Hydrazonoyl Halides: Their Versatile Biological Activities

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Abstract: The various biological activities namely anthelmintic, antiarthropodal, antiviral, antimicrobial, herbicidal, antisarcoptic, acaricidal, insecticidal and miticidal activities exhibited by the hydrazonoyl halides are surveyed. Also, the uses of such halides as pesticides, weed controlling and antihypertensive agents as well as lipoxygenase and cyclooxygenase inhibitors are presented. Furthermore, their contact dermatitis and phytotoxicity effects are pointed out in addition to their metabolic fate.

Keywords: Hydrazonoyl halides, biological activities, metabolism.

1. INTRODUCTION

Hydrazonoyl halides **1** are those compounds which have the characteristic function -C(X):NNH-, where X is a halogen group (e.g. Br or Cl). They are structurally related to hydrazonoic acids **2** in the same way as the imidoyl halides **3** are related to imidoic acids **4**.

1, RC(X)=NNHR' **2, RC(OH)=NNHR'**

3, RC(X)=NR' **4, RC(OH)=NR'**.

The first hydrazonoyl halide was described by Fisher shortly before the begining of the 20th century [1]. Since that time an increasing flow of work has appeared on the chemistry of such a class of compounds so that the output of published work recorded a peak of 261 papers and 53 patents in the eighties. The interest in the chemistry of such halides is a consequence of the fact that they undergo a wide variety of reactions which provide routes to a myriad of both heterocyclic and acyclic compounds. In addition, diverse biological activities such as anthelmintic, antiviral, antiarthropodal, antimicrobial, fungicidal, herbicidal, antisarcoptic, insecticidal, pesticidal, acaricidal, miticidal, etc., have been found to be associated with hydrazonoyl halides. In recent years, interest in the chemistry of this class of compounds has been renewed because of the development of novel synthetic routes and their use as versatile synthons for other compounds that found many applications in both industrial and pharmaceutical fields. At present there are ten review articles by Shawali *et al.* [2-11] covering the various aspects of the chemistry of such halides and their utility in synthesis of heterocycles, Another review by Butler and Scott outlined intermolecular and intramolecular substitution reactions of such halides [12]. In addition, an earlier summary dealing with the chemistry of these compounds had been incorporated by Ulrich in his review of imidoyl chlorides that appeared in 1968 [13]. No comprehensive review on the various biological activities of hydrazonoyl halides has appeared hitherto.

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The goal of the present review is to bring to the reader's attention the scope of the biological activities of hydrazonoyl halides. The literature is covered from 1968 up to mid of 2008. During this period more than 1750 articles and 150 patents making reference to the chemistry and applications of the title compounds have appeared. We hope that this review will stimulate the interest of both chemists and biologists in exploring further the chemistry of such compounds and their biological applications.

2. NOMENCLATURE

The nomenclature applied to hydrazonoyl halides has over the years been somewhat confusing. For example, the following compound was cited in literature under the names indicated below:

$C_6H_5C(Cl)=NNHC_6H_5$

α-Chlorobenzylidene phenylhydrazine

Benzoyl chloride N-phenylhydrazone

N-Phenyl benzhydrazidoyl chloride

α-Chlorobenzaldehyde phenylhydrazone

N-Phenyl benzenecarbohydrazonoyl chloride.

In this review, it is intended to adhere to the nomenclature rules adopted by Chemical Abstracts. According to the latter, the name of a given hydrazonoyl halide, in the absence of higher function or more preferred compound class, is derived from the parent acid by functional group replacement nomenclature. The suffixes appended to the names of molecular skeletons of carboxylic acid, hydrazonoic acid and the corresponding hydrazonoyl halide are as follows:

General Formula	RC(OH)=O	RC(OH)=NNH_2	RC(X)=NNH_2
Suffix	Oic Acid	Hydrazonoic acid	Hydrazonoyl halide
	Carboxylic acid	Carbohydrazonoic acid	Carbohydrazonoyl halide

To illustrate the application of these rules of nomenclature, the following examples are given:

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$CH_3C(Br)=NNHC_6H_4NO_2$-4

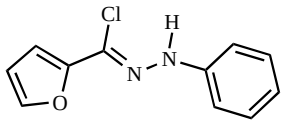
N-(4-Nitrophenyl) ethanehydrazonoyl bromide

4-$BrC_6H_4C(Cl)=NNHC_6H_5$

N-Phenyl 4-bromobenzenecarbohydrazonoyl chloride

$CH_3COC(Cl)=NNHCOC_6H_5$

N-Benzoyl 2-oxopropanehydrazonoyl chloride



N-Phenyl furan-2-carbohydrazonoyl chloride

In the presence of other groups that have priority to hydrazonoic acid group, the hydrazonoyl halide is named as a hydrazono derivative of the parent compound and this is illustrated by the following two examples.

$HOOC-C(Cl)=NNHC_6H_5$

N-Phenylhydrazono-chloroacetic acid

$C_2H_5OCO-C(Br)=NNHCONH_2$

Ethyl N-[(aminocarbonyl)hydrazono]bromoacetate

Also, when the hydrazonoyl halide residue (-C(X):NNH-) is a part of a more preferred class, it is named as halo derivative of the parent compound of such a class. For example, the halide ($C_6H_5N=N-C(Cl)=NNHC_6H_5$), as it belongs to the class of formazans (R-N=N-CH=NNHR') which is ranked highest of all nonfunctional nitrogen compounds, below imines but above nitrogen heterocycles, it is thus named as 3-chloro-1,5-diphenylformazan.

The various types of hydrazonoyl halides whose biological effects were explored are listed in Table **1**.

