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Antifungal Activities of Mono- and Di-$SCCl_3$ Substituted Compounds: Structure–Activity Correlations[1]

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The mono- and di-N-$SCCl_3$ substituted derivatives of lactams, cyclic urea, 5,5-diphenylhydantoin and 5-ethyl-5-phenylbarbituric acid were synthesized. Many of these compounds have not been reported previously. The antifungal activities were determined by spore germination method using *Stemphylium sarcinaeforme, Monilinia fructicola, Helminthosporium maydis* and *Alternaria solani.* Among the lactam and cyclic urea derivatives studied 1,3-bis(trichloromethylthio)-2-imidazolidinone appears to be the most active compound against *S. sarcinaeforme,* and has activity slightly below those of the commercial products captan and folpet. Among the diphenylhydantoin and phenobarbital derivatives the mono-$SCCl_3$ compounds appear to be more potent than the disubstituted compounds in most of the cases examined, but they are not as active as the imidazolidinone derivative. The antifungal activity appears to be highly dependent on the lipophilic character as measured by the 1-octanol/water partition coefficient. Since the bis-$SCCl_3$ compounds are less potent than the mono-substituted compounds in both of the series of compounds studied, it is evident that the whole molecule rather than any decomposition products of the N-$SCCl_3$ moiety is responsible for the fungitoxicity.

Because of the high antifungal activity and the biodegradability, N-$SCCl_3$ containing fungicides like captan, folpet, and difolatan have been very useful in agricultural, cosmetic and industrial applications (1–3). The exact mechanisms of action of these compounds are, however, still open to question (1).

Based on the quantitative structure–activity analysis of imides and their N-$SCCl_3$ compounds, Lien (4) proposed that cyclic ureas with two N-$SCCl_3$ groups may have significant antifungal activity. The main purpose of this report is to test the validity of this hypothesis. Other heterocyclic compounds possessing N-$SCCl_3$ have also been synthesized and tested for their fungitoxicity. Regression analysis is employed to correlate the antifungal activity with 1-octanol/water partition coefficient and the result is compared with the equations obtained from imides, captan, folpet and related compounds. It is hoped that the quantitative structure–activity analysis may shed some light on

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the mechanism of action of R-$SCCl_3$ fungicides.

MATERIAL AND METHODS

1-Trichloromethylthio-δ-valerolactam

δ-Valerolactam (16.6 g, 0.16 mole), NaH oil emulsion (9.6 g of 50% NaH, 0.2 mole) and 220 ml freshly distilled 1,4-dioxane was stirred at room temperature for 45 min. $ClSCCl_3$ (30 g, 0.16 mole) was added dropwise to the reaction mixture kept in an ice bath. Stirring was continued for 1.5 hr then stopped, the reaction mixture was filtered and the solvent of the filtrate was removed in a rotatory evaporator under reduced pressure. The residue was dissolved in 350 ml benzene and purified by column chromatography through activated alumina. The product came out from the 1:1 benzene–chloroform and $CHCl_3$ fractions. Recrystallization from $CHCl_3$–petroleum ether mixture gave 0.89 g (6%) of the product: mp 36–37°, corrected. The structure was confirmed by ir (no N–H stretching, νC=O 5.87 μm; νC–S 12.31 μm; νC–Cl or νC–C 13.4 μm) and elemental analysis.[2]

Anal. Calcd for $C_6H_8Cl_3NOS$: C, 28.99; H, 3.24; N, 5.63; S, 12.89. Found: C, 29.29; H, 2.95; N, 5.84; S, 13.26.

1-Trichloromethylthio-ε-caprolactam

When the similar procedure (*vide supra*) except using dimethylformamide as the solvent was attempted, no desired product but the starting material was obtained. In a second trial 11.3 g (0.1 mole) of ε-caprolactam, 250 ml of fresh dioxane and 18.6 g (0.1 mole) of $ClSCCl_3$ was stirred and heated to 102° for 3 hr. The reaction mixture was passed through activated alumina. The product came out at the last 60 ml of dioxane eluant and the first 140 ml of $CHCl_3$.

