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STUDY OF SYNTHETIC COMPOUNDS AS REPELLENTS AGAINST THE MOSQUITOES *CULEX PIPIENS MOLESTUS* AND *AEDES AEGYPTI*

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A B S T R A C T

Sixty-eight chemicals were synthesized and evaluated as repellents agains 2 species of mosquitoes, *Aedes aegypti* L. and *Culex pipiens molestus* Forskal, by applying the repellents on the shaven belly of a rabbit. The Chemicals were classified into a number of categories according to their repellent effect. Those falling into the best category were then compared in paired tests with deet (/V,/V-diethyl- m-toluamide). 2-Styryl-l ,3-dioxane and 2-methylenedioxyphenyloxazolidine were similar to deet against *Culex pipiens molestus.* The following 7 chemicals were similar to deet against *Aedes aegypti:* N-Butyl-3-fluorobenzamide; 2-methylenedio- xyphenyl-oxazolidine; N-(methylbutyl)-benzamide; N-(sec.Butyl) - 3-fluoroben- zamide; N-(3-methyl butyl)-2-fluorobenzamide; N-pentyl-3-fluorobenzamide and benzyl thiocyanoacetate. Thanite (mixture of fenchyl and isobornyl thiocyano- acetates) was far superior to deet against *Culex pipiens molestus* and also toxic to both species of mosquito.

INTRODUCTION

More than 30,000 organic compounds have been screened as potential insect repellents. This large number stems from the fact that virtually no physicochemical reasoning could be applied to the selection of the chemicals tested. Good repellents were found in almost every class of organic compounds; however, some generalization could

be made from these extensive searches: 1) The molecular weight should be between 150 and 250 a.m.u. 2) The steric-structure could influence the activity (e.g. dimethyl phthalate, a good repellent; dimethyl terephthalate, a poor repellent), giving one isomer a better repelling activity than the other. 3) Some functional groups (e.g. amides, aldehydes, esters etc.) tend to be more active than others. Moreover, it has been suggested that the oxygen(s) containing part of the molecule tested is the site responsible for its activity (Bunker and Hirchfelder, 1925) whereas the other chemical and physical properties of the molecule determine protection time and other parameters e.g., specificity and toxicity (Jonson *et al.*, 1967). Some of these observations could be understood on the basis of the recent works by entomologists who claim that at least in mosquitoes, "repellents repel because they jam the mosquito's sensors so that it is not able to follow the warm and moist air currents given off by a warm-blooded animal' (Wright, 1975). In order to be able to block some of the sensors in the mosquito's antennae the repellent must be adsorbed to the receptor surface in the sensory hairs. From the chemical point of view it is obvious that the more polar atoms such as oxygen and/or nitrogen will increase this adsorption. It has been shown spectroscopically that good repellents have stronger intermolecular forces giving rise to better adsorption properties. The knowledge of the approximate size of the pores and the diameters of the repellents show some correlation (Wright, 1975). Furthermore, the length of interaction between the repellent and the pore, in which the repellent blocks the pore's activity, could be dependent on the chemical nature of the membrane of the chemoreceptor which may differ somewhat in various species of mosquitoes. Therefore one might expect that one chemical will not be an equally effective repellent to all species (Gilbert *et al.*, 1957; Bar-Zeev and Ben-Tamar, 1971).

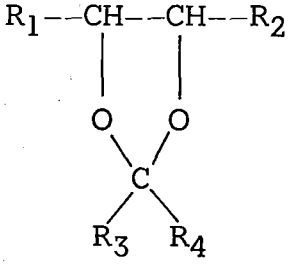
Even before a better understanding of the sensory system was established, some attempts were made to find what determines the best repellency within a given chemical family. The first attempt to correlate the chemical structure with repellency was made by Bunker and Hirchfelder (1925). The effectiveness was correlated with the presence of the oxygen atom. Later Roadhouse (1953) found the best class of compounds to be those with high solubility in water and fat. Alexander and Beroza (1963) prepared some aliphatic amides of cyclic amines and tolylmaleimides and reported the ortho isomer of the tolyl derivative to be the most effective repellent. A more extensive survey on some ring-substituted N, N diethylbenzamide (Johnson *et al.*, 1967) showed that no correlation between repellency and physical properties, such as relative partition coefficient and polarization, exists. However, the repellent's

potency within a given series is obviously dependent upon the availability of the substance to the mosquito via volatilization.

