to be a weeker class of fungicides compared to the above compounds.

The molluscicidal power of coumarin derivatives depends on the concentration of the samples and time of exposure of test animals.

ACKNOWLEDGMENT

We express our sincere thanks to the Head of the Chemistry Department, University of Gorakhpur, for providing necessary facilities. The help received from the Indian Institute of Technology, Kanpur and Central Drug Research Institute, Locknow, in recording NMR spectra and for elemental analysis is gratefully acknowledged.

Registry No. 1, 68454-11-5; 2, 89999-02-0; 3, 89999-03-1; 4, 89999-04-2; 5, 26004-25-1; 6, 89999-05-3; 7, 89999-06-4; 8, 68266-19-3; 9, 89999-07-5; 10, 89999-08-6; 11, 89999-09-7.

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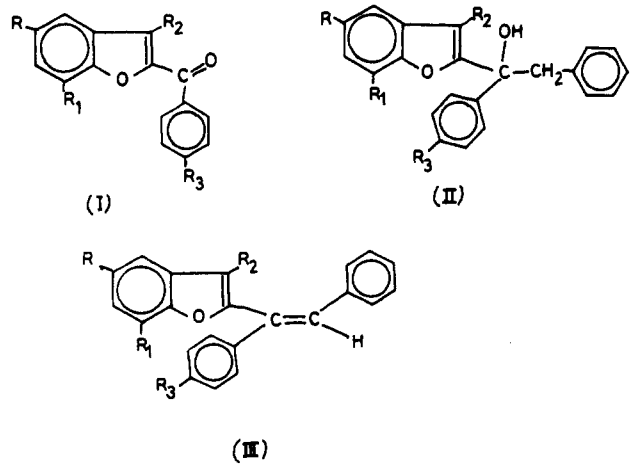
Received for review June 28, 1982. Revised manuscript received June 7, 1983. Accepted January 16, 1984. A.K.M. received financial assistance from C.S.I.R., New Delhi.

Fungicidal and Molluscicidal Activity of Some Heteroarylcarbinols and Ethylenes

Somari Giri* and Awadhesh Kumar Mishra

A number of derivatives comprising 1-aryl-1-(substituted benzofur-2-yl)-2-benzylcarbinols (II) and 1-aryl-1-(substituted benzofur-2-yl)-2-phenylethylenes (III) have been synthesized. Ten such compounds have been screened for their fungitoxicity against *Alternaria tenuis* and *Helminthosporium oryzae*, and two of them have been tested for their molluscicidal activity against *Lymnea acuminata*, a snail. The results have been compared with two commercial fungicides, Dithane M-45 and Bavistin, tested under similar conditions.

A number of benzofuran derivatives have been developed as insecticides (Boell et al., 1974) and fungicides (Grinev et al., 1979; Brooke et al., 1971). Some unsaturated and cyclic alcohols and their ethers have strong insecticidal, fungicidal, bactericidal, and acaricidal (Metcalf, 1948) effects. In view of these observations, it was presumed that the carbinols (II) containing benzofuryl and benzyl moieties should be effective pesticides. The pesticidal properties of some halogenated alkenes is well-known (Melnikov, 1971). Some acrolein (Grassberger and Reinshagm, 1975) and butene (Saikawa and Takano, 1970) derivatives containing a nitrofuryl substituent have been patented as fungicidal, protozoacidal, and antibacterial agents. In view of these records, the alkenes of type III have been synthesized with the anticipation that they might be useful pesticidal agents.



1-Aryl-1-(substituted benzofur-2-yl)-2-benzylcarbinols (II) have been prepared by a general procedure described in the literature (Fuson et al., 1941). Freshly prepared benzylmagnesium chloride in an extremely anhydrous condition was added dropwise to a solution of 2-benzoylbenzofuran in sodium-dried ether. The reaction mixture was kept refluxing in a warm water bath for 2–3 h. After the complex was decomposed with ice and NH_4Cl, the product contained in the ethereal layer was isolated as usual. The IR spectrum of II showed absorption bands in the regions 1600 cm^{-1} (aromatic –C=C– stretching), 1050 cm^{-1}, 815 cm^{-1} (benzofuran ring), 3500 cm^{-1}, 1300 cm^{-1} (tertiary –OH group), and 1445 cm^{-1} ($-CH_2-$ bending).

