L,L diastereoisomer crystd: yield 6.0 g (41.4%); mp 207–210°; $[\alpha]^{25}D$ −66° (*c* 0.4, 0.5 *N* NaOH).

The filtrate, contg the isomer **5**-D-L·HCl in impure form, did not crystallize. The amorphous material had a specific rotation of $[\alpha]^{25}D$ −15° (*c* 0.4, 0.5 *N* NaOH).

L-(−)-α-Methyl-3,4-dimethoxyphenylalanine (3-L). This compd was obtained as the hydrochloride by hydrogenation of (5-L-L) as described for **3**-DL: yield 77.3%; first mp 160–165°; solidifies at 170°; second mp 227–229°; $[\alpha]^{25}D$ −2.88° (*c* 1, 1 *N* HCl); lit.[10] $[\alpha]D$ −2.6° (*c* 1.01, 1 *N* HCl).

D-(+)-α-Methyl-3,4-dimethoxyphenylalanine (3-D). This compd was obtained as the hydrochloride, using the same procedure as for **3**-L replacing L-(−)-α-methylbenzylamine in the preparation of **5** by the D enantiomer: yield 69.5%; first mp 160–165°; second mp 227–229°; $[\alpha]^{25}D$ 2.01° (*c* 1, 1 *N* HCl).

DL-*N*-Formyl-α-methyl-3,4-dimethoxyphenylalanyl-*N*^{1}-D-(+)-α-phenylethylamine (7). A mixt of 3,4-dimethoxyphenylacetone (46.5 g, 0.24 mole), ammonium formate (31.5 g, 0.5 mole), and D-(+)-α-phenylethylisonitrile **(6)**[11] (38.8 g, 0.24 mole) was refluxed in MeOH–H_2O (4:1) (250 ml) for 24 hr. The residue from evapn was extd with $CHCl_3$, washed with H_2O, dried, and evapd. The residue was crystd from Me_2CO: yield 17.8 g (20%); mp 138–139°; $[\alpha]^{25}D$ 28.5° (*c* 1, EtOH). *Anal.* ($C_{21}H_{26}N_2O_4$) C, H, N.

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Synthesis of Insect-Repellent Amino Analogs of 2-Ethyl-1,3-hexanediol (Rutgers 612)†

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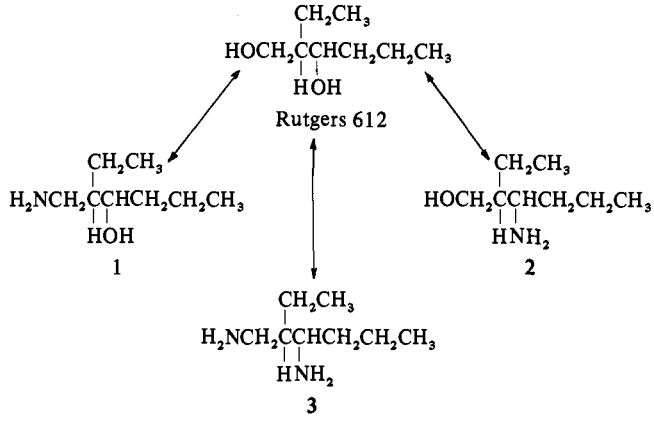
As an extension of our work on the development of insect repellents with dermophilic characteristics and long-lasting efficacy,[1-11] we designed and prepared amino analogs (**1-3**) of the standard repellent 2-ethyl-1,3-hexanediol (Rutgers 612). Since the latter's duration of effectiveness is known to be limited by volatilization from and absorption through the skin,[12] it was envisioned that interaction of the novel compounds' amino groups with acidic functions in the matrix of the epidermis[13] would extend insectifugal activity. The basic groups provide, also, means for linking the new agents to established anchoring components used in precursor molecules, capable of sustained repellent activity.[8]



Chemistry. Amino alcohol **1** was prepared by LAH reduction of 3-cyano-4-heptanone (**4**); the latter was obtained following the procedure described by Ziegler, *et al.*[14] In the synthesis of compds **2** and **3**, 3-amino-2-ethylhexanenitrile (**6**) constituted the key intermediate; it was prepared by the method of Grandberg and Golubeva.[15] LAH reduction of **6** afforded **3**, while ethanolysis of **6** and LAH reduction of the resulting aminoester (**7**) gave **2**. Characterization of compds **1-3** included their conversion to the respective hexachlorophene [2,2′-methylenebis(3,4,6-trichlorophenol)] salts (**8-10**).

