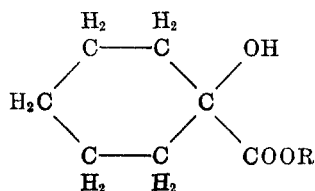


INSECT REPELLENTS. II. ESTERS OF 1-HYDROXYCYCLOHEXANE-CARBOXYLIC ACID¹

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In a previous paper (1) of this series we described the esters of mandelic acid and substituted mandelic acids we prepared for testing as insect repellents. In a continuation of a study of this type of compound, in which a hydroxy group, an ester group, and a ring are the dominant structural elements, we prepared certain esters of 1-hydroxycyclohexanecarboxylic acid:



Drake and coworkers (2) described a number of esters of 1-hydroxycyclohexanecarboxylic acid and patented the more effective repellent compounds in the series they prepared. These esters showed the following repellency to mosquitoes when tested directly on human skin or by cloth impregnation by members of the Orlando, Fla., laboratory of the Bureau of Entomology and Plant Quarantine [Morton, *et al.* (3)]:

ESTER	ON SKIN ^a	ON CLOTH ^a
Acetonyl.....	+++	+++
Propyl.....	+	—
Isoamyl.....	+++	++
2-Ethylbutyl.....	++	—
Cyclopentyl.....	+++	—
Cyclohexyl.....	+++	+++
2-Methoxyethyl.....	++	—
2-Ethoxyethyl.....	+++	+++
2-Butoxyethyl.....	+++++	—
2-Hydroxyethyl.....	Neg.	—
2-Hydroxypropyl.....	Neg.	—
Tetrahydrofurfuryl.....	++	—

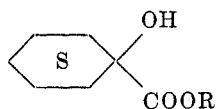
^a These ratings are indicated as follows: +++++, excellent; +++, very good; ++, good; +, fair; neg., little activity.

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TABLE I

ESTERS OF 1-HYDROXYCYCLOHEXANECARBOXYLIC ACID



R	YIELD, ^b %	n_D^{25}	B.P., °C./MM.	ANALYSES ^a				MOSQUITO REPELLENCY	
				C		H		On Skin	On Cloth
				Calc'd	Found	Calc'd	Found		
Methyl ^c	60	1.4585	72/5	—	—	—	—	—	Neg.
Ethyl ^c	74	1.4532	75/5	—	—	—	—	—	Neg.
Isopropyl.....	62	^d	80/5	64.51	64.28	9.63	10.00	—	Neg.
Butyl.....	26	1.4545	103/5	66.00	66.07	10.00	10.25	—	+
Isobutyl.....	64	1.4505	107/6	66.00	66.46	10.00	10.38	—	+
Amyl.....	70	1.4535	110/5	67.28	67.02	10.04	9.70	—	+
Allyl.....	51	1.4681	181-185/20	65.22	65.18	8.70	8.95	—	Neg.
2-Methylcyclo- hexyl.....	40	1.4740	120-125/2	69.49	69.83	10.17	9.92	—	Neg.
4-Methylcyclo- hexyl.....	50	1.4728	113-118/2	69.49	69.92	10.17	10.06	—	Neg.
Benzyl.....	55	1.5400	130/5	71.70	71.60	7.69	7.69	—	Neg.
Phenethyl.....	66	1.5150	164/5	72.58	72.69	8.06	7.98	—	Neg.
2-Propoxyethyl....	35	1.4590	111-113/5	62.60	62.42	9.74	9.60	+++	++++

^a Mary H. Aldridge, of the University of Maryland, made the analyses of some of these esters. ^b Based on 1-hydroxycyclohexanecarboxylic acid as starting material. ^c Tarbouriech, *Compt. rend.*, **149**, 604 (1909); methyl ester, b.p. 103°/17 mm.; ethyl ester b.p. 111°/17 mm. ^d M.p. 42°.

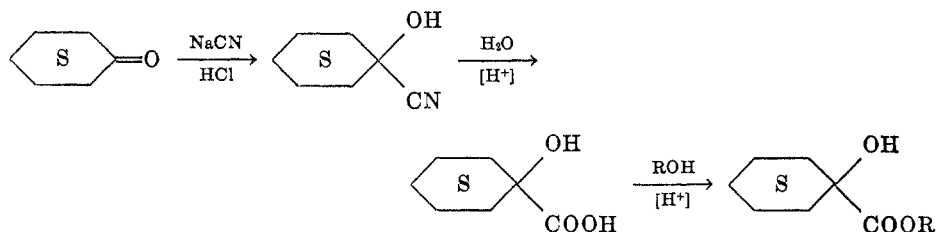
Since the propyl ester was ineffective but the isoamyl ester effective as a repellent, it seemed of interest to complete the series of alkyl esters. It was also of interest to test the methylcyclohexyl and other ring-substituted esters in this series. We therefore prepared these esters which are described in Table I.

It was not possible to establish a clear relationship between the structure and repellent effect. None of the simple alkyl esters except the isoamyl showed appreciable repellent activity. Surprisingly, the 2-methylcyclohexyl and 4-methylcyclohexyl esters exhibited little activity which showed no relationship to the high repellent activity of the cyclohexyl ester previously reported. The 2-propoxyethyl ester was very active, which is in line with the activity of the previously tested 2-ethoxyethyl and the 2-butoxyethyl esters.

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.

Acknowledgment. The authors wish to thank Carroll N. Smith, I. H. Gilbert, and others of the staff of the Orlando, Fla., laboratory of the Bureau of Entomology and Plant Quarantine for conducting the repellency tests. Detailed entomological results on the compounds described in this paper will be reported by members of the Orlando laboratory staff.

EXPERIMENTAL

Preparation of esters of 1-hydroxycyclohexanecarboxylic acid.

This acid was prepared by the method of Bucherer (4) which avoids the use of the sodium bisulfite commonly employed in the preparation of the hydroxynitriles. The nitrile was not purified, but was hydrolyzed directly.

Sodium cyanide, 38 g., was suspended in a solution of 50 g. of cyclohexanone in 150 ml. of ethyl ether in a flask equipped with stirrer and reflux condenser (hood). Concentrated hydrochloric acid (83 g.) was slowly added from a dropping-funnel during 30 minutes while maintaining the temperature at 15–20°. Water was then added to dissolve the precipitated sodium chloride. The ether solution of the nitrile was transferred to a separatory-funnel, washed with water, and dried over sodium sulfate, and the ether was removed on a steam-bath. The oily residue (63 g.) was then heated for 4 hours on the steam-bath with 66 g. of concentrated hydrochloric acid, with stirring. Cold water was added to dissolve the ammonium chloride formed. Upon cooling, the acid crystallized as a brownish-white solid which was filtered and dried; weight 70 g. (95% yield). A portion of the acid recrystallized from water melted at 105–106° [m.p. 107°, according to Bucherer (4)]. The crude acid was used for preparation of the esters.

The esters were made by refluxing the acid with the appropriate alcohol in equimolar (0.1 or 0.2 mole) proportions together with 75 ml. of benzene and about 4 ml. of dilute (1:4) sulfuric acid for 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 then washed with water, dried over sodium sulfate, and the solvent was removed on the steam-bath, the last traces at the water-pump. The crude esters were distilled under a vacuum.

SUMMARY

In continuation of a study of the effect of structure of a compound upon mosquito repellency, 12 esters of 1-hydroxycyclohexanecarboxylic acid were prepared. The 2-propoxyethyl ester is a highly effective mosquito repellent. No definite conclusions could be drawn about the relationship between structure and repellent effect in this series of esters.

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