3. BIOLOGICAL ACTIVITIES

The patent literature contains a large number of hydrazonoyl halides that were reported to have various biological effects. Because of the diversity of structures covered, the discussion is presented according to the biological activity rather than chemical structure of the hydrazonoyl halide.

3.1 Contact Dermatitis

N-Phenyl benzenecarbohydrazonoyl chloride **IA** was reported to cause severe dermatitis in human [14]. Out of 6 people, five-chemistry students were affected following a single contact. The clinical picture of the dermatitis was characterized by a biphasic course. Circumscribed slight lesions, developing usually within one day in directly affected areas were followed after 4 to 12 days by generalized widespread erythema and edema with papules and vesicles [14].

IA, Ar-C(Cl)=NNHAr', Ar = Ar' =C_6H_5

3.2. Anthelmintic Activity

N-phenyl 4-methylbenzenecarbohydrazonoyl chloride **IB** was the first candidate of hydrazonoyl halides that proved effective against gastrointestinal nematodes and cestodes of ovines following a single oral dose of 30-50 mg/kg [15-19]. The sheep developed mild diarrhea and anorexia 10 days after treatment which lasted for 2-4 days, after which the sheep acquired their normal health. No ill signs were observed one week after treatment. N-(4-Chlorophenyl) 4-methoxybenzene-carbohydrazonoyl chloride **IC** has also been found to be an effective potent anthelmintic compound [20].

IB 4-$MeC_6H_4C(Cl)=NNHC_6H_5$

IC 4-$MeOC_6H_4C(Cl)=NNHC_6H_4Cl$-4

In attempt to elucidate the relationship between structure and anthelmintic activity (SAR), Rector and coworkers [21] prepared a series of thirty substituted N-phenyl benzenecarbohydrazonoyl chlorides **I** and evaluated their activity against three mouse helminths, *Syphacia obvelata*, *Nematospiroides dubius* and *Hymenolepis nana*. The dosage used was the highest dose (up to 7.5 mg / mouse / day) which did not elicit toxic effects on the mouse. The structural features required to give the superior anthelmintic activity in the series studied are meta- and/or para- halogen, alkoxy, alkyl, or alkylthio substituent(s) in the acid ring moiety. This is because any compound with an o-substituent in the acid ring residue was found to lack activity. Except for the N-(p-chlorophenyl), any substituent in the N-ring residue gave compounds with little or no activity. Multiple substitution in either ring decreases the activity. Also, the reported data revealed that there did not appear to be the detrimental ortho effect operating in the N-ring substitution as was apparent in the acid ring case.

The anthelmintic activity of other series of N-aryl and N-alkyl benzenecarbohydrazonoyl bromides **IB** (X= Br) and their chloride **IB'** (X = Cl) analogs were tested on mice infected with the nematode *Nippostrongylus braziliensis* [22, 23]. The most active compound was N-(2-bromo-4-

Table 1.

No.	General structure of Hydrazonoyl halide	No.	General structure of Hydrazonoyl halide
I	Ar-C(X)=NNHAr`	**VIII**	ROCO-C(X)=NNHAr
II	Ar-C(X)=$NNHSO_2$Ar`	**IX**	ArNHCO-C(X)=NNHAr
III	R-C(X)=NNHAr	**X**	$(RO)_2P(O)$-C(X)=NNHAr
IV	Het-C(X)=NNHAr	**X1**	R-$(C(X)=NNHAr)_2$
V	HCO-C(X)=NNHAr	**XII**	$(ArNHN=C(X))_2$
VI	RCO-C(X)=NNHAr	**XIII**	NC-C(X)=NNHAr
VII	ArCO-C(X)=NNHAr		

nitrophenyl) benzenecarbohdrazonoyl bromide **IBc** and the least active was N-(4-methylphenylsulfonyl) benzenecarbohydrazonoyl chloride **IBd**.

IBc $C_6H_5C(Br)=NNHC_6H_3Br(NO2)$-2,4

IBd $C_6H_5C(Br)=NNHSO_2C_6H_3Me$-4

Other derivatives such as N-phenyl 4-methylthiobenzenecarbohydrazonoyl chloride **IB** and its N-(4-methylthio) benzenecarbohydrazonoyl chloride **IC** as well as N-(2,4-dibromophenyl) 4-methylthiobenzenecarbohydrazonoyl chloride **ID** were reported to be useful anthelmintics [24].

IB-D ArC(Cl)=NNHAr'

Ar / Ar': B, 4-$MeSC_6H_4$ / Ph; C, Ph / 4-$MeSC_6H_4$;

D, 4-$MeSC_6H_4$ / 2,4-$Br_2C_6H_3$

Also, N-phenyl derivatives of 4-methyl-, 4-nitro- and pentafluoro- benzenecarbohydrazonoyl chlorides as well as N-(2,4-dibromophenyl) benzenecarbohydrazonoyl chloride and N-(2,4,6-trichlorophenyl) 4-chlorobenzenecarbohydrazonoyl chloride were reported to be useful anthelmintics [25].

IB-D Ar-C(X)=NNHAr'

Ar / Ar': **IB**, C_6H_5 / 2,4-$Br_2C_6H_3$;

ICa, 4-MeC_6H_4 / Ph; **ICb**, 4-$O_2NC_6H_4$ / C_6H_5;

ICc, C_6F_5 / C_6H_5;

ID, 4-ClC_6H_4 / 2,4,6-$Cl_3C_6H_2$

Moon *et al.* [26] synthesized a few N-aryl 2-oxopropanehydrazonoyl chlorides **VI** in search of new anthelmintics. The results showed that N-(2,4-dichlorophenyl) derivative **VIa** (250 mg/Kg orally) was effective in sheep and N-(2-chloro-4-nitrophenyl) derivative **VIb** (30 mg/Kg orally) was effective in dogs.

