Topical Mosquito Repellents IV: Alicyclic, Bicyclic, and Unsaturated Acetals, Aminoacetals, and Carboxamide Acetals

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Abstract □ A number of acetals, aminoacetals, carboxamide acetals, and aromatic esters were synthesized and evaluated for topical repellency on human skin against *Aedes aegypti* mosquitoes. The aminoacetals exhibited the highest degrees of repellency, but none of the compounds rivaled *N,N*-diethyl-*m*-toluamide in terms of duration of protection. Repellency was related to volatility, and it is concluded that useful repellency is associated with a volatility range corresponding to a boiling point of 100–150°/0.5 mm. Two benzylic ethers were also examined and one of these was comparable to *N,N*-diethyl-*m*-toluamide in duration of topical repellency.

Keyphrases □ Mosquito repellents, topical, potential—acetals, aminoacetals, carboxamide acetals and esters □ Acetals—synthesis, evaluation as mosquito repellents □ Aminoacetals—synthesis, evaluation as mosquito repellents □ Carboxamide acetals and esters—synthesis, evaluation as mosquito repellents □ Structure–activity relationships—volatility and topical insect repellency □ Repellency, insects—relationship between volatility and topical activity

While *N,N*-diethyl-*m*-toluamide is an excellent topical mosquito repellent, its duration of effectiveness in practical use is somewhat limited owing to loss by evaporation and by rubbing and sweating (1). In a search for longer lasting repellents, preliminary results suggested that acetals or ketals containing an amine function had potentially useful repellent properties (2). In addition, olfactometer screening of compounds for repellent potency (3) as well as evaluation of test data published by the U. S. Department of Agriculture (4) suggested that alicyclic, bicyclic, and polyunsaturated groups were useful moieties for enhancement of repellent potency. These considerations, coupled with the apparently low order of topical toxicity of acetals examined in the past (2), prompted the synthesis and repellency evaluation on humans of a number of high molecular weight, high boiling acetals. In addition, two ethers and a number of esters with similar moieties were synthesized and evaluated for comparison. Low volatility was specifically sought with a view toward enhancement of protection time by minimization of evaporative loss rates. In addition, it was felt that variations in activity among such high boiling compounds might reflect primarily variations in "intrinsic repellency" or equimolar potency independent of variations in vapor concentration.

DISCUSSION

Acetals of *p*-methoxybenzaldehyde were selected for synthesis and evaluation because of the generally good repellency exhibited in the past by compounds containing this aromatic moiety (4). All but the most volatile compound (IV, Table I) in this series failed to exhibit topical effectiveness. Such a finding is consistent with previous results indicating low incidences of effectiveness among acetals and ketals with boiling points in the range of 125–195°/0.5 mm. (2). However, while the benzyl moiety appears to impart some degree of activity to such compounds (2), it may be concluded that the alicyclic and unsaturated moieties examined in the present study were inefficient in imparting sufficient potency for useful activity at low vapor concentrations.

In contrast to the data of Table I, aminoacetals of similar low volatility showed more consistent topical repellency (Table II). The apparent advantage of the amine function is particularly illustrated in Compound XVI, which can be compared directly with the compounds of Table I. Noteworthy, also, is the activity of XVIII in spite of its relatively high volatility. These data appear to confirm the previous inference (2) that an amine function can impart improved repellency characteristics to some compounds. Nevertheless, significant potency was not apparent in the case of carboxamide acetals of similar volatility (Table III). These results, together with those obtained in a previous study (2), suggest that optimum repellency is reached with compounds of this class whose volatilities correspond to a boiling point between 100 and 140°/0.5 mm.

The esters of Table IV were examined in part because extensive studies with this class in the past (4) provide a good basis for structural comparisons. In addition, some current studies[1] suggest that solid repellents may possess certain advantages over liquids, particularly in terms of formulation characteristics. Unfortunately, all of the esters examined were of very low volatility and completely inactive in the standard topical test. The two ethers examined were much more volatile and proved to be active (Table IV).

The present data are of interest in terms of comparative structural attributes associated with variations in topical repellent potency. The findings also provide additional data regarding the relationship of volatility to topical repellency as defined in previous studies (2, 3, 5). For any homologous series of compounds, there exists an optimum volatility range corresponding to maximum duration of topical repellency. While this range varies somewhat between series, data obtained for several classes of compounds suggest that it generally corresponds to a boiling-point range of 100–150°/0.5 mm. Apparently, more volatile compounds are lost too rapidly from the skin surface while less volatile ones do not provide sufficient vapor concentration above the skin surface to repel mosquitoes. Presumably, the latter problem could be overcome by a compound of suitable structure with much greater "intrinsic repellency" (2) or equimolar potency. To date, no evidence of such a structure has been obtained.

