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Synthesis, Characterization and Biological Activities of Some New Hypophosphorous Adducts of Acid Hydrazones Derived from 2, 5-Dichloroanilidoacetohydrazide

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ABSTRACT

A new series of hypophosphorous adducts of acid hydrazones have been synthesized by the reaction of 2, 5-dichloroanilidoaceto hydrazide with various Carbonyl Compounds in 42% to 69% yield. Newly synthesized compounds have been tested for their anti-bacterial activity against gram positive bacteria *S.albus*, *S.aureus* and gram negative bacteria *E.coli* and *Pseudomonas piosineus*. The compound ***1, 4, 11, 12, 13*** *and* ***15*** shown significant activities and compounds *2, 3, 7, 8 and 9* have shown moderate activity. The same compounds were tested for their anti-fungal activity against *Candida albicans, Aspergillus niger and Alternaria alternata* at concentration of 30 mg/ml using Savored dextrose agar media. The compound ***3, 12, 14***, ***15*** shown significant activities and compound *1, 2, 4, 10, 16 and 17* have shown moderate activity against *Candida albicans and Aspergillus niger.* All the other compounds did not show significant activity against the fungi at the concentration used.

Keywords: Malonic ester, dianilide, acid hydrazides, hydrazones, hypophosphorous adducts.

INTRODUCTION

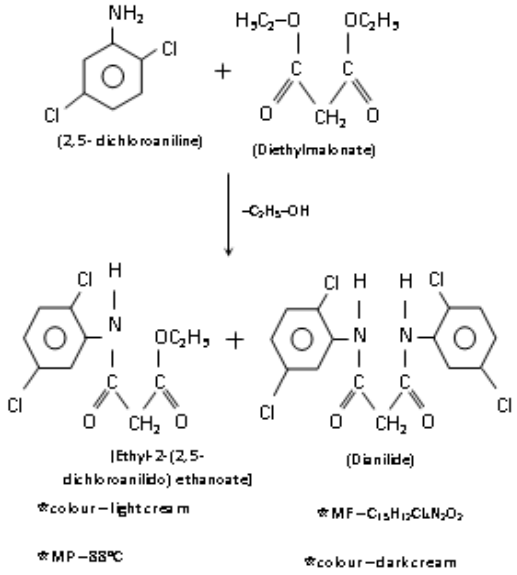
Acid hydrazones and their condensation products possessing an azometine -NHN=CH- proton constitute an important class of compounds for new drug development. In the past several years, numerous compounds with diverse structural features have been reported. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. Hydrazides, hydrazones and their adducts have displayed diverse range of biological properties such as potential biological activities[1-12], anti-viral[13-19], anti-tuberculosis[20-22], anti-tumor [23-28], cardiovascular[29], anti-fungal[30], anti-convulsant[31-34], anti-helminthic[35], anti-leprotic[36], anti-malerial[37-38], anti-depressant[39], analgesic[40], leishmanicidal[41], vasodilator[42] and anti- Inflammatory[43-47] activities. Therapeutic protocols for the treatment of HIV infection are mainly based on the combined use of reverse transcriptase, protease, and more recently, of cell fusion and entry inhibitors. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, the rapid emergence of resistant variants, often cross-resistant to the members of a given class, limits the efficacy of existing antiretroviral drugs. Therefore, it is critical to develop new agents directed against alternate sites in the viral life cycle, anti-cancer[48-56], and anti-HIV[57-64]. Moreover, many selectively chloro-substituted organic compounds show peculiar pharmacological and agrochemical properties. The work reported herein was aimed at the preparation of some new hypophosphorous adducts of acid hydrazones with anticipated biological activities.

