Metabolites and Photoproducts of 3-(2-Butyl)phenyl *N*-Methylcarbamate and *N*-Benzenesulfenyl-*N*-methylcarbamate

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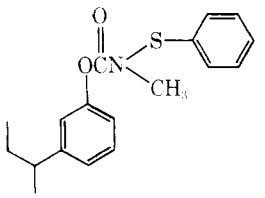
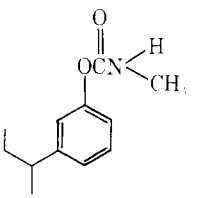
The insecticide chemical, 3-(2-butyl)phenyl *N*-benzenesulfenyl-*N*-methylcarbamate (BPBSMC), is metabolized in orally treated rats to give 72% of the dose as the following urinary metabolites: eight carbamates from cleavage of the benzenesulfenyl group plus hydroxylation or oxidation of any one of the butyl carbons or the *N*-methyl group; the eight corresponding phenols in free or conjugated form. 3-(2-Butyl)phenyl *N*-methylcarbamate (BPMC) yields the same eight carbamate metabolites in the urine of treated rats. Photoalteration of BPBSMC involves oxidation at the sulfur, *N*-methyl, and butyl moieties, and cleavage of the N-S bond and carbamate ester group. Procedures are given for radiosynthesis of BPMC and BPBSMC and for synthesis of many of the metabolites and photoproducts. The biological activity of these derivatives and the liver microsomal metabolism and possible mechanisms for the selective toxicity of BPBSMC relative to BPMC are discussed.

The physical and biological properties of *N*-methylcarbamate insecticide chemicals are modified on derivatization at the nitrogen. The *N*-benzenesulfenyl derivative of 3-(2-butyl)phenyl *N*-methylcarbamate (BPBSMC; Chevron RE 11775) is greatly increased in potency as a mosquito larvicide and yet reduced in oral toxicity to mammals as compared with the nonderivatized compound, 3-(2-butyl)phenyl *N*-methylcarbamate (BPMC; Chevron RE 5365) (Brown and Kohn, 1972; Chevron Chemical Co., 1971). BPBSMC is highly effective in mosquito control, even for strains resistant to organophosphorus insecticide chemicals (Schaefer and Wilder, 1970). This is important because many mosquito-borne diseases of man and livestock are no longer satisfactorily controlled by many of the insecticidal materials currently available, primarily because of resistant strains, and because selective and biodegradable compounds are needed for this use.



BPBSMC



BPMC

The safe and efficient use of any new insecticide chemical, such as BPBSMC or BPMC, is dependent on adequate knowledge of its metabolic and photochemical fate. Previous studies with other alkylphenyl *N*-methylcarbamates (Fukuto, 1972; Kuhr, 1971; Kuhr and Casida, 1967; Miskus *et al.*, 1969; Miyamoto and Fukunaga, 1971; Oonnithan and Casida, 1968; Schlagbauer and Schlagbauer, 1972a,b; Slade and Casida, 1970) and butylphenyl compounds (Bandal and Casida, 1972) provide a basis for speculating on the sites likely to be involved in metabolism and photoalteration of BPBSMC and BPMC. These include, among others, oxidation of the *N*-methyl group and several positions in the butyl moiety, oxidation of the sulfur, and cleavage of the benzenesulfenyl group. In order to implement these investigations, there is need for radioactive preparations of BPBSMC and BPMC and for authentic standard compounds for use in cochromatographic comparisons with metabolites and photoproducts of the labeled materials.

This report considers the radiosynthesis of [^{14}C]carbonyl and [^{14}C]butyl preparations of BPBSMC and BPMC and the synthesis, in unlabeled form, of 24 possible oxidation or cleavage products of these compounds. The modifications involved are at the benzenesulfenyl, *N*-methyl, carbamoyl, and butyl groups. The labeled compounds were administered to rats or mice or incubated with liver microsome mixed-function oxidase systems or exposed to various types of light to evaluate the degradation chemistry of BPBSMC and BPMC. The findings make it possible to suggest tentative metabolic and photoalteration pathways for BPMC and its *N*-benzenesulfenyl derivative.

MATERIALS AND METHODS

All solvents and chemicals were reagent grade and used without further purification. Melting points and boiling points are uncorrected.

Spectral Studies. Infrared (ir) spectra were determined with a Perkin-Elmer Model 456 grating spectrophotometer using 5–10% (w/v) solutions in chloroform. Electron impact mass spectra were obtained on a CEC 21103-C mass spectrometer using a direct introduction probe and an ionization voltage of 70 eV and chemical ionization (ci) spectra were run on The Finnigan Corp. Model 1015D mass spectrometer using a direct introduction probe and methane as the reagent gas at a source pressure of 1 Torr. All nuclear magnetic resonance (nmr) spectra were obtained using a Varian Associates Model T-60 instrument. Samples were run as 5–10% solutions in chloroform-*d*. Tetramethylsilane (TMS) was used as an internal standard and chemical shift values are reported in parts per million (δ) downfield from TMS. Nmr data are given when a sufficient quantity of material was available for spectra to be taken.

Thin-Layer Chromatography (tlc). Thin-layer chromatography utilized 20 × 20 cm silica gel F_{254} precoated chromatoplates (Brinkmann Instruments, Inc., Westbury, N. Y.) with 0.25-mm gel thickness for analysis (unless specified otherwise) and 0.5-, 1.0-, or 2.0-mm gel thickness for preparative isolations. Tlc solvent systems used for analysis of the purity and preparative isolation of the synthesized chemicals and for tentative identification of the ^{14}C metabolites and ^{14}C photoproducts by cochromatography are as follows: A = hexane–ether (2:1); B = benzene–ether–hexane (1:1:1); C = benzene–ether (1:1); D = ether–hexane (2:1); E = benzene saturated with formic acid–ether (10:3); F = carbon tetrachloride–ether–hexane (8:1:1); and G = hexane–ethyl acetate (4:1). R_f values for

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Table I. Code Designations and Tlc R_f Values for Compounds Synthesized to Compare with Metabolites and Photoproducts of 3-(2-Butyl)phenyl *N*-Benzenesulfenyl-*N*-methylcarbamate and 3-(2-Butyl)phenyl *N*-Methylcarbamate

Code	Substituent, R	R_f values in indicated tlc solvent systems				
		A	B	C	D	E
		3-HO-ϕ-R[a]				
BP	$CH_3CH_2CH(CH_3)$–	0.30	0.45	0.56	0.48	0.56
1-CH_2OH-BP	$CH_3CH_2CH(CH_2OH)$–	0.03	0.07	0.23	0.15	0.16
2-COH-BP	$CH_3CH_2C(CH_3)(OH)$–	0.05	0.11	0.31	0.21	0.21
3-CHOH-BP	$CH_3CH(OH)CH(CH_3)$–	0.03	0.08	0.25	0.17	0.17
4-CH_2OH-BP	$HOCH_2CH_2CH(CH_3)$–	0.01	0.05	0.17	0.11	0.14
1-CHO-BP	$CH_3CH_2CH(CHO)$–	0.17	0.30	0.48	0.36	0.42
3-C=O-BP	$CH_3C(O)CH(CH_3)$–	0.13	0.25	0.43	0.31	0.33
1-COOH-BP	$CH_3CH_2CH(COOH)$–	0.02	0.04	0.12	0.09	0.24
4-COOH-BP	$HOOCCH_2CH(CH_3)$–	0.02	0.04	0.11	0.08	0.21
13	$CH_3CH{=}C(CH_3)$–	0.27	0.43	0.55	0.45	0.54
		3-[$CH_3NHC(O)O$]-ϕ-R[a]				
BPMC	$CH_3CH_2CH(CH_3)$–	0.14	0.29	0.45	0.34	0.41
1-CH_2OH-BPMC	$CH_3CH_2CH(CH_2OH)$–	0.01	0.01	0.08	0.05	0.07
2-COH-BPMC	$CH_3CH_2C(CH_3)(OH)$–	0.01	0.04	0.17	0.11	0.11
3-CHOH-BPMC	$CH_3CH(OH)CH(CH_3)$–	0.01	0.02	0.10	0.06	0.07
4-CH_2OH-BPMC	$HOCH_2CH_2CH(CH_3)$–	0.01	0.01	0.08	0.03	0.07
1-CHO-BPMC	$CH_3CH_2CH(CHO)$–	0.01	0.03	0.21	0.10	0.14
3-C=O-BPMC	$CH_3C(O)CH(CH_3)$–	0.03	0.10	0.26	0.16	0.20
1-COOH-BPMC	$CH_3CH_2CH(COOH)$–	0.00	0.02	0.05	0.03	0.08
4-COOH-BPMC	$HOOCCH_2CH(CH_3)$–	0.00	0.02	0.05	0.03	0.06
14	$CH_3CH{=}C(CH_3)$–	0.11	0.26	0.43	0.31	0.41
		3-[$CH_3CH_2CH(CH_3)$]-ϕ-OC(O)-R[a]				
BPC	$-NH_2$	0.07	0.15	0.33	0.23	0.33
BP-CH_2OH-C	$-NHCH_2OH$	0.02	0.05	0.18	0.11	0.14
BPBSC	$-NHS\phi$	0.33	0.53	0.59	0.51	0.62
BPBSMC	$-N(CH_3)S\phi$	0.43	0.57	0.60	0.53	0.65
BPBSOMC	$-N(CH_3)S(O)\phi$	0.23	0.43	0.53	0.41	0.55
$BPBSO_2MC$	$-N(CH_3)S(O_2)\phi$	0.27	0.46	0.58	0.45	0.62
		Other sulfur compounds[a]				
	ϕ-SH or ϕ-SS-ϕ	0.49	0.60	0.60	0.54	0.66
	ϕ-$SS(O_2)$-ϕ	0.30	0.49	0.53	0.44	0.59

[a] ϕ– = phenyl; –ϕ– = 1,3-disubstituted phenyl.

the important chemicals synthesized utilizing one tlc development are given in Table I. Various combinations and sequences of developing solvents were used for adequate resolution of the metabolites and photoproducts. These are designated by the code for the solvent system and the number of times used, thus: C, B × 6 indicates sequential developments once with solvent system C and then six times with solvent system B in the same direction of development.

Product detection involved a variety of procedures. All of the products at 10 μg quenched gel fluorescence when viewed under ultraviolet (uv) light (254 nm), formed blue spots when sprayed with 20% (w/v) phosphomolybdic acid in ethanol followed by heating for 10 min at 110°, and formed yellow spots on exposure to iodine vapor. A spray of $Ce(SO_4)_2$ at 2% (w/v) in 2 *N* H_2SO_4 produced reddish-brown spots on heating for 10 min at 110° with all phenolic compounds and their methylcarbamate derivatives but not with the other compounds. Phenolic compounds were specifically detected by formation of yellow–orange spots on spraying with diazotized benzidine solution [freshly prepared by mixing equal volumes of 0.5% (w/v) of benzidine in 0.15 *N* HCl and 10% (w/v) of aqueous $NaNO_2$ solution at 0°]. A spray of 2,6-dibromo-*N*-chloro-*p*-benzoquinonimine (0.5%, w/v, in ethanol) produced violet spots with phenols and reddish-orange spots with compounds containing an unoxidized thiophenyl moiety. Radioactive products were detected by autoradiography and quantitated by scraping the appropriate gel regions free from the glass support into scintillation vials for determination of radioactivity utilizing a Packard Tri-Carb Model 3003 liquid scintillation spectrometer.

