Synthesis of Possible Metabolites of Methylcarbamate Insecticide Chemicals

Substituted-Aryl *N*-Hydroxymethylcarbamates

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There is a need for authentic preparations of substituted-aryl *N*-hydroxymethylcarbamates because there is reason to believe that these compounds are metabolites of the corresponding substituted-aryl *N*-methylcarbamates. Substituted-aryl *N*-hydroxymethylcarbamates are formed by catalytic hydrogenolysis of substituted-aryl *N*-benzyloxymethylcarbamates, prepared by reaction of the corresponding substituted-phenols with benzyloxymethyl isocyanate. This paper gives two methods for the preparation of benzyloxymethyl isocyanate. It also describes the *N*-benzyloxymethylcarbamates and *N*-hydroxymethylcarbamates of the following phenols: 2-isopropoxyphenol; 3-isopropylphenol; 3-(1-methylbutyl)phenol; 3,5-diisopropylphenol; 2,3,5-trimethylphenol; 3,4,5-trimethylphenol; 4-dimethylamino-3-cresol; 4-dimethylamino-3,5-xylenol; 2-chloro-4,5-xylenol. Difficulties resulting from reduction of the naphthalene ring are encountered in attempts to prepare 1-naphthyl *N*-hydroxymethylcarbamate by the described procedure. The anticholinesterase activity and toxicity to mice of the *N*-hydroxymethylcarbamates generally are less than those of the corresponding *N*-methylcarbamates; so, hydroxylation of the methyl moiety of the methylcarbamoyl grouping generally constitutes a detoxification reaction.

In studies on characterization and toxicity of metabolites of *N*-methylcarbamate insecticide chemicals, there is a need for a variety of authentic compounds as standards for comparison. Metabolism of *N*-methylcarbamates and *N,N*-dimethylcarbamates yields products which appear to be *N*-hydroxymethylcarbamates and *N*-methyl-*N*-hydroxymethylcarbamates, respectively, because these products liberate formaldehyde on acid degradation and they do not appear to be chemically modified on other parts of the molecule (Dorough, 1967; Dorough and Casida, 1964; Dorough *et al.*, 1963; Hodgson and Casida, 1960, 1961; Hook and Smith, 1967; Kuhr and Casida, 1967; Leeling and Casida, 1966; Matthews and Hodgson, 1966; Oonnithan and Casida, 1966, 1968; Shrivastava, 1967; Tsukamoto and Casida, 1967a,b; Tsukamoto *et al.*, 1968; Zubairi and Casida, 1965). Reaction of 1-naphthyl carbamate with paraformaldehyde in acetic acid forms 1-naphthyl *N*-hydroxymethylcarbamate, but the yield is only 2% and there is difficulty in separating the desired compound from a number of other reaction products (Dorough and Casida, 1964).

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The carbamoyl group is resistant to catalytic hydrogenolysis under mild conditions (Abdel-Wahab and Casida, 1967; Hartung and Simonoff, 1953). Therefore, it is reasonable to expect that a variety of *N*-hydroxymethylcarbamates could be prepared by hydrogenolysis of the respective aryl *N*-benzyloxymethylcarbamates, the benzyl moiety acting as a protecting group. Accordingly, benzyloxymethyl isocyanate was synthesized, the desired substituted-aryl *N*-benzyloxymethylcarbamates were prepared, and the respective aryl *N*-hydroxymethylcarbamates were formed by hydrogenolysis.