EXPERIMENTAL

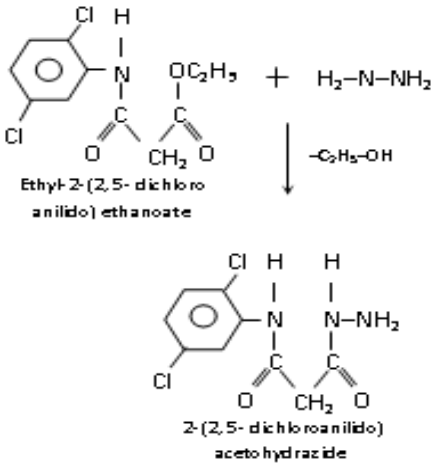
General

Anhydrous solvents and all reagents were purchased from, Sigma-Aldrich, B.D.H., Excel-R, Extra pure E. Merk quality, Acros or Carlo Erba. Reactions involving air or moisture-sensitive compounds were performed under a nitrogen atmosphere using oven-dried glassware and syringes to transfer solutions. Melting points were determined using an electro thermal melting point or a Köfler apparatus and are uncorrected. Infrared (IR) spectra were recorded as thin films or nujol mulls on KBr plates with a Perkin-Elmer-781 IR or 983 -Spectrophotometer and are expressed in ν (cm-^{1}). Nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were determined in $CDCl_3$/DMSO-d_6 (in 3/1 ratio) or DMSO-d_6 and were recorded on a Varian XL-200 (200 MHz) or a Varian VXR-300 (300 MHz). Chemical shifts (δ scale) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) used as internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; brs, broad singlet; dd, double doublet. The assignment of exchangeable protons (-O*H* and -N*H*) was confirmed by addition of D_2O. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel, F-254 plates. For flash chromatography Merck Silica gel-60 was used as stationary phase with a particle size 0.040-0.063 mm (230-400 mesh ASTM). Elemental analyses were performed on a Perkin-Elmer-2400 spectrometer, and were within ±0.5% of the theoretical values.

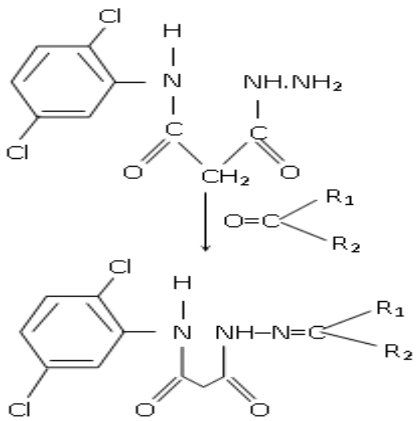
Scheme – I



Scheme –II



Scheme – III



Synthesis of Ethyl-2-(2, 5-dichloroanilido) ethanoate [1]:

Diethylmalonate (20ml) and 2, 5-dichloroaniline (10ml) was refluxed for forty five minutes in a round bottomed flask fitted with an air condenser of such a length (14") that ethanol formed escaped and diethylmalonate flowed back into the flask. Contents were cooled, ethanol (30 ml) was added, when malon-2, 5-dichlorodianilide separated out. It was filtered under suction. The filtrate was poured on to crushed ice (Ca160g) and stirred when ethyl-2-(2, 5-dichloroanilido) ethanoate precipitated as green mass. On recrystallization from aqueous ethanol (50%), ester was obtained as white crystals **(Scheme I).** Yield: 82%, M. P.: 89^0C, M. W.: 276. Anal. Calculation for $\boldsymbol{C_{11}H_{11}N_1O_3Cl_2}$: Found: C 47.7, H: 4.0, O: 17.2, N: 5.1, Cl: 25.4, Calcd. C: 47.8, H: 4.0, O: 17.4, N: 5.1, Cl: 25.7. *IR [KBr]* V_{max} Cm^{-1} : 1665-1660 [C=O diketone], 1290 [-O- Ester], 760-755 [2,5-disubstituted benzene], 1090 [C-Cl Stretching], 1590, 1520 , 1440 [C=C ring stretching], 3150 [N-H Stretching], 3040[C-H aromatic], 1330-1322 [C-H Stretching]. *PMR (DMSO):* δ 4.42 (2H, s, CO-CH_2-CO), 4.0 (2H, s, NH_2), 7.4-8.6 (3H, m, Ar-H), 9.2 (1H, s, CO-NH D_2O exchangeable), 10.6 [1H, s, Ar-NH D_2O exchangeable].