The combined volume of these two fractions was reduced to 5 ml under reduced pressure. A brown precipitate formed upon storage in a freezer. The precipitate was decolorized with charcoal and recrystallized from $CHCl_3$–petroleum ether mixture, giving 2.7 g (11.7%) of the yellow crystals: mp 55–58°, corrected. The identity was confirmed by ir and elemental analysis.[2]

Anal. Calcd for $C_7H_{10}NCl_3OS$: C, 32.01; H, 3.83. Found. C, 31.06; H, 3.50.

1,3-Bis(trichloromethylthio)-2-imidazolidinone

2-Imidazolidinone (8.6 g, 0.1 mole), NaH (50% 9.6 g, 0.2 mole) and 240 ml of freshly distilled 1,4-dioxane were heated briefly to dissolve as much of the 2-imidazolidinone as possible. The reaction mixture was then cooled and kept in an ice bath, 37.2 g (0.2 mole) of $ClSCCl_3$ was added slowly in 1.5 hr to the reaction mixture. Stirring was continued for another 30 min, then allowed to stand overnight; it was then filtered. The filtrate was concentrated in a rotatory evaporator under reduced pressure. Column chromatography (activated alumina) was employed to separate and purify the desired product, which came from the initial 150 ml of benzene eluant. The colorless crystalline product was recrystallized from dil EtOH (80%) first, then from $CHCl_3$–petroleum ether giving 2.5 g (15%): mp 158.5°, corrected. The identity was confirmed by ir (no νN–H absorption, νC=O 5.67 μm; νC–S 12.35 μm; νC–Cl or νC–C 13.30 μm) and elemental analysis.[2]

Anal. Calcd for $C_5H_4Cl_6N_2OS_2$: C, 15.60; H, 1.04. Found C, 15.97; H, 1.09.

3-Trichloromethylthio-5,5-diphenylhydantoin

Twenty-seven grams of 5,5-diphenylhydantoin sodium were dissolved in 300 ml of dioxane and water (1:1). Twenty milliliters $ClSCCl_3$ were added dropwise to keep the temperature around 35°. Then it was refluxed with stirring for 3 hr. The mixture was allowed to stand overnight. The ppt. was filtered off and washed with

[2] Performed by C. F. Geiger, Microanalyst, 312 East Yale St., Ontario, California.

300 ml 5% $NaHCO_3$ solution and dried. Recrystallization from hot $CHCl_3$ and 95% EtOH gave 38 g (94%) of the product: mp 172–173°, corrected (lit.[3] 176°). The identity was confirmed by ir (νN–H 2.95 μm; νC=O 5.7 μm; νC–S 12.35 μm; νC–Cl 13.58 μm) and NMR (Hitachi Perkin-Elmer 24R, 60 MHz, in $CDCl_3$, TMS as internal reference, chemical shift δ in ppm: phenyl protons 7.41; N–H 7.86, exchanged with D_2O).

1,3-Bis(trichloromethylthio)-5,5-diphenylhydantoin

Two grams of 5,5-diphenylhydantoin sodium were dissolved in 200 ml benzene and cooled to 5°. $(Et)_3N$ (0.73 g) was added with constant stirring. $ClSCCl_3$ was added at a rate to keep the temperature below 5°, stirring was continued for 30 min. The mixture was then heated to 50° for 30 min, cooled to 15° and then the ppt. of $(Et)_3N \cdot HCl$ was filtered off. After reducing the volume of the filtrate, the gummy residue was dissolved in $CHCl_3$ and washed with 200 ml of 5% $NaHCO_3$ solution. The volume was reduced again and the crystals were forced out with petroleum ether. The ppt. was collected and recrystallized from 95% EtOH giving 2.5 g (63%) of the product: mp 179–181°, corrected. The identity was confirmed by NMR (chemical shift δ in ppm, phenyl protons 7.48, no N–H peak) and elemental analysis.[2]

Anal. Calcd for $C_{17}H_{10}N_2S_2O_2Cl_6$: C, 37.04; H, 1.81. Found: C, 36.77; H 1.87.