In perspective, the present compounds do not rival *N,N*-diethyl-*m*-toluamide in topical usefulness because the latter compound provides effective protection for 3–10 hr. when tested under similar conditions and even at reduced application rates (5). Of the present compounds, only Compound XXXVIII is noteworthy in this regard.

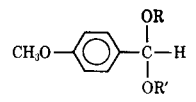
EXPERIMENTAL[2]

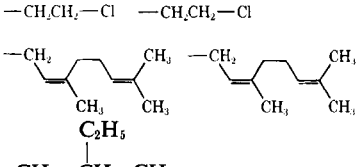
Except where otherwise noted, compounds were purified and boiling points (uncorrected) were determined by vacuum distillation through a 10-cm. Vigreux column. Instability and low volatility frequently necessitated purification by chromatography on basic alumina previously treated with anhydrous K_2CO_3 (pH 10; ethyl acetate–cyclohexane). Structure and purity were verified by NMR spectroscopy. Symmetrical acetals of *p*-methoxybenzaldehyde were obtained by the Claisen method (6), and the unsymmetrical acetals

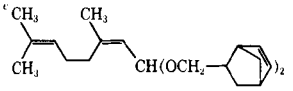
[1] Personal communication, Capt. P. Kurtz, Letterman Army Institute for Research, Letterman General Hospital, San Francisco, Calif.

[2] Elemental analyses are by the Microanalytical Laboratory, Department of Chemistry, Stanford University, Stanford, Calif.

Table I—Acetals of *p*-Methoxybenzaldehyde and Aliphatic Aldehydes



Compound Number	R	R′	Yield, %	Formula	Analysis, % Calc.	Found	Boiling Point (mm.)	Duration of Repellency, hr. (Number of Determinations)
I			39	$C_{18}H_{26}O_3$	C 74.45 H 9.02	74.37 9.03	147° (0.5)	0.25 (2)
II			53	$C_{20}H_{30}O_3$	C 75.43 H 9.50	75.58 9.54	155° (0.25)	0.25 (2)
III			26	$C_{22}H_{30}O_3$	C 77.16 H 8.83	77.40 8.65	171° (0.15)	0.25 (2)
IV	$-CH_3$		48	$C_{16}H_{20}O_3$	C 73.82 H 7.74	73.71 7.98	121° (0.15)	2.5 (1)
V	$-CH_3$	$-CH_2-$ 	41	$C_{17}H_{22}O_3$	C 74.42 H 8.08	74.62 8.20	141° (0.2)	0.25 (1)[a]
VI	$-CH_2-$ 	$-CH_2-$ 	56	$C_{24}H_{30}O_3$	C 78.65 H 8.25	78.62 8.27	207° (0.5)	0.25 (2)
VII	$-CH_2-$ 	$-CH_2-$ 	51	$C_{24}H_{34}O_3$	C 77.80 H 9.25	77.91 9.25	220° (0.5)	0.25 (1)[a]
VIII	$-CH_3$	$-CH_2-$ 	38	$C_{16}H_{18}O_3$	C 74.40 H 7.02	74.87 7.24	131° (0.1)	0.25 (1)
IX	$-CH_2-$ 	$-CH_2-$ 	49	$C_{22}H_{22}O_3$	C 79.02 H 6.67	78.94 6.69	195° (0.25)	0.25 (1)
X	$-CH_3$	$-CH_2CH_2-Cl$	54	$C_{11}H_{15}ClO_3$	C 57.27 H 6.55	57.28 6.51	119° (0.25)	—
XI	$-CH_2CH_2-Cl$	$-CH_2CH_2-Cl$	44	$C_{12}H_{16}Cl_2O_3$	C 51.63 H 5.68	51.79 5.65	146° (0.25)	0.25 (1)
XII			32	$C_{28}H_{42}O_3$	C 78.83 H 9.92	79.23 10.53	208° (0.5)	0.25 (2)
XIII	$-CH_2-CH(C_2H_5)-CH(C_3H_7)-$		85	$C_{16}H_{24}O_3$	C 72.69	72.71	159° (0.1)	—
XIV	—[b]			Derivatives: Table II			150° (0.2)	0.25 (1)
XV	—[c]		49	$C_{26}H_{32}O_2$	C 81.62 H 10.01	81.20 10.04	191° (0.3)	0.25 (1)

