## [CONTRIBUTION FROM THE BUBEAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL Research Administration, U. S. Department of Agriculture]

# INSECT REPELLENTS. I. ESTERS OF MANDELIC AND SUBSTITUTED MANDELIC ACIDS<sup>1</sup>

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The repellent effect against mosquitoes of certain esters (methyl, ethyl, isopropyl, butyl, isobutyl, and hexyl) of dl-mandelic acid has been reported by Morton and co-workers (1). Although all these esters were classed as effective repellents, they were either not effective enough or otherwise unsuitable to replace or supplement standard repellents such as dimethyl phthalate or 2-ethyl-1,3-hexanediol. Piper, *et al.* (2), in reporting results of entomological tests in Canada, rated ethyl mandelate as one of their best repellents against mosquitoes and black flies.

The present paper describes esters in this series, including esters of ethyl mandelate (in which the  $\alpha$ -hydroxy group is esterified) and esters of nuclear-substituted mandelic acids.

The simple esters were made by refluxing mandelic acid with the appropriate alcohol in equimolar proportions together with benzene and a catalytic quantity of dilute sulfuric acid (Method A). Water was removed azeotropically.

The  $\alpha$ -hydroxy group of ethyl mandelate was esterified either by heating with an acyl anhydride (Method B) or by reacting with an acyl or aryl acid chloride in the presence of pyridine (Method C).

Nuclear-substituted mandelates were prepared from the aromatic aldehyde according to one of the following methods:



The esters, together with their physical properties and relative repellency are listed in Tables I–III. It appears that, of the simple mandelates, only those with an alkyl side chain of 6 or less carbon atoms exhibited appreciable repellent effect. It is also evident that a free  $\alpha$ -hydroxy group is essential, since acylation or benzoylation of ethyl mandelate completely destroyed the activity. Substitutions in the nucleus either greatly diminished or destroyed the repellent activity of this series.

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ESTERS OF MANDELIC ACIDCHOHCOOR											
		n <sup>25</sup> <sub>D</sub>	в.р., °С./ <b>мм</b> .	<u>м</u> .р., °С.	\ T			T.			
_	YIELD, <sup>b</sup> %					ANA.	LYSES		MOSQUITO <sup>C</sup>		
ĸ					C		H				
					Calc'd	Found	Calc'd	Found	On Skin	On Cloth	
METHOD A:											
Methyl <sup>d</sup> , •	36		97-106/.01	54						+++	
Ethyl <sup><i>d</i></sup> , <i>f</i>	77	1.5116	149/22	_					++++		
Propyl	74	1.5045	123/4		68.04	67.41	7.22	7.42	++++	+++	
Allyl	77		115/3	32-33	68.75	68.58	6.25	6.25		+++++	
Isopropyl <sup>d</sup>	66	1.4986	97-102/.01		68.04	67.72	7.22	7.03	+++		
Butyl <sup>d</sup>	20	1.4995	104-110/.01	_	69.23	69.59	7.69	7.70	++++		
Isobutyl <sup>d</sup>	28	1.4973	106-107/.01		69.23	69.31	7.69	7.64	+++		
sec-Butyl	74	1.4970	124/3	_	69.23	68.94	7.69	7.71		+++	
Amyl	63	1.4957	174/25		70.27	70.61	8.10	8.41	+++	++++	
Isoamyl	66	1.4924	135/5		70.27	69.67	8.10	8.20		+++	
Hexyl <sup>d</sup>	53	1.4910	133/2		71.19	71.11	8.47	8.65	+++	++	
1-Methylisoamyl.	49		163-167/17	28 - 30	71.19	71.42	8.47	8.51		Neg.	
2-Methylamyl-1.	78	1.4902	136 - 137/3		71.19	71.17	8.47	8.02		Neg.	
Heptyl	56	1.4900	133/2		72.00	72.63	8.80	8.81		Neg.	
3-Heptyl	70	-	150 - 155/5	28 - 30	72.00	72.05	8.80	9.26		Neg.	
Octyl	53	1.4878	181/6		72.73	72.83	9.10	9.04		Neg.	
2-Ethylhexyl	50	1.4837	162 - 164/5	<u> </u>	72.73	73.17	9.10	9.85		Neg.	
1-Isobutyliso-						į					
amyl	40		148 - 151/2	45 - 46	73.38	73.03	9.35	9.24		Neg.	
4-Butyloctyl	77	1.4825	192 - 195/3	-	75.00	74.92	10.00	9.82		Neg.	
2-Ethoxyethyl	33	1.5040	143/3		64.29	63.75	7.14	7.18		Neg.	
Cyclohexyl	77	1.5195	140/2		71.79	71.89	7.69	7.28		Neg.	
2-Phenylcyclo-											
hexyl	72		228 - 238/4	39-40	77.42	77.08	7.10	7.14		Neg.	
Benzyl	50			88	74.36	74.71	5.82	5.74		Neg.	
Phenethyl	82		216-218/8	61 - 62	75.00	75.46	6.25	6.45		Neg.	
3-Phenylpropyl	35	1.5463	118 - 124/5		75.53	75.28	6.71	6.55	-	Neg.	