1-Trichloromethylthio-5-ethyl-5-phenylbarbituric Acid[4]

Twenty-six grams of 5-ethyl-5-phenylbarbituric acid sodium salt were dissolved in 350 ml dioxane and water (1:1). $ClSCCl_3$ (19 g) was added dropwise to keep the temperature at 30°. It was then refluxed with stirring for 3 hr. The mixture was allowed to stand overnight. The two layers were separated, the bottom oily layer was collected and the aqueous layer was extracted with $CHCCl_3$. The combined organic extracts were washed with 300 ml 5% $NaHCO_3$. The volume was reduced under reduced pressure and the gummy residue was dissolved in $CHCCl_3$ and the crystalline powder was forced out with petroleum ether. Recrystallization from 95% EtOH and $CHCCl_3$ gave 36 g (94%) of the product: mp 109–111°. The identity was confirmed by ir (νN–H 3.0 μm; νC=O 5.7μm, 5.85 μm; νC–S 12.25 μm; νC–Cl 13.48 μm) and NMR ($CDCl_3$) δ 0.95 (t, CH_3), 2.50 (q, CH_2), 7.32 (phenyl protons), and 9.31 ppm (N–H, exchanged with D_2O).

1,3-Bis(trichloromethylthio)-5-ethyl-5-phenylbarbituric Acid

$ClSCCl_3$ (13 g) was added dropwise to a mixture of 9 g sodium 5-ethyl-5-phenylbarbiturate and 3.5 g $(Et)_3N$ in 180 ml of benzene. The temperature was kept below 5° and the solution was stirred for 45 min. The mixture was then heated to 50° for 45 min, cooled to 16° and the $(Et)_3N \cdot HCl$ ppt. was filtered off. The volume of the filtrate was reduced and the gummy residue was dissolved in $CHCl_3$ and washed with 300 ml 5% $NaHCO_3$ solution. The volume of the $CHCl_3$ solution was reduced again and 20 ml of 95% EtOH was added. The crystals were forced out with petroleum ether. Recrystallizations from $CHCl_3$, then EtOH gave 12 g (63%) of the product: mp 106–108°. The identity was confirmed by NMR ($CDCl_3$) δ 7.63 (phenyl protons), 2.93 (q, CH_2), and 1.39 ppm (t, CH_3), and elemental analysis.[2]

Anal. Calcd for $C_{14}H_{10}Cl_6N_2S_2O_3$: C, 31.63; H, 1.88. Found: C, 32.13; H, 2.19.

Inhibition of Spore Germination

The spore germination test of Rich and Horsfall (5) was used to determine the

[3] G. P. Lampson and H. O. Singher, *J. Org. Chem.*, **21**, 684 (1956).

[4] Reported by E. Jeney and T. Zsohnai, *Zentralbl. Bakteriol. Parasitenk. Abt. 1. Orig.*, **193**, 516 (1964), no mp was given.

TABLE 1

Inhibition of Spore Germination and Partition Coefficient Data Used in Deriving the Equations in Table 2

A. Lactam, Imide and Urea Derivatives

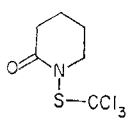
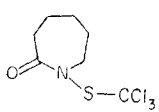
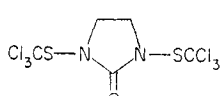
Compound	Log $1/ED_{50}$ vs *S. sarcinaeforme* (Moles/cm²)		(Moles/liter)[a]		Log *P* (octanol/H_2O)
	Observed	Calculated[b]	Observed	Calculated[c]	
 1-Trichloromethylthio-δ-valerolactam	7.11	6.30	3.23	2.42	0.89[d]
 1-Trichloromethylthio-ϵ-caprolactam	7.65	7.59	3.77	3.71	1.51[d]
 1,3-Bis(trichloromethylthio)2-imidazolidinone	8.12	8.23	4.24	4.35	1.99[d]
Phthalimide	6.38[e]	6.90	2.50	3.02	1.15[f]
Tetrahydrophthalimide	5.46[e]	5.44	1.58	1.56	0.57[g]
3,6-Endomethylene-tetrahydrophthalimide	5.19[e]	5.24	1.31	1.36	0.50[g]
Hexahydrophthalimide	5.58[e]	5.92	1.70	2.04	0.74[g]
Folpet	8.58[e]	8.62	4.70	4.74	2.85[f]
Captan	8.70[e]	8.51	4.82	4.63	2.35[f]
Cyclohexane-1,2-dicarboximide-N-$SCCl_3$	8.58[e]	8.60	4.70	4.72	2.98[g]