Insect Repellency. Comparative evaluation of the repellency of several of the novel compds against *Aedes aegypti* (L.) mosquitoes was performed employing methodologies described in preceding communications.[1,3] Forearms of human volunteers, treated with the evaluants or with the standard repellent, were exposed (3 min) to caged mosquitoes at 30-min intervals until a confirmed bite was received. While the data from "round-robin" tests (Table I) reflect the fact that compds **1** and **2** elicit activities paralleling that of 2-ethyl-1,3-hexanediol (Rutgers 612), results from *paired* tests indicate for compd **1** an efficacy surpassing that of the standard Rutgers 612 (Table II). In other paired evaluations, repellency indices for compd **2** and for ethyl 3-amino-2-ethylhexanoate (**7**) were computed at 0.68 and 0.67, respectively, using Rutgers 612 as the standard. Compd **3** was ineffective; the lack of activity was probably associated with the formation of a solid carbonate derivative upon exposure to the atmosphere.

Based upon the results summarized above, amino alcohol **1** appears to offer prominent potentialities as a component of precursor-type repellents. Field tests have been projected

Table I. Protection Effected by Repellents against Biting by *A. aegypti*[a]

Repellent[b]	Protection time, min: Range	Protection time, min: Average[c]	Repellency index[d]
1	30–210	127	0.88
2	60–180	120	0.83
2-Ethyl-1,3-hexanediol	60–270	144	1.00

[a] In standard "round-robin" repellency tests on skin (ref 16). [b] One-half g of the respective repellents in ethanol was applied to the entire forearm of a human volunteer. [c] Average of 8 tests; least significant difference (0.05 level) = 34. [d] The repellency index = average protection time effected by the evaluant:average protection time effected by the 2-ethyl-1,3-hexanediol standard.

†This investigation was supported by the U. S. Army Medical Research and Development Command, Washington, D. C., through Research Contract DA-49-193-MD-2636.

Table II. Protection Effected by Repellents against Biting by *A. aegypti*[a]

Repellent	Protection time, min		Repellency index[c]
	Range	Average[b]	
1	60–300	150	2.22
2-Ethyl-1,3-hexanediol	30–150	68	1.00

[a] In paired repellency tests on skin. One-half g of compd 1 in ethanol was applied to one forearm of a human volunteer, and 0.5 g of the standard 2-ethyl-1,3-hexanediol was applied to the individual's other forearm. [b] Average of 4 tests; least significant difference (0.05 level) = 70. [c] The repellency index = average protection time effected by the evaluant (1):average protection time effected by the 2-ethyl-1,3-hexanediol standard.

for the compound, and further work on derivatives and related compounds is expected to be reported later.

Experimental Section‡

3-Aminomethyl-4-heptanol (1) was prepared by the addn of 29.1 g (0.209 mole) of 3-cyano-4-heptanone **(4)**[14] to a cold, stirred slurry of 11.4 g (0.300 mole) of LAH in 600 ml of dry Et_2O, and then allowing the mixt to stir at room temp for 30 min. Subsequent to work-up of the reaction mixt in the usual manner, the dried residue was distd *in vacuo*, affording 18.0 g (59.3%) of pure product, bp 56–61° (0.05–0.06 mm), n^{25}D 1.4566. *Anal.* ($C_8H_{19}NO$) C, H, N.

The **hexachlorophene salt (8)** of compd 1 was prepared by stirring 2.0 g (0.014 mole) of 1 with 5.6 g (0.014 mole) of hexachlorophene in 215 ml of dry Et_2O at room temp for 48 hr. After removal of the solvent, the crude product was recrystd from EtOH, affording 1.0 g (13%) of **8**, mp 185.5–187.0°. *Anal.* ($C_{21}H_{25}Cl_6NO_3$) C, H, Cl, N.