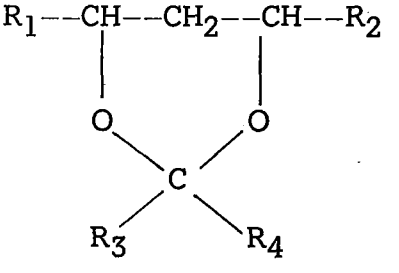
Six hundred synthetic chemicals, most of them obtained from the USDA, were screened on a number of blood sucking insects including mosquitoes (Bar-Zeev and Ben-Tamar, 1971; Bar-Zeev, 1972). On the basis of this study, a group of compunds coded UA were synthesized and evaluated against *C.p. molestus* (Table 6) and it was found that 2-Styryl-1, 3-dioxane (UA 22) was about equal to deet. This led us to concentrate our effort on the compounds coded A P (see following Tables) in the homological series. Three families of compounds were synthesized: 1) m-dioxanes and dioxolanes - derivatives of cinnamaldehyde system. 2) benzamides and fluorobenzamides. 3) thiocyanoacetates.

Effort was devoted to the elaboration of suitable synthetic methods. Selection of the compounds was based on our attempt to rationalize the vast amount of existing data for a methodical search for new repellents.

The m-dioxanes and dioxolanes (family 1) derived from aldehydes could be considered as "masked" carbonyl compounds. In a number of cases, aldehydes and ketones have been found to be effective repellents (benzaldehydes, especially those with alkoxy groups in the *ortho* or *para*-position, capraldehyde, heptanal, cinnamaldehyde, substituted butyrophenones and cyclohexanones). Equally some dioxolanes and m-dioxanes have been found to be effective repellents (I,II)



(I)



(II)

which might be considered as a masked form of the carbonyl compound $R_3 \diagdown C = O$. Most aldehydes though, having intrinsic repellent properties, $\diagup R_4$ tend to have short protection times. Therefore these masked forms might prolong protection time by "slow release agents" acting as precursers of the highly active aldehyde or ketone.

There is no need to elaborate on the importance of the benzamides (family 2). However, since in recent years the effect of fluorine substitution in organic compounds of potential biological interest has been demonstrated, we have employed this approach to the benzamide series. It can be seen (Table 3) that indeed the ortho-alkoxy groups imporove the repellency in the benzamide series.

The thiocyanoacetates (family 3) are a somewhat new group of compounds to be tested. Thanite (mixture of fenchyl and isobornyl thiocyanoacetates) was found (Table 9) to possess outstanding repellent properties against *C.p. molestus* as well as a toxic effect on both species. Furthermore, TMTD (bis-dimethyl thiocarbonyl disulfide) was found to repel wild animals (Radwan, 1969) in addition to its use in pest control.

MATERIALS AND METHODS

Evaluation of repellents

The method of evaluating candidate repellents has been described in detail by Bar-Zeev and Ben-Tamar (1971). The following are the main points of the method: The candidate repellents were applied to the shaven belly of a rabbit. The treated area of the belly was then exposed to several hundred caged mosquitoes for 3 minutes (in the case of *A. aegypti*) or 5 minutes (in the case of *C.p. molestus*) 1 hour after application of the repellent, followed by successive tests at hourly intervals, for a length of time depending on the quality of the repellent. The candidate repellents were classified into the following categories according to the number of mosquitoes feeding after various periods of time after treatment:

