same base composition as the rRNA species extracted from ribosomes, yet they have different sedimentation characteristics (*9*). In most instances, in *E. coli* the difference in sedimentation characteristics between "nascent" and "mature" rRNA is most easily shown for the light rRNA. In the case of cotton the consistent difference relates to the heavy rRNA, whereas the separation of "nascent" and "mature" rRNA of the light species is more difficult to demonstrate on a sucrose gradient. The difference in *E. coli* rRNA in sedimentation properties has been ascribed to a difference in secondary structure between rRNA that has not yet become methylated and rRNA that is derived from the breakdown of ribosomes.

Our data concerning the nature of the labeled RNA from this stage of germinating cotton are open to interpretations other than that of its being "nascent" rRNA. The notion that the labeled particle is indeed a ribosomal precursor particle is based first on the fact that it can be fragmented into two molecular species of RNA whose base composition, within experimental error, corresponds to that of the two species of rRNA from cotton; and secondly on the fact that the labeled RNA species derived from the particle have sedimentation properties distinct from those of mature rRNA, a phenomenon reported by a number of workers to apply to "nascent" rRNA from *E. coli* (*9*). In addition, the germinating cotton particle is very similar to the *E. coli* particles formed during inhibition of protein synthesis with respect to its relative position on sucrose-gradient profiles of ribosomal subunits (*10*). There is the possibility that the 45*S* particles of HeLa cells, the 25 to 30*S* particles in *E. coli*, and the germinating cotton particle may indicate an analogous sequence of events in ribosome synthesis in all organisms.

In any explanation for the synthesis and accumulation of this particle by cotton embryos at this stage of germination one must consider that the synthesis of what is here described as "nascent" rRNA is demonstrable only by isotope incorporation, and probably represents a negligible contribution to embryonic development.

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17 May 1965

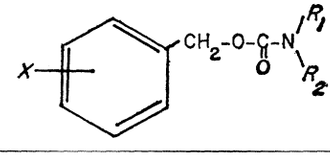
3,4-Dichlorobenzyl Methylcarbamate and Related Compounds as Herbicides

Abstract. *3,4-Dichlorobenzyl methylcarbamate is a selective preemergence herbicide active against both grass and broadleaf weeds. Synthesis of pigment is inhibited in species sensitive to this chemical. Minor structural modifications, such as positioning of the chlorine on the phenyl ring or variations in the* N*-substituent, significantly alter its activity.*

Esters of certain carbanilic acids have been known for many years as regulators of plant growth. Friesen (*1*) was the first to recognize the inhibition of oats and wheat by ethyl carbanilate (phenylurethane). Limited research (*2*) concerning effects of various carbanilates on plant growth continued until the discovery (*3*) of the growth-inhibiting properties of isopropyl carbanilate, IPC. The practical utility of IPC as an herbicide for selective removal of grass weeds from broadleaf crops stimulated additional research that led to the discovery of the herbicidal properties of isopropyl *m*-chlorocarbanilate, CIPC (*4*).

Major efforts have been directed primarily toward the exploration and utilization of carbanilates as herbicides.

Table 1. Herbicidal activities of various benzyl carbamates rated (10 days after treatment) on the following basis: 0, no injury; 1, slight injury, slight reduction in stand, or both; 2, moderate injury, moderate reduction in stand, or both; 3, severe injury, severe reduction in stand, or both; 4, complete kill.



Compound	Substituent			Post-emergence (4 kg/hectare)		Pre-emergence (5 kg/hectare)	
	X	R_1	R_2	Grass*	Broad-leaf†	Grass‡	Broad-leaf§
(A)	H	CH_3	H	0	2	0	0
(B)	2-chloro	CH_3	H	0	2	0	0
(C)	3-chloro	CH_3	H	2	4	4	4
(D)	4-chloro	CH_3	H	2	5	3	6
(E)	2,3-dichloro	CH_3	H	0	2	0	1
(F)	2,4-dichloro	CH_3	H	4	7	0	0
(G)	2,5-dichloro	CH_3	H	0	2	0	0
(H)	2,6-dichloro	CH_3	H	0	2	0	0
(I)	3,4-dichloro	CH_3	H	4	5	7	7
(J)	3,5-dichloro	CH_3	H	2	4	2	2
(K)	3,4-dichloro	H	H	2	6	4	5
(L)	3,4-dichloro	CH_3	CH_3	0	2	2	0
(M)	3,4-dichloro	C_2H_5	H	4	8	1	0
(N)	3,4-dichloro	*i*-C_3H_7	H	2	3	1	1
(O)	3,4-dichloro	*n*-C_4H_9	H	2	3	2	1
(P)	3,4-dichloro	*t*-C_4H_9	H	0	0	0	0
(Q)	3,4-dichloro	allyl	H	2	6	0	0
(R)	3,4-dichloro	phenyl	H	2	4	0	0
(S)	3,4-dichloro	phenyl	CH_3	0	1	0	0
(T)	3,4-dichloro	benzyl	H	0	2	0	0