The triarylethylenes (III) have been obtained in good yield by dehydration of triarylcarbinols (II) using acetic anhydride as the dehydrating agent. The IR spectrum of III reveals the following signals at 3100 cm^{-1} (C–H of the benzofuran ring), 1580 cm^{-1}, 1480 cm^{-1}, 1450 cm^{-1} (aromaticity), 1010 cm^{-1}, 815 cm^{-1} (characteristic of benzofuran), 900 cm^{-1} (C–H bending of trans-substituted alkene), and 1760 cm^{-1} (–C=C– bond stretching of trans-

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0021-8561/84/1432-0762$01.50/0

Table I. 2-Benzoylbenzofurans (Vide Structure I)[a]

compd no.	R	R_1	R_2	R_3	mp, °C	molecular formula	R_f	C, % found	C, % calcd	H, % found	H, % calcd
1	H	H	H	H	89	$C_{15}H_{10}O_2$	0.67	80.89	81.08	4.33	4.50
2	H	H	H	Cl	145–146	$C_{15}H_9O_2Cl$	0.72	70.28	70.31	3.38	3.51
3	H	H	H	Br	140–142	$C_{15}H_9O_2Br$	0.5	59.66	59.8	2.78	2.99
4	Br	Br	H	Cl	94–96	$C_{15}H_7O_2ClBr_2$	0.47	43.32	43.48	1.54	1.69
5	H	H	CH_3	Cl	76–78	$C_{16}H_{11}O_2Cl$	0.58	70.95	71.11	3.89	4.07

[a] Solvent system: ethyl acetate–chloroform–benzene (2:1:3).

Table II. 1-Aryl-1-(substituted benzofur-2-yl)-2-benzylcarbinol (Vide Structure II)

compd no.	R	R_1	R_2	R_3	mp, °C	bp, °C	yield, %	molecular formula	R_f[a]	C, % found	C, % calcd	H, % found	H, % calcd
1	H	H	H	H	95–97		44.2	$C_{22}H_{18}O_2$	0.63	83.37	84.07	5.65	5.73
2	H	H	H	Cl		145–148	36.7	$C_{22}H_{17}O_2Cl$	0.67	75.72	75.86	4.67	4.88
3	H	H	H	Br	121–124		70.3	$C_{22}H_{17}O_2Br$	0.44	67.02	67.17	4.13	4.32
4	Br	Br	H	Cl	125–127		40.98	$C_{22}H_{15}O_2ClBr_2$	0.4	51.95	52.17	2.78	2.96
5	H	H	CH_3	Cl		175–179	49.75	$C_{23}H_{19}O_2Cl$	0.5	76.11	76.24	5.13	5.25

Significant Bands (cm^{-1}) in IR Spectrum (KBr Disk)

compd no.	benzofuran ring	tertiary –OH group	$-CH_2-$ bending	aromatic ring
1	1050, 815	3500, 1300	1445	1600
3	1020, 835	3500, 1250	1460	1600, 1500
4	1020, 840	3400, 1240	1450	1595, 1495

^1H NMR Spectrum of 1 in $CDCl_3$

type of proton	no. of protons	chemical shift, δ	multiplicity
Ar H, benzenoid	15	7–7.5	quadruplet
>C=C<H	1	6.4	singlet
–O–H, alcoholic	1	3.3	quadruplet
$-CH_2-$, alkyl	2	2.4	singlet

[a] Solvent system: ethyl acetate–chloroform–benzene (2:1:3).

Table III. 1-Aryl-1-(substituted benzofur-2-yl)-2-phenylethylene (Vide Structure III)

compd no.	R	R_1	R_2	R_3	mp, °C	bp, °C	yield, %	molecular formula	R_f[a]	C, % found	C, % calcd	H, % found	H, % calcd
6	H	H	H	H	53		71.4	$C_{22}H_{16}O$	0.72	88.87	89.18	5.27	5.40
7	H	H	H	Cl		215–218	71.4	$C_{22}H_{15}OCl$	0.61	79.78	80.00	4.36	4.54
8	H	H	H	Br		248–251	70	$C_{22}H_{15}OBr$	0.58	70.27	70.40	3.83	4.00
9	Br	Br	H	Cl	108–111		52.6	$C_{22}H_{13}OClBr_2$	0.66	53.89	54.09	2.51	2.66
10	H	H	CH_3	Cl		195.9	52.6	$C_{23}H_{17}OCl$	0.78	80.11	80.23	4.87	4.94

Significant Bands (cm^{-1}) in IR Spectrum (KBr Disk)

compd no.	aromaticity	C–H of benzofuran ring	characteristic of benzofuran	C–H bending of trans-substituted alkene	C=C bond stretching of trans-substituted alkene
9	1580, 1480, 1450	3100	1010, 815	900	1760

[a] Solvent system: ethyl acetate–chloroform–benzene (2:1:3).