[a] Tested at approximately 1.5 mg./cm.^{2}. [b] $Cl-CH_2-CH(OCH_2C_6H_5)_2$. [c] 

were obtained by partial transacetalization from *p*-methoxybenzaldehyde dimethyl acetal. The aminoacetals of *p*-methoxybenzaldehyde (XVI and XVII) were obtained from the corresponding β-chlorethyl acetal. The remaining aminoacetals of Table II (XVIII–XXV) were prepared from the diethyl acetal of β-chloracetaldehyde by transacetalization, followed by reaction of the product with the appropriate amine. The carboxamide acetals of Table III were prepared by the method of Arnold and Kornilov (7) from 1,1-dimethoxytrimethylamine (8) and 1,1-dimethoxymethyldiethylamine (9). Esters of *p*-aminobenzoic acid (Table IV) were obtained by transesterification of methyl *p*-nitrobenzoate or by reduction of the corresponding nitro ester with $SnCl_2 \cdot 2H_2O$ and HCl. Nitro esters were prepared from *p*-nitrobenzoyl chloride and the appropriate alcohol in pyridine. Compounds XXXVII and XXXVIII were obtained by the usual Williamson synthesis using benzyl chloride and sodium alcoholates.

Symmetrical *p*-Methoxybenzaldehyde Acetals (Table I)—*p*-Methoxybenzaldehyde (0.1 mole), triethyl orthoformate (0.12 mole), alcohol (0.5 mole), and concentrated hydrochloric acid (8 drops) were heated at 100–110° for 6 hr. with simultaneous removal of the low boiling fraction through a Vigreux column. The temperature was then maintained at 140–150° for 15 hr. After neutralization with NaOMe, the product was distilled under vacuum through a Vigreux column.

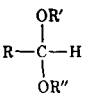
Citral 5-Norbornen-2-methanol Acetal (XV)—A mixture of citral (7.6 g., 0.05 mole), 5-norbornen-2-methanol (32.0 g., 0.25 mole), methyl orthoformate (6.35 g., 0.06 mole), and NH_4Cl (0.2 g.) was heated 48 hr. at 50–60° with periodic removal of volatile products under vacuum. Anhydrous ether was added, and the mixture was washed with water and dried over Na_2SO_4. Following solvent evaporation, the product was distilled through a short Vigreux column.

Asymmetrical *p*-Methoxybenzaldehyde Acetals (Table I)—*p*-Methoxybenzaldehyde dimethyl acetal (0.1 mole), alcohol (0.12 mole), and concentrated hydrochloric acid (4 drops) were heated for 6 hr. at 130–140° with simultaneous elimination of methyl alcohol through a Vigreux column. After neutralization with NaOMe, the product was distilled under vacuum, yielding a small quantity of the aldehyde in the lead fraction and about 20% of the symmetrical acetal.

***p*-Methoxybenzaldehyde Di-(β-*N*-diethylaminoethyl) Acetal (XVII)**—Compound XI (0.1 mole) and anhydrous diethylamine (0.5 mole) were heated in a sealed tube at 90–100° for 4 hr. The mixture was extracted with anhydrous ether and, after evaporation of the solvent, was distilled under vacuum.

α-Chloroacetaldehyde Dibenzyl Acetal (XIV) and Ethyl Benzyl Acetal—A mixture of α-chloroacetaldehyde diethyl acetal, 0.4 mole of benzyl alcohol, and 4 drops of concentrated hydrochloric acid

