Azobenzene Carbamates as Insecticides

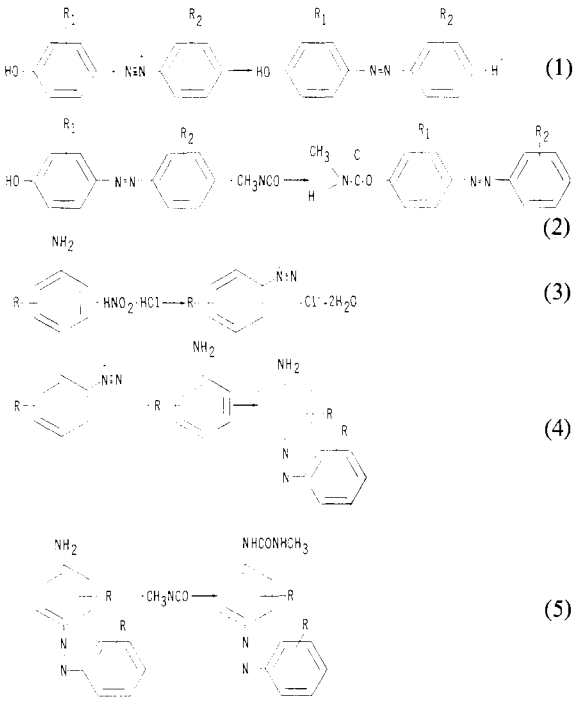
WARREN W. KAEDING[1,3] AND EUGENE E. KENAGA[2]

A series of phenyl carbamates with *para*-azo groups has been prepared. Interesting insecticidal activity has been found in screening tests with Mexican bean beetles and Southern army worms.

Previous papers of this series (Kaeding and Kenaga, 1965; Kaeding *et al.*, 1965) have described the synthesis and insecticidal activity of a number of phenyl-*N*-methylcarbamates. The type and location of various substituents on the aromatic ring were shown to have a profound effect on the insecticidal potency. High activity was observed with the presence of amino and imino (Schiff base) groups. The authors were interested in determining the effect of further changes in substituent groups attached to a nitrogen atom located in the para position. Phenyl carbamates with an azo group were prepared and tested for insecticidal activity (Kaeding, 1961).

Synthesis

Compounds of this series are restricted to derivatives with aromatic rings attached to each nitrogen atom of the azo group because of the characteristic stability of this configuration. Phenols with the desired ortho and meta substituents were coupled with the appropriate benzene diazonium salts (Equation 1). The latter were prepared from the corresponding aniline derivatives.



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A discussion of the many factors which influence the azo coupling reaction is beyond the intended scope of this paper. The comprehensive treatise by Saunders (1949) was a valuable aid for the selection of experimental conditions.

The carbamates were prepared by a reaction between methyl isocyanate and the appropriate hydroxyazobenzene derivative (Equation 2). A rapid reaction occurred in a manner typical for that observed with most phenols. The carbamates were usually red, orange, or yellow and lighter in color than the starting phenol. The compounds are summarized in Tables I and II.

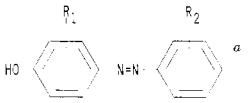
The new compounds were characterized by means of elemental analyses and an interpretation of their infrared spectra. All of the carbamates had strong, sharp absorption bands at the 3.0- and 5.8-micron regions, which were characteristic of the N—H and C=O stretching frequencies.

The position of the azo group on the phenol ring was determined by the isomer formed during the coupling reaction (Equation 1). The position para to the hydroxy group is preferred (Saunders, 1949), but the ortho isomer can be formed under certain conditions. The assignment of a structure to the isomer produced, for the compounds listed in Table I, was based on an interpretation of their infrared spectra.

The infrared spectra of the azophenols were run in anhydrous carbon tetrachloride at dilutions sufficient to eliminate intermolecular association. The results are summarized in Table I. Under these conditions a strong, sharp band (hydroxy stretching frequency) appears in the 3610-cm.$^{-1}$ region. The frequency for phenol itself is 3612 cm.$^{-1}$ (Baker *et al.*, 1964). The presence of ortho substituents influences this absorption frequency, and is especially apparent when hydrogen bonding between the hydroxyl group and the substituent is strong by virtue of favorable steric and electronic factors. The interaction with an ortho olefinic double bond resulted in a substantial decrease in frequency as well as a broadening of the band (Baker and Shulgin, 1964). The authors have concluded that an even stronger interaction takes place between an azo group ortho to the hydroxyl group. Absorption bands were absent from the 3200- to 4000-cm.$^{-1}$ region with the following ortho azo derivatives: 1-(phenylazo)-2-naphthol, 1-(2-methylphenylazo)-2-naphthol, and 2(2-methylphenylazo)-4-methylphenol (obtained from Williams, Ltd., Hounslow, England). Presumably the absorption associated with the hydroxyl stretching frequency of phenols had been shifted to a