Synthesis of 2-(2, 5-dichloroanilido) acetohydrazide [2]:

Ethyl-2-(2, 5-dichloroanilido) ethanoate (9.54 gm; 0.03 mol), ethanol (10 ml) and hydrazine hydrate (15 ml; 80%) were mixed together and stirred for forty five minutes. There were evolution of heat and reaction was spontaneous after 30 minutes, 2-(2, 5-dichloroanilido) acetohydrazide was filtered under suction and recrystallised from ethanol in silver white crystals **(Scheme II).** Yield; 82%, MP = 172°C, MW 262: Analytical calculation for $\boldsymbol{C_9H_9N_3O_2Cl_2}$: Calculated ; N 09.04 ,C 41.32, O 10.33, Cl 15.28, Found; N 09.01, C 41.30, O 10.31, Cl 15.27 IR [KBr] V_{max} cm^{-1}**:** 3160 [N-H Stretching], 3048 [C-H aromatic], 1660 [C=O diketone], 1430 [C-Cl aromatic], 1595, 1520, 1445 [C=C ring stretching]. NMR Spectra (δ DMSO): 2.44 (2H, s, CH_2), 3.2 (3H, s, CH_3), 4.22-4.32 (1H, t, N-H), 7.2-7.6 (3H, m, ArH).

Synthesis of new acidhydrazones [3]:

2-(2, 5-dichloroanilido) acetohydrazide (.001 mol) and (.001 mol) of aromatic aldehyde or ketone (carbonyl compound) dissolved in absolute alcohol and added 2-drops of conc. H_2SO_4 and stirred for 20-25 minutes. It was filtered under suction and recrystallized from hot ethanol. Synthetic strategy has been out lined in scheme I, II & III. Mechanism for the formation of acid hydrazones is given in chart-I.

IR absorption band (cm^{-1}): 3150 (N–H stretching), 2960–2970 (C–H aliphatic), 1665–1660 (C=O Ketone), 785–780 (C–Cl Stretching), 760-755 (2, 5-disubstituted benzene), NMR spectra (δ DMSO), 2.25 (2 H, s, CH_2), 4.21 (1 H, s, NH), 6.95–7.2 (10 H, m, ArH).

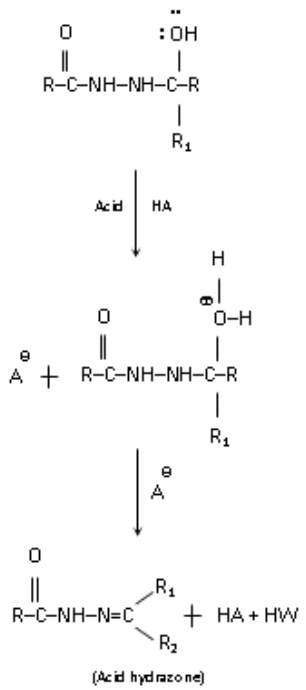


Chart – I: Mechanism of new acidhydrazones

BIOLOGICAL EVALUATION

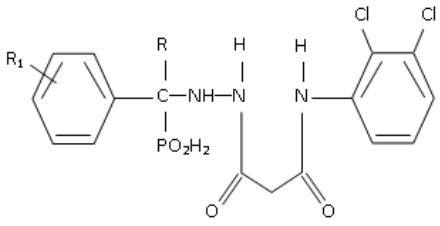
Anti-bacterial activity

Newly prepared hypophosphorous adducts of acid hydrazones were screened for their anti-bacterial activity against the gram positive bacteria *S. albus, S. aureus* and gram negative bacteria *E.Coli* and *Pseudomonas piosineus* by agar plate disc diffusion method at 30 µg/mL concentration. *Ampicillin and tetracycline* were used as a reference compounds. The compound (***1, 4, 11, 12, 13***, ***15***) shown significant activities and compound (*2, 3, 7, 8, 9)* have shown moderate activity.