<sup>o</sup> Mary H. Aldridge of the University of Maryland made the analyses of the esters prepared by Method A. <sup>b</sup> Based on mandelic acid as starting material. <sup>o</sup> Mosquito repellent activity: Tested either directly on human skin or indirectly by cloth impregnation ++++, excellent; +++, very good; ++, good; +, fair; neg., little activity. <sup>d</sup> Morton, et al., U. S. Bur. Entomology and Plant Quar. Pub. No. E-733, Sept. 1947. <sup>e</sup> Acree, Ber., **37**, 2767 (1904) reports b.p. 144°/20 mm., m.p. 57°. <sup>f</sup> Darapsky, J. prakt. Chem., **96**, 298 (1917) reports b.p. 141°/15 mm.

None of these compounds are yet recommended for general use as repellents, as the necessary pharmacological data relating to their practical use have not been obtained.

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TABLE II										
ESTERS OF ETHYL MANDELATE CHORCOOC <sub>2</sub> H <sub>5</sub>										
						ANALY	MOSQUITO REPELLENCY <sup>C</sup>			
R	VIELD, <sup>b</sup>	n <sup>25</sup> <sub>D</sub>	в.р., °С./мм.	м.р., °С.	C					н
					Calc'd	Found	Calc'd	Found	On Skin	On Cloth
METHOD B:										
Acetyl	87	1.4888	173 - 175/29		64.86	64.81	6.31	6.28		Neg.
Propionyl	88	1.4865	175-177/27	-	66.10	66.15	6.78	6.84		Neg.
Butyryl	86	1.4835	185-187/27	—	67.20	67.08	7.20	7.22	-	Neg.
Benzoyl	95	-	169-174/1	29–30	71.83	71.75	5.63	5.54		Neg.
mumoyl	66	1.5052	174-181/1		72.73	72.80	7.88	7.74		Neg.

<sup> $\circ$ </sup> Mary H. Aldridge of the University of Maryland made the analyses of the esters prepared by Methods B and C. <sup>b</sup> Based on ethyl mandelate as starting material. <sup> $\circ$ </sup> See footnote c, Table I.