* Corn, actual rating (0 to 4) × 2. † Tendergreen bean and tomato, total for both. ‡ Perennial rye grass and pearl millet, total for both. § Mustard and pigweed, total for both.

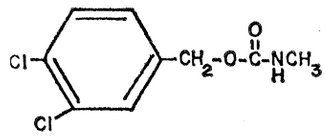


Fig. 1. 3,4-Dichlorobenzyl methylcarbamate.

Variations in either the alcohol or carbanilic acid portions of the molecule cause major changes in herbicidal activity (*5*); however, the most herbicidal carbanilates are primarily grass toxicants with only limited activity against broadleaf weeds.

Certain *N*-alkyl carbamates derived from aromatic alcohols have moderate growth-regulating properties (*6*) but have not found major utility as broad-spectrum herbicides (*7*). Carbamates, however, have been largely used as insecticides [for example carbaryl(1-naphthyl methylcarbamate) (*8*)], and, judged by the number of new carbamate pesticides appearing, most of the effort has been in the area of insecticides. Working on the growth-regulating activity of various *N*-alkyl carbamates, we have discovered the potent, broad-spectrum herbicidal activity against both grass and broadleaf species of various substituted benzyl methylcarbamates, specifically 3,4-dichlorobenzyl methylcarbamate (Fig. 1) (*9*).

The carbamates were synthesized by adding the desired isocyanate to the corresponding alcohol in the presence of catalytic amounts of dibutyltin diacetate. Herbicidal activities of the various compounds were determined by standard preemergence and postemergence treatments under greenhouse conditions. The degree and type of activity varied markedly with variously substituted benzyl methylcarbamates (Table 1). The unsubstituted compound (A) had no preemergence and only slight postemergence herbicidal activity. Substitution of a single chlorine atom in the meta (C) or para position (D) increased both types of activity. Ortho substitution (B) did not alter the minor activity of the unsubstituted compound.

Table 2. Weed and crop tolerances to preemergence applications of 3,4-dichlorobenzyl methylcarbamate; rated on the same scale as in Table 1, but 21 days after treatment.

Plant	Rating	Application (kg/hectare)
	Susceptible	
Barnyard grass	4	2.5
Cantaloupe	3	5.0
Crabgrass	4	1.0
Green foxtail	3	5.0
Lespedeza	4	5.0
Lettuce	3	5.0
Pigweed	3	2.5
Plantain	3	0.5
Sheep sorrel	3	5.0
Wild oats	4	2.0
Yellow foxtail	4	1.0
	Resistant	
Cocklebur	0	10.0
Cotton	0	10.0
Garden peas	0	10.0
Peanuts	1	10.0
Snap beans	0	10.0
Soybean	1	10.0

With one exception, substitution of a second chlorine in the phenyl ring (E, F, G, H, J) decreased preemergence activity to less than that of either the *m*- or *p*-chlorobenzyl methylcarbamate; the exception, 3,4-dichlorobenzyl methylcarbamate (I), showed significantly greater preemergence activity than monosubstituted benzyl methylcarbamates. Interestingly, the most significant postemergence activity was shown by 2,4-dichlorobenzyl methylcarbamate (F), which had no preemergence activity.

Optimum activity with the 3,4-dichloro configuration has been reported for the phenyl ureas (*10*) and anilides (*11*), but the reverse is true of unsubstituted and substituted benzyl acetamides (*12*), in which the 3,4-disubstituted compound was less active than the unsubstituted compound. Of the four dichlorocarbanilates tested for preemergence herbicidal activity by Shaw and Swanson (*5*), only one, isopropyl 2,5-dichlorocarbanilate, was classed "very active"; the others, isopropyl 2,4-dichlorocarbanilate, isopropyl 3,4-dichlorocarbanilate, and isopropyl 3,5-dichlorocarbanilate, were classed "moderately active."