A. Three or more mosquitoes fed 1 hour after application of the repellent in at least 2 replicates.

B. A total of 3 or more mosquitoes fed 1 and 2 hours after application of the repellent in at least 2 replicates.

C. As above after 3 hours.

D. As above after 4 hours.

E. As above after 5 hours.

F. Better results than those mentioned above.

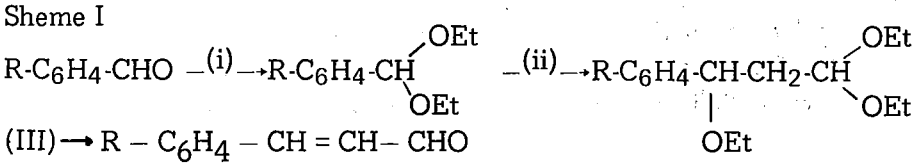
Compounds falling in the above best category (F) were than re-evaluated with 1 percent solution in ethanol and compared in paired tests with deet (*N,N*-diethyl-*m*-toluamide) which is the best repellent against mosquitoes to date. The protection period was taken as the time (hrs) at which no more than 3 feedings were obtained. The relative effectiveness of the repellent as compared to deet was expressed as the ratio of the protection period.

Synthetic procedure

2-cinnamyl-1, 3-dioxanes and 1,3-dioxolanes. The starting cinnamic aldehydes (see Table 1) were prepared as described for the p-methyl compound (Hercel, 1959; see scheme I).

The data of intermediate acetals and products from their reaction with vinyl alkyl ethers are given in Table 1.

Sheme I



R = CH_3O; CH_3; $(CH_3)_2$-CH; Cl; F;

The nitro and cyano derivatives were prepared according to the literature (Waley, 1948; Vecchi and Melone, 1957).

The purity of compounds was established by IR and NMR spectra and elemental analysis.

4-phenylbutyraldehyde. This compound was previously prepared by Kumler et al. (1950) and Gorgues (1967). We synthesized this compound by $LiAlH_4$ reduction of 4-phenylbutyrylimidazolide.

Analysis. Calculated for $C_{15}H_{14}N_2O$: C, 72.9; H, 6.55; N, 13.1

Found: C, 72.0; H, 6.60; N, 12.8

The imidazolide was reduced according to Staab el al. (1962), Staab and Bräunling (1962), and gave a 22% yield of 4-phenylbutyraldehyde.

The m-dioxolanes and m-dioxanes (see Tables 2, 3) were prepared as follows: 0.1 mole of the corresponding aldehyde in dry benzene (150 ml) 0.15 mole of the appropriate diol and 1-2% p-toluenesulphonic acid (w/w to aldehyde) were refluxed in a flask connected to a Dean-Stark trap. After the calculated amount of water was separated the solution was cooled, neutralized with sodium carbonate, washed several times with water and dried. The benzene was removed in a rotory evaporator and the residue either distilled *in vacuo* or crystallized from methanol-water mixture.

For all dioxolanes and dioxanes I.R. and NMR spectra and the elemental analysis were consistent with the structure.

Amides. The starting benzoic acids are commercially available. The acids were converted to chlorides with thionylchloride and then added dropwise (about two hours) at~ 0°C to a stirred solution of 1 M of the corresponding amine and 1 M of triethylamine in dry chloroform. The mixture was left at room temperature overnight, refluxed for one hour, cooled, washed three times with water and dried over Na_2SO_4. The chloroform was removed under reduced pressure and the products were either crystallized or distilled under nitrogen (see Table 4).

Thiocyanoacetates. Alkyl chloracetates were prepared from the respective alcohols and chloroacetic anhydride in dichloromethane - pyridine (Baroni and Marrano, 1933). They were converted to thiocyanoacetates with potassium thiocyanate (Heintz, 1865).

RESULTS

Chemical data as well as repellent properties (categories A to F) of the compounds are given in Tables 2 through 5.

Compounds coded UA which fell into category F were compared in paired tests against *C.p. molestus* (Table 6).

Compounds UA 22 and UA 44 were about equal to deet. Compounds coded AP which fell into category F were unfortunately not compared in paired tests with deet against *C.p. molestus*.