[1] The Dow Chemical Co., Walnut Creek, Calif.
[2] The Dow Chemical Co., Midland, Mich.
[3] Present address, Central Research Laboratory, Mobil Chemical Co., Metuchen, N.J.

Table I. Azo Phenols



R_1	R_2	Formula	M.P., °C.	OH Stretch, $Cm.^{-1}$	Analysis Theory C	Theory H	Theory N	Found C	Found H	Found N
H	H	$C_{12}H_{10}N_2O$	153–4	[b]	[c]	...	...	...	...	...
3-CH_3	H	$C_{13}H_{12}N_2O$	105	3598.6[d]	[e]	...	...	...	...	...
3,5-$(CH_3)_2$	H	$C_{14}H_{14}N_2O$	104	3610	[f]	...	...	...	...	...
3-*t*-C_4H_9	H	$C_{16}H_{18}N_2O$	107–108	3601	75.56	7.13	11.02	75.06	6.88	10.87
3,5-$(CH_3)_2$	2-CH_3	$C_{15}H_{16}N_2O$	108–110	3603	74.97	6.71	11.66	74.88	6.64	12.18
3,5-$(CH_3)_2$	3-CH_3	$C_{15}H_{16}N_2O$	114–115	3610	74.97	6.71	11.66	74.65	6.19	11.84
3,5-$(CH_3)_2$	4-CH_3	$C_{15}H_{16}N_2O$	96–97	3610	74.97	6.71	11.66	74.90	6.67	11.66
3,5-$(CH_3)_2$	2,6-$(CH_3)_2$	$C_{16}H_{18}N_2O$	114–15	3600.1[d]	75.56	7.13	11.02	75.65	7.29	11.02
3,5-$(CH_3)_2$	4-Cl	$C_{14}H_{13}ClN_2O$	113–15	3600	64.49	5.02	10.75	63.53	4.78	11.07
3,5-$(CH_3)_2$	2,5-$(Cl)_2$	$C_{14}H_{12}Cl_2N_2O$	180–2	[b]	24.07	[g]	9.49	24.83	[g]	10.04
3,5-$(CH_3)_2$	3,4-$(Cl)_2$	$C_{14}H_{12}Cl_2N_2O$	146–7	3604	24.02	[g]	9.49	21.88	[g]	9.84
3,5-$(CH_3)_2$	4-NO_2	$C_{14}H_{13}N_3O_3$	167–8	3603	61.98	4.83	15.49	61.60	4.72	15.99
3,5-$(CH_3)_2$	4-$N(CH_3)_2$	$Cl_{16}H_{19}N_3O$	150[d]	3618	71.35	7.11	15.60	71.54	6.73	15.97
3,5-$(CH_3)_2$	4-$N(C_2H_5)_2$	$C_{18}H_{23}N_3O$	156–7	3618	72.69	7.79	14.13	72.84	7.31	14.25
3,5-$(CH_3)_2$	2-OCH_3	$C_{15}H_{16}N_2O_2$	164–5	3610	70.29	6.29	10.93	71.21	6.22	10.95
3,5-$(CH_3)_2$	2,5-$(OCH_3)_2$	$C_{16}H_{18}N_2O_3$	105–106	[b]	67.11	6.34	9.79	67.15	6.68	10.24
3-CH_3	4-$N(CH_3)_2$	$C_{15}H_{17}N_3O_3$	158–9	[b]	70.56	6.71	16.46	70.78	6.68	16.68
2,3-CH=CH—CH=CH—[h]	H	$C_{16}H_{12}N_2O$	200–202	3602	[i]	...	...	...	...	...
3-OC_2H_5	2-OCH_3	$C_{15}H_{16}N_2O_3$	123–5	3320[j]	66.16	5.92	10.29	65.78	6.23	10.36
3,5-$(CH_3)_2$	2-OCH_3-5-CH_3	$C_{16}H_{18}N_2O_2$	124–5	3615	71.09	6.71	10.37	71.38	6.64	10.52
3-*t*-C_4H_9	2-OCH_3	$C_{17}H_{20}N_2O_2$	145–6	3610	71.80	6.03	9.86	69.29	6.54	10.00