Anti-fungal activity

The same compounds were tested for their antifungal activity against *Candida albicans, Aspergillus Niger and Alternaria alternata* at concentration of 30 mg/ml using Savored dextrose agar media. The compound (***3, 12, 14***, ***15)*** shown significant activity and compound (*1, 2, 4, 10, 16 and 17) have* shown moderate activity against *Candida albicans and Aspergillus niger.* All the other compounds did not show significant activity against the fungi at the concentration used.

Reaction conditions for the formation of new hypophosphorous adducts of acidhydrazones.



(i) Quantity of acidhydrazone = 0.001 mol.

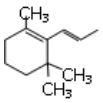
(ii) Quantity of hypophosphorous acid = 3.0 g

(iii) Quantity of absolute alcohol = 20 ml.

(iv) Hours of heating = 3.5 hours.

(v) Solvent for crystallization – ethanol.

Table – I: Physical Characteristics of Acidhydrazones

S.N.	*Acidhydrazones*	*Qtty (g)*	R_1	R_2	*MP (°C)*	*Yield (%)*	*Formula wt.*	*Mol. formula*	*Colour*
01.	Benzaldehyde-2-(2,5-dichloroanilido) acetohydrazone	0.416	H	Ph	251	63	416	$C_{16}H_{16}O_4N_3Cl_2P$	White
02.	Vanilline-2-(2,5-dichloroanilido) acetohydrazone	0.462	H	Ph < OMe (3), OH (4)	229	61	462	$C_{17}H_{18}O_6N_3Cl_2P$	White
03.	5-chloro Salicylaldehyde -2-(2,5-dichloroanilido) acetohydrazone	0.468	H	Ph < OH (2), Cl (5)	237	54	467.5	$C_{16}H_{16}O_5N_3Cl_3P$	White
04.	5-Bromo Salicylaldehyde -2-(2,5-dichloroanilido) acetohydrazone	0.512	H	Ph < OH (2), Br (5)	221	50	512	$C_{16}H_{16}O_5N_3Cl_2BrP$	Silver White
05.	2-Nitro Vanilline-2-(2,5-dichloroanilido) acetohydrazone	0.508	H	Ph < NO_2 (2), OCH_3 (3), OH (4)	234	67	508	$C_{17}H_{18}O_8N_4Cl_2P$	Cream
06.	O-Nitrobenzaldehyde-2-(2,5-dichloroanilido) acetohydrazone	0.462	H	Ph – NO_2 (2)	244	56	462	$C_{16}H_{16}O_6N_4Cl_2P$	White
07.	2-Nitro-5-Bromo Vanillin -2-(2,5-dichloroanilido) acetohydrazone	0.587	H	Ph < NO_2 (2), OMe (3), OH (4), Br (5)	240	45	587	$C_{17}H_{17}O_8N_4Cl_2BrP$	Cream
08.	3,5-dichloro-2-hydroxy benzaldehyde-2-(2,5-dichloroanilido) acetohydrazone	0.502	H	Ph < OH (2), Cl (3), Cl (5)	230	66	502	$C_{16}H_{15}O_5N_3Cl_4P$	White
09.	3-Nitro-6-hydroxy acetophenone-2-(2,5-dichloroanilido) acetohydrazone	0.492	Me	Ph < NO_2 (3), OH (6)	235	46	492	$C_{17}H_{18}O_7N_4Cl_2P$	Cream
10.	Acetone-2-(2,5-dichloroanilido) acetohydrazone	0.368	Me	Me	251	41	368	$C_{12}H_{16}O_4N_3Cl_2P$	Cream
11.	2-Chlorobenzaldehyde -2-(2,5-dichloroanilido) acetohydrazone	0.452	H	Ph – Cl (2)	239	62	451.5	$C_{16}H_{16}O_4N_3Cl_3P$	White
12.	4-N,N-bis-2'-cyanoethylamino benzaldehyde-2-(2,5-dichloroanilido) acetohydrazone	0.538	H	Ph – N – $(CH_2 – CH_2 – CN)_2$	233	69	538	$C_{22}H_{24}O_4N_6Cl_2P$	Light brown
13.	2-Methyl-4-N-N-bis-2'-cyanoethyl aminobenzaldehyde-(2,5-dichloroanilido) acetohydrazone	0.552	H	Ph < CH_3 (2), N $(CH_2 – CH_2 – CN)_2$ (4)	240	43	552	$C_{23}H_{26}O_4N_6Cl_2P$	Brown
14.	2-Methoxy-4-N-N-bis-2'-cyanoethylamino benzaldehyde(2,5-dichloroanilido) acetohydrazone	0.568	H	Ph < OCH_3 (2), N $(CH_2 – CH_2 – CN)_2$ (4)	248	63	568	$C_{25}H_{24}O_5N_6Cl_2P$	Brown
15.	Acetophenone-2-(2,5-dichloroanilido) acetohydrazone	0.430	Me	Ph	220	52	430	$C_{17}H_{18}O_4N_3Cl_2P$	White
16.	Salicylaldehyde-2-(2,5-dichloroanilido)aceto hydrazone	0.433	H	Ph – OH (2)	244	48	433	$C_{16}H_{17}O_5N_3Cl_2P$	White
17.	Anisicaldehyde-2-(2,5-dichloroanilido) acetohydrazone	0.447	H	Ph – OCH_3 (2)	224	55	447	$C_{17}H_{19}O_5N_3Cl_2P$	Yellow
18.	β-Ionone -2- (2, 5-dichloroanilido) acetohydrazone	0.504	Me		232	42	504	$C_{22}H_{32}O_4N_3Cl_2P$	Buff