Compounds coded UA which fell into group F against *A. aegypti* were compared in paired tests with deet (Table 7).

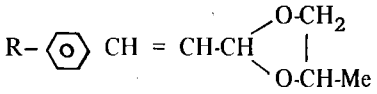
TABLE 1. Substituted cinnamaldehydes and their intermediates

No.	Ar	$ArCH(OEt)_2$		$ArCH(OEt)CH_2CH(OEt)_2$[a]		ArCH=CHCHO[b]	
		B.P. °C/mm or M.P. °C	Yield %	B.P. °C/mm or M.P. °C	Yield %	B.P. °C/mm or M.P. °C	Yield %
1[1,2,3]	MeO-C6H4-	96-98/0.5	92	142-152/2.5	93	121-122/1.0	69
2[4]	Me-C6H4-	78/80/1.0	87	108/110/0.8	84	120-122/0.3	89
3[4]	$(Me)_2CH$-C6H4-	82-83/1.0	94	140-142/3.0	91	118-120/3.0	82
4[5]	Cl-C6H4-	100-101/3.5	91	125-134/2.0	81	61-62	72
5[6]	F-C6H4-	62-64/1.5	91	110-114/1.5	74	88-95/2.0	68
6[7]	O_2N-C6H4-	122-123/1.0	91	148-160/3.0	76	140-141	75
7[8]	NC-C6H4-	120-122/2.0	80	130-140/1.0	75	133-136	56
8[9]	PhCH=CH	114-116/3.0	68	170-180/2.5	73	136-139/1.5	61

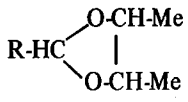
1. Horeau (1948)
2. Poirier and Lozach (1967)
3. Thiele and Giese (1903)
4. Bert and Dorier (1930)
5. Straus (1912)
6. Claisse et al. (1970)
7. Waley (1948)
8. Vecchi and Melone (1957)
9. Mikhailov (1963)

a and b are marked in order to identify the intermediate and aldehyde in the list of analytical results.

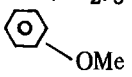
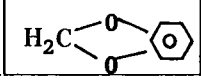
TABLE 2. m-dioxolanes

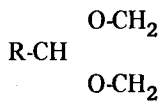


Code	Chemical data				Entomological results	
	R	Yield	B.P. °C/mm	M.P. °C	*C.p. molestus*	*A. aegypti*
AP-24	MeO	93	176-178/6		F	A
AP-43	Me	82	118-120/2		F	E
AP-74	$(Me)_2CH$	76	134-138/1.5		B	B
AP-30	Cl	85	121-123/1.0	44-45	E	B
AP-112	F	84	108-112/2		E	D
AP-114	NO_2	72		78-80	A	F
AP-108	CN	63	150-160/2.5	59-62	F	D



Y indicates 75-85% yield after distillation from the crude

UA-59	$Me(CH_2)_5$	Y	45-58/0.7	A	A
UA-61		Y	68-73/0.5	D	E
UA-63	-CH=CH-Ph	Y	105-114/0.6	F	E
UA-65	Ph	Y	65-70/0.5		
UA-66		Y	102-115/0.6	F	C



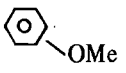
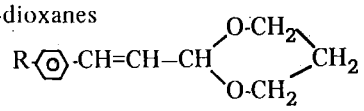
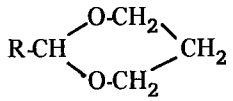
UA-13	Ph	Y	74-77/1	B	B
UA-14	MeO 	Y	60-64/1	F	E
UA-15		Y	156/3	F	F
UA-16	Ph-HC=CH	Y	97-99/1	F	E
UA-18	$Me(CH_2)_6$	Y	56-62/1	A	A

