Topical Mosquito Repellents V: Benzyl Ethers

F. GUALTIERI*, H. JOHNSON, H. TONG, H. MAIBACH†, D. SKIDMORE†, and W. SKINNER▲

Abstract □ A series of benzylic ethers with hydroxyl, epoxy, and unsaturated moieties was synthesized and evaluated on human skin for repellency against female *Aedes aegypti* mosquitoes. Compounds exhibiting the longest durations of repellency were those with boiling points of approximately 125°/0.5 mm. The case of two monobenzyl ethers of 3,4-dihydroxycyclopentene-1 having the same boiling points but different repellent activity is of interest. None of the compounds examined was as effective as *N,N*-diethyl-*m*-toluamide in terms of the duration of topical repellency.

Keyphrases □ Insect repellents, topical—synthesis of benzyl ethers, repellency–volatility relationships □ Benzyl ethers—synthesized and screened as potential insect repellents, repellency–volatility relationships □ Repellency–volatility relationships—benzyl ethers as topical insect repellents

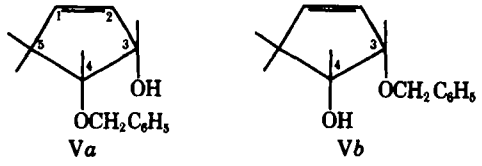
Previous studies (1, 2) suggested that benzyl ethers and polyoxy ethers of the benzyl type were potentially of value in the search for longer lasting topical mosquito repellents. The present compounds were synthesized and evaluated topically on human skin to define the repellency characteristics of such compounds and to determine the effect of other structural moieties such as alicyclic and unsaturated groups.

RESULTS AND DISCUSSION

The compounds (Table I) were obtained by the usual Williamson synthesis using the sodium salt of the alcohol and benzyl chloride; in those cases where a double bond was present, salt formation was *via* sodium hydride in dimethylformamide. With the diols, a double series of compounds, the monobenzyl and dibenzyl ethers, could be obtained using a 1:1 ratio of diol and sodium hydride. The separation of the reaction products by vacuum distillation was not complete, and liquid chromatography was usually required for obtaining suitable analytical samples. The monobenzyl ether fraction of 3,4-dihydroxycyclopentene-1 was further analyzed by VPC, yielding two peaks (FFAP column, 205°, flow rate of 120 ml./min.) with retention times of 10 min. (Compound V*b*, the larger fraction) and 11 min. (Compound V*a*, the smaller fraction).

The indicated structures for the monobenzyl ethers of 3,4-dihydroxycyclopentene-1 were assigned on the basis of NMR as 3-hydroxy-4-benzyloxycyclopentene-1 (V*a*) and 3-benzyloxy-4-hydroxycyclopentene-1 (V*b*). The NMR spectra of these two compounds (Table II) were nearly identical; the major differences were in the τ values of the protons at the 3- and 4-positions.

The 3-proton of Compound V*a* should (5) and does have a lower τ value than the 3-proton of Compound V*b*, since the former is on a carbon with a hydroxyl group and the latter is on a carbon with an ether substituent. Similarly, the 4-proton of Compound V*b* has a lower τ value than that of Compound V*a* for the same reason. Furthermore, the 4-proton of V*a* is a quartet, because of the influence of the 5-methylene protons and the 3-proton. The 4-proton of V*a* also has a higher τ value than its own 3-proton, because the former is an *H*—C—OR proton as compared to an *H*—C—OH proton and because the 3-proton is allylic. In the case of V*b*, its 4-proton should have a lower τ value than its own 3-proton (*H*—C—OH *versus* *H*—C—OR); but since the 3-proton is allylic, it is shifted downfield. The two protons consequently have about the same τ values; 5.6–5.8. The structure of V*b* is further confirmed by its acetyl derivative, whose 4-proton appears at τ 4.65–4.95 as a quartet, having shifted downfield as expected and being split by its neighboring protons; the 3-proton is practically unchanged.



The IR spectrum of the acetate shows the disappearance of the hydroxyl (3 μ) and the appearance of the carbonyl band (5.8 μ). Finally, V*b* is the larger fraction in the reaction product as compared to V*a*, because of the influence of the double bond on the acidity of the 3-hydroxyl group in 3,4-dihydroxycyclopentene-1, thus favoring the formation of the ether derivative in the 3-position.

Similarly, the monobenzyl ether of 3,5-dihydroxycyclopentene-1 was analyzed by VPC. Again, two main peaks were obtained (FFAP column, 210°, flow rate of 120 ml./min., retention times of 17 and 19 min.), collected, and analyzed. Their NMR absorption peaks were identical, suggesting that they are probably *cis*- and *trans*-isomers. Their 4-CH_2 bands (τ 7.8–8.2) confirm the nonallylic nature of these protons in comparison to the 5-CH_2 allylic protons (τ 7.5–7.7) of Compounds V*a* and V*b*.