[a] OH group at 1-position. [b] Not run. [c] Beilstein, 1933a, m.p. 152° C. [d] Obtained with Beckman IR-7, other obtained with IR-10 [e] Beilstein, 1933b, m.p. 109° C. [f] Beilstein, 1933d, m.p. 104° to 105° C. [g] Chlorine. [h] Naphthalene ring. [i] Beilstein, 1933c, m.p., 205–206° C. [j] Structure uncertain, hydrazobenzene derivative suggested.

widely separated region of the spectrum. The absence of an absorption band in the 3200- to 4000-cm^{-1} region was interpreted as being characteristic of an azo group located ortho to the hydroxyl group on the aromatic ring. On the other hand, the appearance of a strong, sharp band in the 3600-$cm.^{-1}$ region was taken as evidence of the absence of an ortho azo group. Since coupling meta to the hydroxy group is highly unlikely (Saunders, 1949), these compounds were assigned the para configuration.

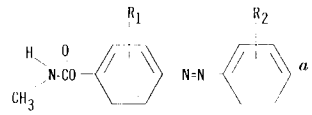
When an attempt was made to prepare the carbamate of an *o*-hydroxyazobenzene derivative in the usual manner, the authors observed that a reaction did not take place. This also suggests an unusually strong interaction between the hydroxyl and azo groups. This is consistent with the spectra and the high electron density associated with nitrogen atoms and the double bond.

When aromatic diazonium salts were prepared (Equation 3) which contained substituents which tended to increase the ring electron density strongly, coupling with the starting aniline (Equation 4) was an important side reaction. The reaction product of the latter with methyl isocyanate (Equation 5) gave the corresponding urea derivative. These isosteric compounds did not possess insecticidal activity.

The selection of compounds for synthesis should be designed to provide a systematic variation of substituents on the parent structure, *p*-(phenylazo)-phenyl *N*-methyl carbamate, compound I, and relate this to insecticidal activity. The nine positions available in this series impose a formidable synthetic problem and the selection of derivatives for this initial survey must be somewhat arbitrary. The relative ease of synthesis, availability of starting materials, and previously established, broad guide lines relating chemical structure to activity also influenced the choice of compounds.

Metcalf and Fukuto have developed an elegant theory for the mode of insecticidal action of aromatic carbamates (1965). Convincing evidence has been presented that these materials compete with acetylcholine in the cholinesterase enzyme system of insects. Stated simply, the carbamate blocks the site on the enzyme surface to acetylcholine and interrupts a vital life process. Molecular models provided a demonstration of this hypothesis. An impression was made in a plaster cast, which represented the enzyme surface, by a molecular model of

