Synthesis of Mannich Bases and Sulphides Derived from 5-(*p*-)-Chlorophenyl 1,3,4-Oxadiazol-2-thione

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A series of seventeen Mannich bases and some new sulphides have been prepared from 5-(*p*-)chlorophenyl-1,3,4-oxadiazol-2-thione. The site of the substituent in Mannich bases has been confirmed by stepwise synthesis, interconversion and spectral comparison with 2-alkylthio-5-(*p*-)chlorophenyl-1,3,4-oxadiazoles.

The hypoglycemic,^{1,2)} carcinostatic,³⁾ bacteriostatic,⁴⁾ diuretic,⁵⁾ antiviral,⁶⁾ antitubercular⁷⁾ and antifungal^{8,9)} inhibiting properties exhibited by cyclic compounds such as oxadiazoles, thiadiazoles and mercaptotriazoles have made them important chemotherapeutic agents. 5-Substituted 1,3,4-oxadiazol-2-ones are known to possess interesting biological property like antimycobacterial activity.^{9,10)} On this basis a study on oxadiazoles was considered to be of interest as they themselves may show pharmacodynamic properties. Compounds of the type (I) were subjected to Mannich reaction. The resulting 3-substituted-aminomethyl-5-substituted-1,3,4-oxadiazol-2-ones (II) as well as parent compounds (I) were found to be highly active against *Mycobacterium tuberculosis*^{9,10)} in animals and human beings.

A comparative study of oxo analogues (I) and 1,3,4-oxadiazol-2-thiones (III) has revealed that thio analogues are less reactive and more stable. Hence it was thought to improve the biological activity by exotic combination of groups obtainable from the Mannich reaction on III. The key intermediate 5-(*p*-)chlorophenyl-1,3,4-oxadiazol-2-thione was prepared by following the method of Young

and Wood¹¹⁾ and subjected to Mannich reaction by condensing them in ethanol with formaldehyde (40%) and various primary and secondary amines to give 3-substituted-aminomethyl-5-(*p*-)chlorophenyl-1, 3, 4-oxadiazol-2-thiones (IV). During the synthesis of Mannich bases it was observed that reaction of III with aliphatic primary and secondary amines was accomplished after 24 hr while heterocyclic secondary amines gave Mannich bases after 2~3 hr in freezing mixture except piperazine with which Mannich base was obtained immediately. The aromatic and heterocyclic primary amines gave Mannich bases within an hour; but with aliphatic and aromatic amines having hydroxyl groups such as diethanolamine and aminophenols, the Mannich bases were obtained after two days. The yield of Mannich bases with aminophenols was found to be very poor due to hydroxyl group attached to the benzene nucleus which reduces the basicity of compounds.

The site of the substituents of Mannich bases was confirmed by synthesis and interconversions. Compound III on condensation with formaldehyde and primary or secondary amine in ethanolic medium, afforded product (IV) which was hydrolysed with 10% HCl at room temperature in to parent compound (III). Several attempts were made to hydrolyse the compound (IV) in to (V) with 90% acetic acid by following the method of Vakula and Srinivasan¹²⁾ but were unsuccessful, always parent compounds (IV) were obtained

TABLE I

Type IV				
S. No.	R	R'	$\nu_{\max}$ in cm^{-1}	
1	(<i>p</i> -)Anisyl	H	1080	(Sharp and strong)
2	(<i>p</i> -)Tolyl	H	1090	(— do —)
3	(<i>p</i> -) <i>n</i> -Butylcarboxylate phenyl	H	1090	(— do —)
4	2-Pyridyl	H	1080	(— do —)
Type VII				
1	Carboxylic methyl	—	1060	(Sharp and weak)
2	Benzyl	—	1070	(— do —)

inspite of varying the reaction conditions. Mixed melting point with authentic 3-substituted aminomethyl-5-(*p*-)chlorophenyl-1, 3, 4-oxadiazol-2-thione (V) was undepressed. Synthesis of 2-alkyl-thio-5-(*p*-)chlorophenyl-1,3,4-oxadiazol (VII) from III with alkyl halide in ethanolic sodium hydroxide (10%) revealed that compound III exists in tautomeric structure (VI). These transformations are depicted in the above scheme.