Compound VI was prepared *via* epoxidation of a mixture of V*a* and V*b*; similarly, the other epoxy compounds were prepared from the corresponding unsaturated ethers. No attempt was made to determine their steric structures.

As in previous studies (1, 2), the present series of compounds exhibited a rather restricted volatility–repellency relationship. Compounds with boiling points higher or lower than those of Compound IV, V*a*, V*b*, and VII did not yield appreciable repellency duration (Table I and Fig. 1). Nonalicyclic benzyl ethers (Compounds XIII–XVIII) of a wide range of boiling points are completely ineffective. Together with previous data (2), the present results suggest that a volatility region corresponding to a boiling point of approximately 115–135°/0.5 mm. is optimal for alicyclic benzyl ethers in terms of topical mosquito repellency. The striking difference in the protection times of Compounds V*a* and V*b*, which are isomeric with the same boiling point, suggests a case of specific structure–activity relationship not commonly reported in insect repellent studies. Similarly, it is of interest that Compounds XIII–XVIII uniformly exhibited poor repellency in spite of the variation in volatility (Table I). The presence of an OH group, an epoxy ring, or a second benzylic moiety does not appear to significantly enhance repellent potency. In terms of duration of protection, Compound V*a* approaches but is inferior to the performance of *N,N*-diethyl-*m*-toluamide (2).

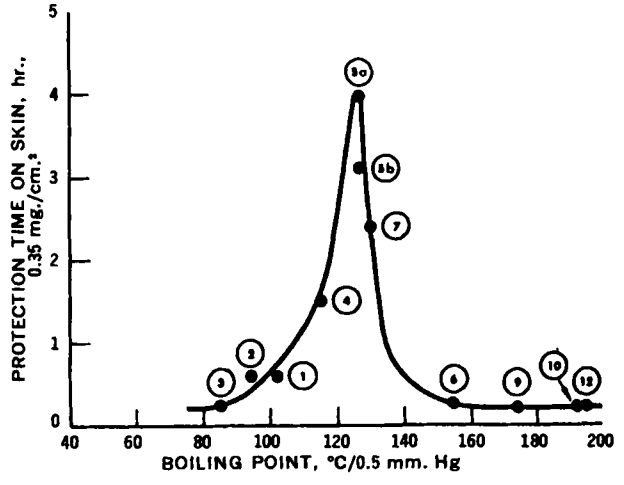
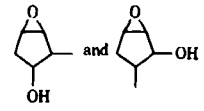
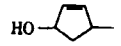
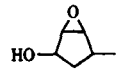
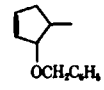
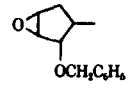
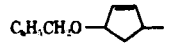
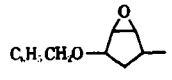
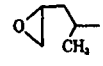
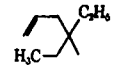
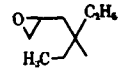
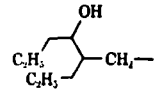
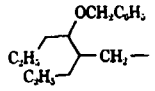


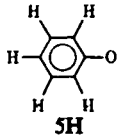
Figure 1—*Alicyclic benzyl ethers.*

Table I—Benzyl Ethers $ROCH_2C_6H_5$

Compound	R	Yield, %	Formula	Analysis, % Calc.	Found	Boiling Point (mm.)	Duration of Repellency, hr. (Number of Determinations)
I		—[a]	—	—	—	127° (2.6)	0.6 (2)
II		—[b]	—	—	—	88° (0.35)	0.6 (5)
III		49	$C_{13}H_{16}O$	C 82.94 H 8.57	83.83 8.75	89° (0.6)	0.25 (2)
IV							
V*a*		37	$C_{12}H_{14}O_2$	C 75.69 H 7.42	76.62 7.46	114° (0.25)	4.0 (4)
V*b*		—	$C_{12}H_{14}O_2$	C 75.69 H 7.42	75.62 7.46	114° (0.25)	2.9 (4)
VI		77	$C_{12}H_{14}O_3$	C 69.89 H 6.84	69.76 6.83	141° (0.25)	0.25 (2)
VII		23	$C_{12}H_{14}O_2$	C 75.69 H 7.42	75.76 7.42	125° (0.4)	2.4 (4)
VIII		71	$C_{12}H_{14}O_3$	C 69.89 H 6.84	69.76 6.85	147° (0.35)	—
IX		45	$C_{19}H_{20}O_2$	C 81.40 H 7.19	81.18 7.39	169° (0.4)	0.25 (2)
X		67	$C_{19}H_{20}O_3$	C 77.00 H 6.80	76.98 6.74	186° (0.35)	0.25 (2)
XI		18	$C_{19}H_{20}O_2$	C 81.40 H 7.19	81.28 7.38	167° (0.4)	—
XII		41	$C_{19}H_{20}O_3$	C 77.06	77.03	187° (0.3)	0.25 (2)
XIII		52	$C_{12}H_{16}O$	C 81.77 H 9.15	81.91 9.26	73° (1.75)	0.25 (2)
XIV		56	$C_{12}H_{16}O_2$	C 74.97 H 10.2	75.09 10.1	99° (1.25)	0.25 (1)
XV		59	$C_{16}H_{22}O$	C 82.52 H 10.2	82.83 10.1	88° (0.25)	0.25 (2)
XVI		86	$C_{16}H_{22}O_2$	C 76.88 H 9.46	76.82 9.67	119° (0.35)	0.25 (4)
XVII		50	$C_{16}H_{24}O_2$	C 76.23 H 10.2	76.17 10.4	111° (0.15)	0.25 (3)
XVIII		50	$C_{22}H_{30}O_2$	C 80.34 H 9.26	80.38 9.45	173° (0.2)	0.25 (3)