TABLE 1—*Continued*

B. Lactam, Urea and Imide Derivatives

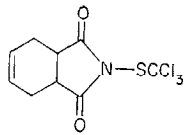
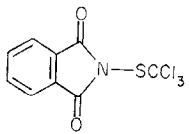
Compound	Log $1/ED_{50}$(moles/liter) vs M. fructicola		Log $1/ED_{50}$(moles/liter) vs H. maydis		Log $1/ED_{50}$(moles/liter) vs A. solani		Log P (octanol/H_2O)
	Observed	Calculated[h]	Observed	Calculated[i]	Observed	Calculated[j]	
1-Trichloromethylthio-δ-valerolactam	3.56	3.06	3.16	2.81	3.17	3.05	0.89
1-Trichloromethylthio-ε-caprolactam	3.12	3.85	3.61	3.78	3.68	3.91	1.51
1,3-Bis(trichloromethylthio)-2-imidazolidinone	4.39	4.46	3.51	4.53	4.27	4.58	1.99
Captan 	5.00	4.92	5.92	5.09	5.77	5.08	2.35
Folpet 	5.76	5.55	5.87	5.87	5.52	5.78	2.85

TABLE 1—*Continued*

C. Hydantoin and Barbiturate Derivatives

Compound	Log $1/ED_{50}$ (moles/liter) vs S. sarcinaefore		Log $1/ED_{50}$ (moles/liter) vs M. fructicola		Log $1/ED_{50}$ (moles/liter) vs H. maydis		Log $1/ED_{50}$ (moles/liter) vs A. solani		Log P (oct/w)
	Observed	Calculated[k]	Observed	Calculated[l]	Observed	Calculated[m]	Observed	Calculated[n]	
3-Trichloromethylthio-5,5-diphenylhydantoin	3.15	3.29	4.54	4.59	3.22	3.16	3.02	3.14	4.17
1,3-Bis(trichloromethylthio)-5,5-diphenylhydantoin	2.96	2.89	3.54	3.55	2.96	2.91	3.29	2.96	5.87
1-Trichloromethylthio-5-ethyl-5-phenylbarbituric acid	3.63[p]	3.54	3.49	3.48	3.33	3.32	3.50	3.25	3.12
1,3-Bis(trichloromethylthio)-5-ethyl-5-phenylbarbituric acid	3.12	3.14	4.66	4.61	2.95	3.07	2.61	3.07	4.82

[a] Log $1/ED_{50}$ (moles/liter) = log $1/ED_{50}$ (moles/cm^2) − 3.88, since 1.3 μg/cm^2 = 0.01 g/liter.

[b] Calculated from Eq. 2b.

[c] Calculated from Eq. 2a.

[d] Calculated from the log P values of the lactam and the π value of $SCCl_3$. The log P values of the lactams were taken from Lien *et al.*, *J. Med. Chem.* **14**, 846 (1971). The value of $SCCl_3$ was calculated as the following: π_{SCCl_3} = log P_{folpet} − log $P_{phthalimide}$ = 2.85 − 1.15 = 1.70. π—CH_2— = 0.62 between δ-valerolactam and ε-caprolactam.

[e] From Lien, *J. Agr. Food Chem.* **17**, 1265 (1969).

[f] Experimentally determined value by Leo *et al.*, *Chem. Rev.* **71**, 525 (1971).

[g] Calculated from the following equation of Leo *et al.* (see *f*): log $P_{octanol/H_2O}$ = (log $P_{oleyl\ alc./H_2O}$ + 0.575) × (1/0.999). The log $P_{oleyl\ alcohol}$ values were from Lien (see *e*).

[h] Calculated from Eq. 5.

[i] Calculated from Eq. 3.

[j] Calculated from Eq. 4.

[k] Calculated from Eq. 8.

[l] Calculated from Eq. 7.

[m] Calculated from Eq. 9.

