 1517,1448,(C=C). ^{1}H NMR (DMSO-d_6),; 2.6 (s,1H-CH), 4.25, (s,1H,CHCl), 7.20-8.22, (m,9H,Ar-H),13.2, (s,1H,Ar-OH), MS (m/z): 660(M$^+$). Anal. Calcd for $C_{22}H_{15}N_2O_4I_2Cl$: C,40.00, H, 2.27, N, 4.24, Found C, 40.05, H, 2.22, N,4.28.

3-chloro-4-(4-hydroxy-5-iodo biphenyl-3-yl)-1-(4-carboxylic-2-iodo phenyl) azetidin-2-one (IIh)

Yield 62%; mp 212°C; IR (KBr,cm^{-1}): 3355(OH), 1738 (C=O),1725 (C=O), 1615,1600, 1550 (C=C). ^{1}H NMR (DMSO-d_6),; 2.1, (s,1H-CH), 4.2, (s,1H-CHCl), 7.3-8.3 (m,10,Ar-H),11.1(s,1H-OH), 13.2 (s,1H,Ar-OH), MS (m/z): 645(M$^+$). Anal. Calcd for $C_{22}H_{14}NO_4I_2Cl$: C,40.93, H, 2.17, N, 2.17, Found C, 41.01; H, 2.23, N,2.22.

3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1-(2,6-dichloro-4-iodophenyl)azetidin-2-one (IIm)

Yield 72%; mp 204°C; IR (KBr,cm^{-1}), 3320(OH), 1725 (C=O),1615,1545,1490, (C=C). ^{1}H NMR (DMSO-d_6),; 2.2 (s,1H,-CH), 4.1 (s,1H,-CHCl),7.0-8.3 (m,9H,Ar-H), 13.1 (s,1H,Ar-OH), MS (m/z): 670(M$^+$). Anal. Calcd for $C_{21}H_{12}NO_2I_2Cl_3$: C,37.61, H, 1.79, N, 2.08, Found C, 37.68, H, 1.84; N,2.02.

Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity using *Xanthomonas citri, Escherichia coli, Erwinia Carotovora* and *Bacillus subtilis* as bacteria. The activity of these compounds was tested by disc diffusion method [17] at 200 ppm concentration using 5mm filter disc. Penicillin was used as a standard antibiotic as control for comparison. The zone of inhibition of compounds Ic, Id, Ie, If, Ii, Ik, Im, IIc, IId, IIe, IIf, IIi, IIk and IIm were measured and it showed significant antibacterial activity. The remaining other compounds showed moderate to less activity.

RESULTS AND DISCUSSION

Structures of compounds have been elucidated by elemental analysis, IR measurements. Schiff bases shows IR absorption peak at 1615-1530 cm^{-1} (C=N stretching). The azetidinones were characterized by their absorption bands at 1710-1673 cm^{-1} (C=O stretching) of β- lactum ring and band around 1572,1563,1524 due to aromatic stretching. All the compounds show NMR signals for different kinds of protons at their respective positions. Newly synthesized compounds were screened against four bacterial pahogens. The bacteria tested were *Xanthomonas citri, Escherichia coli, Erwinia carotovora* and *Bacillus subtilis.* It is clear from results presented in table-1 that the majority of compounds tested showed antibacterial activity but compounds like Id, Ii, Ik, Im, IIi, IIk and IIm were at par against all the bacteria tested except *Bacillus subtilis.*

Table 1. Analytical, physical data and antibacterial activity of compounds I (a-m) and II (a-m)

Entry	Molecular formula	M.P.°C	Yield %	Antibacterial Activity.			
				Xc.	E.coli	Ec.	Bs.
Ia.	$C_{19}H_{13}N_2O_3I_2$	155	80	05.00	04.00	05.03	00.00
Ib.	$C_{19}H_{13}N_2O_3I_2$	70	78	03.20	03.50	03.00	02.50
Ic.	$C_{19}H_{13}NOI_2Cl$	130	75	11.08	11.00	10.10	00.00
Id.	$C_{19}H_{13}NOI_2Cl$	110	80	20.01	21.80	19.05	00.02
Ie.	$C_{20}H_{15}NOI_2$	120	75	18.70	18.00	17.70	00.04
If.	$C_{19}H_{12}N_2O_3I_2$	90	70	12.00	10.00	11.20	00.02
Ig	$C_{20}H_{15}N_2O_3I_2$	160	72	07.00	06.50	06.90	00.05
Ih.	$C_{20}H_{14}NO_3I_2$	130	78	8.50	08.02	07.20	01.90
Ii.	$C_{20}H_{12}NO_3I_2$	180	70	20.90	21.80	20.02	00.01
Ij.	$C_{19}H_{13}N_2O_3I_2$	110	70	02.00	04.00	02.50	01.50
Ik.	$C_{20}H_{14}NO_3I_2$	120	78	20.70	21.08	19.10	04.00
Il.	$C_{20}H_{14}NO_3I_2$	80	82	03.50	04.00	03.50	00.02
Im.	$C_{19}H_{12}NOI_2Cl_2$	75	80	20.00	22.00	20.50	01.00
IIa.	$C_{21}H_{13}N_2O_4I_2Cl$	234	72	05.00	00.00	05.02	00.01
IIb.	$C_{21}H_{13}N_2O_4I_2Cl$	240	85	04.00	00.00	04.08	00.04
IIc.	$C_{21}H_{13}NO_2I_2Cl_2$	214	60	16.00	15.60	16.03	01.00
IId.	$C_{21}H_{13}NO_2I_2Cl_2$	232	68	13.00	13.02	12.50	10.00
IIe.	$C_{22}H_{15}NO_2I_2Cl$	240	65	11.00	15.00	12.00	00.00
IIf.	$C_{21}H_{12}N_2O_4I_3Cl$	256	63	10.50	09.00	10.50	06.00
IIg.	$C_{22}H_{15}N_2O_4I_3Cl$	246	68	01.00	02.00	01.00	07.00
IIh.	$C_{22}H_{14}NO_4I_2Cl$	212	62	01.70	02.00	01.60	00.00
IIi.	$C_{22}H_{13}NO_4I_3Cl$	260	66	20.60	21.70	18.90	05.00
IIj.	$C_{21}H_{13}N_2O_4I_2Cl$	236	68	08.20	10.00	08.50	00.00
IIk.	$C_{21}H_{13}NO_2I_2Cl_2$	244	66	20.02	21.02	19.10	00.00
IIl.	$C_{22}H_{14}NO_4I_2Cl$	218	64	05.20	06.00	05.00	03.00
IIm.	$C_{21}H_{12}NO_2I_2Cl_3$	204	72	21.80	22.40	23.50	00.05
Penicillin (200 ppm.)				21.00	22.00	19.00	23.00

CONCLUSION

Schiff bases and 2-azetidinones have been synthesized and tested for their antibacterial activity. Some of the compounds Id, Ii, Ik, Im, IIi, IIk and IIm were found to be nearly equal or more active than standard antibiotics used for comparison (Table 1). Hence, further study of antimicrobial activity may become fruitful.

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