The structure of Mannich bases was further proved by comparative study of infrared spectra of IV with those of 2-alkylthio 5-(*p*-)chlorophenyl-1,3,4-oxadiazoles (VII), obtained by reaction of III with alkyl halide in alkali. The IR spectra of IV revealed the presence of $\text{C}=\text{S}$ bands as sharp and strong peaks in the region $1050\sim 1090\text{ cm}^{-1}$ while 2-alkylthio-5-(*p*-)chlorophenyl-1, 3, 4-oxadiazoles (VII) showed sharp and weak bands in the same region. This gave an evidence for designating

the Mannich bases as 3-substituted aminomethyl derivatives. Absorption maxima of few compounds of the type IV and VII in the region $1050\sim 1090\text{ cm}^{-1}$ have been presented in Table I. Some of the compounds were tested as fungicide on *Aspergillus niger* and few of them showed significant activity. Presence of carboxyl group, ester group and halogens enhances the activity.

EXPERIMENTAL

All melting points are uncorrected.

5-(p-Chlorophenyl)-1,3,4-oxadiazol-2-thione (III). It was prepared by the method described by Young and Wood¹¹ in 72% yield, mp, 172°C (Rep.¹¹) $176\sim 8^\circ\text{C}$.

3-(n-Butylaminomethyl)-5-(p-chlorophenyl)-1, 3, 4-oxadiazol-2-thione. Compound III (0.5 g, 0.0025 mole) was dissolved in ethanol and treated with formaldehyde (0.5 ml, 40%). To this mixture *n*-butyl amine (0.25 g, 0.0025 mole) was added dropwise with swirling and the

content was left overnight in ice-mixture. The precipitated Mannich base was filtered and washed with little ethanol, yield (0.62 g, 86%). Crystallization with water-ethanol mixture afforded analytical sample, mp 120°C. *Anal.* Calcd. for $C_{13}H_{16}ClN_3OS$: C, 52.4; H, 5.38; N, 14.1. Found: C, 52.6; H, 4.9; N, 14.5.

3-Diethanolaminomethyl-5-(*p*-chlorophenyl-1,3,4-oxadiazol-2-thione). To a cold ethanolic solution of III (0.5 g, 0.0025 mole), formaldehyde (0.5 ml) was added and left in ice-mixture for half an hour. To this mixture a ethanolic solution of diethanolamine (0.27 g 0.0025 mole) was added slowly with swirling and left in ice-mixture for two days with occasional scratching. A white crystalline solid obtained which was filtered and washed with little ethanol, yield (0.5 g, 65%). Compound was crystallised with water-ethanol mixture, mp 150°C. *Anal.* Calcd. for $C_{13}H_{16}ClN_3O_3S$: N, 12.67. Found: N, 12.5.

1, 4-Bis(3-methylene-5-(*p*-chlorophenyl-1, 3, 4-oxadiazol-2-thione)piperazine. Piperazine (0.11 g, 0.0012 mole) and 5-(*p*-chlorophenyl-1,3,4-oxadiazol-2-thione (0.5 g, 0.0025 mole) were dissolved in ethanol separately and later was treated with formaldehyde (1 ml, 40%) and cooled. To this mixture solution of piperazine was added dropwise with swirling. A white pre-

cipitate obtained within few minutes which was left in ice-bath for an hour and filtered. The product was crystallised with ethanol, mp 225°C, yield (0.45 g, 72%). *Anal.* Calcd. for $C_{22}H_{20}Cl_2N_6O_2S_2$: C, 50.0; H, 3.7; N, 15.7. Found: C, 50.5; H, 4.1; N, 15.71.