Metabolism in Living Mammals. Male albino rats (160 g, Sprague–Dawley strain, Horton Laboratories, Oakland, Calif.) were treated orally by stomach tube with [^{14}C]carbonyl- and [^{14}C]butyl-labeled preparations of BPBSMC and BPMC using 100 μl of dimethylsulfoxide as the administration vehicle and 150 μl of this solvent as the wash for the stomach tube. The dose for the [^{14}C]carbonyl- and [^{14}C]butyl-labeled preparations was 3.6 to 4.4 and 5.5 to 7.0 μmol/kg, respectively, and one or two rats were treated with single doses of each labeled preparation. Immediately after treatment, the rats were placed in metabolism chambers (Krishna and Casida, 1966) designed for the separate collection of urine, feces, and expired carbon dioxide ([^{14}C]carbonyl preparations only) and then held there for 48 hr. During the experiment the animals received normal laboratory rations and water *ad libitum*.

Urinary metabolites of [^{14}C]butyl-BPBSMC excreted by three rats within 48 hr after single oral treatments at a dose of 57 μmol/kg were fractionated by solvent partitioning and the fractions were subjected to tlc analysis for metabolite identification. The urine (about 100 ml) was acidified by addition of 20% HCl to pH 1, saturated with $(NH_4)_2SO_4$, then extracted with ether (50 ml × 2). The ether extract was separated into three fractions for direct tlc analysis without further cleanup: acidic components removed by extraction with 5% $KHCO_3$ solution (10 ml × 3); phenolic components removed by extraction with cold 5% KOH solution (10 ml × 3); and neutral components

remaining in the ether phase. The acidic and phenolic components were recovered by acidification of the aqueous medium, addition of $(NH_4)_2SO_4$, and extraction with ether. The ether-unextractable portion of the original acidified urine was lyophilized to dryness, the residue extracted with methanol, the methanol extract evaporated, and the resulting residue dissolved in water. This solution was subjected to cleanup on a Bio-Bead column (Bandal and Casida, 1972) and then one-dimensional tlc with two developments (first C, second E) to move trace amounts of unconjugated metabolites from the origin, and finally recovery of the conjugated metabolites by extraction of the gel from the origin using methanol. The conjugates were dissolved in aqueous acetate buffer (pH 4.5) and cleaved by the action of β-glucuronidase and then glusulase, according to Bandal and Casida (1972). The products of enzymatic cleavage were fractionated into acidic, phenolic, and neutral components as before. The tlc solvent systems used for tentative identification of metabolites are given in Table II.

Another study involved analysis of the urine collected within 48 hr after single oral treatments of individual rats with [^{14}C]carbonyl-BPBSMC or -BPMC at a dose of 5.1 and 2.7 μmol/kg, respectively. The procedure for metabolite analysis was identical to that used in the [^{14}C]butyl-BPBSMC investigation except that the ether extract was fractionated prior to tlc into only two fractions: the acidic components from washing with 5% $KHCO_3$ solution; and the neutral components remaining in the ether. This modified procedure is appropriate for the [^{14}C]carbonyl metabolites because they are likely to be almost entirely neutral or acidic carbamates. Thus, the extraction does not involve treatment with KOH solution so the neutral metabolites are not subjected to potential hydrolysis by this alkaline treatment, and therefore a better estimate of the amount of neutral carbamate metabolites is possible by this approach. The conjugated carbamates were then recovered from the ether-unextractable portion of the original acidified urine by saturation with $(NH_4)_2SO_4$ and extraction three times with equal volumes of ether–ethanol (2:1) mixture.

A similar but less extensive study was made with male albino mice (20 g, Horton Laboratories) administered single doses of [^{14}C]carbonyl- or [^{14}C]butyl-BPBSMC at 1.4 to 1.7 μmol/kg, both intraperitoneally and by the oral route, using one animal per treatment schedule and collecting urine and expired 14-carbon dioxide for 24 or 48 hr. The urine following [^{14}C]butyl-BPBSMC administration was adjusted to pH 1 with H_2SO_4 and extracted with dichloromethane to obtain organosoluble metabolites for tlc analysis.

Metabolism by Rat Liver Microsomes. [^{14}C]Carbonyl-BPBSMC or -BPMC (0.04 μmol) was incubated with rat liver microsomes (7 mg of microsomal protein) in phosphate buffer (2.0 ml, 0.10 *M*, pH 7.4) containing $MgCl_2$ (21 μmol) with or without reduced nicotinamide-adenine dinucleotide phosphate (NADPH) (0.2 μmol) at 37° for 1 hr. Alternatively, a comparable amount of "boiled microsomes" (held at 100° for 15 min and then cooled) was used in place of the "fresh microsomes." The products were recovered from the incubated mixtures by extraction with ether (10 ml × 1, 5 ml × 1) and then the ether was dried (Na_2SO_4), concentrated, and spotted for tlc analysis as indicated in Table III.

Photoalteration. Four sets of conditions were used: midday sunlight during late December; two short-wavelength (254 nm) uv lamps (15-W germicidal lamp G15T8, Sylvania Electric Products, Inc., Danvers, Mass.) at a distance of 5 cm; one sunlamp (275 W, General Electric Co., Cleveland, Ohio) at a distance of 31 cm; no exposure to light, serving as a control. The studies were of three types. First, unlabeled BPBSMC or BPMC (10 mg) in methanol (5 ml) was exposed in a petri dish (5.5 cm diameter) to uv, sunlamp, or sunlight irradiation for 1 hr and then the photoproducts were analyzed by tlc using solvent systems A, B, G, and others. Second, [^{14}C]carbonyl-BPBSMC was coated on glass or silica gel (origin of tlc chromatoplate) surfaces at 0.5 and 5 μg/cm^2, respectively, and exposed to sunlight or uv irradiation for various periods with qualitative product analysis by two-dimensional tlc (first A × 2, second G × 2). Finally, [^{14}C]carbonyl- and [^{14}C]butyl-labeled preparations of BPBSMC and BPMC were exposed at 5 μg/cm^2 on silica gel surfaces for 5 min to uv light or 0.5 hr to sunlamp irradiation. The photoproducts were then separated by the tlc solvent systems given in Table IV and quantitated by liquid scintillation counting.

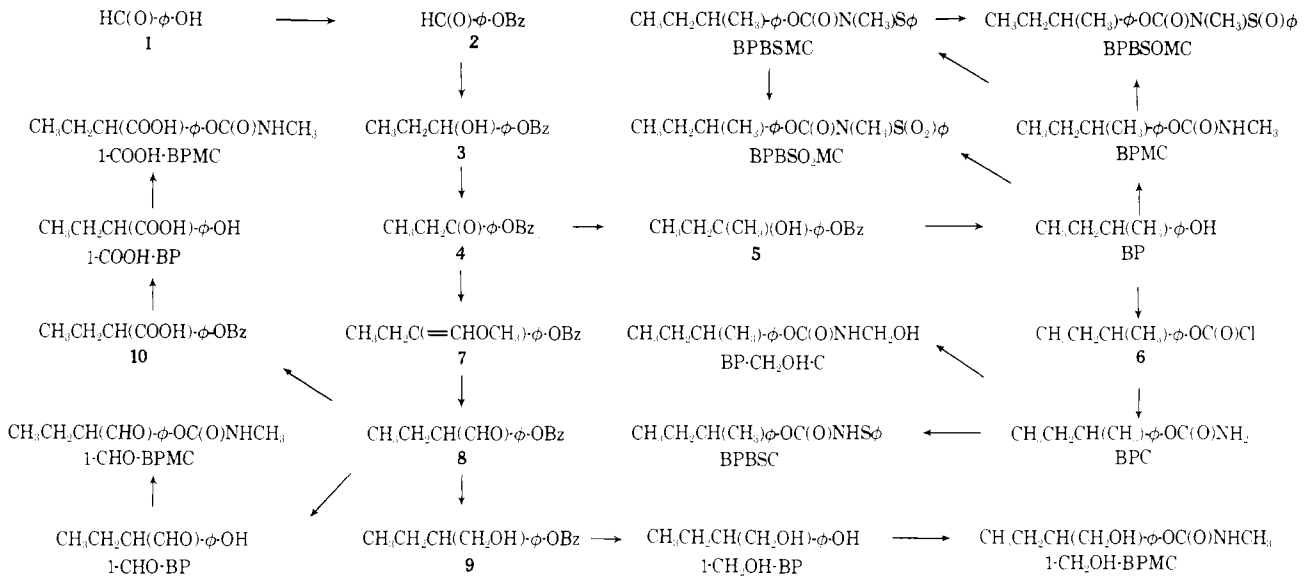
Bioassays. The reagents and procedure described by Ellman *et al.* (1961) were used for assay of human plasma cholinesterase activity. The carbamate was deposited on the bottom of the assay tube by evaporation of an acetone solution, buffer (3.0 ml), chromogenic reagent (100 μl),

Table II. Products in Urine of Rats 48 Hr after Oral Administration of [^{14}C]Butyl-Labeled 3-(2-Butyl)phenyl *N*-Benzenesulfenyl-*N*-methylcarbamate