ANALYTICAL METHODS

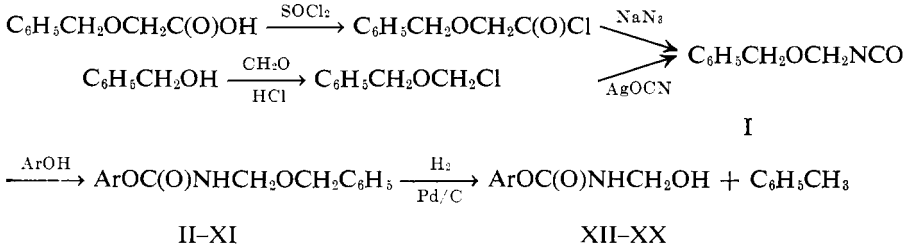
The methods used for purification, isolation, and characterization of the products and comparison of these materials with metabolites of methylcarbamate-carbonyl-C^{14} insecticide chemicals were the same as those described by Balba and Casida (1968). All reported R_f values for thin-layer chromatography (TLC) were determined using silica gel F_{254} precoated plates (Brinkmann Instrument, Inc., Westbury, N. Y.) and ether-hexane (4 to 1) mixture as the developer. Chromogenic reagents used for detection of compounds on the TLC plates were as follows: ninhydrin, after alkaline hydrolysis on the plates (Krishna *et al.*, 1962), to detect *N*-benzyloxymethylcarbamates as pink spots and *N*-hydroxymethylcarbamates as orange spots; chromotropic acid, in sulfuric acid (Beroza, 1963), to give purple spots with each of the abovementioned compounds as a result of their acid degradation to formalde-

hyde; Gibbs' reagent or ferric chloride–potassium ferricyanide, before and after alkaline treatment, to detect the phenolic moiety liberated on alkaline hydrolysis (Krishna *et al.*, 1962). The amount of formaldehyde liberated, on acid degradation of certain compounds in chromotropic–sulfuric acid solution, was also determined colorimetrically (Menzer and Casida, 1965).

Anticholinesterase activity is expressed as the minimum detectable level (MDL) which shows an inhibitory spot on the TLC assay plate, using the in situ procedure with human blood plasma. Male white mice were used for the intraperitoneal toxicity studies (Balba and Casida, 1968).

METHODS OF SYNTHESIS

The reaction sequences used were as follows:



The numbered products are identified in Tables I and II.

Benzyloxymethyl Isocyanate (I) by the Azide Route. Benzyloxyacetic acid was prepared by benzylation of ethyl glycolate followed by saponification with alkali according to Brenner *et al.* (1958), and by reacting methyl chloroacetate with benzyl alcohol according to Gröger and Waldmann (1958), followed by saponification. In the first reaction, glycolic acid (2 moles) gave ethyl glycolate (b.p. 156° C.; lit. b.p. 160° C., Weast, 1964), in 60% yield, on acid catalyzed esterification in ethanol: this was treated with benzyl chloride in the presence of sodium ethoxide to give ethyl benzyloxyacetate which, in turn, was saponified to yield benzyloxyacetic acid (52 to 57%). In the second procedure, methyl chloroacetate (0.5 mole) gave methyl benzyloxyacetate (b.p. 131–8° C. per 11 to 14 mm.; lit. b.p. 135–8° C. per 14 mm., Gröger and Waldmann, 1958) which on alkaline hydrolysis gave benzyloxyacetic acid (23%), identical as determined by infrared spectrum and chromatographic characteristics with the product obtained by the first method.

Benzyloxyacetic acid (0.25 mole) and thionyl chloride (0.5 mole) in petroleum ether (100 ml.) were stirred for 18 hours at 25° C., using a drying tube to protect the reaction mixture from moisture. The solvent and excess thionyl chloride were evaporated under reduced pressure and the product was distilled to yield benzyloxyacetyl chloride (b.p. 135–8° C. per 18 to 20 mm. and 74–5° C. per 0.5 to 0.6 mm.), a colorless oil which darkened slowly on standing. In separate preparations, the yields ranged from 52 to 79%.

Benzyloxymethyl isocyanate was formed by addition of benzyloxyacetyl chloride (0.1 mole) to a suspension of activated sodium azide (0.14 mole) (Smith, 1946) in benzene (100 ml.) at 5° C., followed by refluxing and stirring for 24 hours. The reaction mixture was cooled and filtered, the solvent was evaporated under reduced pressure, and the residue was distilled to give a colorless liquid (b.p. 120–2° C. per 18 to 20 mm. and 65–8° C. per 0.6 mm., n_D^{24} 1.5154) in 38% yield. The infrared spectrum of the product (Figure 1) showed the expected features, and the crystalline *N*-benzyloxymethylcarbamates produced on reaction with phenols gave satisfactory analytical results, confirming the identity of the isocyanate.