VI $CH_3COC(Cl)=NNHAr$

Ar: a, 2,4-$Cl_2C_6H_3$; b, 2-Cl,4-$O_2NC_6H_3$

Some N-aryl C-heteroarylmethanehydrazonoyl chlorides **IV** were also reported to be useful as anthelmintics [27, 28].

IV Het-C(Cl)=NNHAr

Het: A, 2-furyl; B, 5-Br-2-(5-Br-furyl); C, 2-thienyl;

G, 3-pyridyl, M, 2-Cl-(pyrid-3-yl)

Ar: a, Ph; b, 2,4,6-$Cl_3C_6H_2$

3.3. Antiarthropodal Activity

Several N-aryl benzenecarbohydrazonoyl chlorides **I** were reported active against anthropod pests and worms [29]. For example, N-(4-methylthiophenyl) benzenecarbohydrazonoyl chloride **IB**, N-phenyl 4-methylthiobenzenecarbohydrazonoyl chloride **ICa** and its N-(2,4-dibromophenyl) analog **ID** [30] and N-phenyl 3-trifluromethylbenzocarbohydrazonoyl bromide **ICb** [31] were found useful for control of anthropodal pests such as insects, spiders, ticks and mites.

IB, Ph-C(Cl)=NNH C_6H_4-SMe-4

ICa, 4-$MeSC_6H_4$-C(Cl)=NNHPh

ICb, 3-$F_3CC_6H_4$-C(Cl)=NNHPh

ID, 4-$MeSC_6H_4$-C(Cl)=NNH $C_6H_3Br_2$-2,4

3.4. Antiviral Activity

A series of N-aryl 2-aryl-2-oxo-ethanehydrazonoyl bromides **VII** were tested as antiviral agents. The results showed that all compounds investigated succeeded to reduce the number of local lesions induced by tomato mosaic virus on detached *Datura metel* leaves [32]. The order of activity was found to be Y/X: 4-Br / H = H / 4-Cl > H / 4-Me = 4-Me /H > H / 4-NO_2. Analysis of the results obtained revealed that the activity of the studied compounds is more than that found for N-(4-nitrophenyl) benzenecarbohydrazonoyl bromide **I**. This result was considered to indicate that the presence of the 2-oxo group enhances the antiviral activity [32].

VII YC_6H_4-CO-C(Br)=$NNHC_6H_4X$

Y/X: a, 4-Br / H; b, H / 4-Cl; c, H / 4-Me; d, 4-Me /H; e, H / 4-NO_2

3.5. Antimicrobial Activity (Fungicidal and Bactericidal)

Twenty seven hydrazonoyl halides of types **I, III** and **VI** were examined for their toxicity, fungicidal, fungistatic and bactericidal activities. The fungicidal activity was found to depend on the acid residue R [33]. The toxicity of the studied halides **I, III** and **VI** in warm blooded animals decrease in the order of substituents H > 4-NO_2 > 4-Cl > 4-Br > 2- or 3-NO_2 [33, 34].

I, YC_6H_4-C(X)=$NNHC_6H_3R'R''$-2,4

Y = H, 4-Br, 4-F, 4-Cl, 3-O_2N, 4-O_2N; X = Cl, Br

III, R-C(X)=$NNHC_6H_3R'R''$-2,4

R: Me, Et, Pr; X: Cl, Br

VI, MeCO-C(Cl)=$NNHC_6H_3R'R''$-2,4

R' = H, Br, O_2N; R'' = H, Br, Cl, O_2N, H_2NSO_2

Dubenko *et al.* [35] reported that some N-aryl derivatives of, 2-oxo-2-phenylethanehydrazonoyl chlorides **VII**, 2-amino-2-oxoethanehydrazonoyl chlorides **IX** and cyanomethanehydrazonoyl chlorides **XIII** showed activity against wheat stem rust, phytophora infection of tomatoes and cucumber powdery mildew. Both systemic and contact activities were reported. Activities of these compounds were correlated with their structure.

VII PhCO-C(Cl)=$NNHC_6H_4X$

IX ArNHCO-C(Cl)=$NNHC_6H_4X$

XIII NC-C(Cl)=$NNHC_6H_4X$

X: a, H; b, Cl; c, Br; d, I; e, O_2N; f, $AcNHSO_2$; g, EtOCO

Also some N-aryl 2-oxopropanehydrazonoylchlorides **VI** were reported to be useful fungicides [36].

VI, $CH_3COC(Cl)=NNHAr$; Ar = $RR'C_6H_3$,

R = H, 2-Cl, 2-Me, 3-F_3C

R' = H, 2-, 3-, 4-Cl, 5-F_3C, 6-Me, 4-O_2N

3.6. Phytotoxicity Activity

Kukota *et al.* [37] tested fifteen N-(4-substituted phenyl) 3-bromo-2-oxopropanehydrazonoyl bromides **VI** and their 3-

pyridinio bromide analogs **IV** as plant growth regulators at 0.01, 0.001 and 0.0001 %. The N-(4-methylphenyl)-, N-(4-chlorophenyl)- and N-(4-nitrophenyl)- derivatives depressed the growth of roots, stalks and leaves of lettuce and Oats.