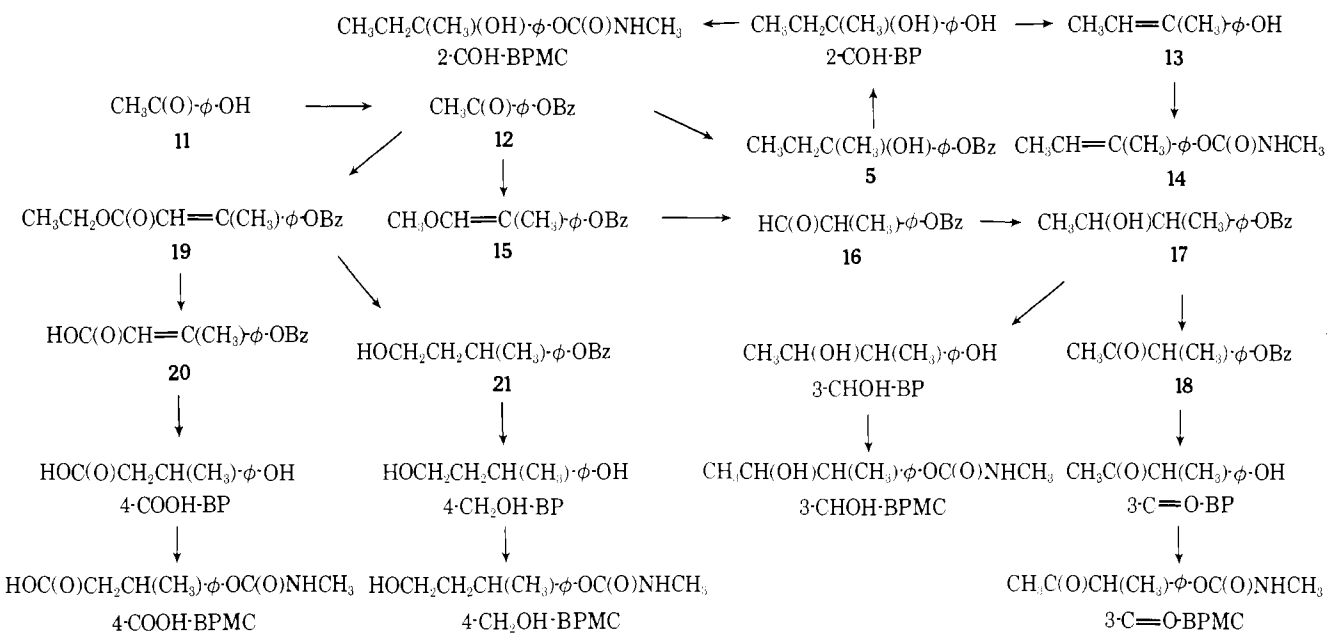
Metabolite	Tlc system for cochromatography	Amount of administered radiocarbon recovered, %, in indicated fraction: Unconjugated	Conjugated[a]	Total
Butyl group unmodified, 2.54%				
BP	A, F, B	1.44	1.08[c]	2.52
BP-CH_2OH-C	C, E	0.02[b]	0.00	0.02[b]
Butyl group oxidized at 1 position, 12.04%				
1-CH_2OH-BPMC	C, D, E	0.05[b]	0.00	0.05[b]
1-COOH-BPMC	E × 4, D	1.81	0.23[c]	2.04
1-CH_2OH-BP	C, B × 6	1.29	5.77[e]	7.06
1-COOH-BP	E × 2, D	0.83	2.06[d]	2.89
Butyl group oxidized at 2 position, 26.08%				
2-COH-BPMC	C, D, E	0.99	0.00	0.99
2-COH-BP	C, B × 3	7.84	17.25[e]	25.09
Butyl group oxidized at 3 position, 17.32%				
3-CHOH-BPMC	C, D, E	0.13	0.00	0.13
3-C=O-BPMC	C, D, E	0.03[b]	0.00	0.03[b]
3-CHOH-BP	C, B × 6	2.57	8.58[e]	11.15
3-C=O-BP	C, B × 2	1.23	4.78[d]	6.01
Butyl group oxidized at 4 position, 14.38%				
4-CH_2OH-BPMC	C, D × 3	0.01[b]	0.00	0.01[b]
4-COOH-BPMC	E × 4, D	4.84	0.14[c]	4.98
4-CH_2OH-BP	C, B × 3	0.52	2.50[d]	3.02
4-COOH-BP	E × 2, D	2.94	3.43[d]	6.37
Unknowns,[f] 26.60%				
Phenolic (2 or 3)		0.51	7.72[d]	8.23
Acidic (6 to 8)		2.45	10.13[d]	12.58
Water-soluble			5.79	5.79
Total		29.50	69.46	98.96

[a] A portion of the conjugates are cleaved by β-glucuronidase and the remainder by glusulase. [b] There is a possibility that carbamates appearing in such small amounts might be artifacts resulting from the analytical procedure used. However, this does not appear to be the case, because these compounds are also found, again in small amounts, in studies with [^{14}C]-carbonyl-BPBSMC where noncarbamate metabolites are not detected. [c] More than 98% cleaved by β-glucuronidase. [d] From 50 to 76% cleaved by β-glucuronidase. [e] From 41 to 42% cleaved by β-glucuronidase. [f] The unknowns do not include any BPBSMC, BPMC, or any of the phenolic or acidic compounds available as authentic standards. A separate study with [^{14}C]carbonyl-BPBSMC and -BPMC confirmed that the parent compounds are not excreted in unmetabolized form.

Scheme I. Syntheses from 3-Hydroxybenzaldehyde (1)



Scheme II. Syntheses from 3-Hydroxyacetophenone (11)



and plasma (40 μl) were added, mixed, and held for 5 min at 25°, and then acetylthiocholine solution (20 μl) was added with 20 min incubation at 25° prior to colorimetric determination of the thiocholine liberated on enzymatic hydrolysis.

Several compounds were also assayed for toxicity to fourth instar mosquito larvae (susceptible strain, *Culex pipiens quinquefasciatus* Say). The carbamate dissolved in acetone (5 μl) was added to water (5 ml) with mixing and then ten larvae were added, with mortality determinations after 48 hr.

SYNTHESES

The reaction sequences starting from 3-hydroxybenzaldehyde (1) are shown in Scheme I for the ^{14}C-labeled compounds, the 3-(2-butyl)phenyl carbamates with various N substituents, and the alcohol, aldehyde, and carboxylic acid derivatives at the 1 position of 3-(2-butyl)phenol and their *N*-methylcarbamates. Scheme II shows the routes of conversion from 3-hydroxyacetophenone (11) to alcohol, keto and carboxylic acid derivatives at the 2, 3, and 4 positions of 3-(2-butyl)phenol and their *N*-methylcarbamates and to two butenyl derivatives. These schemes and Table I also give the code designations used for the compounds. The abbreviations are: φ- = phenyl; -φ- = 1,3-disubstituted phenyl; Bz = benzyl.

^{14}C-Labeled Compounds. *3-Benzyloxybenzaldehyde* (2). To 24.4 g (0.20 mol) of recrystallized 3-hydroxybenzaldehyde (1) in 60 ml of ethanol were added 63 g (0.50 mol) of benzyl chloride and 13 g (0.22 mol) of KOH. This mixture was refluxed for 5 hr, after which time the ethanol was removed using a vacuum rotary evaporator. The residue was extracted with benzene and then the benzene-soluble portion was washed with 5% (w/v) KOH in H_2O, and H_2O saturated with NaCl and dried over anhydrous Na_2SO_4. After removal of the benzene by distillation, the residue was distilled under vacuum to obtain 37 g (90% yield) of pure 3-benzyloxybenzaldehyde (2), which solidified upon standing: bp 119–120° (0.025 mm); mp 45° (reported mp 54°; Bristow, 1957).

3-Benzyloxypropiophenone (4). To a magnetically stirred solution of 32 g (0.15 mol) of 2 in 150 ml of anhydrous ether was added 0.20 mol of ethylmagnesium bromide (Alfa Products, Beverly, Mass.) in 150 ml of anhydrous ether over a period of 20 min. When the reaction was judged complete (*tlc monitoring*), hydrolysis of the mixture was accomplished using 100 ml of 25% (w/v) NH_4Cl in H_2O. The ether phase was washed twice with 50-ml portions of H_2O saturated with NaCl and dried over anhydrous

Na_2SO_4. Removal of the ether by distillation gave 36 g (99% yield) of 1-(3-benzyloxyphenyl)propanol (**3**), which was used directly without further purification. To 500 mg (0.19 mmol) of **3** in 15 ml of dry benzene was added 2.0 g (23 mmol) of activated MnO_2 in accordance with described procedures (Attenburrow *et al.*, 1952; Turner, 1954). The mixture was stirred magnetically and protected from moisture. After 2 hr at 25°, the MnO_2 was removed by filtration. Evaporation of the benzene gave an oil which, when subjected to preparative tlc using several developments with hexane–ether (8:1) mixture, yielded a light yellow liquid. Distillation of this liquid gave compound **4** in 96% yield: bp 135° (0.035 mm); mass spectrum (70 eV) *m/e* (rel intensity) 240 (67), 211 (7), 92 (34), 91 (100). The ir spectrum showed no absorption at 3595 cm^{-1} characteristic of compound **3** but a strong band at 1680 cm^{-1} was present. 3-Benzyloxypropiophenone (**4**) was also prepared *via* oxidation of **3** with a CrO_3–pyridine complex or with aluminum isopropoxide (Oppenauer oxidation).

3-(1-[^{14}C]2-Butyl)phenol ([^{14}C]Butyl-BP). To a 10-ml flask fitted with a $CaCl_2$ drying tube was added 500 mg of Mg chips, then 370 mg (2.6 mmol) of unlabeled methyl iodide in 4 ml of anhydrous ether, and a small crystal of I_2. When the reaction had begun, as noticed by a color change from brown to white and a small degree of bubbling, 47.3 mg (0.33 mmol) of [^{14}C]methyl iodide (3.0 mCi/mmol; New England Nuclear Corp., Boston, Mass.) in 1 ml of anhydrous ether was added and this mixture was refluxed for 1 hr. The resulting mixture was cooled and 720 mg (3.0 mmol) of compound **4** in 2 ml of anhydrous ether was added dropwise with continuous stirring. The reaction mixture was then kept at 25° for 30 min, after which time the unreacted Mg was removed, the mixture shaken vigorously with H_2O saturated with NH_4Cl (2 ml), and the desired product recovered by extraction into ether. Tlc analysis revealed that over 99% of the radiocarbon was present as **5**, with traces of 2-(3-benzyloxyphenyl)-2-butene and unlabeled **4** also being present. Preparative tlc using several developments with hexane–ether (4:1) mixture and then two developments with hexane–ether (8:1) mixture yielded pure ^{14}C-**5** (59% yield based on starting radioactivity) with a specific activity of 0.29 mCi/mmol. Properties such as ir of this labeled **5** were identical to an unlabeled preparation synthesized by a different method described in a later section.

Compound ^{14}C-**5** (384 mg, 1.50 mmol) was then added in a small amount of absolute ethanol to a 200-ml hydrogenation flask containing 40 ml of absolute ethanol, 1 drop of concentrated H_2SO_4, and 200 mg of 10% Pd on charcoal. After 24 hr with the H_2 pressure at 30 lb/in.^{2}, the mixture was filtered and the solid washed several times with ethanol, and the combined ethanol washings (*ca.* 100 ml) were removed using a vacuum rotary evaporator. The resulting oil was redissolved in dichloromethane (1 ml) and preparative tlc purification was carried out. Development three times with hexane–ether (4:1) mixture yielded pure ^{14}C-BP (201 mg; 89% yield) with a specific activity of 0.29 mCi/mmol, the remainder being [^{14}C]3-(2-hydroxy-2-butyl)phenol (2-COH-BP). The ^{14}C-BP had identical properties to that of unlabeled BP synthesized by a method similar to that described above. Some of the properties of unlabeled BP are: bp 63° (0.05 mm); nmr ($CDCl_3$) δ 0.82 (t, 3 H), 1.21 (d, 3 H), 1.58 (m, 2 H), 2.58 (m, 1 H), 6.6–7.3 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 150 (46), 135 (5), 122 (18), 121 (100), 107 (18), 91 (13), 77 (17).

