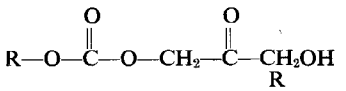
Unsymmetrical Carbonates as Potential Long-Lasting Insect Repellents

LORRIN R. GARSON and DANIEL D. GARNER

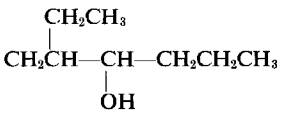
Abstract □ The synthesis of unsymmetrical carbonates of 1,3-dihydroxy-2-propanone with mono- and difunctional insectifugal alcohols is described. The compounds were designed to provide perdurable insect repellency upon topical application.

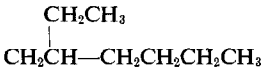
Keyphrases □ Repellents, insect, potential—1,3-dihydroxy-2-propanone carbonates, synthesis □ 1,3-Dihydroxy-2-propanone carbonates—synthesis, insect repellents, potential □ Carbonates, unsymmetrical, 1,3-dihydroxy-2-propanone—insect repellents, potential

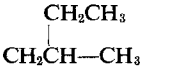
Due to the insect repellent efficacy of several monoesters of 1,3-dihydroxy-2-propanone[1] (1, 2), this study sought to incorporate the standard insect repellent 2-ethyl-1,3-hexanediol (Rutgers 612) and other insectifugal alcohols (3) into "precursor molecules" through a carbonate-connecting linkage with 1,3-dihydroxy-2-propanone. The rationale of this approach (4) and the structural features of several monoacyl and diacyl derivatives of 1,3-dihydroxy-2-propanone were previously discussed in detail (5).



Compound

I 

II 

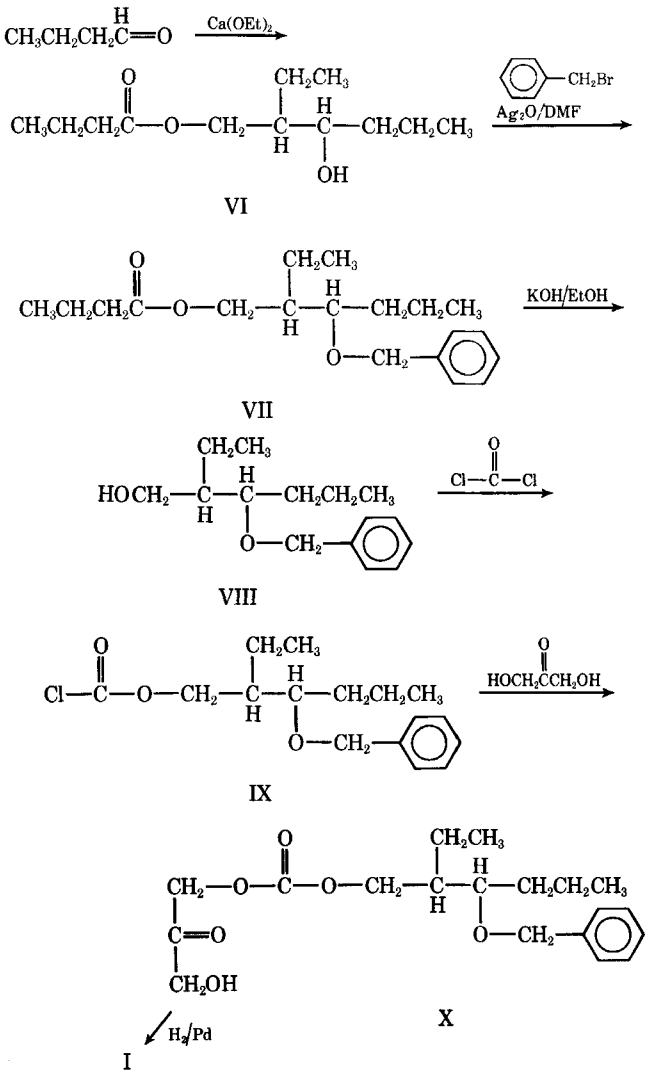
III 

IV $CH_2CH_2—O—C_6H_5$

Compounds I–IV are designed to release the respective repellent alcohols *via* hydrolysis of the carbonate function subsequent to dermal application. Cleavage should be facilitated by the influence of both the secondary alcohol function in I (6, 7) and the ketone group (8) present in each of the precursor molecules. Compounds II and III are, obviously, structural relatives of I. They were designed to ascertain the influence of the hydroxyl function and that of the chain length in the repellent component.

The preparation of Compounds II–IV is accomplished by reacting ROH with phosgene in ether to give the corresponding chlorocarbonate R—O—CO—Cl, which in turn is allowed to react with an excess of 1,3-dihydroxy-2-propanone in pyridine. The resulting unsymmetrical carbonates are sufficiently stable to permit purification, and separation from the accompanying biscarbonates, by distillation. In preparing IV, the bisester [1,3-di(2-phenoxyethylcarbonato)-2-propanone, V] was isolated and fully characterized.