Table IV. Fungicidal Data

compd no.[a]	average % inhibition after 96 h: *A. tenuis* 1000 ppm	*A. tenuis* 100 ppm	*A. tenuis* 10 ppm	*H. oryzae* 1000 ppm	*H. oryzae* 100 ppm	*H. oryzae* 10 ppm
1	78.7	65.6	45.5	79.3	68.2	49.2
2	87.1	75.3	56.1	88.0	77.4	42.0
3	88.1	70.3	52.5	85.1	69.3	27.6
4	90.4	87.1	75.3	89.3	75.5	53.7
5	93.1	88.2	76.7	92.9	79.3	63.5

[a] Number of the compounds corresponds to that given in Table II.

Table V. Fungicidal Data

compd no.[a]	average % inhibition after 96 h: *A. tenuis* 1000 ppm	*A. tenuis* 100 ppm	*A. tenuis* 10 ppm	*H. oryzae* 1000 ppm	*H. oryzae* 100 ppm	*H. oryzae* 10 ppm
6	85.1	73.2	59.7	84.5	72.5	54.7
7	89.5	79.3	61.5	90.6	83.5	49.2
8	92.4	77.4	64.0	87.3	76.5	43.4
9	90.8	86.6	71.0	88.8	78.3	61.2
10	92.4	85.6	61.5	94.1	82.7	53.6
Bavistin	98.9	96.6	94.7	94.2	91.2	84.3
Dithane M-45	99.2	98.5	94.9	96.7	93.2	95.7

[a] Number of the compounds corresponds to that given in Table III.

substituted alkene). On the basis of a study of IR absorption spectra of III, the phenyl groups around the alkene bond have been put in the trans position.

The compounds thus prepared were screened for antifungal activity against *Helminthosporium oryzae* and *Alternaria tenuis*.

EXPERIMENTAL SECTION

2-Benzoylbenzofurans (I). These were prepared according to a standard method (Stoermer et al., 1924). To an alcoholic solution of appropriate *o*-hydroxyaldehyde or

Table VI. Molluscicidal Data

no. of animals	compd no.[a]	dose, mg/L	% mortality (M ± SE) at indicated time intervals after treatment		
			24 h	48 h	96 h
60	4	1.0	35.0 ± 0.45	46.67 ± 6.12	51.67 ± 5.24
60	4	3.0	38.33 ± 3.37	48.33 ± 3.37	58.o3 ± 3.37
60	4	5.0	56.67 ± 3.66	65.00 ± 4.7	78.33 ± 3.37
60	9	1.0	6.67 ± 3.66	15.00 ± 4.7	25.00 ± 3.75
60	9	3.0	11.67 ± 3.37	23.33 ± 3.66	35.00 ± 3.75
60	9	5.0	41.67 ± 4.41	50.00 ± 4.91	60.00 ± 4.01

[a] Numbers correspond to those given in Tables II and III.

ketone (1.0 M) was added an ethanolic solution of KOH (1.1 M), and the mixture was warmed. To this was added an alcoholic solution of ω-bromoacetophenone (1.1 M), and the reaction mixture was refluxed for 5 h. The precipitated KBr was filtered, and the bulk of alcohol was distilled out. The residue upon cooling gave the crude product, which was recrystallized from aqueous ethanol and purified by TLC using a benzene, chloroform, and ethyl acetate solvent system. These compounds are given in Table I.

1-Aryl-1-(substituted benzofur-2-yl)-2-benzylcarbinols. Benzylmagnesium chloride prepared by reacting benzyl chloride (1.0 M) with clean dry magnesium turning (1.1 M) in anhydrous ether (100 ml) was added gradually to a solution of 2-benzoylbenzofuran (1.0 M) in sodium-dried ether. The reaction mixture was carefully refluxed in a warm water bath for 3 h. It was decomposed with ice and NH_4Cl, and the ethereal layer was washed with water and dehydrated over anhydrous Na_2SO_4. Removal of ether gave the desired product. The carbinols (II) thus synthesized were purified by repeated crystallization and TLC and are given in Table II.

1-Aryl-1-(substituted benzofur-2-yl)-2-phenylethylenes. Carbinols (II) (1.0 M) were mixed with acetic anhydride (5.0 M), and the mixture was refluxed for 3 h. Nearly two-thirds of acetic anhydride was distilled out, and the residue after usual treatment yielded the desired product (III). The compounds thus prepared were recrystallized from ethanol and purified by TLC and are recorded in Table III.