3-(1-[^{14}C]2-Butyl)phenyl N-Methylcarbamate ([^{14}C]Butyl-BPMC). To a flask containing 201 mg (1.34 mmol) of [^{14}C]butyl-BP, 5 ml of anhydrous ether, and 2 drops of triethylamine was added 300 mg (5.3 mmol) of methyl isocyanate. The flask was stoppered and kept at 25° for 18 hr. Evaporation of the ether and excess methyl isocyanate under a gentle stream of dry N_2 and further purification by preparative tlc (solvent system A × 2) gave a colorless solid in 95% yield. Recrystallization from hexane gave pure [^{14}C]butyl-BPMC, which had properties including an ir spectrum identical to that of unlabeled BPMC: mp 53°; nmr ($CDCl_3$) δ 0.82 (t, 3 H), 1.22 (d, 3 H), 1.59 (m, 2 H), 2.6 (m, 1 H), 2.82 (d, 3 H, NCH_3), 5.2 (bm, 1 H, NH), 6.8–7.2 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 207 (6), 150 (72), 135 (6), 121 (100), 107 (8). Further characterization of both the unlabeled and [^{14}C]butyl-BPMC was obtained by comparing their mass spectra (ci) *m/e* (rel intensity) 208 (M + 1) (65), 152 (11), 151 (100), 150 (22), 123 (22), 95 (50).

[^{14}C]Carbonyl-BPMC. The [^{14}C]carbonyl preparation of BPMC was synthesized in a similar manner to that of [^{14}C]butyl-BPMC but using methyl [^{14}C]isocyanate (10.5 mg, 0.184 mmol; 5.4 mCi/mmol; New England Nuclear Corp.) and unlabeled BP. The properties, including mp, ir, and mass spectra (ci), were identical to those of [^{14}C]butyl-BPMC and unlabeled BPMC. The final product, obtained in 95% yield, had a specific activity of 5.4 mCi/mmol.

[^{14}C]Carbonyl-BPBSMC and [^{14}C]Butyl-BPBSMC. Into a 2-ml ampoule were placed 34 mg (0.164 mmol) of [^{14}C]carbonyl-BPMC, 60 mg of pyridine, 100 mg (0.69 mmol) of freshly prepared and distilled benzenesulfenyl chloride, and 1 ml of dichloromethane. The ampoule was sealed and kept at 25° for 24 hr. The resulting mixture was purified by preparative tlc utilizing two developments with hexane–ether (4:1) mixture and then two developments with hexane–ether (6:1) mixture. The light yellow oil obtained consisted of pure [^{14}C]carbonyl-BPBSMC (97% yield) with a specific activity of 5.4 mCi/mmol. A similar procedure using [^{14}C]butyl-BPMC (61 mg, 0.295 mmol) gave [^{14}C]butyl-BPBSMC (95% yield; specific activity 0.29 mCi/mmol). The identity of both [^{14}C]carbonyl-BPBSMC and [^{14}C]butyl-BPBSMC was confirmed by tlc, ir, and nmr comparison with pure unlabeled BPBSMC prepared in a manner similar to that described above. A few of the properties of unlabeled BPBSMC are as follows: nmr ($CDCl_3$) δ 0.82 (t, 3 H), 1.21 (d, 3 H), 1.59 (m, 2 H), 2.6 (m, 1 H), 3.4 (s, 3 H, NCH_3), 6.8–7.2 (m, 4 H, aromatic), 7.2–7.4 ppm (s, 5 H, S aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 315 (60), 258 (76), 229 (13), 201 (30), 166 (32), 150 (10), 149 (24), 121 (40), 109 (100). The unlabeled and the [^{14}C]carbonyl and [^{14}C]butyl preparations of BPBSMC gave identical mass spectra (ci) *m/e* (rel intensity) 316 (M + 1) (20), 203 (16), 167 (12), 166 (100), 151 (20), 141 (12), 137 (16), 109 (76).

The radiochemical purity of each radiolabeled preparation of BPMC and BPBSMC was greater than 99.5% (tlc analysis). Each labeled compound was repurified by tlc immediately prior to use in metabolism or photodecomposition experiments.

3-(2-Butyl)phenyl Carbamates with Various N Substituents. *3-(2-Butyl)phenyl N-Benzenesulfinyl-N-methylcarbamate (BPBSOMC).* To 65 mg (0.206 mmol) of BPBSMC in 1 ml of dichloromethane was added 40 mg (0.255 mmol) of 3-chloroperoxybenzoic acid. After 24 hr at 25°, preparative tlc cleanup was carried out. Two developments with hexane–ethyl acetate (5:1) mixture and then twice with hexane–carbon tetrachloride–ether (4:1:1) mixture gave pure BPBSOMC (67% yield) as a colorless paste: ir ($CHCl_3$) 1105 and 1075 cm^{-1} (SO); nmr ($CDCl_3$) δ 0.82 (t, 3 H), 1.22 (d, 3 H), 1.6 (m, 2 H), 2.61 (m, 1 H), 2.8 (s, 3 H, NCH_3), 6.8–7.3 (m, 4 H, aromatic), 7.4–7.8 ppm (m, 5 H, SO aromatic). BPBSOMC was also prepared in 60% yield by reaction of BPMC with benzenesulfinyl chloride by a method similar to that used in synthesizing BPBSMC.

3-(2-Butyl)phenyl N-Benzenesulfonyl-N-methylcarbamate (BPBSO$_2$MC). Two different procedures were used to prepare BPBSO$_2$MC. The first involved the treatment of BPBSMC with a large excess of 3-chloroperoxybenzoic acid in dichloromethane. Use of the preparative tlc method described earlier for BPBSOMC gave BPBSO$_2$MC in a 30% yield. The second method involved a series of steps and initial preparation of *N*-methyl benzenesulfonamide from the reaction of benzenesulfonyl chloride with methylamine. The methyl benzenesulfonamide was then reacted with an excess of phosgene in the presence of K_2CO_3 to prepare *N*-benzenesulfonyl-*N*-methylcarbamoyl chloride. This carbamoyl chloride (*ca.* 240 mg, *ca.* 1.0 mmol) was mixed with 240 mg (1.6 mmol) of BP and 240 mg (3.0 mmol) of pyridine in 5 ml of dichloromethane and held at 25° for 4 hr. Tlc workup of the reaction mixture gave 175 mg (50% yield) of pure BPBSO$_2$MC: mp 75–76°; ir ($CHCl_3$) 1360 and 1170 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 0.80 (t, 3 H), 1.19 (d, 3 H), 1.57 (m, 2 H), 2.57 (m, 1 H), 3.5 (s, 3 H, NCH_3), 6.6–7.3 (m, 4 H, aromatic), 7.3–7.7 (m, 3 H, SO_2 aromatic), 7.9–8.1 ppm (m, 2 H, SO_2 aromatic).

3-(2-Butyl)phenyl Carbamate (BPC). BPC was obtained by reacting 212 mg (1.0 mmol) of the chloroformate (**6**), prepared by the reaction of BP with phosgene in the presence of K_2CO_3, in 4 ml of benzene with 1 ml of 28% NH_4OH. The mixture was shaken for 5 min, followed by preparative tlc (solvent system B × 2) of the benzene phase. Recrystallization from hexane gave pure BPC in 50% yield: mp 107–108°; ir ($CHCl_3$) 3500, 3420, 3340, 3270, 3160 cm^{-1} (NH_2); mass spectrum (70 eV) *m/e* (rel intensity) 193 (4), 150 (76), 135 (7), 121 (100), 107 (31), 91 (18), 77 (23), 43 (24).

3-(2-Butyl)phenyl N-Benzenesulfenylcarbamate (BPBSC). To 50 mg (0.28 mmol) of benzenesulfenyl chloride in 0.1 ml of dichloromethane was added a mixture of 30 mg (0.155 mmol) of BPC and 40 mg (0.50 mmol) of pyridine in 0.9 ml of dichloromethane.

The resulting mixture was kept at 25° for 3 hr, after which time preparative tlc cleanup was carried out with benzene–chloroform (1:1) and then benzene–hexane (2:1) mixtures. Pure BPBSC was obtained in 38% yield as a colorless oil: ir ($CHCl_3$) 3400 (NH), 1745 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 301 (M^+ absent), 151 (35), 150 (43), 121 (100), 109 (46), 91 (26), 77 (34), 65 (19), 43 (22); mass spectrum (ci) *m/e* (rel intensity) 342 (M + 41) (8), 330 (M + 29) (19), 302 (M + 1) (100).

3-(2-Butyl)phenyl N-Hydroxymethylcarbamate (BP-CH_2OH-C). The synthesis procedure used was similar to that of Fahmy and Fukuto (1972). To 4 mg (0.044 mmol) of paraformaldehyde in 1 ml of dimethoxyethane in an ampoule were added 15 mg (0.067 mmol) of BPC and a catalytic amount (3 μl) of 37% HCl in H_2O. The ampoule was sealed and the mixture heated and stirred magnetically at 50–60° for 1 hr. Preparative tlc (solvent system B × 3) of the resulting liquid gave 8 mg (62% yield) of pure BP-CH_2OH-C as an oil: ir ($CHCl_3$) 3580 (OH), 3450 cm^{-1} (NH); mass spectrum (70 eV) *m/e* (rel intensity) 223 (1), 205 (2), 193 (10), 176 (4), 150 (85), 135 (9), 122 (41), 121 (100), 107 (32), 91 (19), 77 (24), 65 (9).

Aldehyde, Alcohol, and Carboxylic Acid Derivatives at the 1 Position of 3-(2-Butyl)phenol and Their *N*-Methylcarbamates. *2-(3-Benzyloxyphenyl)butanal* (**8**). To 5.0 g (14.6 mmol) of methoxymethyltriphenylphosphonium chloride in a freshly prepared methanolic sodium methoxide solution (0.8 g of Na metal in 30 ml of absolute methanol) was added 1.5 g (6.25 mmol) of compound **4**. This mixture was kept at 45–50° under N_2 for 48 hr, after which time the crude product (*ca.* 1.8 g) was passed through a Florisil column (40 × 2.8 cm, 140 g), eluting the desired material with hexane–ether (4:1) mixture. Preparative tlc of the resulting oil with multiple developments in hexane–ether (8:1) mixture gave pure 2-(3-benzyloxyphenyl)-1-methoxybutene (**7**) in 81% yield. Hydrolysis of 1.0 g (3.73 mmol) of **7** in a mixture of 10 ml of dimethoxyethane and 8 ml of 25% HCl in H_2O under N_2 for 4 hr at 25° gave pure **8** (60% yield) upon workup and preparative tlc development in hexane–ether (6:1) mixture: ir ($CHCl_3$) 2820 and 2720 (CHO), 1720 cm^{-1} (C=O).

3-(1-Formyl-1-propyl)phenol (1-CHO-BP) and 3-(1-Formyl-1-propyl)phenyl N-Methylcarbamate (1-CHO-BPMC). Catalytic hydrogenation of 200 mg (0.87 mmol) of compound **8** in the manner described earlier gave, after tlc cleanup (solvent system C), 120 mg (85% yield) of pure 1-CHO-BP as a viscous oil: ir ($CHCl_3$) 3590–3100 (OH), 2830 and 2720 cm^{-1} (CHO); mass spectrum (70 eV) *m/e* (rel intensity) 164 (19), 136 (15), 135 (35), 121 (21), 107 (100), 91 (19).