TABLE 3. m-dioxanes

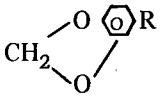


Code	Chemical data				Entomological results	
	R	Yield	B.P. °C/mm	M.P. °C	*C.p. molestus*	*A. aegypti*
AP-78	MeO	86	152-156/1.5	68-69	C	A
AP-117	Me	79		66-67	F	A
AP-106	$(Me)_2CH$	80	149-157/2.5		B	A
AP-67	Cl	88	140-145/2.5	98-100	E	D
AP-132	F	72	130-131/2.5	58-59	E	B
AP-111	NO_2	76		122-123	C	B
AP-147	CN	67		112-114	A	D



Y indicates 75-85% yield after distillation from the crude

AP-91	$PhCH{=}CH{-}CH{=}CH$	72	150-158/3	54-56	D	D
AP-84	$PhCH_2CH_2$	70	102-106/1.5		D	C
AP-86	$PhCH_2$	74	92-94/2		A	C
AP-220	$Ph(CH_2)_3$	75	116-118/0.5		F	B
UA-19	Ph	Y	80-96/1		D	B
UA-21		Y	141-145/1		E	F
UA-22	Ph-CH=CH-	Y	128-129/2		F	E
UA-24	$Me(CH_2)_6$	Y	78-82/1		C	B
UA-32	$Me(CH_2)_5$	Y	61-63/2		B	A
UA-51	MeO -	Y	76-86/1		F	C



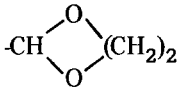
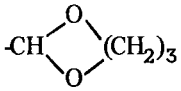
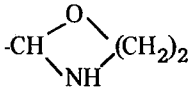
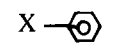
UA-40		Y	95-106/0.6	F	F
UA-41		Y	110-125/0.6	F	F
UA-44		Y	150-165/1	F	F

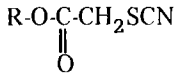
TABLE 4. Amides (benzamides)

 – CONR

Y indicates 75-85% yield after distillation from crude

Code	Chemical data					Entomological results	
	X	R	Yield %	B.P. °C/mm	M.P. °C	*C.p. molestus*	*A. aegypti*
AP-126	H	$(CH_2)_3CHMe_2$	70	158-160/2		C	B
AP-129	H	$(CH_2)_2CHMe_2$	62	150-152/3	48-49	D	F
AP-134	2-Me	$(CH_2)_3CHMe_2$	69	160-162/2.5	43-45	A	C
AP-137	2-Me	$(CH_2)_2CHMe_2$	72	154-156/3.0	45-47	D	C
AP-141	3-F	$CH_2CH(Me)_2$	81		72-73	D	A
AP-143	3-F	$(CH_2)_2Me$	82	131-132/2.0	51-52	E	F
AP-144	3-F	$CH(Me)CH_2Me$	78	128-129/2.0	59-60	F	F
AP-145	3-F	$(CH_2)_2CH(Me)_2$	78	151-152/3.0	30-31	C	E
AP-150	3-F	$C(Me)_3$	84		104	F	D
AP-151	3-F	$(CH_2)_5Me$	78		37-38	B	D
AP-152	H	$CH(Me)CH_2CH\text{-}(Me)_2$	76		92-93	A	A
AP-154	$2\text{-}CH_3$	$CH(Me)CH_2CH\text{-}(Me)_2$	75		54-55	F	E
AP-157	2-F	$(CH_2)_2CH(Me)_2$	81	142-143/1.0		F	F
AP-159	2-F	$CH(Me)CH_2CH\text{-}(Me)_2$	77	140-141/1.5		F	F
AP-161	4-F	$CH(Me)CH_2CH\text{-}(Me)_2$	79		98-99	D	B
AP-163	4-F	$(CH_2)_2CH(Me)_2$	75	182-184/6	59-61	A	C
AP-195	3-F	$CH(Me)CH_2CH\text{-}(Me)_2$	69		88-89	A	B
AP-216	3-F	$(CH_2)_4Me$	80	142-144/5		F	F
UA-1	4F	$CH_2C_6H_5$	Y		142	A	A
UA-2	2F	$CH_2C_6H_5$	Y		46	A	A
UA-6	3F	$CH_2C_6H_5$	Y		90	A	A
UA-3	4F	N-Bu	Y		58	F	C
UA-4	2F	N-Bu	Y		52	F	F
UA-5	3F	N-Bu		157/3		F	F
UA-35	4F	$Cy^c\text{-}C_6H_{11}$	Y			A	A
UA-57	4F	adamantyl	Y		d.p.	A	A

TABLE 5. Thiocyanoacetates.