Benzyloxymethyl Isocyanate (I) by the Silver Cyanate Route. Benzyl chloromethyl ether was prepared by a simplification of the procedure of Mamedov *et al.* (1962). The homogeneous solution resulting from addition of aqueous formaldehyde (37%, 1 mole) to benzyl alcohol (1 mole) was chilled in an ice bath and then hydrogen chloride gas was bubbled into the solution for one hour. The organic phase which separates during the reaction was recovered, dried over calcium chloride, and excess hydrogen chloride was removed under reduced pressure. Distillation gave benzyl chloromethyl ether (b.p. 48–52° C per 0.2 to 0.4 mm.; lit. 92–3° C. per 9 mm.) in 71% yield.

Although silver cyanate from commercial sources is adequate, the material used was freshly prepared by the following method. Silver nitrate (0.5 mole) in 75 ml. of acetonitrile was added with vigorous stirring to a warm solution of potassium cyanate (0.5 mole) in 1 liter of 80% ethanol. The precipitate which formed on the addition was filtered and washed with water (3 × 200 ml.) and acetone (4 × 100 ml.). (This washing must be thorough because, in the presence of benzyl chloromethyl ether, silver nitrate forms a product, probably benzyloxymethyl nitrate, which is difficult to separate from the desired benzyloxymethyl isocyanate.) The yield of silver cyanate was quantitative after drying at 40° C. per 15 mm. for 16 hours in the dark.

Benzyl chloromethyl ether (0.5 mole, stored over calcium chloride) was dissolved in acetonitrile (200 ml., dried with calcium chloride) and added to a slurry of silver cyanate (0.5 mole) in 300 ml. of dry acetonitrile over a period of 30 minutes, using a drying tube and aluminum foil to protect the reaction from moisture and light. The mixture was then warmed to 60° C. and stirred for one hour. Filtration to remove silver chloride, evaporation of the solvent, and distillation of the residue gave benzyloxymethyl isocyanate (b.p. 71–4° C. per 0.65 mm.) in 26% yield. The infrared spectrum and behavior on gas chromatography for this product are identical to those for the product formed by the azide route; in addition, they both react in the same way to give *N*-benzyloxymethylcarbamates. Higher yields of benzyloxymethyl isocyanate were occasionally obtained, but further studies were not made to determine optimal reaction conditions. Up to half of the starting material appears in the distillation residue and is probably *N*,*N*′-bis(benzyloxymethyl)urea.

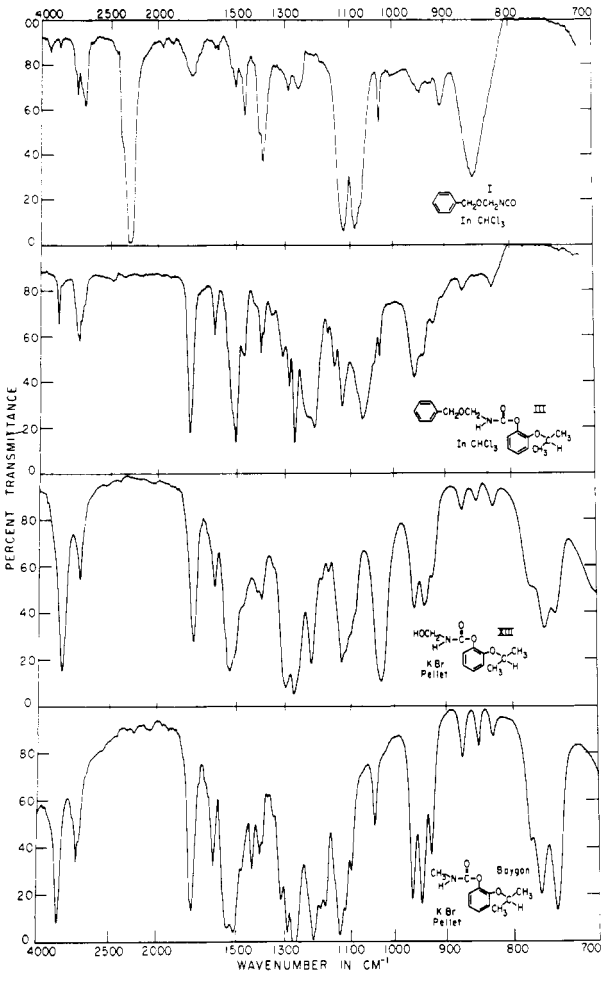


Figure 1. Infrared spectra of benzyloxymethyl isocyanate (I), 2-isopropoxyphenyl *N*-benzyloxymethylcarbamate (III), 2-isopropoxyphenyl *N*-hydroxymethylcarbamate (XIII), and 2-isopropoxyphenyl *N*-methylcarbamate (Baygon)