The reaction of 50 mg (0.3 mmol) of 1-CHO-BP with 46 mg (0.8 mmol) of methyl isocyanate in 1 ml of anhydrous ether containing 20 mg (0.2 mmol) of triethylamine gave, after tlc workup with benzene–ether (2:1) mixture, 28 mg (42% yield) of pure 1-CHO-BPMC: ir ($CHCl_3$) 3450 and 3200 (NH), 2820 and 2720 (CHO), 1730 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 221 (6), 164 (10), 135 (14), 122 (30), 121 (52), 107 (100), 57 (49).

3-(1-Hydroxy-2-butyl)phenol (1-CH_2OH-BP) and 3-(1-Hydroxy-2-butyl)phenyl N-Methylcarbamate (1-CH_2OH-BPMC). Reduction of 240 mg (0.94 mmol) of compound **8** with 20 mg (0.50 mmol) of $LiAlH_4$ in anhydrous ether gave in a quantitative yield 2-(3-benzyloxyphenyl)butanol (**9**). Hydrogenation of **9**, as described above, followed by tlc isolation (solvent system C) gave a 96% yield, based on starting **8**, of 1-CH_2OH-BP: mp 81–82°; ir ($CHCl_3$) 3580–3100 cm^{-1} (OH); mass spectrum (70 eV) *m/e* (rel intensity) 166 (39), 148 (2), 136 (25), 135 (68), 121 (8), 120 (12), 107 (100), 91 (22).

The corresponding *N*-methylcarbamate, 1-CH_2OH-BPMC, was prepared by reacting 75 mg (0.45 mmol) of 1-CH_2OH-BP with methyl isocyanate in the usual manner. Preparative tlc workup (solvent system C) gave 76 mg (75% yield) of pure 1-CH_2OH-BPMC: mp 44–45°; ir ($CHCl_3$) 3580 (OH), 3460 (NH), 1730 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 223 (2), 205 (4), 193 (20), 166 (66), 148 (6), 136 (65), 135 (76), 121 (31), 120 (55), 107 (100), 57 (44).

3-(1-Carboxyl-1-propyl)phenol (1-COOH-BP) and 3-(1-Carboxyl-1-propyl)phenyl N-Methylcarbamate (1-COOH-BPMC). To a stirred suspension of 1.0 g (5.9 mmol) of $AgNO_3$ and 0.5 g (10 mmol) of NaOH in 3 ml of water was added 0.3 g (1.2 mmol) of compound **8** in 2 ml of methanol. This mixture was stirred rapidly for 3 hr at 25°, after which time the solution was acidified with 8 ml of 10% HCl in H_2O and extracted with ether, and the ether was dried and evaporated yielding a viscous oil. Preparative tlc (solvent system A) gave pure 2-(3-benzyloxyphenyl)butanoic acid (**10**) (56% yield). This compound was reacted further *via* hydrogenation, in the manner described earlier, and tlc workup (solvent system C), giving 83% yield of pure 1-COOH-BP: ir ($CHCl_3$) 3580 (OH), 3500–2500 (*COOH*), 1710 (C=O), 1280 cm^{-1} (CO).

Formation of the *N*-methylcarbamate from 1-COOH-BP was carried out in the usual manner obtaining, after tlc workup (solvent system E), 1-COOH-BPMC (52% yield) as a pasty liquid: ir ($CHCl_3$) 3450 (NH), 3200–2500 (*COOH*), 1730 (C=O, carbamate ester), 1705 cm^{-1} (*COOH*).

Alcohol Derivative at the 2 Position of 3-(2-Butyl)phenol, its *N*-Methylcarbamate and Their Dehydration Products. *3-(2-Hydroxy-2-butyl)phenol (2-COH-BP) and 3-(2-Hydroxy-2-butyl)phenyl N-Methylcarbamate (2-COH-BPMC).* 3-Benzyloxyacetophenone (**12**) was synthesized in a manner similar to that of compound **2** but using 3-hydroxyacetophenone (**11**) as starting material. Compound **5**, a precursor to 2-COH-BP, was prepared by the action of ethylmagnesium bromide on **12** in a manner similar to that described in the preparation of compound **3** giving a 95% yield of **5** after tlc workup with hexane–ether (4:1) mixture. Hydrogenation of 1.0 g (4 mmol) of **5** in 40 ml of ethanol over 0.5 g of 10% Pd on charcoal for 1 hr at a pressure of 20 lb/in.^{2} led to a 90% yield, based on starting **5**, of 2-COH-BP: mp 89–90°; mass spectrum (70 eV) *m/e* (rel intensity) 166 (39), 149 (13), 148 (38), 137 (100), 133 (21), 121 (38), 107 (13).

Reaction of 166 mg (1 mmol) of 2-COH-BP in the usual manner with 60 mg (1.2 mmol) of methyl isocyanate gave, after tlc workup (solvent system C) and recrystallization from hexane–ether, a quantitative yield of pure 2-COH-BPMC: mp 101–102°; ir ($CHCl_3$) 3590 (OH), 3460 (NH), 1730 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 223 (4), 194 (38), 166 (47), 148 (30), 137 (100), 133 (17), 121 (18), 107 (11).

3-(2-Buten-2-yl)phenol (**13**) *and 3-(2-Buten-2-yl)phenyl N-Methylcarbamate* (**14**). Dehydration was accomplished by treating 1.66 g (10 mmol) of 2-COH-BP with 50 mg of concentrated H_2SO_4 in 30 ml of absolute ethanol and refluxing the resulting mixture for 4 hr. The reaction was worked-up by neutralization with 0.2 g of $KHCO_3$, removal of the solvent under reduced pressure, and two preparative tlc developments with benzene. The resulting oily liquid (81% yield) consisted of two products detected on tlc with multiple benzene developments, the higher R_f product in about a ninefold greater amount than the lower R_f product. It appears likely that the higher R_f material consists of a mixture of *trans-* and *cis*-3-(2-buten-2-yl)phenol (**13**): ir ($CHCl_3$) 3580 cm^{-1} (OH); mass spectrum (70 eV) *m/e* (rel intensity) 148 (100), 133 (68), 121 (17), 107 (16), 91 (20). The lower R_f material is 3-(1-buten-2-yl)phenol on the basis of the ratio of the products, their expected chromatographic behavior, and the fact that each of the tlc-separated products is converted to BP on hydrogenation over Pd on charcoal.

Methylcarbamoylation of the mixture of dehydration products referred to as compound **13** (0.50 g, 3.4 mmol) with methyl isocyanate in the usual manner and preparative tlc (first B × 2, second benzene × 2) yielded 452 mg (2.2 mmol; 65% yield) of pure compound **14**: mp 51–52°; ir ($CHCl_3$) 3460 (NH), 1730 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 205 (29), 148 (100), 133 (47).

Alcohol and Keto Derivatives at the 3 Position of 3-(2-Butyl)phenol and Their *N*-Methylcarbamates. *3-(3-Hydroxy-2-butyl)phenol (3-CHOH-BP) and 3-(3-Hydroxy-2-butyl)phenyl N-Methylcarbamate (3-CHOH-BPMC).* In a Wittig reaction similar to that described in the preparation of compound **7**, 1.5 g (6.6 mmol) of compound **12** was reacted with 5.0 g (15 mmol) of methoxymethyltriphenylphosphonium chloride in a methanolic sodium methoxide solution. Purification was accomplished using a Florisil column with hexane–ether (3:1) mixture and then preparative tlc using a 4:1 mixture of hexane–ether. Isolated in 83% yield was 2-(3-benzyloxyphenyl)-1-methoxypropene (**15**). Compound **15** (1.0 g, 3.9 mmol) was hydrolyzed using the same procedure as in the preparation of compound **8** giving, after preparative tlc, a 64% yield of a colorless oil identified as 2-(3-benzyloxyphenyl)propanal (**16**). Reaction of **16** (400 mg, 1.67 mmol) with methylmagnesium iodide in the usual manner, followed by preparative tlc isolation using hexane–ether (4:1) mixture for development, gave 2-(3-benzyloxyphenyl)-3-butanol (**17**) (99% yield). This intermediate (320 mg, 1.25 mmol) was then debenzylated in the usual manner, followed by preparative tlc (solvent system A × 2), giving 96% yield of 3-CHOH-BP as a mixture of diastereomers: ir ($CHCl_3$) 3600–3200 (OH), 1260 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.06 (d, 3 H), 1.22 (q, 3 H), 2.6 (m, 1 H), 3.8 (m, 1 H), 6.6–7.3 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 166 (29), 122 (100), 121 (34), 107 (78), 91 (12).

The methylcarbamate derivative, 3-CHOH-BPMC, was obtained by the reaction of 120 mg (0.72 mmol) of 3-CHOH-BP with 43 mg (0.75 mmol) of methyl isocyanate in 1 ml of anhydrous ether containing 50 μl of triethylamine. After 1 hr at 5°, preparative tlc work-up (solvent system C × 2) gave a 93% yield of pure 3-CHOH-BPMC: mp 75–76°; ir ($CHCl_3$) 3580 (OH), 3460 (NH), 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.06 (d, 3 H), 1.22 (q, 3 H), 2.6 (m, 1 H), 2.82 (d, 3 H, NCH_3), 3.75 (m, 1 H), 5.2 (bs, 1 H, NH), 6.8–7.4 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 223 (M^+ absent), 179 (73), 166 (9), 122 (100), 121 (38), 107 (74), 57 (20); mass spectrum (ci) *m/e* (rel intensity) 264 (M + 41) (1), 252 (M + 29) (7), 224 (M + 1) (12), 206 (100).

3-(1-Acetylethyl)phenol (3-C=O-BP) and 3-(1-Acetylethyl)-phenyl N-Methylcarbamate (3-C=O-BPMC). To 200 mg (2.3 mmol) of activated MnO_2 in 5 ml of anhydrous benzene was added 20 mg (0.078 mmol) of compound **17**. The mixture was kept at 25° for 24 hr. Removal of the MnO_2 by filtration and preparative tlc purification by two developments with hexane–ether (6:1) mixture gave a 90% yield of 2-(3-benzyloxyphenyl)-3-butanone (**18**). Catalytic hydrogenation of 18 mg (0.07 mmol) of compound **18** in the usual manner and purification by tlc involving two developments with hexane–ether (4:1) mixture produced a 77% yield of 3-C=O-BP: ir ($CHCl_3$) 3580 (OH), 1710 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 164 (4), 121 (32), 91 (32), 77 (36), 43 (100).