RESULTS AND DISCUSSION

Hypophosphorous adducts of various acid hydrazones have been synthesized by the reaction of 2-(2, 5-dichloroanilido) acetohydrazide with various Carbonyl Compounds in 42% to 69 % yield. Hydrazonephosphorous adducts are white, brown and yellow colour solids, having high melting points. The structure of all the compounds are confirmed by IR, PMR, and Mass spectral data and are further supported by correct elemental analysis. Newly synthesized compounds have been tested for their *antibacterial activity* against gram positive bacteria *S. albus, S. aureus* and gram negative bacteria *E.Coli* and *Pseudomonas piosineus*. The compound (***1, 4, 11, 12, 13***, ***15***) shown significant activities and compound (*2, 3, 7, 8, 9)* have shown moderate activity. The same compounds were tested for their *antifungal activity* against *Candida albicans, Aspergillus niger and Alternaria alternata* at concentration of 30 mg/mL using savored dextrose agar media. The compound (***3, 12, 14***, ***15)*** shown significant activities and compound (*1, 2, 4, 10, 16 and 17) have* shown moderate activity against *Candida albicans and Aspergillus Niger*. All the other compounds did not show significant activity against the fungi at the concentration used.

CONCLUSION

Newly synthesized compounds have been tested for their ***antibacterial activity*** against gram positive bacteria *S. albus, S. aureus* and gram negative bacteria *E.coli and Pseudomonas piosineus* by agar plate disc diffusion method at 30 µg/mL concentration. *Ampicillin and tetracycline* were used as a reference compounds. The compound (***1, 4, 11, 12, 13***, ***15***) shown significant activities and compound (***2***, ***3, 7, 8***, ***9)*** have shown moderate activity. The same compounds were tested for their ***antifungal activity*** against *Candida albicans, Aspergillus niger and Alternaria alternata* at concentration of 30 *albicans and Aspergillus niger.* All the other compounds did not show significant activity mg/mL using Savored dextrose agar media. The compound (***3, 12, 14***, ***15)*** shown significant activities and compound (*1, 2, 4, 10, 16 and 17)* have shown moderate activity against *Candida* against the fungi at the concentration used.

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