Table II. Carbamates



	R1	R2	Formula	M.P., °C.	Analysis Theory C	Theory H	Theory N	Found C	Found H	Found N	Insecticidal Activity MBB[b] LD_{50}	MBB[b] LD_{95}	SAW LD_{50}	SAW LD_{95}
I	H	H	$C_{14}H_{13}N_3O_2$	155–6	65.87	5.13	16.46	65.73	5.18	16.56	>500	>500	>500	>500
II	3-CH_3	H	$C_{15}H_{15}N_3O_2$	138–9	66.90	5.61	15.60	66.67	6.09	15.06	6.5	11.0	45	>500
III	3,5-$(CH_3)_2$	H	$C_{16}H_{17}N_3O_2$	120–1	67.82	6.05	14.83	67.45	6.13	14.76	75	180	70	160
IV	3-*t*-C_4H_9	H	$C_{18}H_{21}N_3O_2$	146–7	69.43	6.80	13.49	69.04	6.51	12.93	80	180	>500	>500
V	3,5-$(CH_3)_2$	2-CH_3	$C_{17}H_{19}N_3O_2$	125–7	68.67	6.44	14.15	67.94	6.28	14.30	0.22	0.35	>500	>500
VI	3,5-$(CH_3)_2$	3-CH_3	$C_{17}H_{19}N_3O_2$	109	68.67	6.44	14.15	68.03	6.47	14.06	1.3	1.8	>500	>500
VII	3,5-$(CH_3)_2$	4-CH_3	$C_{17}H_{19}N_3O_2$	145–6	68.67	6.44	14.15	68.08	6.48	14.10	70	300	>500	>500
VIII	3,5-$(CH_3)_2$	4-Cl	$C_{16}H_{16}ClN_3O_2$	178–9	60.47	5.08	13.22	61.34	5.21	13.87	16	20	>500	>500
IX	3,5-$(CH_3)_2$	2,5-$(Cl)_2$	$C_{16}H_{15}Cl_2N_3O_2$	208–209	54.56	4.29	11.93	54.33	4.43	12.20	3.2	4.2	>500	>500
X	3,5-$(CH_3)_2$	3,4-$(Cl)_2$	$C_{16}H_{15}Cl_2N_3O_2$	169–70	20.13[c]	...	11.93	19.88[c]	...	12.02	4.0	6.0	>500	>500
XI	3,5-$(CH_3)_2$	4-NO_2	$C_{16}H_{16}N_4O_4$	195–6	58.53	4.91	17.07	58.67	4.94	16.96	47	95	88	180
XII	3,5-$(CH_3)_2$	4-$N(CH_3)_2$	$C_{18}H_{22}N_4O_2$	144–6	66.23	6.80	17.17	66.60	6.51	17.16	2.8	3.7	50	95
XIII	3,5-$(CH_3)_2$	4-$N(C_2H_5)_2$	$C_{20}H_{26}N_4O_2$	148–50	67.77	7.39	15.81	68.38	7.43	15.88	2.8	3.7	45	65
XIV	3,5-$(CH_3)_2$	2-OCH_3	$C_{17}H_{19}N_3O_3$	124–5	65.16	6.11	13.41	67.91	6.29	12.33	80	170	70	190
XV	3,5-$(CH_3)_2$	2,5-$(OCH_3)_2$	$C_{18}H_{21}N_3O_4$	131–4	62.96	6.17	12.24	62.26	6.42	11.0	7.0	11.0	40	60
XVI	3-CH_3	4-$N(CH_3)_2$	$C_{17}H_{20}N_4O_2$	154–6	65.36	6.45	17.94	68.16	6.70	17.55	4.5	7.0	55	100
XVII	2,3-CH=CH—CH=CH—[d]	H	$C_{18}H_{15}N_3O_2$	168–70	70.80	4.95	13.76	70.10	4.97	13.16	>500	>500	>500	>500
XVIII	3-OC_2H_5	2-OCH_3[e]	$C_{17}H_{19}N_3O_4$	138–40	61.99	5.81	12.76	61.87	5.68	12.64	100	200	>500	>500
XIX	3,5-$(CH_3)_2$	2-OCH_3-5-CH_3	$C_{18}H_{21}N_3O_3$	137–8	66.04	6.47	12.84	65.95	6 45	13.20	0.78	1.0	220	310
XX	3-*t*-C_4H_9	2-OCH_3	$C_{19}H_{23}N_3O_3$	117–19	66.84	6.79	12.31	65.67	6.78	12.15	7.0	12.0	>500	>500

[a] Carbamate group at No. 1 position.
[b] Concentration of insecticide in parts per million to give 50 and 95% lethal dose for Mexican bean beetle (MBB) and Southern army worm (SAW).
[c] Chlorine.
[d] Naphthalene ring.
[e] Structure uncertain.

acetylcholine. A direct relationship was established between the degree of fit in the cavity of the plastic cast of analogous models of a large number and variety of aromatic carbamates and their insecticidal activity.

In addition to a physical fit of the carbamate molecule in the enzyme surface, an electrostatic attraction was proposed to keep it in position and thereby deny access to acetylcholine (Metcalf and Fukuto, 1965). In the enzyme, a positively charged esteratic and negatively charged anionic site, separated by a distance of about 5 A., were matched and held in place by oppositely polarized portions of the carbamate substrate. The carbamic acid portion of the latter was held by the esteratic site, while a positively polarized portion of the aromatic ring in the vicinity of the ortho or meta position was held by the anionic site.