VI, $BrCH_2COC(Cl)=NNHC_6H_4X$

IV, $[C_5H_5N^+\text{-}C(Cl)=NNH\ C_6H_4X]\ Br^-$

X = 4-Me, 4-Cl, 4-O_2N

3.7. Herbicidal Activity

Kaugars and his coworkers [27, 28] prepared two series of N-aryl hetarylcarbohydrazonoyl chlorides **IV** and indicated that they are primarily useful as herbicides.

IV, Het-C(Cl)=NNHAr

Het: A, 2-furyl, B, 2-(5-Br-furyl), C, 2-thienyl, D, 2-picolinyl,

E, nicotinyl, F, 4-pyridinyl

Ar = XC_6H_{5-n}; X: a, H, b, 2,4,6-Cl_3

N-(2,4-Dichlorophenyl) propanehydrazonoyl chloride **IIIa** and its N-(2,4,6-trichlorophenyl) analog **IIIb** were reported to have, at 1Ib/acre, postemergence contact herbicidal activity against bread leaf weeds, and to a lesser degree against grasses [38]. Some other N-aryl (C_{2-4})alkanehydrazonoyl chlorides **IIIA** were reported to be useful herbicides [39].

CH_3CH_2-C(Cl)=NNHAr

III, Ar: a, 2,4-$Cl_2C_6H_3$; b, 2,4,6-$Cl_3C_6H_2$

IIIA, $R\text{-}C(Cl)=NNHC_6H_{5-n}X_n$

R = C_{2-4}; X = H, 4-Cl, 2,4-Cl_2, 4-Me

Also a series of N-aryl cyanomethanehdrazonoyl chlorides **XIII** was prepared and tested on lettuce and Oat cultured on agar [40]. Of these hydrazonoyl chlorides only N-(4-nitrophenyl)- and N-(2,4-dichlorophenyl)- derivatives **XIIIa** and **XIIIb** were reported to be the most effective herbicides, decreasing germination and inhibiting growth to the highest extent. Both compounds acted as herbicides at 0.0001% [40]. N-(4-methylphenyl) cyanomethanehydrazonoyl chloride **XIIIc** at 0.0001% was reported to stimulate lettuce stem growth to the highest extent [40].

XIII, NC-C(Cl)=NNHAr

Ar: a, 4-$O_2NC_6H_2$; b, 2,4-$Cl_2C_6H_3$; c, 4-MeC_6H_4

Twelve N-aryl alkanehydrazonoyl chlorides **IIIA** were also prepared and found useful as herbicides (e.g., against crabgrass, wild oats, yellow foxtail) [41]. N-(4-Chlorophenyl) 2,2-dimethylpropanehydrazonoyl chloride **IIIB** was reported to exhibit the highest activity against crabgrass, wild oats and yellow foxtail [41].

IIIA, R-CX)=NNHAr, R = Et, Pr, Me_2CH, Me_3C

IIIB, $(CH_3)_3C\text{-}C(Cl)=NNHC_6H_4Cl\text{-}4$

Some other derivatives of N-Phenyl benzenecarbohydrazonoyl chloride **I** were prepared as useful herbicides [42]

I, $XC_6H_4\text{-}C(Cl)=NNHC_6H_4Cl\text{-}2$

X: alkyl, alkoxy, alkenyl, halo, CN, O_2N

3.8. Antisarcoptic Activity

Strinadkin *et al.* [43] reported that of the twenty derivatives of N-aryl substituted benzenecarbohydrazonoyl-, ethanehydrazonoyl-, 3-pyridinecarbohydrazonoyl-, 4-pyridinecarbohydrazonoyl- and 2-oxopropane-hydrazonoyl halides **I-VI**, respectively N-(2-nitrophenyl) benzene-carbohydrazonoyl chloride was the most effective as antisarcoptic. A single application (5-10 ml 0.05%) of such a chloride or 0.5% of N-(2,4-dibromophenyl) benzenecarbohydrazonoyl bromide **I** to rabbit's ears eradicated psoroptosis within 10 days.

I Ar-C(Cl)=NNHAr'

III CH_3-C(Cl)=NNHAr

IV Het-C(Cl)=NNHAr

VI CH_3CO-C(Cl)=NNHAr

Het: F, 4-Pyridyl G, 3-Pyridyl

Also, Buzykin *et al.* [44] studied the antisarcoptic activity of twenty one hydrazonoyl halides of types **I, III** and **X** against *Psoroptos Cuniculi* and reported that the activity of **I** increases with increasing electron donating properties of the substituent in the Ar' group, 4-MeO > 4-Cl > 4-Br > 3-NO_2 > 4-NO_2 > 2-NO_2. They found that one application of 0.05% of a 13.6% compositon emulsion of N-phenyl benzenecarbohydrazonoyl chloride **Ia** to rabbit ears 100% eradicated psoroptosis. LD_{50} of hydrazonoyl halides studied for mice was 0.4-13.5 ml/kg vc. a 0.5-10.9M LC_{50} for *P. Cuniculi*. Both N-(2-nitrophenyl) benzenecarbohydrazonoyl chloride **Ib** and N-phenyl 4-bromobenzenecarbohydrazonoyl chloride **Ic** were strongly allergenic to rabbits.

I, Ar-C(Cl)=NNHAr'

Ar' = XC_6H_4; X = 4-MeO, 4-Cl, 4-Br, 3-NO_2, 4-NO_2, 2-NO_2

III, HC(Cl)=NNHAr'

X, $(RO)_2PO\text{-}C(Cl)=NNHAr'$

3.9. Acaricidal and Miticidal Activity

N-Phenyl 4-methylthiobenzenecarbohydrazonoyl chloride **Ia**, N-(4-methylthiophenyl) benzenecarbohydrazonoyl chloride **Ib** and N-(2,4-dibromophenyl) 4-methylthiobenzenecarbohydrazonoyl chloride **Ic** [24, 25, 45] and N-(4-chlorophenyl) 3,3-dimethyl-2-oxopropanehydrazonoyl chloride **VI** [41] were reported to be useful as acaricides and miticides.