Reaction of 3 mg (0.02 mmol) of 3-C=O-BP with an excess of methyl isocyanate in the usual manner gave, essentially in a quantitative yield, 3-C=O-BPMC: ir ($CHCl_3$) 3460 (NH), 1735 (C=O), 1710 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 221 (M^+ absent), 164 (7), 122 (11), 121 (45), 107 (6), 103 (13), 91 (64), 77 (36), 57 (17), 43 (100); mass spectrum (ci) *m/e* (rel intensity) 262 (M + 41) (3), 250 (M + 29) (12), 222 (M + 1) (100).

Carboxylic Acid and Alcohol Derivatives at the 4 Position of 3-(2-Butyl)phenol and Their *N*-Methylcarbamates. *3-(3-Carboxyl-2-propyl)phenol (4-COOH-BP) and 3-(3-Carboxyl-2-propyl)-phenyl N-Methylcarbamate (4-COOH-BPMC).* To 1.2 g (5.4 mmol) of triethyl phosphonoacetate in a solution of 0.5 g of Na metal in 30 ml of absolute methanol was added 1.1 g (5 mmol) of compound **12**. The resulting mixture was stirred under N_2 for 12 hr at 50°. Reaction workup was done by evaporation of the solvent and acidification by pouring the reaction mixture into 50 ml of 10% HCl in H_2O. This was then extracted three times with 15-ml portions of dichloromethane. Evaporation of the dichloromethane and preparative tlc using a hexane–ether (3:1) mixture gave 1.2 g (82% yield) of pure ethyl 3-(3-benzyloxyphenyl)crotonate (**19**). Hydrolysis of 180 mg (0.61 mmol) of **19** in 7% (w/v) KOH in ethanol for 2 hr at 50–60° yielded, after workup, 150 mg (0.56 mmol; 92% yield) of pure 3-(3-benzyloxyphenyl)crotonic acid (**20**). Hydrogenation of 150 mg (0.56 mmol) of compound **20** in methanol by the usual procedure and preparative tlc (solvent system C) gave 76 mg (75% yield) of 4-COOH-BP: ir ($CHCl_3$) 3580, 3400–2500 (COOH), 1705 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 180 (90), 135 (22), 134 (36), 121 (100), 107 (7), 59 (56), 45 (27).

The *N*-methylcarbamate was prepared in the usual manner to give, after workup, a 50% yield of 4-COOH-BPMC: ir ($CHCl_3$) 3455 (NH), 1735 (C=O, carbamate ester), 1710 cm^{-1} (COOH).

3-(4-Hydroxy-2-butyl)phenol (4-CH_2OH-BP) and 3-(4-Hydroxy-2-butyl)phenyl N-Methylcarbamate (4-CH_2OH-BPMC). To 152 mg (3.9 mmol) of $LiAlH_4$ in 100 ml of anhydrous ether at 0–5° was added dropwise and slowly 800 mg (2.7 mmol) of **19** in 40 ml of anhydrous ether. After normal workup, 600 mg (87% yield) of pure 3-(3-benzyloxyphenyl)butanol (**21**) was obtained. Compound **21**, upon catalytic hydrogenation in the usual manner and tlc purification (solvent system D), gave 240 mg (93% yield) of 4-CH_2OH-BP: ir ($CHCl_3$) 3590 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.22 (d, 3 H), 1.8 (m, 2 H), 2.8 (m, 1 H), 3.56 (t, 2 H), 6.6–7.3 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 166 (100), 148 (6), 147 (6), 133 (20), 122 (94), 121 (61), 107 (29), 91 (11), 77 (15).

Reaction of 60 mg (0.36 mmol) of 4-CH_2OH-BP with methyl isocyanate in the normal manner gave, after tlc purification (solvent system C × 3), 40 mg (50% yield) of pure 4-CH_2OH-BPMC: ir ($CHCl_3$) 3600 (OH), 3460 (NH), 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.22 (d, 3 H), 1.78 (m, 2 H), 2.8 (m, 1 H), 2.82 (d, 3 H, NCH_3), 3.5 (t, 2 H), 5.2 (bs, 1 H, NH), 6.8–7.3 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 223 (3), 166 (55), 135 (6), 122 (100), 121 (40), 107 (19), 57 (30).

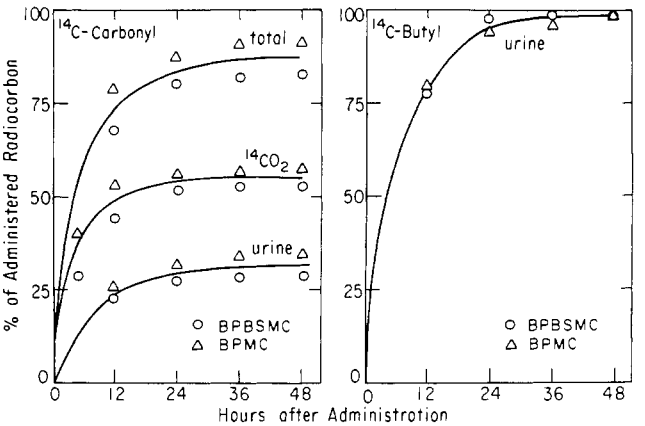


Figure 1. Rate of excretion of radiocarbon in urine and carbon dioxide of rats after oral administration of [^{14}C]carbonyl- and [^{14}C]butyl-labeled 3-(2-butyl)phenyl *N*-benzenesulfenyl-*N*-methylcarbamate and 3-(2-butyl)phenyl *N*-methylcarbamate.

METABOLISM AND PHOTOALTERATION

Metabolism of BPBSMC and BPMC in Living Mammals. The carbamate group of BPBSMC and BPMC undergoes extensive cleavage in rats treated orally with the [^{14}C]carbonyl compounds, based on the large amount of expired 14-carbon dioxide relative to urinary radiocarbon (Figure 1). The [^{14}C]butyl-labeled preparations yield essentially all of the administered radioactivity in the urine (Figure 1) and little if any in the feces within 48 hr. So, the metabolites of both BPBSMC and BPMC are quickly excreted from the body with up to 30% of the dose accounted for by compounds retaining the carbamate moiety. The similarity in results with BPBSMC and BPMC suggests that the same compounds may be excreted following treatment with either chemical. On this basis, BPBSMC was selected for a critical examination of the urinary products.

The identified urinary metabolites of [^{14}C]butyl-BPBSMC in rats account for 72% of the administered dose and 27% is present as unidentified metabolites, including those not extractable into organic solvent (Table II). The neutral fraction contains neither BPBSMC nor BPMC, but instead it consists of six butylphenyl methylcarbamates modified by monohydroxylation or, in the case of 3-C=O-BPMC, hydroxylation and then oxidation to a ketone. The acidic fraction consists of two methylcarbamates with butyric acid side chains and the phenolic fraction consists of BP and seven phenols modified by oxidation in the butyl moiety. The aldehyde intermediates leading to the carboxylic acids are not found, probably being transitory intermediates. The major urinary metabolite is 2-COH-BP, followed by 3-CHOH-BP and 1-CH_2OH-BP. The oxidation of the butyl side chain in the combined methylcarbamate and phenol products occurs at the 2, 3, 4, and 1 positions in the ratio of 100:66:55:46, respectively. About 70% of the urinary metabolites are present as conjugates cleaved by glucuronidase and glusulase. The major metabolites retaining the carbamoyl moiety are 1- and 4-COOH-BPMC; these two carboxylic acids are the only methylcarbamates excreted in part as conjugates, suggesting that the carboxylic acid moiety is more easily conjugated than the hydroxyalkyl moiety in the other methylcarbamate metabolites. The metabolites yielding 1- and 4-COOH-BPMC on enzymatic hydrolysis are almost entirely cleaved by β-glucuronidase, so they are possibly glucuronides. The identified metabolites retaining the carbamate moiety account for 8.3% of the administered radiocarbon. This is well below the value of up to 30% indicated from the balance study with the [^{14}C]carbonyl compounds described above. There are two possible

Table III. Metabolites of [^{14}C]Carbonyl-Labeled 3-(2-Butyl)-phenyl *N*-Benzenesulfenyl-*N*-methylcarbamate and 3-(2-Butyl)phenyl *N*-Methylcarbamate Formed by the Rat Liver Microsome–NADPH System

Compound	R_f[a]	Amount of initial radiocarbon recovered, %, in indicated fraction: BPBSMC[b]	BPMC[c]
BPBSMC	0.85	35.3	
BPMC	0.71	42.6	49.7
BPC	0.57	0.1	0.2
3-C=O-BPMC	0.47	0.2	0.4
BP-CH_2OH-C	0.36	1.0	9.0
2-COH-BPMC	0.31	2.0	9.0
3-CHOH-BPMC	0.21	0.8	7.9
1- and/or 4-CH_2OH-BPMC	0.17	1.9	13.1
Other organosoluble carbamates	*d*	1.0	2.1
Water-soluble products		1.1	2.1
Loss[e]		14.0	6.5

[a] Developed twice in one dimension with solvent system C. [b] Less than 2% of the BPBSMC is converted to BPMC in buffer alone or buffer containing NADPH but this conversion takes place to the extent of 33 to 71% with either fresh or boiled microsomes in the presence or absence of NADPH. The addition of NADPH decreases the extent of N–S cleavage with fresh microsomes but increases this cleavage with boiled microsomes. [c] No products other than BPMC detected after incubation in mixtures containing only one but not both of microsomes and NADPH. [d] R_f values of 0.00, 0.05, 0.07, 0.09, and 0.43. [e] A portion of this loss may occur by hydrolysis but experiments were not made to detect 14-carbon dioxide, if any.

Table IV. Photoalteration Products of [^{14}C]Carbonyl-Labeled 3-(2-Butyl)phenyl *N*-Benzenesulfenyl-*N*-methylcarbamate and 3-(2-Butyl)phenyl *N*-Methylcarbamate Formed on Tlc Chromatoplates Exposed to Ultraviolet Light or Sunlamp Irradiation

Compound	R_f[a]	Amount of applied radiocarbon recovered, %, in indicated fraction[a]: Uv light, 5 min BPB-SMC	Uv light, 5 min BPMC	Sunlamp, 0.5 hr BPB-SMC	Sunlamp, 0.5 hr BPMC
BPBSMC	0.71	42.4		75.7	
$BPBSO_2MC$	0.55	0.3		0.1	
BPBSOMC	0.49	2.5		2.5	
BPMC	0.39	18.6	84.7	7.7	92.3
BPC	0.30	1.0	0.1	0.1	<0.1
BP-CH_2OH-C	0.18	3.7	0.3	0.8	<0.1
2-COH-BPMC	0.15	0.3	0.2	0.1	<0.1
Unknowns					
Above origin	c	6.2	0.8	2.1	0.1
At origin	0.00	6.9	0.3	1.4	<0.1
Loss[d]		18.1	13.6	9.5	7.6

[a] No products other than applied compound detected after comparable exposure periods in the dark. [b] Developed in one dimension with three solvent systems used in sequence as follows: first, E for 50% of distance; second, D for 60% of distance; third, hexane–ether (9:1) used three times for development to the front, *i.e.*, 100% of distance. [c] R_f values of 0.33, 0.42, 0.46, 0.52, 0.57, 0.59, and 0.66 as derived from BPBSMC; unknown photoproducts of BPMC represent total areas of R_f 0.05 to 0.12 and 0.20 to 0.37. [d] About two-thirds of the loss appears to result from photolysis to BP and other phenols (which results in loss of the carbonyl label) and about one-third from volatilization based on comparable studies with [^{14}C]butyl-BPBSMC and -BPMC.

explanations for this difference. First, a portion of the unidentified metabolites may be carbamates. Second, the urine fractionation involved brief treatment with cold 5% KOH solution, a procedure that may have hydrolyzed a portion of the carbamates in the urine so that these products would appear in the phenolic fraction.