Code	Chemical data			Entomological results	
	R	Yield %	B.P. ^{o}C/mm	*C.p. molestus*	*A. aegypti*
AP-228	$(Me)_2C=CH(CH_2)_2$ - $C(Me)=CHCH_2$-	73	115-120/1	F	A
AP-240	$Me(CH_2)_7$-	82	122-123/0.5	F	A
AP-242	$Ph(CH_2)_2$-	86	150-152/0.5	F	D
AP-244	$PhCH_2$-	85	144-146/O.8	F	F

TABLE 6. Relative effectiveness of repellents of category F in paired tests with deet against *C.p. molestus*. (Concentration: 1% in ethanol)

Code No. *	No. of replicates	Av. protection period (hrs.)		
		Experimental repellent	Deet	Ratio to deet
UA15	2	1.0	4.5	0.22
UA16	2	2.0	5.0	0.40
UA14	2	2.5	6.0	0.41
UA40	2	1.5	3.5	0.42
UA41	6	1.8	4.0	0,45
UA5	2	2.5	4.5	0.55
UA63	2	3.5	6.0	0.58
UA51	2	3.0	5.0	0.60
UA66	4	2.5	4.0	0.62
UA3	2	4.5	6.0	0.75
UA4	2	3.0	3.5	0.85
UA22	6	4.0	4.3	0.93
UA44**	5	4.2	4.0	1.05

*For chemical structure see tables 2, 3, 4.

**UA-44: 2-Methylene dioxyphenyl-oxazolidine

TABLE 7. Relative effectiveness of repellents of category F in paired tests with deet against *A. aegypti*. (Concentration: 1% in ethanol)

Code No. *	No. of replicates	Av. protection period (hrs.)		
		Experimental repellent	Deet	Ratio to deet
UA40	2	1.0	4.0	0.25
UA41	2	1.0	3.5	0.28
UA15	2	1.5	5.0	0.30
UA4	2	1.5	4.0	0.37
UA21	2	2.5	6.0	0.42
UA44	4	4.5	5.0	0.90
UA5	4	5.2	5.7	0.91

*For chemical structure see tables 2, 3, 4.

TABLE 8. Relative effectiveness of repellents of category F in paired tests with deet against *A. aegypti*. (Concentration: 1% in ethanol. Two replicates)

Code No.*	Av. protection period (hrs.)		
	Experimental repellent	Deet	Ratio to deet
A.P. 159	2.5	5.5	0.45
A.P. 143	3.5	6.0	0.58
A.P. 114	3.0	5.0	0.60
A.P. 157	5.0	5.5	0.90
A.P. 144	5.5	6.0	0.92
A.P. 129	5.5	5.5	1.00
A.P. 244	6.0	6.0	1.00
A.P. 216	5.5	5.0	1.10

*For chemical structure see tables 2, 4, 5.

TABLE 9. The effect of thanite, mixture of fenchyl and isobornyl thiocyanoacetates on *Culex pipiens molestus* and *Aedes aegypti* (paired tests on rabbits). (Concentration: 1% in ethanol.)