Activity of the most active preemergence compound, 3,4-dichlorobenzyl methylcarbamate, proved very sensitive to variation of the *N*-substituent. When the *N*-methyl group was removed, the resulting *N*-unsubstituted compound (K) was moderately active. Replacement of the *N*-methyl group with higher alkyl (M, N, O, P), alkenyl (Q), aryl (R), or alkaryl (T) groups caused loss of preemergence activity, although in certain instances (Q) postemergence activity was observed. *N*, *N*-disubstitution (L, S) substantially reduced activity. The preemergence inactivity of 3,4-dichlorobenzyl carbanilate (R) agrees essentially with the results of Shaw and Swanson (*5*) with benzyl carbanilate against the same species, pigweed and mustard.

Carbanilates differ widely in ability to alter normal chlorophyll content. CIPC increased chlorophyll (*13*), while isopropyl 5-chloro-2-methylcarbanilate, isopropyl 5-chloro-2-methoxycarbanilate, isopropyl 3-trifluoromethylcarbanilate, and isopropyl 3-methylcarbanilate induced various degrees of chlorosis (*5*). Ability of these compounds to inhibit synthesis of chlorophyll was a function of plant species, and the property of inhibition of chlorophyll did not appear to be associated with total herbicidal activity (*5*).

The most characteristic response of sensitive plants to 3,4-dichlorobenzyl methylcarbamate is appearance of extreme chlorosis or discoloration. The ability of 3,4-dichlorobenzyl methylcarbamate to inhibit synthesis of chlorophyll is limited to crops and weeds that are sensitive to the compound as an herbicide. Concentrations as low as 1.1 kg/hectare (1 lb/acre) completely inhibited synthesis of chlorophyll by sensitive species (yellow foxtail, crabgrass), but there was no such inhibition by 10 times that concentration with resistant species (cotton, peas, beans, and cocklebur).

The property of inhibiting formation of chlorophyll appears to be associated with herbicidal activity. This specificity can be utilized, and 3,4-dichlorobenzyl methylcarbamate can be used to control sensitive weeds in several crops. Table 3 illustrates the degree of selective toxicity. Both grassy and broadleaf weeds are sensitive to 3,4-dichlorobenzyl methylcarbamate.

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5 April 1965

Carboxyhemoglobin: Hemodynamic and Respiratory Responses to Small Concentrations

Abstract. *Hemodynamic and respiratory measurements were made on humans before and after inhalation of sufficient carbon monoxide to raise the carboxyhemoglobin to between 5 and 10 percent of saturation. Arterial and mixed-venous oxygen tensions decreased on average 7.3 and 13.3 percent, respectively. One of five subjects developed evidence of mild left-ventricular dysfunction.*

The recent report on smoking by the Surgeon General (*1*) summarized the known effects of smoking on the cardiovascular system. Most investigators have attributed these effects to the action of nicotine and miscellaneous coal tars, although certain observations are not thus conveniently explained. For example, the significant increase in the oxygen debt during exercise, observed in smokers (*2*), cannot be attributed to these agents. It is remarkable that carbon monoxide, a known toxicant constituting 4.2 percent of tobacco smoke (*1*), has not been considered as an explanation of the diverse effects of tobacco smoke on the circulation. Reluctance to indict carbon monoxide has probably derived from Hanson and Hastings's observations that saturation of carboxyhemoglobin in smokers ranged from 3 to 4 percent (*3*) and from Haldane's observations that physiologic effects did not occur until carboxyhemoglobin reached 20 to 30 percent of saturation (*4*). Recent evidence suggests that both these observations may be inaccurate (*5, 6*).

A sensitive and rapid gas-chromatographic method for the measurement of carbon monoxide in blood (*6*) has permitted extensive study of the concentration of carboxyhemoglobin in the blood of smokers. We have found the carbon monoxide content of blood in 28 normal nonsmokers to range from 0.01 to 0.36 percent by volume (average saturation, 0.9 percent). In 25 smokers, carbon monoxide content ranged from 0.15 to 2.39 percent (average saturation, 4.2 percent) and was related to the amount of tobacco smoked. However, smaller individuals, and those whose blood showed lower hematocrits, showed higher contents of carboxyhemoglobin in their blood after similar inhalation of tobacco smoke; in one heavy smoker the value was 17 percent of saturation.