The synthesis of I, however, does not lend itself to the same reaction sequence. While, as in the preparation of mephenesin carbamate (9), it may be possible to obtain selectively the chlorocarbonate of the primary alcohol of



Scheme I

[1] The term dihydroxyacetone frequently appears in the literature.

2-ethyl-1,3-hexanediol, cyclization to the corresponding 1,3-dioxane-2-one would appear to be a serious side reaction; furthermore, such a synthesis would not be unambiguous. Accordingly, Compound I was prepared by protecting the secondary alcoholic function of 2-ethyl-1,3-hexanediol by conversion to a benzyl ether moiety (Scheme I). All intermediates in this sequence, being oily liquids, were subjected to distillation at reduced pressures. Compound X was readily purified by high-vacuum distillation (molecular still); however, Compound I was not amenable to this procedure. A small sample (about 0.4 ml.) of I was successfully distilled using this technique, but decomposition occurred when attempts were made to distill larger quantities.

Compounds I–IV were tested for insectifugal activity against *Aedes aegypti* (L.) mosquitoes subsequent to application on the forearms of human volunteers. Experimental details were previously described (1). In comparing the insect repellency of these agents with the standard repellent *N,N*-diethyl-*m*-toluamide ("deet"), the compounds elicited an unexpected low level of activity; they provided 10% or less duration of protection than that afforded by the standard. The length of protection for these agents was not significantly increased upon subjecting the treated volunteers to conditions inducing sweating (27° at 80% relative humidity). The data reflect a lack of significant repellency for the intact precursor molecules and suggest that the desired hydrolytic cleavage of the carbonate linkage does not occur at a sufficiently rapid rate.

EXPERIMENTAL[2]

2-Ethyl-1,3-hexanediol 1-Butanoate (VI)—By employing a modification of the Villani and Nord method (10), 15.4 g. (0.384 mole) of calcium and a few crystals of mercuric chloride and iodine were added to 650 ml. of absolute EtOH. The ensuing exothermic reaction, which required heating to initiate, was occasionally quenched in an ice bath; the reaction mixture was heated at reflux 2 hr. and allowed to stand at ambient temperatures for 20 hr. The excess solvent was removed by distillation *in vacuo*, and the calcium ethoxide was dried for 16 hr. (25°/1.5 mm.). To the ethoxide was *cautiously* added 1000 ml. (810 g., 11 moles) of freshly distilled (b.p. 74.5°) cold butanal[3]; the mixture was cooled, with difficulty, in an ice–EtOH bath and allowed to stand at −10 to 15° for 3 hr. and then at room temperature for 4.5 hr. After removal of the metal catalyst by filtration, the reaction mixture was distilled *in vacuo*, employing an 80-cm. Vigreaux column, affording 168 g. (20.6%) of VI: b.p. 95–96° (0.2 mm.); n_D^{25} 1.4406; ρ^{25} 0.9405 [lit. (1) b.p. 100–102° (0.5 mm.); n_D^{21} 1.4462; ρ^{21} 0.9492]; $\nu_{max.}^{CHCl_3}$ 3571, 3460 (OH), and 1727 cm.$^{-1}$ (carbonyl).

Anal.—Calc. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.58; H, 11.09.

3-Benzyloxy-2-ethyl-1-hexanol Butanoate (VII)—A mixture of 40.4 g. (0.187 mole) of VI, 63.9 g. (0.374 mole) of benzyl bromide, 43.4 g. (0.187 mole) of silver oxide, and 100 ml. of anhydrous *N,N*-dimethylformamide was protected from light and stirred at room temperature for 1 week. The reaction mixture was filtered through a bed of Celite, the residue was washed with *N,N*-dimethylformamide (2 × 20 ml.), and the filtrate was distilled *in vacuo* (40-cm. Vigreaux column). The fraction boiling at 154–159° (0.7 mm.) was redistilled, yielding pure VII; consistent yields of 66–73% were obtained: b.p. 123–127° (0.15 mm.); n_D^{25} 1.4791; ρ^{25} 0.9700; $\nu_{max.}^{CHCl_3}$ 1724 cm.$^{-1}$ (carbonyl); $\lambda_{max.}^{EtOH}$ 210 nm. (ϵ 7320).

Anal.—Calc. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.42; H, 9.88.