Hours after treatment	Number of Mosquitoes fed			
	Culex	Aedes	Culex	Aedes
1	0	2[a]	0	0
2	0	2[a]	0	0
3	0	3[b]	0	2[c]
4	0		0	0
5	0		0	2
6	0		0	2
7	0	0[g]		
8	0[d]	0[h]		
9	0[e]	0[i]		
10	0	0[j]		
11	0[f]	0[k]		
12	0	0[l]		

a) 2 mosquitoes died soon after feeding had been completed.
b) 1 mosquito died soon after feeding had been competed.
c) 1 mosquito died soon after feeding had been completed.
d) 4 males died on contact with the treated skin.
e) 1 male died on contact with the treated skin.
f) 1 male died on contact with the treated skin.
g) 3 males and 1 female died on contact with the treated skin.
h) 3 males and 1 female died on contact with the treated skin.
i) 2 males and 1 female died on contact with the treated skin.
j) 3 males and 1 female died on contact with the treated skin.
k) 4 males died on contact with the treated skin.
l) 5 males and 2 females died on contact with the treated skin.

Compounds UA5 and UA 44 were about equal to deet. It should be noted that compound UA 44 was also about equal to deet against *C.p. molestus* (see Table 6).

Compounds coded AP which fell into group F against *A. aegypti* were compared in paired tests with deet (Table 8).

Five compounds (AP 216, AP 244, AP 129, AP 144, and AP 157) were about equal to deet.

Tests with thanite, mixture of fenchyl and isobornyl thiocyanoacetates (ent. 92-1).

This mixture was found to possess outstanding repellent properties against *C.p. molestus* as well as a toxic effect on the 2 species of mosquitoes tested. In paired tests of this chemical with deet (6 replicates) against *C.p. molestus* at 1% concentration in ethanol, it was found that deet was effective for an average of 2½ hours, whereas thanite was effective for more than 12 hours (the maximum testing time). During these tests it was noted that this chemical had a strong toxic effect on the mosquitoes. Some mosquitoes that touched the treated surface died immediately, before being able to engorge blood. Additional tests were carried out on rabbits with this chemical to determine its effect in paired tests against *C.p. molestus* and *Aedes aegypti*. Results are given in Table 9. It can be seen that this chemical is toxic to both species of mosquitoes, but much more toxic to *Culex* than to *Aedes*. It has a very strong repellent effect on *Culex* but much less on *Aedes*. In the case of *Aedes*, some mosquitoes did feed one or more hours after application of the repellent, but died during feeding or as soon as feeding was completed.

DISCUSSION

From the results obtained it may be concluded that the combined efforts of entomological and chemical reasoning narrow down the type of organic compounds to be tested for superior repellent properties. The family of the dioxanes and dioxolanes could be considered as the combination of diols and aldehydes. Both aldehydes (Christophers, 1945) and diols (Piper *et al.*, 1951) were found to be highly active as repellents. Moreover, the products are also of the heterocyclic family containing oxygen (Roadhouse, 1953). The results obtained with com-

pounds coded UA (Table 6) led us to concentrate our effort on the dioxanes and dioxolanes derived from cinnamic aldehydes. The results indicate no correlation between physical properties and repellency; also no enhancing of the intrinsity with the introduction of a fluorine atom (aromatic moiety) could be recorded. However, the introduction of ***methoxy*** and ***cyano*** groups (A P 24 and A P 108) at the para position brought about higher activity (in the case of ***C.p. molestus***) which is in contradiction to "Hammett-like" formulation.

Out of the three chemical families studies, the benzamides are the most extensively studied potential repellents (Garson and Winnike, 1968). We have focused our synthetical efforts on the substitution of alkyl and aryl groups on the nitrogen atom and some aromatic fluorine substituents. The results indicate that potency of the repellent of the benzamide structure depends on both the substituent on the nitrogen atom and the position of the fluorine atom at the benzenic moiety. High activity was recorded when the alkyl groups were ethyl, propyl, butyl and to a lesser extent, pentyl. However, if the alkyl group is replaced by alycyclic or aromatic substituents the activity drops drastically (Table 4). The replacement of aromatic hydrogen by a fluorine atom in the ***ortho*** position seems to increase the intrinsic repellency as compared to the ***meta*** and ***para*** substituents. In some cases this observation is true for one mosquito species and differs for another (Table 4).

The thiocyanoacetates proved to be very active (Table 5). However, their toxicity in skin tests has not yet been determined. No correlation between physical properties and repellent potency was found (see Tables for specific data).

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