I Ar-C(Cl)=NNHAr'

VI $Me_3CCOC(Cl)=NNHC_6H_4Cl\text{-}4$

Ar / Ar': a, H/ 4-$MeSC_6H_4$; b, 4-$MeSC_6H_4$ / H;

c, 4-$MeSC_6H_4$/2,4-$Br_2C_6H_3$

Kaugars *et al.* [46, 47] screened seventy N-aryl benzenecarbohydrazonoyl chlorides **I** for miticidal activity and repellency, using the two-spotted spider miet. They reported that such activities depend to a large extent on the nature, position and number of substituents in either or both aromatic rings, the highest activity was shown by N-(2-chlorophenyl) derivatives of 4-chloro- and 4-bromo-benzenecarbohydrazonoyl chlorides **Ia,b** and N-(3-trifluoromethyl) benzene-

carbohydrazonoyl chloride **Ic**. Replacement of the hydrazone NH by $N(CH_3)$ decreased the activity [48].

I Ar-C(Cl)=NNHAr'

Ar / Ar': a, 4-ClC_6H_4 / 2-ClC_6H_4H; b, 4-BrC_6H_4/ 2-ClC_6H_4; c, C_6H_5 / 3-$F_3CC_6H_4$

Kaugers and Germrich [15, 49] indicated that N-aryl benzene-carbohydrazonoyl chlorides **I** are highly active as miticides. One of these compounds, namely N-(2,4,6-trichlorophenyl) benzenecarbohydrazonoyl chloride **IB**, has been extensively field tested and has been assigned the trade mark *Banomite*. The latter was reported to decrease significantly Texas citrus mite *(Euteranychus banksi)* eggs and adults [50]. Other derivatives of benzenecarbohydrazonoyl chloride having methylthio group in either the C-phenyl or the N-phenyl groups were reported to be useful as acaricides [25].

IB Ph-C(Cl)=$NNHC_6H_2Cl_3$-2,4,6

Several other N-aryl alkanehydrazonoyl chlorides **III** were also reported to be useful as acaricides [39, 51].

III RC(Cl):NNHAr

R = Me, Et, n-Pr, i-Pr, t-Bu

Ar = 2,4-$Cl_2C_6H_3$; 4-Cl,2-$NO_2C_6H_3$, 2,4,6-$Cl_3C_6H_2$

Also, N-phenyl methylthio-substituted benzenecarbohydrazonoyl chlorides **IA,B** were useful as acaricides [24, 52].

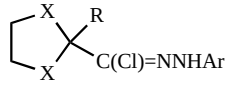
IA,B $RC_6H_4C(Cl):NNHC_6H_4R'$

R/R': 4-MeS / H, 4-Cl,2-MeS / H, H / 4-MeS, 4-MeS / 2,4-Br_2

N-(2,4,6-Trichlorophenyl) benzenecarbohydrazonoyl chloride **IB** (*banamite*) was found more toxic (LC_{50} 12 ppm) to the two spotted spider mite (*Tetranychus urticae*) than were nine of its potenrial metabolites. It inhibited rat liver *monoamine oxidase* at medium inhibitory concentrations (I_{50}) of 4.7 x 10^{-5}, 1.2 10^{-4} > 1.0 x10^{-3} and 1.4 x 10^{-3} M, respectively. Compounds relatively nontoxic to mites were usually ineffective *monoamine oxidase* inhibitors [53].

IB, Ph-C(Cl)=$NNHC_6H_2Cl_3$-2,4,6

In another report [54], it was indicated that the acaricidal activity of the dithioketal of N-(2,4-dichlorophenyl) 2-oxopropanehydrazonoyl chlorides **IVA** against the 2-spotted spider mite *(Tetranychus urticae)* on lima bean plants depended on R group, and was in the descending order R: Me, Et, Ph, H and C_5H_{11}, that is the most active compound thus being the chloride **IVAa**. The thioketal **IVAa** was reported to be much more active than the corresponding ketal **IVBa**. Of the series **IV**, the most active halides were those having 3-F3C, 4-Brsubstituents in the N-aryl group.



R = a, Me, b, Et, c, Ph, d, H, e C_5H_{11}

Ar = 2,4-$Cl_3C_6H_2$, 3-F_3C; 4-Br

IV X : A, S / S; B, O / O

Emmel *et al.* [55, 56] prepared nineteen derivatives of ethyl N-arylhydrazonochloroacetates **VIIIA** and their methyl analogs **VIIIB** and used against red spiders on beans and apple trees. Also, N-(2,4-dibromophenyl) benzenehydrazonoyl bromide **I** was reported to be effective gave 100% control of houseflies in 48 h [57].

VIII $ROCOC(Cl):NNHC_6H_4X$

I $PhC(Br)=NNHC_6H_3Br_2$-2,4

R: **A**, Et; **B**, Me

X: H, 3-F_3CO, 3-FCH_2-CF_2-O, 3-Cl_2CH-CF_2-O, 2-Me-4-Cl_2CH-CF_2-O

N-Phenyl and N-(2,4,6-trichlorophenyl) derivatives of 2-furyl-, 2-thienyl, 2- or 3-pyridyl- and 2-chloro-4-pyridyl-carbohydrazonoyl chlorides **IV** were also proved to have acaricidal activity [58].