4, 4'-Bis(3-methylene-5-(*p*-chlorophenyl-1, 3, 4-oxadiazol-2-thione) benzidine. I was prepared by the reaction of III (0.5 g, 0.0025 mole) with benzidine (0.23 g, 0.0012 mole) and formaldehyde (0.5 ml, 40%) in ethanol and keeping the mixture in freeze for 2~3 hr. Crystallization with acetone afforded analytical sample mp 190°C dec., yield (0.5 g, 64%). *Anal.* Calcd. for $C_{30}H_{22}Cl_2N_6O_2S_2$: C, 56.9; H, 3.4; N, 13.27. Found: C, 57.4; H, 3.7; N, 13.18.

Several Mannich bases were prepared by the procedure described above and their relevant data are recorded in Table II.

Hydrolysis of Mannich bases

Typical examples are given below.

I) Hydrolysis of the Mannich bases with 10% hydrochloric acid. 3-(*p*-Bromophenylaminomethyl-5-(*p*-chlorophenyl-1,3,4-oxadiazol-2-thione (0.25 g) was treated with hydrochloric acid (5 ml, 10%) and left to stand at room temperature, for half an hour. The product was filtered and washed with distilled water

TABLE II. ELEMENTAL ANALYSIS AND YIELD OF MANNICH BASES

S. No.	R	Yield (%)	Mp (°C)	Molecular formula	Calcd. (%)			Found (%)		
					C	H	N	C	H	N
1	Piperidinomethyl	65	123	$C_{14}H_{16}ClN_3OS$	54.3	5.17	13.57	54.6	5.3	13.8
2	(<i>p</i> -Chlorophenyl-aminomethyl	70	135	$C_{16}H_{11}Cl_2N_3OS$	51.14	3.1	11.9	51.5	3.3	11.8
3	(<i>p</i> -Bromophenyl-aminomethyl	62	154	$C_{16}H_{11}ClBrN_3OS$	45.4	2.8	10.6	45.6	3.1	10.5
4	(<i>p</i> -Anisylaminomethyl	68	132	$C_{16}H_{14}ClN_3O_2S$	55.25	4.03	12.08	55.6	4.35	11.6
5	(<i>p</i> -Phenethylaminomethyl	72	175	$C_{17}H_{16}ClN_3O_2S$	56.4	4.4	11.6	56.8	4.2	12.1
6	2-Pyridylaminomethyl	70	185	$C_{14}H_{11}ClN_3OS$	52.7	3.45	17.6	53.1	3.6	17.17
7	(<i>p</i> -Dimethylamino-phenyl-aminomethyl	65	125	$C_{17}H_{17}ClN_4OS$	56.6	4.7	15.5	56.8	5.1	15.4
8	(<i>p</i> -Tolylaminomethyl	78	180d	$C_{16}H_{14}ClN_3OS$	57.9	4.2	12.67	57.6	3.97	13.1
9	3-Hydroxy-4-carboxy-phenyl-aminomethyl	50	195	$C_{16}H_{12}ClN_3O_4S$	50.86	3.18	11.12	51.1	3.5	11.3
10	(<i>p</i> - <i>n</i> -Butoxycarbonyl phenyl-aminomethyl	70	165	$C_{20}H_{20}ClN_3O_3S$	57.5	4.8	10.06	57.75	4.7	10.2
11	(<i>p</i> -Isobutoxycarbonyl phenyl-aminomethyl	75	164	$C_{20}H_{20}ClN_3O_3S$	57.5	4.8	10.06	57.4	4.9	10.2
12	(<i>m</i> -Nitrophenyl aminomethyl	80	162	$C_{15}H_{11}ClN_4O_3S$	49.65	3.03	15.4	50.1	3.3	15.52

d=decompose.

three times and crystallised from ethanol. The mixed melting point with starting mercaptan was undepressed, 172°C.