3-Amino-2-ethylhexanenitrile (6) was prepared, in accordance with the procedure reported by Grandberg and Golubeva,[15] from 225 g (1.60 moles) of 4-ethyl-5-propyl-2-pyrazoline **(5)**.[15] The crude liquid product was distd *in vacuo* affording 43.6 g (19.4%) of **6**, bp 55° (0.2 mm) [lit.[15] bp 103–106.5° (11 mm)]. The **phenylisothiourea derivative,** prepared in the conventional manner, melted at 109.2–110.2° after recrystn from EtOH (lit.[15] mp 108–109°).

Ethyl 3-Amino-2-ethylhexanoate (7). This compd was prepared, utilizing a procedure described by Dupre, *et al.*,[17] for the synthesis of another aminoester, from 34.5 g (0.246 mole) of **6**. The crude oily liquid product was distd *in vacuo*, affording 18.1 g (39.3%) of pure **7**, bp 57.2–59.0° (0.7–0.8 mm), n^{20}D 1.4437. *Anal.* ($C_{10}H_{21}NO_2$) C, H, N.

3-Amino-2-ethyl-1-hexanol (2) was prepared by addn of 25.9 g (0.138 mole) of **7** to a cold, stirred slurry of 7.82 g (0.206 mole) of LAH in 170 ml of dry Et_2O. The mixt was then stirred at room temp for 30 min, and worked up in the usual manner. After removal of Et_2O solvent, the residual liquid product was distd *in vacuo* affording 10.3 g (51.5%) of pure **2**, bp 57.0° (0.4 mm), n^{25}D 1.4643. *Anal.* ($C_8H_{19}NO$) C, H, N.

The **hexachlorophene salt (9)** of compd **2** was prepared from 2.0 g (0.014 mole) of **2** and 5.6 g (0.014 mole) of hexachlorophene in the same manner as described for **8**. The crude product was recrystd from C_6H_6 yielding 2.0 g (29.0%) of pure **9**, mp 170.5–171.5°. *Anal.* ($C_{21}H_{25}Cl_6NO_3$) C, H, Cl, N.

2-Ethyl-1,3-hexanediamine (3) was synthesized by adding 82.0 g (0.585 mole) of **6** to a cold, stirred mixt of 25.0 g (0.659 mole) of LAH in 1320 ml of dry Et_2O, and then allowing the mixt to stir at room temp for 2 hr. After work-up of the mixt in the usual manner, the dried oily liquid product was distd *in vacuo*, giving 43.2 g (51.2%) of **3**,§ bp 50° (0.5 mm). *Anal.* ($C_8H_{20}N_2$) C, H, N.

The **hexachlorophene salt (10)** of compd **3** was prepared from 0.8 g (0.006 mole) of **3** and 4.5 g (0.011 mole) of hexachlorophene as described for **8**. The crude product was recrystd from Et_2O–petroleum ether (bp 30–75°) affording 1.2 g of **10**, mp 148.8–150.0°. *Anal.* ($C_{21}H_{26}Cl_6N_2O_2$) C, H, Cl, N.

‡ Boiling points are uncorrected. Melting points are corrected; they were determined with a Büchi melting point apparatus. Ir spectra consistent with the stipulated molecular constitutions of the synthetic entities were obtained with Perkin-Elmer Model 137B or Beckman Model IR33 spectrophotometers. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.3% of the theoretical value.

§ The compd readily formed a white solid when exposed to air, or when CO_2 was passed through a solution in Et_2O.

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Synthesis of the Phosphonic Acid Isostere of Glycerol 3-Phosphate

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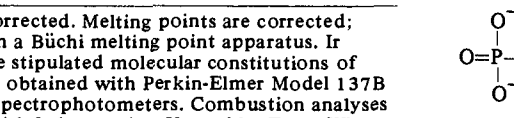
As glycerol 3-phosphate acts as a precursor in phospholipid synthesis, it was of interest to investigate the action of an isostere (substituting CH_2 for O in the ester linkage) in which cleavage of the phosphorus portion from the carbon chain would not readily occur. To this end the synthesis of the dilithium salt of 3,4-dihydroxybutyl-1-phosphonic acid (**6**) was undertaken by the route described below.



6

The uptake of **6** by *Escherichia coli* requires an active glycerol 3-phosphate transport system. Its inhibitory effects are not offset by the presence of either glucose or a high