IV Het-C(Cl)=NNHAr

Het: A, 2-furyl; B, 5-Br-2-furyl; C, 2-thienyl; G, 3-pyridyl;

H, 2-pyridyl; I, 2-Cl-4-pyridyl;

Ar: Ph, 2,4,6-$Cl_3C_6H_2$

Also, eighteen N-aryl 2-oxopropanehydrazonoyl chlorides **VI** were prepared and found useful acaricides [36].

VI, $CH_3COC(Cl)=NNHC_6H_3RR'$

R = H, 2-Cl, 2-Me, 2-Et R' = H, Me, Et

N-(4-Fluorophenyl) 2-chlorobenzenecarbohydrazonoyl chloride **IC** was prepared and reported to control totally *Plutella maculipennis* larvae on cabbage leaves when 0.01% concentration of it was used [42].

IC, 4-F-$R_nC_6H_{4-n}C(Cl)=NNHC_6H_5$

R = alkyl, alkoxy, alkenyl, halo, CN, O_2N; n = 0, 1-4

Also, thirty four alkanehydrazonoyl chlorides **III**, **IV**, **IB** and **V** were found useful as acaricides and insecticides [27, 28, 59-64].

III, R-C(Cl)=NNHAr

R = C_{1-7} alkyl; Ar = 2-Cl-4-R"-5-R'C_6H_2: R' = C_{1-4} alkoxy, $CH_2=CHCH_2O$, $HC\equiv CCH_2O$, or Cl, R" = Cl, Me or $HC\equiv CCH_2O$

IV, Het-C(Cl)=NNHAr;

Het: A, 2-furyl, B, 5-Bromo-2-furyl; C, 2-thienyl, D, picolinyl, E, nicotinyl; I, 2-Cl-4-pyridyl;

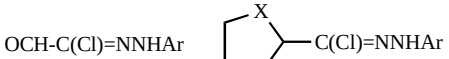
Ar: Ph, 2,4,6-$Cl_3C_6H_2$

IB, $PhC(Cl)=NNHC_6H_2Cl_3$-2,4,6

V, $OCH\text{-}C(Cl)=NNHC_6H_3Cl_2$-3,4

3.10. Pesticides

N-Aryl 2-oxoethanehydrazonoyl chlorides **V** and their ketal and thioketal derivatives **IV** were reported to have strong pesticidal effects [65].



J, X = O; K, X= S

Kaugars *et al.* [46, 66] reported that various substituted N-phenyl benzenecarbohydrazonoyl chlorides **I** have pesticidal properties.

I, Ar-C(Cl)=NNHAr'

N-Phenyl 3-trifluoromethylbenzenecarbohydrazonoyl chloride **IAa** was found by Kaugars *et al.* to be useful pesticide for controlling arthropods [31]. In addition, it was reported that N-phenyl 4-methylthiobenzenecarbohydrazonoyl chloride **IAb** and N-(4-methylthiophenyl) benzenecarbohydrazonoyl chloride **IBa** are useful for control of arthropodal pests such as insects, spiders, ticks and mites [63].

IAa, 3-$CF_3C_6H_4$-C(Cl)=NNHPh

IAb, 4-$MeSC_6H_4$-C(Cl)=NNHPh

IBa, Ph-C(Cl)=$NNHC_6H_4$SMe-4

3.11. Insecticidal Activity

Eighteen N-aryl 2-oxopropanehydrazonoyl chlorides **VI** were prepared and reported to be useful insecticides [36].

VI, MeCO-C(Cl)=$NNHC_6H_3RR'$

R: H, 2-Cl, 2-Me, 3-F_3C

R': H, Me, Et

N-Phenyl and N-(2,4,6-trichlorophenyl) derivatives of 2-furan-, 2-thiophene-, 2-pyridine-, 3-pyridine- and 2-chloro-4-pyridine- carbohydrazonoyl chorides **IV** were found useful as insecticides because of their insect metamorphosis-inhibiting activity [27, 58, 59]. Tests on cabbage looper and three other insects were given.

IV Het-C(Cl)=NNHAr

Het: A, 2-furyl; C, 2-thienyl; G, 3-pyridyl; I, 2-Cl-4-pyridyl

Ar: Ph, 2,4,6-$Cl_3C_6H_2$

N-Phenyl 2-substituted-propanehydrazonoyl chlorides of type **IIIA** and **IIIB** were also reported to be useful as insecticides because of their insect metamorphosis-inhibiting activity [41, 67].

IIIA, Me-CH(SR)-C(Cl)=NNHPh

R = Me, Et, i-Pr, t-Bu, 4-ClC_6H_4

IIIB, R'C(Cl)=NNHAr

R': Et, Pr, Bu, i-Pr, t-Bu

Ar = XC_6H_4; X: H, 2-Me, 4-O_2N, 4-Cl, 2,4-Cl_2, 2,4,6-Cl_3

In addition, substituted N-phenyl benzenecarbohydrazonoyl halides **I** and N-aryl (C_{2-4})-alkanehydrazonoyl chlorides **III** were reported to be useful as insecticides and miticides [25, 39, 46, 49, 66]. For example N-(2,4-dibromophenyl) benzenecarbohydrazonoyl bromide **1** gave 100% control of houseflies in 48 h.