## TABLE III

R'《

ESTERS OF NUCLEAR-SUBSTITUTED MANDELIC ACIDS

>CHOHCOOR

	R′	vield,ª %	n <sup>25</sup> <sub>D</sub>	в,р., °С./ мм.			ANALY	MOSQUITO <sup>f</sup> REPELLENCY			
R					м.р., °С.	Cl				н	
						Calc'd	Found	Calc'd	Found	On Skin	On Cloth
METHOD D											
Ethyl	o-Chloro	60	1.5240	154/4		16.55	16.65				++
Isopropyl	o-Chloro	50	1.5128	126/4		15.53	15.64				++
Cyclohexyl.	o-Chloro	47	1.5283	176/4		13.22	13.39				Neg.
Ethyl	p-Chloro	40		128/4	63	16.55	16.58	-			Neg.
Ethyl	2,4-Dichloro	40	1.5380	145/4		28.51	28.15		—		++
						CAR	BON				
Ethvl	o-Methoxv <sup>b</sup>	33	1.5220	140/5		_					Neg.
Methyl	p-Methoxy	58	1.5305	162/8		61.22	60.90	6.12	6.31		B-
Ethyl	p-Methoxy <sup>c</sup>	67	_	169/9	47.						÷-
Propyl	<i>p</i> -Methoxy	55	1.5150	173/9		64.28	64.20	7.14	7.59		+
Isopropyl.	p-Methoxy	31	1.5100	151/6		64.28	64.07	7.14	7.34		+
Allyl	p-Methoxy	42	1.5286	176/8		64.86	64.66	6.30	6.45		Neg.
Methyl	3,4-Methylenedioxy <sup>d</sup>	67		161/4	95						Neg.
Ethyl	3,4-Methylenedioxy	55		175/6	70			—			Neg.
Propyl	3,4-Methylenedioxy	89		184/5	58	60.50	60.52	5.88	6.10		Neg.
Isopropyl	3,4-Methylenedioxy	77		190/6	88	60.50	60.30	5.88	6.30		Neg.
Allyl	3,4-Methylenedioxy	37		175/4	42	61.01	60.97	5.08	5.40	—	Neg.

<sup>a</sup> Based on aldehyde as starting material. <sup>b</sup> Levy and Pernot, Bull. soc. chim., **49**, 1721 (1931) report b.p. 168°/14 mm.,  $n_{\rm p}^{\rm T}$  1.521. <sup>c</sup> Knorr, Ber., **37**, 3173 (1904) reports m.p. 47-48°. <sup>d</sup> Slotta and Haberland, J. prakt. Chem., **139**, 211 (1934) report m.p. 99°. <sup>e</sup> Barger and Ewins, J. Chem. Soc., **95**, 552 (1909) report b.p. 179-181°/8 mm., m.p. 72°. <sup>f</sup> See footnote c, Table I.

be reported in separate publications by members of the Orlando Laboratory staff.

#### EXPERIMENTAL

Simple esters of mandelic acid. Method A. dl-Mandelic acid,  $^{\circ}$  0.2 mole, with an equimolar quantity of anhydrous ethanol was refluxed in a 500-ml. flask with 75 ml. of benzene and 4 ml. of dilute sulfuric acid 2 to 8 hours or until water was no longer separating in the moisture trap. The mixture was then transferred to a separatory-funnel, cooled, and shaken with 150 ml. of cold tap water and 75 ml. of ether. After the water layer had been drawn off, the ether extract was washed with 50 ml. of 5% sodium hydroxide solution until the aqueous layer remained alkaline to phenolphthalein. The ethereal extract was washed with water and dried over sodium sulfate, the solvent was removed on the steam-bath, the last traces at the water pump, and the crude esters were distilled at the vacuum pump.

Acylation of ethyl mandelate with an acid anhydride. Method B. Ethyl mandelate, 0.2 mole (prepared by method A), was placed in a beaker with 0.4 mole of acetic (or other) anhydride and 0.5 g. of anhydrous sodium acetate. The mixture was heated on the steam-bath for 2 hours, cooled, and 200 ml. of cold water was added. It was then transferred to a separatoryfunnel, extracted with 150 ml. of ether, and the extract was washed twice with water and then with 5% sodium hydroxide solution. The extract was dried over sodium sulfate and the ether was removed on the steam-bath. The crude ester was distilled in a vacuum and the higher-boiling fraction was collected.