II) *Hydrolysis of the Mannich bases with 90% acetic acid.* Two Mannich bases, (i) 3-(*p*-)bromophenyl-aminomethyl-5-(*p*-)chlorophenyl-1,3,4-oxadiazol-2-thione and (ii) 3-(*p*-)n-butoxycarbonyl phenylaminomethyl-5-(*p*-)chlorophenyl-1,3,4-oxadiazol-2-thione were tried to hydrolyse with 90% acetic acid following the method given by Vakula and Sriniwasan.¹²¹ After maintaining different reaction conditions, the parent compound was always obtained in each case. The mixed melting with parent compound was undepressed.

Preparation of 2-alkylthio-5-(p-)chlorophenyl-1,3,4-oxadiazol (VII)

As typical examples in this series the preparation of 1,2-bis(5-(*p*-)chlorophenyl-1,3,4-oxadiazol-2-thio)ethylene and 2-ethylthio 5-(*p*-) chlorophenyl-1,3,4-oxadiazol

are described below.

Procedure A

1,2-Bis(5-(p-)chlorophenyl-1,3,4-oxadiazol-2-thio)ethylene. A mixture of III (log, 0.005 mole), ethylene chloride (0.25 gn, 0.0025 mole) and fused sodium acetate (0.8 g, 0.01 mole) in ethanol (8 ml) was refluxed for 3 hr. The reaction mixture was poured in to cold water, filtered and washed with distilled water. Product was crystallised with water-ethanol mixture, yield (0.74 g, 70%), mp 222°C. *Anal.* Calcd. for C₁₈H₁₂Cl₂N₄O₂S₂: N, 12.4. Found: N, 12.6.

Procedure B

2-Ethylthio-5-(p-)chlorophenyl-1,3,4-oxadiazol. Compound III (0.5 g, 0.0025 mole) was dissolved in 10% ethanolic sodium hydroxide (5 ml) and to this solution of ethylbromide (0.26 g, 0.0025 mole) was

TABLE III.

S. No.	R	Yield (%)	Mp (°C)	Molecular formula	N(%)	
					Calcd.	Found
1	<i>n</i> -C ₃ H ₇	68	130 ^a	C ₁₁ H ₁₁ ClN ₂ OS	11.0	11.3
2	-CH ₂ C ₆ H ₅	60	155 ^a	C ₁₅ H ₁₁ ClN ₂ OS	9.26	9.53
3	-CH ₂ COOH	62	142 ^b	C ₁₀ H ₇ ClN ₂ O ₃ S	10.35	10.6
4	-CH ₂ CH ₂ COOH	52	95 ^b	C ₁₁ H ₉ ClN ₂ O ₃ S	9.8	10.1
5	-CH-COOH CH ₃	—	Gummy mass	C ₁₁ H ₉ ClN ₂ O ₃ S	—	—

^a Prepared from procedure A; ^b Prepared from procedure B.

TABLE IV.

Compound	Width of zone in control (mm)	Width of zone of inhibition in mm after 96 hr Concentrations used ^b		
		1: 1000	1: 10000	1: 100000
1	38	11	14	18
2	40	10	13	22
3 ^a	41	8	12	16
4 ^a	40	10	12	18
5	40	15	18	25
6	42	14	20	22
7	39	20	20	30
8	41	18	22	25
9	43	15	15	23
10	42	13	13	19

^a The S. No. of compounds corresponds to those recorded in Table III and rest-corresponds to those recorded in Table II.

^b No. of replications=3.

added. The whole mixture was refluxed for 3 hr and poured into cold water. The residue obtained was filtered and washed several times with distilled water, yield (0.4 g, 71%). Crystallization with ethanol afforded analytical sample mp 120°C. *Anal.* Calcd. for $C_{10}H_9ClN_2OS$: N, 11.64. Found: N, 11.5.

Other sulphides were also prepared by following the procedure A and B given above. The melting points, yields and other data of the compounds thus prepared are listed in Table III.

Fungicidal activity

Ten compounds were tested for their fungicidal action against *Aspergillus niger* by agar-plate technique¹³⁾ at three different concentrations namely 1: 1000, 1: 10,000 and 1: 100,000. At the close of incubation period, the width of the zone of the inhibition surrounding each test compound was noted. The result of this screening are recorded in Table IV.

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