I, XC_6H_4-C(Cl)=$NNHC_6H_4Y$

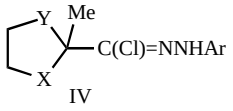
X: H, 3-, 4-Me, 4-F, 2-, 3-, 4-Cl, 4-Br, 4-I, 2-Me, 4-i-Pr, 2,4-Cl_2, 3,4-Cl_2, 2,6-Cl_2, 2,4-Cl(NO_2), 3,4-Me(NO_2), 3,4-Me_2, 2,5-Me_2, 3,5-Me_2, F_5

Y: 2,4-Br_2, 2,5-Cl_2. 2-Me, 4-Cl, 4-O2N,

III, R-C(Cl)=NNHAr

R = C_nH_{n-1}, n = 2,3,4

Furthermore, ketal, thioketal and dithioketal derivatives of N-aryl 2-oxopropanehydrazonoyl chlorides **IVJ**-L were reported to be useful insecticides for European red mites and double-spotted spider mites [65, 68].



IV

X / Y : J, O / O; K, O / S; L, S / S;

N-Phenyl and N-(4-methylthiophenyl) derivatives of benzenecarbohydrazonoyl chloride and its 2- and 4-methylthio analogs **I** were also reported to be useful as insecticides and acaricides [15, 24, 42, 52].

I, Ar-C(Cl)=NNHAr'

Ar = Ph, 2-$MeSC_6H_4$, 4-$MeSC_6H_4$

Ar' = Ph, 4-$MeSC_6H_4$

Kaugars prepared a series of N-aryl C-heteroarylmethanehydrazonoyl chlorides **IV** and found that such halides are useful as insecticides [28, 60].

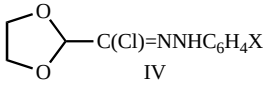
IV, Het-C(Cl)=$NNHC_6H_{5-n}Cl_n$

Het: A, 2-furyl, C, 2-thienyl, D, 2-pyridyl, G, 3-pyridyl, I, 4-pyridyl n = 1, 2, 3

Also, N-(2,4-dibromophenyl) benzenecarbohydrazonoyl bromide **Ie** was reported to be effective as insecticide as it gave 100% control of house flies in 48 hr [57].

I, Ph-C(Br)=$NNHC_6H_3Br_2$-2,4

In another report, it was indicated that the ketal derivatives of N-aryl 2-oxoethanehydrazonoyl chloride **IV** are effective insecticide [69].

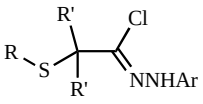


IV

X = 4-Cl, 4-Br, 4-F_3C

Also, N-(4-chlorophenyl) 2,2-dimethylpropanehydrazonoyl chloride **III** was found useful as insecticide against housefly, cotton weevil and Mexaican beanbeetle [41].

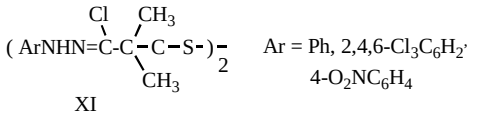
III $(CH_3)_3C$-C(Cl)=$NNHC_6H_4$Cl-4



III

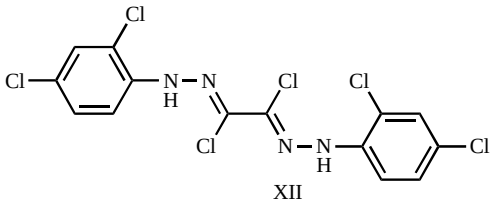
Ar = 2,4,6-$Cl_3C_6H_2$,

R = Me, Et, t-Bu; R' and R' = H, Me



XI

Ar = Ph, 2,4,6-$Cl_3C_6H_2$, 4-$O_2NC_6H_4$



XII

Also, several N-(2,4,6-trichlorophenyl) 2-alkylthioalkanehydrazonoyl chlorides **III** were found to be useful as insecticides having morphogenic hormonal mimetic activity [70-72]. The *bis*-hydrazonoyl chlorides **X1** were reported to have insecticidal activity against cabbage looper and alfafa weevil larvae [39].

The *bis*-hydrazonoyl chloride **XII** was reported to be useful insecticide for fertilizers [73].

3.12. Weed Controlling Agents

Kaugars [41] indicated that tweleve N-aryl (C_{3-5})alkane hydrazonoyl chlorides **III** are useful as miticides, insecticides against housefly, cotton ball weevi, mexican bean beetle and as herbicides against crabgrass, wild oats and yellow foxtail.

III, R-C(Cl)=NNHAr; R = C_nH_{n-1}, n = 3,4, 5

In addition, Moon [74] prepared a series of 1'-formyl-4'-halobenzeneazamethanes **VI** and indicated that they are useful as weed controlling agents.

VI, RCOCR'(X)-N=N-Ar;

R = Lower alkyl, cycloalkyl, cycloalkoxy, haloalkyl, haloalkoxy

R' = Lower alkyl, cycloalkyl, Ph

X = Br, Cl

The hydrazonoyl chlorides **VII, IX** and **XIII** showed also activity against wheat stem rust, phytophora infection of tomatoes and cucumber powdery mildew [34].

VII, PhCO-C(Cl)=NNHAr **IX**, H_2NCO-C(Cl)=NNHAr

XIII, NC -C(Cl)=NNHAr

In addition, the hydrazonoyl bromides **VI** were tested as plant growth regulators. They depressed the growth of roots, stalks and leaves of lettuce and oats [37].