Some information is also available from studies on the rat urinary metabolites of [^{14}C]carbonyl-BPBSMC and -BPMC which fully confirms and extends the findings with [^{14}C]butyl-BPBSMC relative to the carbamate metabolites excreted in unconjugated form. The same unconjugated carbamates in almost the same amounts are found following administration of [^{14}C]butyl-BPBSMC (Table II) or [^{14}C]carbonyl-BPBSMC or -BPMC; these are BP-CH_2OH-C, 1-CH_2OH-BPMC, 1-COOH-BPMC, 2-COH-BPMC, 3-CHOH-BPMC, 3-C=O-BPMC, 4-CH_2OH-BPMC, 4-COOH-BPMC, and five unidentified acidic metabolites. The very small amounts of several monohydroxylated carbamates (BP-CH_2OH-C, 1-CH_2OH-BPMC, and 4-CH_2OH-BPMC) excreted in the urine indicate that these compounds are transient intermediates in the metabolism, undergoing subsequent oxidation or carbamate ester cleavage. The findings with the [^{14}C]carbonyl preparation establish that little or no loss of unconjugated carbamate metabolites occurs during the alkaline wash used in studies on the [^{14}C]butyl metabolites. Conjugated carbamate metabolites account for 15 to 20% of the administered dose based on the [^{14}C]carbonyl studies, so a major portion of the unknown conjugates found in the [^{14}C]butyl investigations are carbamates rather than phenols. The unidentified carbamate metabolites, after conjugate cleavage, are for the most part more polar compounds than the identified materials; so they may involve two or more sites of oxidation at different positions on the molecule such as at both the *N*-methyl and butyl moieties.

In studies with mice, the carbamate group is cleaved more rapidly following intraperitoneal than oral administration of [^{14}C]carbonyl-BPBSMC since the 14-carbon dioxide expired after 0.5 and 24 hr is 34 and 57%, respectively, by the intraperitoneal route and 16 and 70%, respectively, when administered orally. The urinary radioactivity from [^{14}C]carbonyl-BPBSMC accounts for 8 to 13% of the administered dose within 24 hr. [^{14}C]Butyl-BPBSMC yields, within 48 hr, 94% of the radiocarbon in the urine, almost none in the feces, and none as 14-carbon dioxide. Two of the urinary products present in unconjugated form were identified as BP and 2-COH-BP.

Metabolism of [^{14}C]Carbonyl-BPBSMC and -BPMC by Rat Liver Microsomes. The carbamate metabolites of BPBSMC detectable by tlc are the same as those of BPMC when these compounds are incubated with the rat liver microsome–NADPH system (Table III). The major metabolites are formed by oxidation at the *N*-methyl group, yielding BP-CH_2OH-C which partially degrades to BPC, and at the butyl group, yielding mainly the alcohols formed by hydroxylation at each carbon of the side chain. Little if any 1- and 4-COOH-BPMC are formed because these would appear in the water-soluble products, which are in a small amount. The chromatographic behavior (R_f values of 0.05, 0.07, and 0.09) of three minor metabolites and the larger amounts of BP-CH_2OH-C and hydroxybutyl-BPMC derivatives suggest that these unidentified carbamates of low R_f may be compounds hydroxylated at both the *N*-methyl and butyl moieties. The degree of hydrolysis is uncertain, although a portion of the loss of radiocarbon on incubation of these [^{14}C]carbonyl-labeled compounds may have resulted from carbamate cleavage.

There are four remarkable features of the microsomal metabolism of BPBSMC. First, the conversion to BPMC occurs with fresh or boiled microsomes in the presence or

absence of NADPH; so, the N–S cleavage may involve a nonenzymatic reaction with a microsomal component, such as a sulfhydryl group, in some cases and an oxidative cleavage by the action of microsomal enzymes in other cases. Second, the greater loss of labeled material from BPBSMC than BPMC occurs only when both microsomes and NADPH are present in the incubation mixture. This suggests that oxidative cleavage may be involved for a portion of the BPBSMC as might occur *via* the hydrolytically unstable BPBSOMC as an intermediate. Third, the addition of NADPH to fresh microsome preparations reduces the extent of conversion of BPBSMC to BPMC. One possible mechanism for this phenomenon is the release of an oxidation product, such as benzenesulfenic acid from BPBSOMC, at a critical site in the microsomal oxidase system, resulting in inhibition by combination with a component important to oxidase action. Fourth, the oxidation of BPBSMC to hydroxy-BPMC derivatives is less extensive than that of BPMC, a finding that has several possible explanations: differences in liposolubility may influence the relative rates of oxidation at various sites of BPBSMC and BPMC; the rate-limiting step with BPBSMC may be cleavage of the N–S bond, producing the more readily oxidized BPMC; oxidation at the sulfur may be favored over *N*-methyl or butyl oxidation; nonenzymatic or enzymatic conversion of BPBSMC to BPMC may involve release of the phenyl-S or phenyl-SO moiety in a form and at a site in the microsomes that leads to inhibition of mixed-function oxidase activity, such as by reaction with an important sulfhydryl group. If this latter proposal is correct, then microsomal oxidation of BPBSMC releases not only the active insecticide BPMC but also an oxidase-inhibiting or synergist fragment to reduce the subsequent rate of BPMC detoxification.

Photoalteration of BPBSMC. Preliminary studies involving the exposure of unlabeled BPBSMC in methanol solution to uv, sunlamp, or sunlight irradiation for 1 hr showed that it yields at least six photoproducts, the same ones with each light source, as detected with various chromogenic reagents after tlc resolution. BPMC is more stable under these conditions, undergoing extensive decomposition only on uv irradiation, in which case six or more photoproducts are formed. The photoproducts, based on tlc R_f values and chromogenic responses, are: BP and BP-CH_2OH-C but no detectable BPC from BPMC; BPMC, BP-CH_2OH-C, BPC, BP, and diphenyldisulfide but no detectable 2-COH-BPMC, 2-COH-BP, or phenyl benzenethiosulfonate from BPBSMC. Thus, BPBSMC is more photolabile than BPMC, BPMC is a major photoproduct of BPBSMC, and large amounts of BPC are formed as a photoproduct of BPBSMC but not of BPMC.

[^{14}C]Carbonyl-BPBSMC undergoes rapid decomposition when exposed on glass surfaces or silica gel tlc chromatoplates to uv light or sunlight. The photodecomposition is about 99 and 50% complete on 5 min exposure to uv light on glass and silica gel surfaces, respectively, and 20 and 30% complete on 30 min exposure to winter sunlight on these same surfaces, respectively. At least 13 carbamate photoproducts are evident when the photoalteration conditions are such that little BPBSMC remains. There is some information relevant to the likely sequence for formation of various photoproducts: the first products detected in large amounts are BPMC and BPBSOMC; more extensive decomposition then yields BP-CH_2OH-C and small amounts of BPC, 2-COH-BPMC, and $BPBSO_2MC$; almost complete decomposition of BPBSMC is always accompanied by the disappearance of four to seven carbamate photoproducts retaining the N–S bond (tlc R_f between BPBSMC and BPMC), these products apparently being quite unstable. The use of [^{14}C]butyl-BPBSMC permits the detection of small amounts of BP and 2-COH-BP, in addition to the carbamate photoproducts indicated above.

Quantitative data on the photoalteration of [^{14}C]carbonyl-BPBSMC and -BPMC exposed on tlc chromatoplates to uv light or sunlamp irradiation (Table IV) confirm the photoinstability of BPBSMC relative to BPMC, the ease of oxidation of the sulfur (particularly to BPBSOMC), the rapid and extensive cleavage of the N–S bond, and the larger amounts of BP-CH_2OH-C and BPC formed on photoalteration of BPBSMC than of BPMC. At least a portion of the loss of radiocarbon resulting on photodecomposition of [^{14}C]carbonyl-BPBSMC occurs by ester cleavage, since comparable studies with [^{14}C]butyl-BPBSMC produce a small amount of [^{14}C]butyl-BP.

Biological Activity of Metabolites, Photoproducts, and Related Compounds. BPMC is a potent plasma cholinesterase inhibitor (molar concentration for 50% inhibition equals 2×10^{-7} *M*) but 4-CH_2OH-BPMC and BPBSC are at least three times more potent. Three other compounds (BPBSMC, BPC, and BP-CH_2OH-C) are 0.1 to 0.3 times the potency of BPMC, while the following nine other compounds are less than 0.1 times as active: 1-CH_2OH-BPMC, 1-CHO-BPMC, 1-COOH-BPMC, 2-COH-BPMC, 2-CHOH-BPMC, 3-C=O-BPMC, 4-COOH-BPMC, BPBSOMC, and compound **14**. The high potency of 4-CH_2OH-BPMC relative to other hydroxybutyl-BPMC derivatives is a remarkable feature in this series.

Four of the compounds (BPBSMC, BPBSOMC, BPBSC, and BPMC) show high mosquito larvicidal activity (concentration for 50% mortality or LC_{50} below 0.04 ppm) and, of these, BPBSMC is most potent. Intermediate larvicidal activity (LC_{50} 0.1–3 ppm) is found with BP-CH_2OH-C, BPC, 2-CHOH-BPMC, 3-C=O-BPMC, and compound **14**. The other compounds tested are inactive at 10 ppm and these include $BPBSO_2MC$, 1-CH_2OH-BPMC, 1-CHO-BPMC, 1-COOH-BPMC, 3-CHOH-BPMC, 4-CH_2OH-BPMC, 4-COOH-BPMC, and three phenols (BP, 2-COH-BP, and compound **13**).

DISCUSSION

Several alkylphenyl *N*-methylcarbamates are under development or in use as insecticide chemicals; these include the *N*-methylcarbamates of 3,4-xylenol (Meobal), a mixture of 3,4,5- and 2,3,5-trimethylphenols (Landrin), 3-methyl-5-isopropylphenol (promecarb), 2-(2-butyl)phenol (Bassa), a mixture of 3-(1-ethylpropyl)- and 3-(1-methylbutyl)phenol (Bux), and 3,5-di-*tert*-butylphenol (Butacarb). The metabolism of these compounds, where it is known, includes modification of the alkyl substituent to form alcohol, aldehyde, and carboxylic acid derivatives. The present report outlines methods applicable to synthesis of the phenolic intermediates for the anticipated metabolites of several of these compounds, starting from hydroxybenzaldehydes, hydroxyacetophenones, and the corresponding higher alkyl aldehydes and ketones. Selective methylcarbamoylation of the phenolic hydroxyl group in dihydroxy intermediates is achieved by controlling the conditions and reactant ratios with consideration that the reactivity of the alcoholic hydroxyl group decreases in the order of primary, secondary, and tertiary. The carbamates synthesized do not include those with aromatic hydroxyl groups; previous studies (Kuhr and Casida, 1967; Miyamoto and Fukunaga, 1971; Oonnithan and Casida, 1968; Slade and Casida, 1970) on alkylphenyl methylcarbamates failed to detect significant amounts of ring-hydroxylated carbamates as metabolites in various organisms and enzyme systems.

