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Attempt in the Synthesis of 2-[(2,6-Disubstitutedthiocarbamidophenyl)Amino] Benzeneacetic Acid and their Antimicrobial Study

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Heteroacyclic and Heterocyclic nucleus containing drugs showed remarkable and noticeable drug absorption, transmission and drug activity and effects; hence they created their own status in chemical, pharmaceutical, medicinal, agricultural and drug sciences. Thioamido, benzaimido heterocycles showed an assortment of significances, applications and importances in industrial, pharmaceutical, medicinal and drug chemistry. Considering all these facts into consideration it was thought interesting to synthesize Substitutedthiocarbamides, 2-[(2,6-Disubstitutedthiocarbamidophenyl)amino] benzeneacetic acid by interacting 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid,monosodium salt with various thiourea in isopropanol medium .The justification and identification of the structure of these newly synthesized compounds had been established on the basis of chemical characterization, elemental analysis, and through spectral data.

Key words: Substitutedthiocarbamides, 2[(2,6Disubstitutedthiocarbamidophenyl) Amino]Benzeneacetic Acid and Isopropanol.

Recently in this laboratory the synthetic applications of dicyandiamide and 1, 3-diformamido-thiocarbamide had been briefly explored[1]. As evident from structure of 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt, it possesses chloro, and carboxylo reactive sites for various reactions. As a wider program of this laboratory in the synthesis of nitrogen, sulphur and nitrogen and sulphur containing heteroacyclic and heterocyclic compounds the interactions of dicyandiamide with various thiourea and isothiocynates have been investigated in sufficient details [2-8]. Some of these compounds showed remarkable pharmaceutical and biological activities[9-13].

An exhaustive literature survey on thiocarbamides[3-6] and 2-[(2,6-Disubstitutedthiocar bamidophenyl) amino] benzeneacetic acid [14-16] showed that these nucleus containing drugs play an important role in pharmaceutical, medicinal and drug chemistry having remarkable pharmaceutical, medicinal and biochemical applications. By considering all these facts into consideration, the interactions of 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid,monosodium salt with various thiourea and sodium bicarbonate in isopropanol medium were investigated to isolate yet new series of 2-[(2,6-Disubstitutedthiocarbamidophenyl) amino] benzeneacetic acid. (Scheme 1) For investigating the medicinal and pharmaceutical applications. The antimicrobial activities of synthesized compounds were also studied.

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EXPERIMENTAL

The melting point of the all synthesized compounds was recorded using hot Paraffin bath. The carbon and hydrogen analysis were carried out on Carlo-Ebra 1106 analyzer. Nitrogen estimation was carried out on Colman-N-analyzer-29. IR spectra were recorded on Perkin Elmer Spectrometer in range 4000-400 cm^{-1} in KBr pellets. PMR spectra were recorded on Bruckner Ac 300 F Spectrometer with TMS as internal standard using $CDCl_3$ and DMSO–d_6 as solvent. The purity of compound was checked on silica Gel-G Pellets by TLC with layer thickness of 0.3 mm. All chemicals used were of AR-grade.

2-[(2,6-Dithiocarbamidophenyl)amino] benzeneacetic acid (3a)

A mixture of 2-[(2,6-dichlorophenyl) amino]benzeneacetic acid, monosodium salt (1) (0.1M), thiourea (2a),sodium bicarbonate(1gm) and isopropanol (40ml) was refluxed on boiling water bath for 4 hrs. During boiling suspended 2-[(2,6-dichlorophenyl) amino]benzeneacetic acid, monosodium salt went into the solution and the new product was found to be gradually separated out ,which on basification with dilute ammonium hydroxide afforded white crystals. It was filtered in hot conditions and recrystallized with aqueous ethanol to obtained (3a), yield74.34%, melting point 278 °C. (D)

Properties

It is pink, crystalline solid having melting point 278°C. (D). It gave positive test for nitrogen and sulphur. Desulphurised with alkaline plumbite solution. It formed picrate, melting point 295 ^{0} C.

Elemental analysis

C [(found 51.03%) calculated 51.33%], H [(found 4.11%) calculated 4.27%], N [(found 17.69%) calculated 18.71%], S [(found8.23%) calculated 8.55%].

IR Spectra

The IR spectra was carried out in KBr pellets and the important absorptions can be correlated as, (cm^{-1}) 3382.1 (N-H stretching), 2924.6 [C-H (Ar)] stretching, 1217 (C-N stretching), 1576 (=C=NH imino), 1010.1 (=C=S).