VI $BrCH_2COC(Br)=NNHC_6H_4X$

X = 4-Me, 4-Cl, 4-NO_2

3.13. Lipoxygenase and Cyclooxygenase Inhibitors

N-(2,4,6-Trichlorophenyl) benzenecarbohydrazonoyl chloride (*banamite*) **IB** was reported to be more toxic (LC_{50} 12 ppm) to the twospotted spider mite (*Tetranychus urticae*) and it inhibits rat liver manoamine oxidase at median inhibitory concentrations [53]. Compounds relatively nontoxic to the mites were usually ineffective monoamine oxidase inhibtors

IB $PhC(Cl)=NNHC_6H_2Cl_3$-2,4,6

4. METABOLIC FATE

The metabolism of the acaricide *Banamite* (N-(2,4,6-trichlorophenyl) benzenecarbohydrazonoyl chloride) was reported. It was indicated that it is metabolized slowly by the two-spotted spider mite (*Tetranychus urticae*). The major metabolites identified were benzaldehyde N-(2,4,6-trichlorophenyl)hydrazone and benzoic N-(2,4,6-trichloro)hydrazide. Minor metabolites identified were 2,4,6-trichloroaniline, benzaldoxime, 2,4,6-trichlorophenylhydrazine and benzoic acid [61].

Also, the metabolism of one of the anthelmintic hydrazonoyl halides was studied in sheep and rats by Jaglan and coworkers [75-79]. For this purpose, the authors used ^{14}C-(Phenylhydrazine) and ^{14}C-(carboxy) labeled N-phenyl p-toluenecarbohydrazonoyl chloride (TCPH-I) and (TCPH-II), respectively. Ten days after a single oral therapeutic dose of 50 mg/kg, 93% of the radioactivity was recovered, 19% in urine and 74% in feces. The ^{14}C residues were higher and persisted longer in blood and blood rich organs such as liver, lung, kidney and spleen compared to other tissues. The ^{14}C residues were largely present in the hemoglobin. Such residues could neither be extracted into organic solvents nor separated from hemoglobin by dialysis, gel filtration or electrophoresis. Administration of TCPH-II resulted in a lower concentration of ^{14}C in the blood. Most of the ^{14}C residue in the blood was found in the plasma rather than in the erythrocytes which demonstrated that only the phenylhydrazine part of the molecule was bound to erythrocytes. Chromic acid oxidation of heme or globin from TCPH-I experiment produced ^{14}C-benzoic acid. This finding was considered to indicate that the phenyl part of TCPH was bound to hemoglobin and that the carboxyl carbon of benzoic acid comes from heme or globin [75].

In another report [76], it was indicated that both labels TCPH-I and TCPH-II cleared the gastrointestinal tract of treated sheep within ten days with the fecal radioactivity levels being 3-4 times greater than those for urine. Fractionation of blood from TCPH-I treated sheep showed that the majority of the radioactivity (66%) was associated with protein with erythrocytes having ten times the radioactivity of plasma. Although plasma levels were approximately equal for both TCPH-I and TCPH-II, ^{14}C levels in erythrocytes from the form TCPH-I treatment were 15 times greater than with TCPH-II treatment suggesting cleavage of the molecule with only phenylhydrazine moiety being retained. Erythrocytic ^{14}C was bound to hemoglobin [76].

An analytical procedure, to measure the level of phenyl groups incorporated in heme, based on their oxidation to benzoic acid, was developed to monitor the residues in treated animals [77]. Relay metabolism in rats was studied by feeding sheep blood containing ^{14}C residues from ^{14}C-TCPH treatment. No retention of ^{14}C residues in rat tissues was observed, which contrasted with the TCPH metabolism. A 90-day relay toxicity study in rats, which were fed dried blood from treated sheep containing up to 2000 times the potential exposure to residues in human diet, indicated no observable toxic responses. It was concluded tat these data support a tolerance of 6 ppm TCPH equivalents in blood [77].

Furthermore, it was indicated that benzene was characterized as a volatile metabolite of p-toluic acid phenylhydrazide in rats. The relationship of benzene as the volatile metabolite of p-toluic acid phenylhydrazide and the phenyl groups bound to haemoglobin from treatment of sheep with ^{14}C-(carboxy labeled) hydrazonoyl chloride (TCPH-I) was discussed [78].

In an attempt to identify the metabolites of TCPH in the urine and feces of treated sheep, Jaglan and coworkers [79] indicated that thin layer chromatography of ethyl acetate extracts of feces showed that about 12 % of the dose was present unchanged TCPH and < 2% as p-toluic acid phenyl-

hydrazide (TAPH) and aniline. A major feal metabolite (27% of the dose) was characterized as 1-phenyl-1-acyl-2-p-tuolylhydrazine (where the acyl group was a mixture of stearyl, palmityl, myristyl and lauryl groups). Both TCPH and TAPH were not found in urine. Small amounts (< 1% of the dose) of p-toluic acid, α-ketoglutaric acid phenylhydrazone and pyruvic acid phenylhydrazone were also observed, based on cochromatography with synthetic compounds. The major urinary radioactivity (about 10 % of the dose) was characterized as p-methylhippuric acid, indicating molecular cleavage of TCPH [79].

5. CONCLUSION

From the previous literature survey, it is clear that hydrazonoyl halides are very useful chemical-biology tools. In addition, we now have in hand an impressive number of biologically active candidates that can be used for treatment of various diseases. Less attention, however, was directed toward the synthesis and biology of C-alditolyl hydrazonoyl halides which are expected to have more penetrating power in the living cells. Further studies along this line may lead to products with better biological properties. For those who will be interested in exploring the chemistry and biology of such class of hydrazonoyl halides, the various review articles by one of the authors and mentioned in the introduction will be of help. In the light of the present review, there is every reason to believe that additional new and important biological applications of hydrazonoyl halides are just waiting to be discovered. It is hoped that this review will further stimulate interest in the biology of this class of organic compounds.

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