Acylation of ethyl mandelate with an acid chloride. Method C. Ethyl mandelate (0.2 mole), 15 ml. of dry pyridine, and 75 ml. of petroleum ether (b.p. 28-38°) were placed in a flask fitted with a reflux condenser, calcium chloride tube, and dropping-funnel. The acid chloride (0.2 mole) was slowly dropped in while the contents of the flask were stirred with a magnetic stirrer. After standing overnight the mixture was taken up in 75 ml. of ether, transferred to a separatory-funnel, washed with 5% sodium hydroxide, water, dilute acid, and then twice with water; the extract was dried over sodium sulfate. After removal of ether on the steambath, the residual oil was distilled under a vacuum and the higher-boiling fraction was collected.

Ethyl 2,4-dichloromandelate. Method D. The acid was prepared essentially by the method of Speigel (3). A solution of 170 g. (approximately 1 mole) of 2,4-dichlorobenzaldehyde in 200 ml. of ether was placed in a flask containing 60 g. of sodium cyanide. The stirred mixture was kept at 15° while 150 ml. of concentrated hydrochloric acid was added dropwise during 1.5 hours. Water sufficient to dissolve the precipitated sodium chloride was added. The reaction mixture was transferred to a separatory-funnel, the ether layer was separated, and the ether was removed on the steam-bath. The crude nitrile (120 g. of a brown oil) was heated on the steam-bath with 200 ml. of concentrated hydrochloric acid for 3 to 4 hours. Water was then added to dissolve the ammonium chloride. The acid, after cooling, was extracted with ether. The 2,4-dichloromandelic acid was extracted from the ether with 10% sodium carbonate solution and was recovered from the extract by precipitating with enough dilute sulfuric acid to make the mixture acid to Congo Red. The acid was filtered and dried; yield, 100 g. (45%) of a semisolid mass.

The ethyl ester was prepared by refluxing 40 g. of the crude acid with 150 ml. of absolute ethanol and 15 g. of concentrated sulfuric acid for 6 hours when the solution was cooled, added to water in a separatory-funnel, and extracted with ether. The ether was washed successively with water, 10% sodium carbonate, and water, and then dried over sodium sulfate. The ether was removed and the ester was distilled; b.p. 145°/4 mm.; yield 18 g. (40%).

The esters of o-chloro- and p-chloromandelic acid were prepared in the same manner as those of the 2,4-dichloroacid.

Methyl p-methoxymandelate. Method E. p-Methoxymandelonitrile was prepared as in

<sup>3</sup> Mandelic acid, N. F., purchased from the New York Quinine & Chemical Works, Inc.

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Method D. The crude nitrile from 70 g. of anisaldehyde weighed 84 g. (practically quantitative) and was dissolved in 100 ml. of anhydrous ether and 16 g. (0.5 mole) of anhydrous methanol. This solution was cooled to 15° and maintained at this temperature while dry hydrogen chloride was bubbled through for approximately one-half hour. The reaction was complete when the mixture became solid with crystalline iminoester hydrochloride. The hydrochloride was filtered and then washed with a little cold ether; m.p. 150°, yield 76 g. (64%). The iminoester hydrochloride in 120 ml. of water was hydrolyzed by heating on the steambath for 15 minutes. The mixture was cooled and extracted with ether in a separatoryfunnel. The ether layer was washed with water, then with 10% sodium bicarbonate solution, and dried over sodium sulfate. After removal of the ether the methyl p-methoxymandelate distilled at 162°/8 mm.; yield 50 g. (51% based on anisaldehyde).

#### SUMMARY

Esters of mandelic acid and substituted mandelic acids were prepared for repellent tests against mosquitoes and other insects. Substitution of methoxy, methylenedioxy, or chlorine in the ring or acylation or benzoylation of the  $\alpha$ -hydroxy group decreased or destroyed the repellent effect. The maximum repellent effect was observed with simple alkyl esters of mandelic acid containing six carbons or less. Most of the esters described are new compounds.

### BELTSVILLE, MARYLAND

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