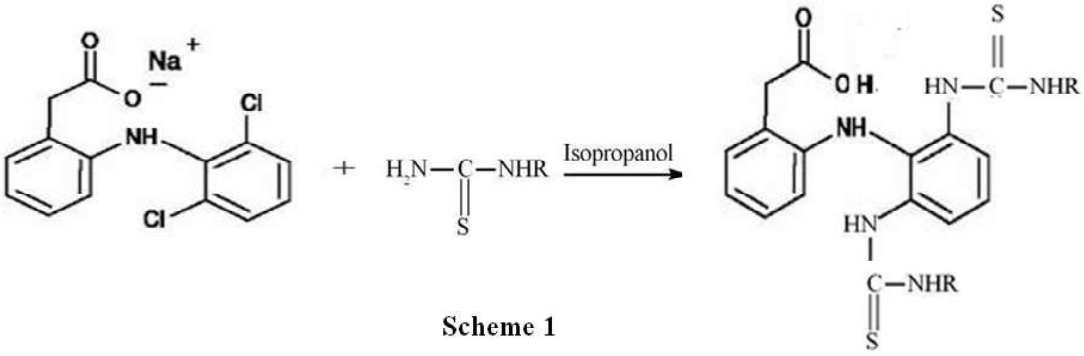
PMR Spectra

The spectrum was carried out in $CDCl_3$ and DMSO-d_6 .This spectrum distinctly displayed the signals due to Ar-H, protons at Δ 8.5551-8.016 ppm. Ar-NH protons at Δ 6.6928-6.6719 ppm, -NH_2 proton at Δ 3.8 ppm. Ar–CH_2 protons at Δ 7.8484-7.1293 ppm. –OH proton at Δ10.1521 ppm

Similarly, 2-[(2,6-Diphenylthiocarb-amidophenyl) amino] benzeneacetic acid (3b), 2-[(2,6 Dimethylthiocarbamidophenyl)amino] benzeneacetic acid (3c), 2-[(2,6-Diethylthiocar bamidophenyl)amino] benzeneacetic acid (3d) and 2-[(2,6-Diallylthiocar bamidophenyl) amino] benzeneacetic acid (3e) were synthesized by interacting phenylthiourea (2b), methylthiourea (2c), ethylthiourea (2d) and allylthiourea (2e) with 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (1) and sodium bicarbonate in isopropanol medium by above mentioned method and are mentioned in Table 1.

Antimicrobial and Antifungal Activities

The antimicrobial and antifungal activities[17-18] of all these compounds were screened by using cup-plate agar diffusion method in DMF,



Scheme 1

Where R = -H, -phenyl, -methyl,-ethyl, -allyl

using standard Co-Trimazin 25 µg/ml against gram positive and gram negative bacteria such as *E. coli, S. typhi, S. abony, P. aeruginosa* and *B. subtilis*. All compounds were also screened for their antifungal activities by using standard Greseofulvin (10µg/ml) against A. *niger* and C. *albicans*.

Cup-plate method

A medium used throughout the experiment was HI-Media (India make) having composition of [Pepton-5gm/lit, NaCl -5gm/lit,Yeast extract -1.5gm/lit, Agar powder -20gm/lit, pH - 7.4 ± 0.1]

The medium used for antibacterial and antifungal activities were prepared [N-agar for bacterial and Sabourands dextrose agar for fungi] by dissolving 26 gms of ingredients in one liter of distilled water and sterilized in autoclave at 121°C at 15 Ibs/inch pressure in an autoclave for 154 minutes. Then microbes were inoculated with requisite quantity to the medium at temperature 40-50°C and immediately poured the inoculate medium into sterilized petridishes to give a depth of 3-4 mm of uniform thickness. After solidification the well or holes were prepared by well borer. The dimethylformamide solution of the compound was added in sufficient amount to fill the well. Then it was kept at room temperature for 4 hrs as a pre-incubation and then plates of bacteria were inoculated for 18-24 hrs, at 36-38°C and all plates fungi were inoculated 48 hrs at 20-25 °C. After the period of inoculation, zones of inhibition were recorded around the wells. The results are cited in Table 2.

All the seven organisms studied are human pathogens; from the results it is clear that all the synthesized compounds showed remarkable and considerable antimicrobial activities. These thiocarbamides showed highly activity against *E. coli, S. typhi, S. abony, P. aeruginosa, B. subtilis* While inactive against *A. niger* and *C. albicans.* Hence study of these compounds is required in biochemical and medicinal directions. From the above data it is concluded that this compounds showed remarkable antibacterial activity that antifungal activity. *S. typhi* causes typhoid while *E. coli* causes diarrhoea and *S. abony* causes pus formation. It is observed from literature survey of medicinal sciences that in the last two decades the patients of typhoid and diarrhoea throughout the world are common. Lower drugs of typhoid are now totally rejected and higher drugs are now given to the patients. As newly synthesized thiocarbamides showed remarkable and considerable activities so these compounds can be used as alternative for the treatment of diseases caused by the above mentioned pathogens only if they do not have toxic and other side effects after the details study. The potency of the drug is increased due to substitution of thiocarbamido moiety on the previous drug.

Table 1.

S. No.	Expt. No.	"4-(p-Substitutedthiocarbamidophenyl)-N, N-dimethyl-3-pyridin-2-yl-propan-1-amine."	Yield %	m.p. °C
3b	2	Phenyl	79.97	178
3c	3	Methyl	80.65	192
3d	4	Ethyl	82.57	158
3e	5	Allyl	79.43	127

Table 2.

Comp. No	S.*typhi* (mm)	E.*coli* (mm)	S. *abony* (mm)	P.*aeruginosa* (mm)	B. *subtilis* (mm)	A. *niger* (mm)	C. *albicans* (mm)
3a	1.3	1.1	1.3	0.9	0.5	-	-
3b	1.9	1.7	1.9	1.2	1.3	-	-
3c	1.5	1.2	1.2	0.8	0.7	-	-
3d	1.2	1.0	0.7	0.7	0.7	-	-
3e	1.7	1.3	1.4	1.1	0.9	-	-

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