Aryl *N*-Benzyloxymethylcarbamates (II-XI). Benzyloxymethyl isocyanate (10 mmoles) and the appropriate phenol (10 mmoles) were refluxed in anhydrous benzene (50 ml.), containing triethylamine (0.2 ml.), for 18 hours, under a drying tube. The solvent was evaporated under reduced pressure, and the residual oil or solid was purified on a Florisil column, using hexane followed by ether-hexane (2 to 1) for elution. Compound VI required additional clean up by TLC. When crystalline materials were obtained, ether-hexane mixture was the recrystallizing solvent. The products formed a single major spot on TLC if not crystalline, or a single spot if crystalline. Elemental analyses on the crystalline materials were appropriate for the proposed structures (Table I). Each compound showed the infrared spectral features expected of an aryl *N*-benzyloxymethylcarbamate; by using the compound with the 2-isopropoxyphenyl moiety (compound III) as an example, these features can be seen in Figure 1.

Aryl *N*-Hydroxymethylcarbamates (XII–XX). Each *N*-benzyloxymethylcarbamate (4 mmoles) was hydrogenated in a Parr hydrogenator over 10% palladium-on-charcoal catalyst (3 grams) in isopropanol (50 ml.) at 20° C. and atmospheric pressure. When the compound was pure, hydrogenation proceeded smoothly to the theoretical uptake after correction for hydrogen absorption by solvent and catalyst; however, in the case of *N*-benzyloxymethylcarbamates which were not pure, it was necessary to filter, wash the catalyst with isopropanol, evaporate the combined filtrate to 50 ml., add fresh catalyst, and continue the hydrogenation until theoretical uptake was accomplished. The times required for hydrogenolysis were: 6 hours or more for III and V, 2 to 3 hours for IV and VI to XI, and 2 minutes for XII. The *N*-hydroxymethylcarbamates were isolated by filtering the reaction mixture, evaporating the filtrate under reduced pressure, and chromatographing the residue on a Florisil column with ether-hexane (2 to 1) followed by ether-hexane (4 to 1). Recrystallization from ether-hexane mixture gave the compounds, with elemental analyses as expected for the proposed structures. The responses to chromogenic reagents on TLC plates and the chromotropic acid test for formaldehyde were also as expected. Examination of the infrared spectrum and comparison with that of the parent *N*-methylcarbamate of each product also supported the proposed structures. Figure 1 shows 2-isopropoxyphenyl *N*-methylcarbamate (Baygon) and its *N*-hydroxymethylcarbamate derivative (XII) as an example of this point.