Fungicidal Test. The fungicidal activity of 10 compounds synthesized in the present investigation was evaluated by the agar growth technique against two different species of fungi used as the test organism. The fungus was planted in agar medium mixed with the test compound. The diameter of the fungus colony was measured by a millimeter scale at three different concentrations, 1000, 100, and 10 ppm. Inhibition of fungus growth was determined as the difference in growth between the control plates and those treated with the toxicant. Three repetitive experiments were performed for each concentration of the test chemical, and the same number of replicates of controls was provided. The percentage inhibition was calculated as

$$\% \text{ inhibition} = \frac{C - T}{C} \times 100$$

where C = the average diameter of fungus colony (in mm) in the control plate and T = the average diameter of fungus colony (in mm) in the treated plate.

The fungicidal performance of test compounds was compared with that of two commercial fungicides, Dithane M-45 and Bavistin, by using similar conditions and same fungus species. The fungicidal data are recorded in Tables IV and V.

Molluscicidal Activity Test. The molluscicidal activity of two compounds was evaluated against a snail, *Lymnea acuminata*. The aquarium containing the snails was intoxicated by different concentrations of the chemicals, and the mortality studies were carried out after different time intervals. Each aquarium contained 10 experimental animals. Six aquariums were set up for each concentration of the toxicant. A equal number of control animals were kept in a similar manner without the chemical (toxicant). The snails were exposed to three different concentrations of each chemical for different periods of several hours. The results obtained were worked up to their percentage mortality by mathematical calculations, which are given in Table VI.

RESULTS AND DISCUSSION

An examination of fungitoxic data reveals that all carbinols and ethylenes under investigation were active against *A. tenuis* and *H. oryzae* at concentrations of 1000 ppm, the activity falling with a decrease in concentration. Thus, at a concentration of 100 ppm only two compounds (4 and 5) could retain fungitoxic behavior comparable to that of commercial fungicides. At a concentration of 10 ppm all the test samples proved to be weaker fungicides. The ethylenes in general were more toxic to test fungi than the carbinols.

The results of molluscicidal tests indicate that the activity depends on the concentration of the test chemical as well as on the total time of exposure. If a minimum dose was used, the mortality rate was minimum but it increased gradually with a increase in the time of exposure. However, a relatively higher initial dose of the compound brought about a considerable increase in mortality rate even on exposure for the minimum time period. The ethylene derivatives were found to be relatively more toxic to the snails under investigation than the carbinol compounds.

CONCLUSION

The heteroarylcarbinols and ethylenes incorporating benzofuran moieties proved to be weaker fungicides when tested against *A. tenuis* and *H. oryzae*.

The molluscicidal power of above compounds depends on the concentration of the samples and time of exposure of the test animals.

ACKNOWLEDGMENT

We express our sincere thanks to the Head, Chemistry Department, University of Gorakhpur, for providing necessary facilities. The help received from Indian Institute of Technology, Kanpur, and Central Drug Research Institute, Lucknow, in recording NMR spectra and for elemental analysis is gratefully acknowledged. A.K.M. is grateful to C.S.I.R., New Delhi, for the award of a Junior Research Fellowship.

Registry No. I ($R = R_1 = R_2 = R_3 = H$), 6272-40-8; I ($R = R_1 = R_2 = H$, $R_3 = Cl$), 27052-20-6; I ($R = R_1 = R_2 = H$, $R_3 = Br$), 29555-25-7; I ($R = R_1 = Br$, $R_2 = H$, $R_3 = Cl$), 83806-70-6; I ($R = R_1 = H$, $R_2 = CH_3$, $R_3 = Cl$), 67534-79-6; II ($R = R_1 = R_2 = R_3 = H$), 89998-94-7; II ($R = R_1 = R_2 = H$, $R_3 = Cl$), 82158-26-7; II ($R = R_1 = R_2 = H$, $R_3 = Br$), 89998-95-8; II ($R = R_1 = Br$, R_2

= H, R_3 = Cl), 89998-96-9; II (R = R_1 = H, R_2 = CH_3, R_3 = Cl), 89998-97-0; III (R = R_1 = R_2 = R_3 = H), 89998-98-1; III (R = R_1 = R_2 = H, R_3 = Cl), 89998-99-2; III (R = R_1 = R_2 = H, R_3 = Br), 89999-00-8; III (R = R_1 = Br, R_2 = H, R_3 = Cl), 89999-01-9; III (R = R_1 = H, R_2 = CH_3, R_3 = Cl), 90028-85-6.