[n] Calculated from Eq. 10.

[o] Calculated from the following values: log $P_{diphenylhydantoin}$ = 2.47, log $P_{phenobarbital}$ = 1.42, π_{SCCl_3} = 1.70 (from Lien *et al.*, *J. Pharm. Sci.* **62**, 246 (1972).

[p] The average of 4 separate runs.

TABLE 2

Equations Correlating Antifungal Activities with the 1-Octanol-water Partition Coefficients

Equation		n^a	r^b	s^c	log $P_0{}^d$ (±95% c.l.)
N-$SCCl_3$ derivatives of imides, lactams and urea vs *Stemphylium sarcinaeforme*					
1a	$\log 1/ED_{50} = 1.379 \log P + 1.114$ (moles/liter)	10	0.927	0.553	
1b	$\log 1/ED_{50} = 1.379 \log P + 4.994$ (moles/cm²)	10	0.927	0.553	
2a	$\log 1/ED_{50} = -0.659 (\log P)^2 + 3.649 \log P - 0.303$ (moles/cm²) ($F_{1,7} = 8.67$; $F_{1,7_{0.975}} = 8.07$)	10	0.968	0.395	2.77 (2.26–7.07)
2b	$\log 1/ED_{50} = -0.659 (\log P)^2 + 3.649 \log P + 3.577$ (moles/cm²) vs *Helminthosporium maydis*	10	0.968	0.395	2.77 (2.26–7.06)
3	$\log 1/ED_{50} = 1.559 \log P + 1.424$ (moles/liter) ($F_{1,3} = 8.87$; $F_{1,3_{0.90}} = 5.54$) vs *Alternaria solani*	5	0.865	0.791	
4	$\log 1/ED_{50} = 1.394 \log P + 1.807$ (moles/liter) vs *Monilinia fructicola*	5	0.929	0.485	
5	$\log 1/ED_{50} = 1.275 \log P + 1.920$ (moles/liter) ($F_{1,3} = 13.3$; $F_{1,3_{0.95}} = 10.1$)	5	0.904	0.528	
N-$SCCl_3$ derivatives of barbiturates and hydantoin vs *Monilinia fructicola*					
6	$\log 1/ED_{50} = 0.027 \log P + 3.936$ (moles/liter)	4	0.050	0.769	
7	$\log 1/ED_{50} = -0.608 (\log P)^2 + 5.495 \log P - 7.745$ (moles/liter) ($F_{1,1} = 214.1$; $F_{1,1_{0.95}} = 161$) vs *Stemphylium sarcinaeforme*	4	0.998	0.075	4.52 (3.79–5.39)
8	$\log/ED_{50} = -0.233 \log P + 4.263$ (moles/liter) ($F_{1,2} = 13.00$; $F_{1,2_{0.90}} = 8.53$) vs *Helminthosporium maydis*	4	0.931	0.129	
9	$\log 1/ED_{50} = -0.149 \log P + 3.787$ (moles/liter) ($F_{1,2} = 9.29$; $F_{1,2_{0.90}} = 8.53$) vs *Alternaria solani*	4	0.906	0.098	
10	$\log/ED_{50} = -0.106 \log P + 3.580$ (moles/liter) ($F_{1,2} = 0.29$, not significant)	4	0.318	0.446	

[a] n = number of data points used in the regression.
[b] r = correlation coefficient.
[c] s = standard deviation.
[d] Determined by setting $(d \log 1/ED_{50})/(d \log P) = 0$.

fungitoxicity against the following fungi: *Stemphylium sarcinaeforme, Monilinia fructicola, Helminthosporium maydis* Race T., and *Alternaria solani*. The results are summarized in Table 1. Unless otherwise stated the values are the average of two runs. The ED_{50} was determined from the dose–response curve by the graphic method (6).