1-Naphthyl *N*-hydroxymethylcarbamate is not reported in Table I because the described procedure is not appropriate for preparing this material. Although the benzyl group of 1-naphthyl *N*-benzyloxymethylcarbamate readily cleaves on hydrogenolysis, the naphthalene ring is also reduced under the same conditions. When 1-naphthyl *N*-methylcarbamate (R_f = 0.55) is reduced under comparable conditions, it converts to a material of higher R_f value (0.66) which was isolated in 50% yield and is identical with 5,6,7,8-tetrahydro-1-naphthyl *N*-methylcarbamate prepared via the chloroformate as reported by Lambrech (1963) (m.p. 108–9° C.; material prepared by the procedure of Lambrech gave m.p. and mixed m.p. of 108° C.). Three products are obtained on reduction of 1-naphthyl *N*-benzyloxymethylcarbamate, and these products have R_f values of 0.28, 0.31, and 0.79 as compared to 0.74 for the original material. The major product (R_f = 0.31) was isolated in 34% yield and gives analyses appropriate for 5,6,7,8-tetrahydro-1-naphthyl *N*-hydroxymethylcarbamate (Calculated C = 65.14%, H = 6.83%, N = 6.33%; Found C = 65.04%, H = 6.77%, N = 6.51%). The product of R_f = 0.79 was not isolated but is probably 5,6,7,8-tetrahydro-1-naphthyl *N*-benzyloxymethylcarbamate because with longer reduction times it converts to 5,6,7,8-tetrahydro-1-naphthyl *N*-hydroxymethylcarbamate. The product of R_f = 0.28 is the desired 1-naphthyl *N*-hydroxymethylcarbamate as determined by isolation in yields of less than 2% and comparison by TLC analysis with authentic material prepared by acid cleavage of 1-naphthyl *N*-(2-tetrahydropyranyloxymethyl)carbamate (Hoover *et al.*, 1963; Slade and Casida, 1968). Attempts to obtain the desired product by varying the conditions of hydrogenolysis of 1-naphthyl *N*-benzyloxymethylcarbamate were not successful; these included variations in catalyst, solvent, and reaction time.

ANALYTICAL RESULTS

All elemental analyses were performed by the Microchemical Laboratory, Department of Chemistry, University of California, Berkeley, and the results obtained for the synthesized aryl *N*-benzyloxymethylcarbamates and aryl *N*-hydroxymethylcarbamates are given in Table I. The infrared spectra were measured, using potassium bromide pellets or chloroform solutions, on a Beckman IR-4 spectrophotometer; certain of these spectra are presented in Figure 1. Balba (1967) gives more details and data pertaining to the infrared and ultraviolet spectra of most of these compounds.

Table I. Analytical Data Found for New Aryl *N*-Benzyloxymethylcarbamates and Aryl *N*-Hydroxymethylcarbamates

Compound				Elemental Analyses, %		R_f Values
No.	Phenyl moiety	Yield, %	M.P., ° C.	Calculated	Found	for TLC
			N-Benzyloxymethylcarbamate Derivatives			
II	1-Naphthyl	74	98–9	C 74.25	74.06	0.74
				H 5.58	5.46	
				N 4.56	4.76	
III	2-Isopropoxyphenyl	84	60.5–2	C 68.55	68.57	0.78
				H 6.71	6.41	
				N 4.44	4.53	
IV	3-Isopropylphenyl	(84)	Oil			0.82
V	3-(1-Methylbutyl)phenyl	88	Oil	C 73.37	73.40	0.80
				H 7.70	8.05	
				N 4.28	4.12	
VI	3,5-Diisopropylphenyl	80	56.5–7	C 73.87	73.52	0.86
				H 7.97	7.75	
				N 4.10	4.30	
VII	2,3,5-Trimethylphenyl	53	89–90	C 72.24	72.14	0.83
				H 7.02	7.20	
				N 4.68	4.76	
VIII	3,4,5-Trimethylphenyl	72	78–9	C 72.24	72.15	0.83
				H 7.02	7.17	
				N 4.68	4.75	
IX	4-Dimethylamino-3-cresyl	70	62.5–4	C 68.77	68.97	0.76
				H 7.05	7.05	
				N 8.91	8.94	
X	4-Dimethylamino-3,5-xylenyl	(100)	Oil			0.82
XI	2-Chloro-4,5-xylenyl	80	113–5	C 63.85	64.02	0.79
				H 5.67	5.77	
				N 4.38	4.47	
			N-Hydroxymethylcarbamate Derivatives			
XII	2-Isopropoxyphenyl	67	95–6.5	C 58.66	58.26	0.23
				H 6.71	6.87	
				N 6.22	6.03	
XIII	3-Isopropylphenyl	12	84–6	C 63.14	63.71	0.24
				H 7.23	7.31	
				N 6.69	6.83	
XIV	3-(1-Methylbutyl)phenyl	34	Oil	C 65.80	65.39	0.29
				H 8.07	8.20	
				N 5.90	5.20	
XV	3,5-Diisopropylphenyl	15	82.5–4	C 66.91	66.92	0.32
				H 8.42	8.19	
				N 5.57	5.51	
XVI	2,3,5-Trimethylphenyl	32	134–5	C 63.17	63.22	0.32
				H 7.18	7.43	
				N 6.70	6.51	
XVII	3,4,5-Trimethylphenyl	28	156–7[a]	C 63.17	62.95	0.32
				H 7.18	7.21	
				N 6.70	7.02	
XVIII	4-Dimethylamino-3-cresyl	28	90–1	C 58.91	58.52	0.16
				H 7.19	6.88	
				N 12.49	12.67	
XIX	4-Dimethylamino-3,5-xylenyl	42	106–6.5	C 60.49	60.39	0.22
				H 7.61	7.57	
				N 11.76	11.71	
XX	2-Chloro-4,5-xylenyl	49	144.5–7	C 52.29	52.48	0.24
				H 5.27	5.30	
				N 6.00	6.15	