3-Benzyloxy-2-ethyl-1-hexanol (VIII)—A solution of 5.00 g. (0.0163 mole) of VII in 16.3 ml. of 2 *N* alcoholic KOH was heated at reflux for 3 hr., cooled, treated with charcoal, and filtered; the filtrate was distilled *in vacuo*, leaving a brown, semisolid material. The residue was partitioned between H_2O (50 ml.) and $CHCl_3$ (50 ml.), and the aqueous phase was extracted with $CHCl_3$ (3 × 30 ml.). The combined $CHCl_3$ phases were dried ($MgSO_4$), filtered, concentrated, and distilled *in vacuo*, yielding 2.50 g. (64.8%) of VIII: b.p. 121-122° (0.05 mm.); n_D^{25} 1.4954; $\nu_{max.}^{CHCl_3}$ 3472 cm.$^{-1}$ (OH); $\lambda_{max.}^{EtOH}$ 210 nm. (ϵ 6920).

Anal.—Calc. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.10; H, 10.35.

3-Benzyloxy-2-ethyl-1-hexyl Chlorocarbonate (IX)—To a solution of 29.6 g. (0.299 mole) of phosgene in 100 ml. of anhydrous ether was added 29.3 g. (0.124 mole) of VIII. After heating at reflux for 12.5 hr., a stream of dry air was passed through the system, removing excess phosgene and HCl; the residue was concentrated and dried overnight *in vacuo*. No attempt was made to purify IX before subsequent use: $\nu_{max.}^{CHCl_3}$ 1773 cm.$^{-1}$ (carbonyl), OH bands not present.

1-(3-Benzyloxy-2-ethylhexyl-1-carbonato)-3-hydroxy-2-propanone (X)—To a cooled (−8 to −1°), well-stirred solution of 44.7 g. (0.496 mole) of dry 1,3-dihydroxy-2-propanone in 200 ml. of anhydrous pyridine was slowly added a solution of 37.1 g. (0.124 mole) of chlorocarbonate IX in 200 ml. of freshly distilled (from P_2O_5) $CHCl_3$. After warming to room temperature and stirring for an additional hour, the reaction mixture and 500 ml. of 6 *N* HCl were simultaneously added dropwise to 250 ml. of 3 *N* HCl and 500 g. of ice, taking care to maintain a reaction temperature of −10 to −1°. After separating the organic phase, the aqueous layer was extracted with $CHCl_3$ (3 × 50 ml.); the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*, affording a yellow liquid. Purification of the oil by molecular distillation (130–135° at 0.010–0.015 mm.) yielded a viscous yellow product in 20.5 g. (46.9%) yield: n_D^{25} 1.4982; $\nu_{max.}^{CHCl_3}$ 3472 (OH) and 1742 cm.$^{-1}$ (carbonyl); $\lambda_{max.}^{EtOH}$ 208 nm. (ϵ 7520).

Anal.—Calc. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.67; H, 8.13.

1-(2-Ethyl-3-hydroxyhexyl-1-carbonato)-3-hydroxy-2-propanone (I)—With a Brown hydrogenator (12), 410 mg. (1.16 mmoles) of X in 20 ml. of 95% EtOH was catalytically reduced (24 hr.), employing 500 mg. of 10% palladium on charcoal. After removing the catalyst by filtration (Celite), the filtrate was concentrated *in vacuo* and the residue was purified by molecular distillation (135° at 0.004 mm.) to yield 97.0 mg. (31.8%) of I: n_D^{25} 1.4630; $\nu_{max.}^{CHCl_3}$ 3460 (OH) and 1745 cm.$^{-1}$ (carbonyl).

Anal.—Calc. for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.98; H, 8.93.

1-(2-Ethylhexyl-1-carbonato)-3-hydroxy-2-propanone (II)—In a manner analogous to the preparation of IX, 36.2 g. (0.278 mole) of freshly distilled [b.p. 60-61° (1.6 mm.)] 2-ethyl-1-hexanol was converted to the chlorocarbonate by reaction with 83.6 g. (0.845 mole) of phosgene. As in the preparation of X, the chlorocarbonate was allowed to react with 1,3-dihydroxy-2-propanone (100 g., 1.11 moles) to yield 36.4 g. (53.1%) of analytically pure II after molecular distillation (107° at 0.020 mm.): n_D^{25} 1.4565; $\nu_{max.}^{CHCl}$ 3472 (OH) and 1748 cm.$^{-1}$ (carbonyl).

Anal.—Calc. for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.61; H, 9.20.

1-(2-Methylbutyl-1-carbonato)-3-hydroxy-2-propanone (III)—Similarly, 24.5 g. (0.278 mole) of 2-methyl-1-butanol and 50.1 g. (0.506 mole) of phosgene afforded the desired chlorocarbonate. This, in turn, was allowed to react with 100 g. (1.11 moles) of 1,3-dihydroxy-2-propanone to yield, after molecular distillation (93° at 0.005–0.010 mm.), 36.7 g. (64.6%) of III: n_D^{25} 1.4460; $\nu_{max.}^{CHCl_3}$ 3497 (OH) and 1745 cm.$^{-1}$ (carbonyl).