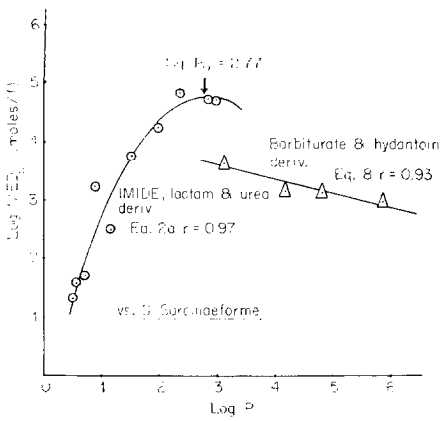


FIG. 1. *Plot of log* $1/ED_{50}$ *vs log* P (*octanol/water*). *Note the parabolic dependence of the activity on log* P *for the imide, lactam and urea derivatives, and the negative dependence for the barbiturate and hydantoin derivatives.*

Regression Analysis

The method of least squares (7) was used to derive the equations listed in Table 2, using an IBM 370/155 computer.

RESULTS AND DISCUSSION

From Table 1 one can see that among the lactam and cyclic urea derivatives studied 1,3-bis(trichloromethylthio)-2-imidazolidinone appears to be the most active

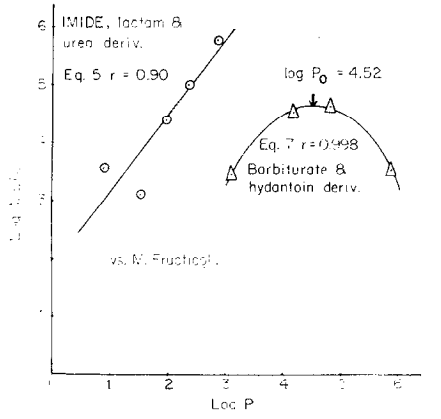


FIG. 2. *Plot of log* $1/ED_{50}$ *vs log* P (*octanol/water*). *Note in this case a linear equation was obtained for five imide, lactam and urea derivatives, while a parabolic equation was obtained for the barbiturate and hydantoin derivatives.*

compound against *S. sarcinaeforme*, and has activity about half log unit below those of captan and folpet. From Eq. 1 and 2 it appears evident that the antifungal activities of the N-$SCCl_3$ derivatives of imides, lactams and ethyleneurea (2-imidazolidinone) can all be correlated by the 1-octanol-water partition coefficient (see Fig. 1). The $(\log P)^2$ term in Eq. 2a and b are significant at 97.5% level as indicated by an *F* test. The ideal lipophilic character ($\log P_0$) of 2.77 in octanol-water is equivalent to 2.19 in oleyl alcohol/water[5] which is slightly below the previously reported value (4). For the five compounds we synthesized and/or tested in this study, linear equations (Eq. 3–5) were obtained for the activities vs *H. maydis*, *A. solani* and *M. fructicola*. This is primarily due to the relatively narrow range of log *P* values of these compounds. The linear equations (see Fig. 2–4) suggest that more lipophilic compounds may have higher antifungal activities within a certain limit, i.e., if they do not go beyond the apex of the parabola. The linear equations should be considered as special cases of the more general parabolic equations (8, 9). For the phenobarbital and diphenylhydantoin derivatives the mono-N-$SCCl_3$ compounds have been reported previously (10, 11). The di-N-$SCCl_3$ substituted compounds were prepared for the first time. From Table 1 it appears that for the dilantin derivatives the mono-substituted compound is more active than the disubstituted one except in the case of *A. solani*. For the phenobarbital derivatives the mono-N-$SCCl_3$ derivative is more active than the disubstituted one except in the case of *M. fructicola*. From these findings and the fact that 1,3-bis(trichloromethylthio)-2-imidazolidinone is less active than the mono-$SCCl_3$ compounds like captan and folpet even though they fit in the same regression line, it appears quite evident that the whole molecule rather than the decom-

[5] Calculated from the equation $\log P_{(\text{oleyl alc.})} = 0.575 + 0.999 \log P_{(\text{octanol})}$, from Leo *et al.*, *Chem. Rev.*, 71, 525 (1971).

position products of N-$SCCl_3$ (e.g., thiophosgene) is responsible for the fungitoxicity.