[a] This material is dimorphic, giving a m.p. of 134–5° C. when recrystallized from 2-propanol (personal communication, Juan Morales, Shell Development Co., Modesto, Calif.).

Table II. Comparative Biological Activities of *N*-Methylcarbamates and *N*-Hydroxymethylcarbamates

Compound, Name or Number	Biological Activities: AntiChE, MDL, μg.	Biological Activities: IP toxicity to mice, LD_{50}, mg./kg.
2-Isopropoxyphenyl *N*-methylcarbamate (Baygon)	0.5	12
2-Isopropoxyphenyl *N*-hydroxymethylcarbamate (XII)	2.0	>167
3-Isopropylphenyl *N*-methylcarbamate (Hercules 5727)	0.004	3.1
3-Isopropylphenyl *N*-hydroxymethylcarbamate (XIII)	0.04	111
3-(1-Methylbutyl)phenyl *N*-methylcarbamate (RE 9659)		7.4
3-(1-Methylbutyl)phenyl *N*-hydroxymethylcarbamate (XIV)		54
3,5-Diisopropylphenyl *N*-methylcarbamate (Hooker HRS-1422)	0.03	17
3,5-Diisopropylphenyl *N*-hydroxymethylcarbamate (XV)	0.1	111
2,3,5-Trimethylphenyl *N*-methylcarbamate (SD 8786)		305
2,3,5-Trimethylphenyl *N*-hydroxymethylcarbamate (XVI)		>500
3,4,5-Trimethylphenyl *N*-methylcarbamate (SD 8530)		420
3,4,5-Trimethylphenyl *N*-hydroxymethylcarbamate (XVII)		>1000
4-Dimethylamino-3-cresyl *N*-methylcarbamate (Matacil)	1.0	10
4-Dimethylamino-3-cresyl *N*-hydroxymethylcarbamate (XVIII)	1.0	83
4-Dimethylamino-3,5-xylyl *N*-methylcarbamate (Zectran)	0.02	7.8
4-Dimethylamino-3,5-xylyl *N*-hydroxymethylcarbamate (XIX)	0.2	>56
2-Chloro-4,5-xylyl *N*-methylcarbamate (Banol)	0.03	4.6
2-Chloro-4,5-xylyl *N*-hydroxymethylcarbamate (XX)	0.15	53

BIOLOGICAL ACTIVITIES AND COCHROMATOGRAPHY CHARACTERISTICS WITH METABOLITES

The biological activity of the various synthesized *N*-hydroxymethylcarbamates generally is less, and frequently is much less, than that of the corresponding *N*-methylcarbamates, as demonstrated by the anticholinesterase activity and toxicity results given in Table II.

Each of the *N*-hydroxymethylcarbamates (XII, XIII, XV, XVIII–XX) prepared cochromatographs with one of the metabolites of the corresponding *N*-methylcarbamate as formed in the rat liver microsome-reduced nicotinamide-adenine dinucleotide phosphate enzyme system (Oonnithan and Casida, 1966, 1968) and with one of the aglycones released on incubation with β-glucosidase of the metabolites produced in bean plants from the corresponding *N*-methylcarbamate (Kuhr and Casida, 1967). Two of the other *N*-hydroxymethylcarbamates (XVI and XVII) also appear in plants as glycosides which are cleaved by β-glucosidase when the beans are treated with the corresponding *N*-methylcarbamate.

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