Anal.—Calc. for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 53.08; H, 7.99.

1-(2-Phenoxyethylcarbonato)-3-hydroxy-2-propanone (IV) and 1,3-Di(2-phenoxyethylcarbonato)-2-propanone (V)—By employing the procedures used in the preparation of IX and X, the chlorocarbonate from 42.1 g. (0.305 mole) of 2-phenoxyethanol and 31.3 g.

[2] Melting points are corrected; they were determined with a Büchi melting-point apparatus. Boiling points are uncorrected. UV and IR spectra were obtained with the Perkin-Elmer model 202 and 137B spectrophotometers, respectively. Molecular distillations were performed employing a Rota-Film model 50-2 apparatus. The mass spectral analysis was carried out by the Morgan–Schaffer Corp., Montreal, Canada. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

[3] Addition of the catalyst to butanal, as described by Villani and Nord (10), frequently led to an uncontrollable exothermic reaction.

(0.316 mole) of phosgene, when allowed to react with 100 g. (1.11 moles) of 1,3-dihydroxy-2-propanone, afforded 61.2 g. of a mixture of IV and V. The crude product was extracted with boiling ether (6 × 200 ml.) to remove the bisester. The ether-insoluble material was recrystallized three times from 95% EtOH, yielding 25.0 g. (32.3%) of analytically pure IV: m.p. 121–126°; $\nu_{max.}^{mineral\ oil}$ 3356 (OH) and 1739 cm.$^{-1}$ (carbonyl); $\lambda_{max.}^{EtOH}$ 219, 266, 273, and 280 nm. (ϵ 7570, 1220, 1630, and 1390).

Anal.—Calc. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.64; H, 5.69.

The combined ethereal extracts were evaporated *in vacuo*. The solid residue was recrystallized five times from 95% EtOH, affording pure V: m.p. 101–102°; $\nu_{max.}^{CHCl_3}$ 1751 cm.$^{-1}$ (carbonyl); $\lambda_{max.}^{EtOH}$ 218, 264, 271, and 278 nm. (ϵ 1420, 2320, 3100, and 2590); mass spectrum, *m/e* (relative intensity) 418 (6.3), 325 (5.6), 237 (50), 143 (41), 121 (92), and 94 (100); isotope distribution calc. for $C_{21}H_{22}O_9$, *m/e* (relative intensity) 418 (100), 419 (23.3), 420 (4.38), found 418 (100), 419 (23.5), 420 (4.30).

Anal.—Calc. for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30. Found: C, 60.15; H, 5.05.

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Structure Elucidation of Maytenonic Acid, a New Triterpene from *Maytenus senegalensis* (Celastraceae)

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Abstract □ Evidence for the structure of a new triterpene from *Maytenus senegalensis*, named maytenonic acid, is presented. The structure was postulated mainly on the basis of interpretation of IR, NMR, and mass spectral data.

Keyphrases □ Maytenonic acid, triterpene from *Maytenus senegalensis*—structure elucidation □ *Maytenus senegalensis* (Celastraceae)—structure elucidation of maytenonic acid □ Spectroscopy, IR, NMR, mass—structure elucidation of maytenonic acid from *Maytenus senegalensis*

Previously, the isolation and identification of β-amyrin, lupenone, β-sitosterol, β-sitosterol xyloside, wilforine, dulcitol, and two new triterpenes from *Maytenus senegalensis* (Lam.) Excell. were reported (1). Extracts and fractions from the plant were shown to have reproducible activity against the 9KB carcinoma of the nasopharynx in cell culture, as well as the L-1210 leukemia and PS leukemia tumor systems in mice. Dulcitol was shown to be responsible for a part of the antitumor activity. At this time, evidence is presented for the structure elucidation of one of the triterpenes previously isolated, triterpene A (1).

DISCUSSION

Maytenonic acid (I) (triterpene A), m.p. 262°, $[\alpha]_D^{26}$ −32 (c, 0.5, MeOH) was shown to have a molecular formula of $C_{30}H_{48}O_3$ by

Table I—Mass Spectrometric Data for Maytenonic Acid[a]

m/e	Percent	*m/e*	Percent
456	8.7	163	32.6
441	6.5	155	63.5
410	4.3	135	22.3
395	2.0	121	33.4
371	4.3	109	100.0
273	32.6	95	61.8
250	16.2	81	52.7
221	8.7	69	42.8
218	13.0	55	60.5
205	6.5	43	52.7
189	10.0	41	34.5

[a] Spectra were determined using a mass spectrometer LKB-9000 (LKB Produkter, Stockholm, Sweden) at 70 e.v.