Table II—Aminoacetals



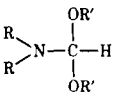
Compound Number	R	R′	R″	Yield, %	Formula	—Analysis, %— Calc.	Found	Boiling Point (mm.)	Duration of Repellency, hr. (Number of Determinations)
XVI	CH_3O-C$_6$H$_4$-	$-CH_3$	$-CH_2CH_2N(CH_3)_2$	57	$C_{13}H_{21}NO_3$	C 65.27 H 8.77 N 5.74	65.25 8.84 5.85	125° (0.2)	1.5 (3)
XVII	CH_3O-C$_6$H$_4$-	R″	$-CH_2CH_2N(C_2H_5)_2$	63	$C_{20}H_{36}N_2O_3$	C 68.15 H 10.29 N 7.85	68.88 10.41 7.96	151° (0.25)	2.0 (1)[a]
XVIII	$(CH_3)_2NCH_2-$	$-CH_2-C_6H_4-$	C_2H_5	57	$C_{13}H_{21}NO_2$	C 69.92 H 9.48 N 6.27	69.93 9.49 6.29	83° (0.2)	2.0 (1)
XIX	$(CH_3)_2NCH_2-$	$-CH_2-C_6H_4-$	$-CH_2-C_6H_5$	52	$C_{18}H_{23}NO_2$	C 75.76 H 8.12 N 4.91	75.75 8.08 4.97	143° (0.3)	3.5 (1)[a] 0.25 (2)
XX	$(C_2H_5)_2NCH_2-$	$-CH_2-C_6H_4-$	$-CH_2-C_6H_5$	53	$C_{20}H_{27}NO_2$	C 76.64 H 8.68 N 4.47	76.69 8.58 4.55	150° (0.2)	0.25 (2)
XXI	N-CH_2-	$-CH_2-C_6H_4-$	$-CH_2-C_6H_5$	76	$C_{20}H_{25}NO_2$	C 77.14 H 8.09 N 4.50	77.23 8.05 4.46	166° (0.15)	0.5 (3)
XXII	O,N-CH_2-	$-CH_2-C_6H_4-$	$-CH_2-C_6H_5$	68	$C_{20}H_{25}NO_3$	C 73.37 H 7.70 N 4.28	73.51 7.63 4.33	182° (0.25)	0.25 (2)
XXIII	N-CH_2-	$-CH_2-C_6H_4-$	C_2H_5	65	$C_{16}H_{25}NO_2$	C 72.97 H 9.57 N 5.32	73.45 9.99 5.46	121° (0.25)	—
XXIV	n-C_4H_9, H_3C, N-CH_2-	$-CH_2-C_6H_4-$	$-CH_2-C_6H_5$	60	$C_{21}H_{29}NO_2$	C 77.02 H 8.93 N 4.28	76.74 8.92 4.33	157° (0.2)	0.25 (2)
XXV	H_3C, H_3C, NCH_2CH_2N, CH_3	$-CH_2-C_6H_4-$	C_2H_5	67	$C_{16}H_{23}N_2O_2$	C 68.53 H 10.06 N 9.99	68.44 10.12 9.91	115° (0.2)	—

[a] Tested at approximately 1.5 mg./cm.^{2}.

was heated for 18 hr. at 130–135° with simultaneous removal of ethanol through a Vigreux column. After neutralization with NaOMe, vacuum distillation yielded the ethyl benzyl acetal in the first fraction (20%, b.p. 92–93°/0.3) and the dibenzyl acetal in the second fraction (54%, b.p. 150–151°/0.2). When a 1:1 ratio of the diethyl acetal and benzyl alcohol was used, the main compound obtained was the ethyl benzyl acetal (45%) with about 20% of the dibenzyl acetal.

α-*N*-Dialkylaminoacetaldehyde Dibenzyl Acetals (Table II)—Compound XIV (0.1 mole) and 0.4 mole of amine were heated in a sealed tube for 12 hr. at 95–100°. Following extraction with anhydrous ether and evaporation of the solvent, the product was ob-

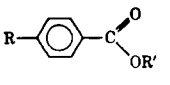
Table III—Carboxamide Acetals

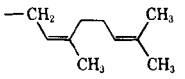
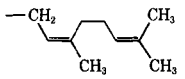
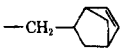


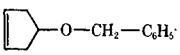
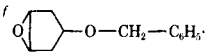
Compound Number	R	R′	Yield, %	Formula	——Analysis, %—— Calc.	Found	Boiling Point (mm.)	Duration of Repellency, hr. (Number of Determinations)
XXVI	CH_3	$-CH_2-C_6H_5$	—[a]	—	—	—	141° (0.75)	0.25 (2)
XXVII	CH_3	$-CH_2-C_6H_4-$	61	$C_{19}H_{29}NO_2$	C 75.21 H 9.63	75.17 9.54	149° (0.75)	—
XXVIII	CH_3	$-CH_2-C_6H_4-$	58	$C_{17}H_{29}NO_2$	C 73.07 H 10.46	73.15 10.27	118° (0.3)	0.25 (2)
XXIX	C_2H_5	$-CH_2-C_6H_5$	49	$C_{19}H_{25}NO_2$	C 76.21 H 8.42	76.00 8.49	141° (0.3)	0.5 (2)
XXX	C_2H_5	$-CH_2-C_6H_4-$	47	$C_{21}H_{33}NO_2$	C 76.09 H 10.03	76.04 10.14	140° (0.3)	0.25 (2)

[a] See *Reference 7*.