Previous work has demonstrated that *p*-amino and -imino groups markedly increase insecticidal activity by comparison with the corresponding unsubstituted compounds (Kaeding and Kenaga, 1965; Kaeding *et al.*, 1965). The basic nature of the nitrogen atom (negative character), rather than size of the substituent, appears to be significant here, since activity was preserved when the nitrogen was bonded to a total of eight saturated carbon atoms. This suggests an electrostatic attraction to a cationic (positive) surface of the enzyme, in the vicinity of the para position.

The *p*-phenylazo group is a relatively large, linear substituent which approximately doubles the length of the phenyl carbamates. Although reduced mobility would be anticipated, interactions with a much larger portion of the enzyme surface are possible.

Substituents on the azophenyl ring could alter the polar nature of the *p*-azo group or interact directly with other surfaces of the enzyme, probably by electrostatic forces, and affect the ability of the carbamate molecule to stick on the active site.

Dialkylamino groups in the para position of the azophenyl group, compounds XII and XIII, have significantly greater activity than the parent compound, III. Alkoxy groups, compounds XV and XIX, also potentiate activity, but to a lesser extent. Perhaps these groups with relatively higher electron density interact with a cationic site on the enzyme surface considerably removed from the esteratic position. They could also enrich the electron density of the azo group by resonance.

With Mexican bean beetles, methyl groups in the azophenyl ring, (compounds V, VI, and VII) display an effect similar to that shown by the single-ring aromatic carbamates studied earlier (Metcalf and Fukuto, 1965), ortho, meta > para.

In contrast with the phenyl carbamate series (Metcalf *et al.*, 1964), electron-withdrawing groups, such as nitro or chlorine (compounds VIII, IX, X, and XI) increased activity with Mexican bean beetles but reduced the effect with Southern army worms, when compared with the parent compound, III. Perhaps electrostatic interactions between the carbamate substrate and the enzyme surface, with areas of different negative and positive character, account for this. Subtle differences of this nature could explain the variations in activity observed with different insect species and the inability to establish firm rules relating structure to activity.

Experimental

Primary leaves of Cranberry bean plants, *Phaseoleus vulgaris* L. (var. Cran.), were dipped in aqueous dilutions containing the carbamates. The leaves, when dry, were infested with third instar larvae of the Mexican bean beetle (MBB), *Epilachna varivestis* Muls., or third instar larvae of the Southern army worm (SAW), *Prodenia eridania* (Cran). The infested plants were caged and held at greenhouse temperatures of about 80° F. for 6 days before mortality counts were made. These counts were corrected for natural mortality by the use of Abbott's formula.

Synthesis of Compounds

Phenols. A specific example of the azo coupling reaction is shown to illustrate the method (Blatt, 1943).

4(2-Methylphenylazo)-3,5-xylenol. Solution A was prepared by dissolving 10.7 grams (0.1 mole) of *o*-toluidine in a solution of 30 ml. of concentrated HCl and 100 ml. of water and cooling to 0° C. Solution B was prepared by dissolving 6.9 grams of sodium nitrite (0.1 mole) in 25 ml. of water and cooling to 0° C. Solution C was prepared by dissolving 12.2 grams (0.1 mole) of 3,5-xylenol in a solution of 12.0 grams of NaOH in 100 ml. of water. After heating to form a solution the temperature was reduced to 0° C. Solutions A and B were combined and allowed to stand for 45 minutes in an ice bath. Then AB was poured into C with agitation and allowed to stand for 20 minutes. The addition of some pentane appeared to assist the crystallization of the product. The latter was removed by filtration, washed with water and pentane, and recrystallized from hexane to give orange-brown crystals, m.p. 108–110° C.

***N*-Methylcarbamates.** The phenol used for preparing each carbamate was dissolved in either dry hexane, ether, or methylene chloride to give a solution approaching saturation at room temperature and treated with a 10 to 100% molar excess of methyl isocyanate and a trace of triethylamine catalyst. An exothermic reaction usually took place, and if amounts of phenol in excess of 50 grams were used, an ice bath was necessary to control the temperature. The crude product was purified by recrystallization from an appropriate solvent such as hexane, carbon tetrachloride, or chloroform.

The infrared spectra were obtained with either a Beckman IR-7 or Beckman IR-10 spectrophotometer. A precision of ± 0.2 and ± 5 cm.$^{-1}$, respectively, was obtained. The cell length was 1.0 cm. and the concentrations, in anhydrous CCl_4, were approximately $5 \times 10^{-3} M$. The cell temperature was ambient (about 25° C.).

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