[a] See *Reference 3*. [b] See *Reference 4*.

Table II—NMR τ Values of Derivatives of 3,4-Cyclopentenediol

	Aromatic  5H	Vinyl  2H	Benzyl —$OCH_2C_6H_5$ 2H	3-Position  1H	4-Position  1H	5-Methylene  2H	Hydroxyl[a] —OH 1H	Acetate —$OCCH_3$ 3H
4-Benzyl ether	2.70	4.2	5.4	5.5	5.8–6.1 (quartet)	7.5–7.7	7.4–7.6	—
5-Benzyl ether	2.70	4.0–4.3	5.4	5.6–5.8	5.6–5.8	7.5–7.7	7.2–7.4	—
4-Acetate of 3-benzyl ether	2.75	4.1–4.3	5.5	5.6	4.6–4.95 (quartet)	7.4–7.6	—	8.05

[a] Confirmed by D_2O exchange and integration.

EXPERIMENTAL

The starting materials of the best mosquito repellents in this series, 3,4-dihydroxycyclopentene-1 (b.p. 55–65°/0.5 mm. Hg) and 3,5-dihydroxycyclopentene-1 (b.p. 90–100°/0.6 mm. Hg), were obtained commercially[1] as a mixture and were separated by spinning band distillation. The 3,4-dihydroxy fraction (n_D^{25} 1.4971) was further purified by VPC (FFAP column, 205°, flow rate of 120 ml./min.) and had a retention time of 5 min.; the 3,5-dihydroxy fraction (n_D^{25} 1.5012), under the same GC conditions, had a retention time of 11 min. The 3,5-dihydroxy fraction was oxidized to the dione as previously described (5), and the melting point agreed with that reported. A comparison of the NMR spectra of the derivatives V*a*, V*b*, and VII indicated that the assigned structures as 3,4- and 3,5-dihydroxy compounds were correct.

The alcohol (0.1 mole) was added slowly to a stirred suspension of sodium hydride (0.1 mole) in 50 ml. of anhydrous dimethylformamide. After 3 hr. at room temperature, benzyl chloride (0.1 mole) was added dropwise with stirring and cooling. After 24 hr. at room temperature, the mixture was partitioned between hexane and water. The hexane layer was washed and dried (sodium sulfate), yielding primarily the dibenzyl ether, while extraction of the aqueous phase with ethyl acetate gave primarily the monobenzyl ether following fractionation of the oils resulting from the evaporation of the solvents. In some cases (Compounds V, VII, IX, and XI), chromatography on silica gel (eluant 20:80, ethyl acetate–cyclohexane) was necessary to obtain pure analytical samples. Boiling points are uncorrected.

The compounds were tested on the forearm of human subjects as described previously (1, 2) at a concentration of 0.35 mg./cm.[2].

[1] Research Organic.

REFERENCES

(1) P. Tsakotellis, H. L. Johnson, W. A. Skinner, D. Skidmore, and M. J. Maibach, *J. Pharm. Sci.*, **60**, 84(1971).

(2) F. Gualtieri, H. Johnson, H. Maibach, D. Skidmore, and W. A. Skinner, *ibid.*, **61**, 577(1972).

(3) J. Loerenich, H. Utsch, P. Moldricky, and E. Schaeffer, *Chem. Ber.*, **62B**, 3084(1929).

(4) P. Shorigin, *ibid.*, **58B**, 2028(1925).

(5) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1963, p. 84.

(6) C. H. DePuy and E. F. Zoweski, *J. Amer. Chem. Soc.*, **81**, 4920(1959).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 26, 1971, from the *Department of Pharmaceutical Chemistry, Life Sciences, Stanford Research Institute, Menlo Park, CA 94025*

Accepted for publication October 4, 1972.

Supported by U. S. Army Medical Research and Development Command Contracts DADA-170-70-C-0112 and DADA-170-70-C-0109.

The authors acknowledge the cooperation of Dr. Lester Pope and Dr. Eugene Prait, California State Department of Corrections.

• Present address: University of Camerino, Camerino, Italy.

† Present address: Division of Dermatology, School of Medicine, University of California, San Francisco Medical Center, San Francisco, Calif.

▲ To whom inquiries should be directed.