Table IV—Esters and Ethers



Compound Number	R	R′	Yield, %	Formula	Analysis, % Calc.	Found	Melting Point or Boiling Point (mm.)	Duration of Repellency, hr. (Number of Determinations)
XXXI	NO_2		80[a]	$C_{17}H_{21}NO_4$	C 67.31 H 6.88 N 4.62	67.81 6.52 4.63	175° (0.25)	0.25 (1)
XXXII	NH_2		52[b]	$C_{17}H_{23}NO_2$	C 74.69 H 8.48 N 5.12	74.62 8.63 5.26	51–52°	0.25 (1)
XXXIII	NH_2		20[b]	—[c]	—	—	54–55°	0.25 (1)
XXXIV	NO_2		94[d]	$C_{14}H_{15}NO_4$	C 64.36 H 5.49 N 5.36	64.46 5.48 5.35	78–79°	0.25 (1)
XXXV	NH_2		68[b]	$C_{14}H_{17}NO_2$	C 72.70 H 7.41 N 6.06	72.85 7.46 5.97	84–85°	0.25 (1)
XXXVI	NH_2		32[b]	$C_{15}H_{17}NO_2$	C 74.05 H 7.04 N 5.75	74.24 7.09 5.67	89–90°	0.25 (1)
XXXVII	—[e]		74	$C_{12}H_{14}O$	C 82.72 H 8.10	82.34 8.09	67° (0.5)	2.0 (1)
XXXVIII	—[f]		55	$C_{12}H_{14}O_2$	C 75.76 H 7.42	75.44 7.39	98° (0.2)	8.0 (1)

[a] See *Reference 10*. [b] Recrystallized from *n*-hexane. [c] See *Reference 11*. [d] Recrystallized from ethanol. [e]  [f] 

tained by vacuum distillation.

1,1-Dialkoxymethyldialkylamines (Table III)—1,1-Dimethoxytrimethylamine or 1,1-dimethoxymethyldiethylamine (0.1 mole), 0.24 mole of the alcohol, and 20 ml. of anhydrous benzene were refluxed with simultaneous removal of the methanol–benzene mixture through a short Vigreux column. Vacuum distillation yielded a product which required chromatographic purification (basic alumina, ethyl acetate–cyclohexane, 10:90) for suitable analysis.

***p*-Aminobenzoic Acid Esters**—*Transesterification (XXXII, XXXIII, and XXXVI)*—Methyl *p*-aminobenzoate (0.01 mole) and 0.1 mole of the alcohol were heated at 140–150° for 24 hr. After removal of excess alcohol, the product was chromatographed on a silica column (ethyl acetate–cyclohexane, 30:70).

Reduction of Nitro Esters (XXXII and XXXV)—To 0.01 mole of ester in 20 ml. of ether was added 0.02 mole of $SnCl_2 \cdot 2H_2O$ in 8 ml. of concentrated hydrochloric acid and 40 ml. of alcohol in portions with stirring and cooling. After 1 hr. at room temperature, 50 ml. of water was added and the mixture was extracted with ether. The aqueous acidic solution was made alkaline and extracted with ether. The ether extract was washed with water, dried over $NaSO_4$, and evaporated to yield the pure product.

Biological Evaluation—Repellency duration testing was conducted by uniform application of compounds in EtOH to an exposed area of the arm of a human subject as described previously (5). The compounds were applied at a rate of approximately 0.3 mg./cm.^{2} except where otherwise noted. Female *Aedes aegypti* (nonblood-fed) mosquitoes (5–7 days old) were used in all tests. Exposure testing was begun after an initial 15-min. period to allow evaporation of solvent and at 30–60-min. intervals thereafter. Protection times noted are times to the first bite confirmed by one or more bites 30 min. later. Where indicated, values are means of more than one determination. Simultaneous testing of *N,N*-diethyl-*m*-toluamide at an application rate of 0.3 mg./cm.^{2} yielded protection times of 3–5 hr.

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