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Received for review July 1, 1982. Revised manuscript received June 7, 1983. Accepted February 21, 1984.

Formation of Alkoxysulfenyl Derivatives of Carbofuran by Acid-Catalyzed Alcoholysis of Carbosulfan

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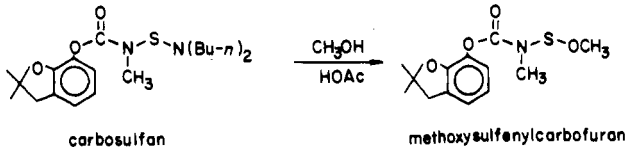
The behavior of carbosulfan [2,3-dihydro-2,2-dimethylbenzofuran-7-yl *N*-[(dibutylamino)thio]-*N*-methylcarbamate] in alcohol–acid mixtures was examined. In methanol- or ethanol-containing acetic acid, carbosulfan was converted into a number of products, the major product being the solvolysis product in which the dibutylamino group is substituted by the methoxy or ethoxy moiety to give the respective alkoxysulfenyl derivative of carbofuran. The methoxysulfenyl derivative was also the principal alteration product of carbosulfan in methanolic hydrogen chloride, but in this case a number of polysulfide analogues of this derivative were observed. The alkoxysulfenyl derivatives showed good insecticidal activity against the house fly and were less toxic to the white mouse than carbofuran, the parent methylcarbamate.

Carbosulfan or 2,3-dihydro-2,2-dimethylbenzofuran-7-yl *N*-[(dibutylamino)thio]-*N*-methylcarbamate is a sulfenylated derivative of carbofuran (2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate), which is being developed as a broad-spectrum insecticide. Previous papers from this laboratory described the acid-catalyzed alteration of carbosulfan via N–S bond cleavage and formation of the polysulfide derivatives of carbosulfan and biscarbosulfan *N,N'*-disulfide, along with carbofuran and several other alteration products (Umetsu et al., 1981a,b; Umetsu and Fukuto, 1982). In these studies aprotic, inert solvents such as acetonitrile and dichloromethane were used.

A subsequent study of the behavior of carbosulfan in



carbosulfan methoxysulfenylcarbofuran

protic solvents, e.g., methanol–acetic acid (9:1), revealed solvent participation in the alteration reaction with significant amounts of the methoxysulfenyl derivative of carbofuran being formed, along with other alteration products. Examination of the toxicological properties of (methoxysulfenyl)carbosulfan revealed this compound to have insecticidal activity comparable to that of either carbosulfan or carbofuran. Because of our interest in new carbamate derivatives and the possible significance of acid-catalyzed solvolysis on the chemical and toxicological properties of carbosulfan, further probe into the nature of the alcoholysis reaction was made. This paper is concerned with the isolation, identification, and toxicological evaluation of the (alkoxysulfenyl)carbofuran derivatives formed from carbosulfan in alcohol-containing acid.

MATERIALS AND METHODS

Chemicals. [*carbonyl*-^{14}C]Carbosulfan (sp act. 25.20 mCi/mmol) was available from previous studies (Umetsu et al., 1979). The radiolabeled material was 99.5% pure and contained 0.2% carbofuran and 0.3% unknown components. Biscarbofuran *N,N'*-disulfide (CFS_2CF), biscarbofuran *N,N'*-polysulfide (CFS_nCF, $n \geq 3$), and polysulfide analogues of carbosulfan (CFS_nNBu_2, $n \geq 2$) were also available from previous studies (Umetsu et al., 1980, 1981a,b; Umetsu and Fukuto, 1982). Other chemicals were analytical reagent grade, and redistilled solvents were used.

Stability of Carbosulfan in Acidic Solvent Mixtures. In a preliminary examination of the stability of carbosulfan in different acidic solvents, samples of [*carbonyl*-^{14}C]carbosulfan (10.0 mg, 1.13 μCi) were dissolved in 0.2 mL of the following solvent mixtures and kept at 23 °C: acetonitrile–acetic acid (9:1), methanol–acetic acid (9:1), and ethanol–acetic acid (9:1). All solvent–acetic acid mixtures were prepared volume/volume. At different time intervals, duplicate 5-μL samples were removed and the contents were examined by thin-layer chromatography (TLC).

Acid-Catalyzed Alcoholysis of Carbosulfan. A mixture of 10.0 mg of purified carbosulfan (nonradioactive) and 18.6 μg of [*carbonyl*-^{14}C]carbosulfan (1.28 μCi) dissolved in 200 μL of methanol was added to 200 μL of a 4:1

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0021-8561/84/1432-0765$01.50/0