Cardiorespiratory responses to small amounts of carbon monoxide were determined by transvenous catheterization of the heart. A cardiac catheter was positioned in the main pulmonary artery to measure intracardiac pressures and to sample mixed venous blood; arterial blood was obtained by Cournand needle from a brachial artery. Oxygen tensions of the bloods were measured (*7*) before and 5 to 7 minutes after inhalation of carbon monoxide at 0.4 percent in air.

Table 1 shows that oxygen tensions of arterial and mixed-venous bloods decreased on average 7.3 and 13.3 percent, respectively, when the carboxyhemoglobin rose to between 4.95 and 9.69 percent of saturation. Neither cardiac output, oxygen consumption, nor body-surface ventilation per minute changed consistently, but the difference in oxygen pressure in arterial and venous bloods, which reflects extraction of oxygen by tissue, increased in all five subjects. Intracardiac pressures did not change in four of the subjects; in the individual that received the greatest amount of carbon monoxide, left atrial pressure rose and cardiac output fell, indicating development of abnormal left ventricular function.

These studies demonstrate that small amounts of carboxyhemoglobin decrease oxygen tension in both arterial and mixed-venous bloods. Oxygen tension of arterial blood is a function of the oxygen concentration in the inspired air, the resistance to diffusion of oxygen imposed by alveolar membrane and red blood cells, and the shunting of venous blood directly to systemic arteries. Such shunts occur through collapsed or inadequately ventilated alveoli and through anatomic pulmonary arteriovenous comunications (*7*). The concentration of oxygen in inspired air was unchanged after the inhalation of carbon monoxide, and no evidence suggested an increase in venoarterial shunting. Two explanations may be advanced: (i) decrease in the capacity of the blood to carry oxygen can be shown to magnify the effect of physiologic venoarterial shunting, and (ii) carboxyhemoglobin containing red cells may impose abnormal resistance to diffusion of oxygen. Roughton and Forster have stressed the importance of oxygen distribution within the blood (*8*); we postulate that binding of heme groups with carbon monoxide may further hinder distribution of oxygen.

The partial pressure of oxygen in venous blood, an index of maximum oxygen tension in tissue, decreased to a greater degree than arterial oxygen tension because of changes in the hemoglobin dissociation curve. Haldane demonstrated in 1912 that the partial combination of hemoglobin with carbon monoxide makes the remaining hemoglobin bind oxygen with abnormal tenacity (*9*). Thus, unloading of oxygen results only from exposure to lower oxygen tensions. This effect may be particularly harmful in a vascular bed,

Table 1. Hemodynamic and respiratory responses of five normal subjects to carboxyhemoglobin. The first of each pair of lines shows values before the breathing of CO at 0.4 percent in air; the second, values after breathing. COHb, carboxyhemoglobin; sat, saturation; LA, left artium; PA, pulmonary artery; Ar, arterial; t_{O_2}, oxygen tension; Ven, mixed venous; Ar-ven diff, arterial-venous difference; Vent, ventilation per square meter of body-surface area per minute; t_{CO_2}, carbon dioxide tension.

COHb (% sat)	Pressure (mm-Hg)				Ar-ven diff (% by vol.)	Cardiac output (lit./min)	Vent (liter)	t_{CO_2} (mm-Hg)
	LA (wedge)	PA (mean)	Ar t_{O_2}	Ven t_{O_2}				
0.48	28	9	89	45	3.40	5.23	4.23	34
8.84	28	9	81	42	3.82	4.46	4.23	36
			86	37	3.96	4.37	4.68	36
6.29			80	30	4.55	4.35	5.72	36
	3	14	74	42	3.92	4.31	2.55	36
	3	12	68	37	4.24	4.17	3.11	40
0.37	9	13	84	49	4.00	5.32	5.43	39
4.95	9	13	79	42	4.66	6.54	7.36	38
0.96	7	12	77	41	4.02	6.00	4.87	36
9.69	11	18	72	35	4.81	4.68	4.24	39