Many products are generated on biodegradation and photoalteration of the new carbamate insecticide BPBSMC, a compound that contains seven sites susceptible to attack: the sulfur; the *N*-methyl group; the car-

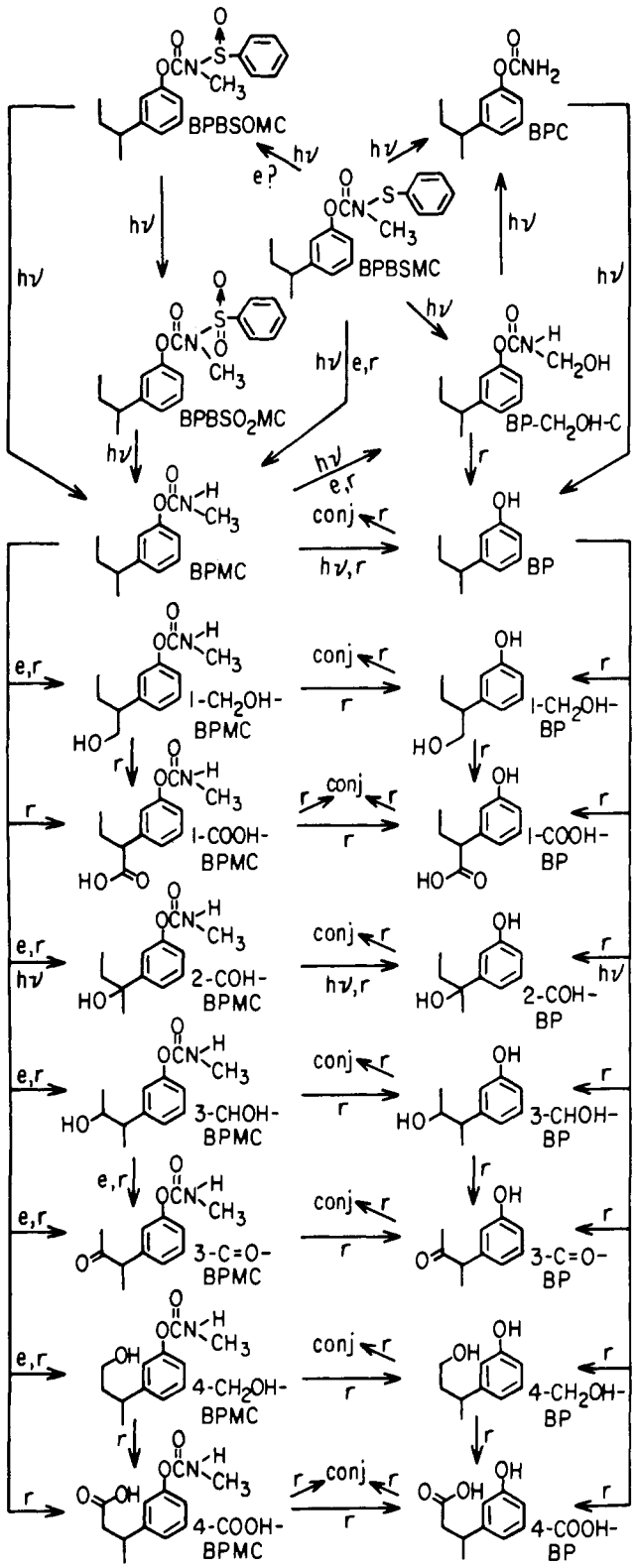


Figure 2. Tentative pathways of photoalteration ($h\nu$) and metabolism in living rats (r) and the liver microsome–NADPH system (e) for 3-(2-butyl)phenyl *N*-benzenesulfenyl-*N*-methylcarbamate and 3-(2-butyl)phenyl *N*-methylcarbamate.

bamoyl group; and each carbon of the butyl moiety. While Figure 2 defines the major pathways for formation of the carbamate and phenol metabolites and photoproducts tentatively identified by cochromatography, it does not show a number of transient intermediates that must be involved and does not include many other metabolites and photoproducts, most of which appear in small amounts, that remain to be identified. It is possible that some of the additional carbamate and phenolic metabolites are formed by two or more sites of hydroxylation at positions already defined or, less likely, by attack on the phenyl group.

The fate of the metabolically-released thiophenol was not determined in this study, but it is known from other investigations that in rats it is methylated to thioanisole, which is then oxidized to sulfoxide and sulfone derivatives with or without hydroxylation in the 3 and 4 positions of the phenyl group (McBain and Menn, 1969; McBain *et al.*, 1971). Photodecomposition involves cleavage of the N-S bond with release of the thiophenyl radical which is oxidized to diphenyldisulfide. Several sulfur-containing photoalteration products remain unidentified and these may be formed by one or more of: oxidation of diphenyldisulfide; cleavage of BPBSOMC or $BPBSO_2MC$; addition of a thiophenyl moiety to BPBSMC or a carbamate derived from BPBSMC by attack of a liberated thiophenyl radical. The *N*-methyl group of BPBSMC is particularly susceptible to photooxidation yielding $BP\text{-}CH_2OH\text{-}C$ and BPC possibly *via* BPBSOMC, BPBSC, or the *N*-hydroxymethyl derivative of BPBSMC as intermediate(s).

The present study establishes that BPBSMC is not likely to be a persistent chemical in the environment or to pass unmetabolized through food chains. A number of the metabolites and photoalteration products retain a relatively high degree of biological activity and so must be considered in evaluating persisting residues. This is particularly true of BPMC and certain of its monohydroxybutyl derivatives. It is not known if these compounds form in plants, but this would not be surprising in light of previous studies comparing the plant and animal metabolism of methylcarbamates (Fukuto, 1972; Kuhr, 1971; Kuhr and Casida, 1967; Schlagbauer and Schlagbauer, 1972a,b; Slade and Casida, 1970).

The findings with BPBSMC and BPMC indicate that comparable studies on related alkylphenyl methylcarbamates are likely to reveal many metabolites and photoproducts. Optimum anticholinesterase and insecticidal activities are found with C_3–C_5 branched-alkyl substituents in the ortho or meta positions (Kohn *et al.*, 1965; Metcalf, 1971). These are the very types of substituents that lead to a variety of metabolites, among which those retaining the methylcarbamoyl group and those with hydroxyalkyl substituents are most likely to have a significant level of toxicity to mammals. Thus, high potency for the parent carbamate of this type leads to biodegradable compounds, yielding some active intermediates in the detoxification process.

Substitution of the proton on the carbamoyl moiety with appropriate groupings yields derivatized *N*-methylcarbamates that are sometimes equal to or greater in insecticidal activity than the underivatized compounds and yet have greatly reduced mammalian toxicity. Alterations in physical properties and partitioning characteristics on derivatization might contribute to the changes in biological activity. There is already speculation and evidence from studies with *N*-phosphorothioyl and *N*-acetyl derivatives that the carbamate ester moiety may be preferentially cleaved in mammals leading to detoxification, while the phosphorothioyl or acetyl group is more readily removed by insects yielding the toxic *N*-methylcarbamates (Fahmy *et al.*, 1970; Miskus *et al.*, 1969). A third hypothesis, involving interaction of the derivatizing group with the microsome mixed-function oxidase system, is also worthy of consideration. This hypothesis is based, in part, on the observed ability of selected phosphorothionates to preferentially inhibit microsomal oxidations, insect microsomes being more sensitive to this inhibition than mammalian microsomes (Oppenoorth *et al.*, 1971). Perhaps this inhibition results from appropriate localization

of the liberated sulfur-derived moiety interfering with the pathway of microsomal electron transport. Peracid oxidation of *N*-methyl-*N*-phosphorothioylcarbamates liberates sulfur and the *N*-methylcarbamate among other products (Fahmy and Fukuto, 1972). Microsomal metabolism of the *N*-benzenesulfenyl-*N*-methylcarbamate examined in the present investigation results in release of the *N*-methylcarbamate, apparently with inhibition of subsequent microsomal oxidations. Possibly the sulfur- or thiophenyl-derived moiety released on oxidation of the *N*-methyl-*N*-phosphorothioylcarbamate or *N*-benzenesulfenyl-*N*-methylcarbamate inhibits subsequent detoxification of the liberated *N*-methylcarbamate, resulting in a greater overall level and persistence of the toxic *N*-methylcarbamate in some insects than in mammals. This hypothesis warrants further investigation.

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Photochemistry of Bioactive Compounds. Kinetics of Selected *s*-Triazines in Solution

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The rate constants (k) for several 2-methylthio and 2-halo-4,6-bis(alkylamino)-*s*-triazines have been calculated in methanol, *n*-butyl alcohol, and water solutions. The rate of disappearance of the starting material (I–XII) has been found to be dependent on the nature of the halogen and alkyl substituents and the solvent employed. A decrease in k was observed in the order I-Br-Cl-F and $-C_2H_5 > -C_3H_7$. All photoreactions showed zero-order rate constants. The rate constant in methanol was found to be considerably greater than that calculated in *n*-butyl alcohol.

Effects of sunlight and laboratory ultraviolet light on pesticides have been investigated with renewed interest in the past decade (Dilling, 1966). Changes in the ultraviolet spectra of photolyzed solutions of *s*-triazines and a decrease in the phytotoxicity of unidentified photoproduct mixtures have been reported (Comes and Timmons, 1965; Jordan *et al.*, 1963, 1965). Jordan *et al.* (1970) summarized the literature on *s*-triazine photochemistry to that date.

Recent investigations in this laboratory (Pape and Zabik, 1970, 1972) have demonstrated the generality of the photochemical solvolysis of 2-halo and 2-methylthio-*s*-triazines. Irradiation of the former in water, methanol, and *n*-butyl alcohol solutions resulted in the formation of the corresponding 2-hydroxy and 2-alkoxy derivatives. Photolysis of 2-methylthio-*s*-triazines resulted in photoreduction *via* intramolecular elimination with hydrogen transfer.

The purpose of the present investigation was to extend the knowledge of the photochemistry of symmetrical substituted triazines. The rate variations caused by solvent and substituent effects indicate certain characteristics of the excited state which will be useful in the understanding of their photoreactions.

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MATERIALS AND METHODS

s-Triazines. Authentic samples of I–V and IX–XI were supplied by Geigy Agricultural Chemicals, Ardsley, N. Y.

2-Iodo-*s*-triazines (VI–VIII) were supplied by Z. D.