From Fig. 1–4, one can see that at an isolipophilic point of log $P = 3$ the barbiturate and hydantoin derivatives are less active than the imide, lactam and urea derivatives. The difference is about one log unit or more. This is probably due to the difference in the overall electronic property of the parent molecules, as reflected by the different dipole moments: ethyleneurea (2-imidazolidinone) 4.01 D (12), ε-caprolactam 3.88 D (13), phthalimide 2.12 D (14), diphenylhydantoin 1.74 D and phenobarbital 0.87 D (15). Since the dipole moment data of the N-$SCCl_3$ compounds are not available no quantitative assessment can be made at the present. An alternate possibility is that the 2 groups attack different sites in the fungal cell.

For Eq. 6–10 in Table 2, only four data points are included, the addition of $(\log P)^2$ term is not justifiable except in Eq. 7, where the linear equation of log P gives no correlation at all (Eq. 6, $r = 0.05$) and the $(\log P)^2$ term is significant at 95% level as indicated by an F test ($F_{1,1} = 214.1$). The ideal lipophilic–hydrophilic character ($\log P_0$) of 4.52 with *M. fructicola*[6] is considerably higher than that of *S. sarcinaeforme* indicating different membrane characteristics (16–18). Equations 8 and 9 are significant at 90% level while Eq. 10 is not statistically significant. The negative coefficients associated with log P in Eq. 8 and 9 suggest that increased lipophilicity would only decrease the activity further. In view of the fact that the log P values of diphenylhydantoin and phenobarbital are 2.47 and 1.42, resp., one would expect them to have some antifungal activity (see Eq. 7–10 and Fig. 1–4). However, our experimental results indicate that less than 50% inhibition of the spore germination could be achieved at concentrations ranging from

[6] Previously designated as *Sclerotinia*, it was changed to *Monilinia* after 1951.

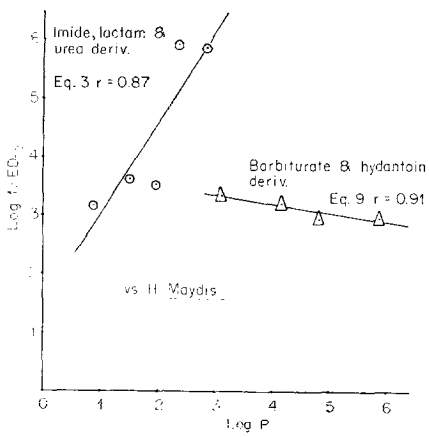


FIG. 3. *Graph showing positive dependence of the antifungal activity on log* P *for the imide, lactam and urea derivatives and negative dependence for the barbiturate and hydantoin derivatives.*

0.01–10 g/liter. This is in contrast to the previous finding of imides and their $SCCl_3$ derivatives, i.e., both the imides and the $SCCl_3$ compounds can be correlated by the same regression line [Eq. 2 of Table 2, Eq. 2 of Ref. (4)]. Lack of activity of diphenylhydantoin and phenobarbital suggests that the fungitoxicity of their N-$SCCl_3$ derivatives is contributed mainly by the $SCCl_3$ moiety, while in the case of captan and folpet both the imide and N-$SCCl_3$ moieties appear to serve as toxicophores.

Some of the equations of Table 2 (6–10)

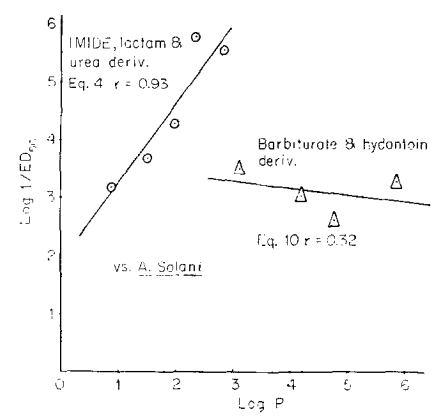


FIG. 4. *Graph showing positive dependence of the antifungal activity on log* P *for the imide, lactam and urea derivatives and poor correlation for the barbiturate and hydantoin derivatives.*

have only four data points and thus one should not place too much emphasis on the correlations and statistics obtained (19). Nevertheless, the repeated patterns of these correlations as seen from Fig. 1–4 tend to substantiate the validity of the dependence of the fungitoxicity on log P. In other words the correlations obtained may be useful guidelines in designing new fungicides.

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