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.

Acknowledgments. We would like to thank Messrs. D. Godwin, N. Smith, D. Smith, J. Jackson, K. H. Posey, and I. H. Gilbert for their participation in the evaluations of insect repellency.

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Synthesis of the Phosphonic Acid Isostere of Glycerol 3-Phosphate

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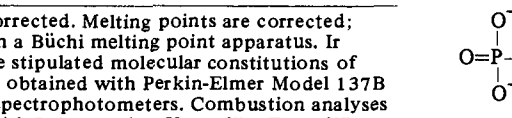
Received April 14, 1972

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

concentration of inorganic phosphate in the growth medium.[1] It is capable of exerting an inhibitory effect on cells containing an active glycerol-3-phosphate dehydrogenase.[1] Recent studies indicate that lipid synthesis *in vivo* is more sensitive to inhibition by **6** than DNA, RNA, and protein synthesis.† It appears to be a competitive inhibitor of glycerol 3-phosphate in the glycerol 3-phosphate:CMP phosphatidyl transferase reaction.† It is also a substrate for rabbit muscle glycerol-3-phosphate dehydrogenase.‡

Experimental Section§

3-Butenyl Bromide (2). A prior synthesis of this compound is reported by Juvala.[2] To 651 g (1.386 moles) of freshly prepared triphenyl phosphite dibromide were added 54.8 g (0.693 mole) of 3-buten-1-ol, **1** (prepared according to the method of Linstead and Rydon[3]), and 55.7 g (0.705 mole) of pyridine, and the mixt was stirred for 2 hr. The precipitate of pyridine hydrobromide was removed with suction filtration and the volatile components of the filtrate were collected in a cold trap under vacuum. Upon fractional distillation there was isolated 44.9 g (48%) of pure **2**, bp 32° (47 mm).

Diethyl 3-Butene-1-phosphonate (3). To the refluxing bromide, **2** (49.9 g, 0.333 mole), was added dropwise 66.4 g (0.400 mole) of freshly distilled triethyl phosphite, and the mixt was refluxed for 2 hr. The reaction mixture was then distilled using an 18-in. spinning band column, EtBr being removed first at atmospheric pressure. Under reduced pressure was then isolated 43.6 g (68%) of pure **3**, bp 78° (1.75 mm). The ir and nmr spectra were in accord with the proposed structure. *Anal.* ($C_8H_{17}O_3P$) C, H.

Dilithium 3,4-Dihydroxybutyl-1-phosphonate (6). To 28.5 g (0.150 mole) of phosphonate **3** were added 76 ml of 88% formic acid and 22.1 ml of 30% H_2O_2. The reaction mixture was maintained overnight in the temperature range 40–50°. Volatile materials were removed under reduced pressure on a rotary evaporator leaving as a syrupy, clear liquid, impure diethyl 3,4-dihydroxybutyl-1-phosphonate, **4**. This material was not purified but hydrolyzed directly. To it was added 220 ml of hot, saturated LiOH solution. The reaction mixture was heated in an autoclave at 120° for 5 hr. Volatile components were removed under reduced pressure to give a syrupy liquid which upon washing with three 300-ml portions of acetone yielded a white precipitate, isolated by suction filtration, and dried under vacuum. Spectra indicated this to be the partial ester, lithium ethyl 3,4-dihydroxybutyl-1-phosphonate, **5**, although further purification was not attempted. This material was dissolved in 350 ml of water with 20 ml of saturated LiOH solution, and the reaction mixture was heated in an autoclave for 3 hr at 120°. A white precipitate formed which was isolated by suction filtration. The filtrate was returned to the autoclave for 2 hr at 120°; the second crop of crystals was isolated and combined with the first. The combined materials were washed with several portions of 95% ethanol and ether and dried under vacuum to yield 11.0 g (49%) of **6**. The ir and nmr spectra were in accord with the proposed structure. *Anal.* ($C_4H_9O_5PLi_2$) C, H.

Acknowledgment. The authors wish to thank Dr. Arthur Rosenthal for numerous helpful discussions and suggestions. This investigation was supported by a grant from the City University of New York Faculty Research Program and a Biomedical Sciences Support Grant from NIH.

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§All nmr spectra were measured using a Varian A60-A instrument. The ir spectra were measured on a Perkin-Elmer 237B spectrophotometer. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Structures were confirmed by ir and nmr spectra, all of which agreed with those predicted. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

Synthesis and Antiviral Activity of 4′-Hydroxy-5,6,7,8-tetramethoxyflavone

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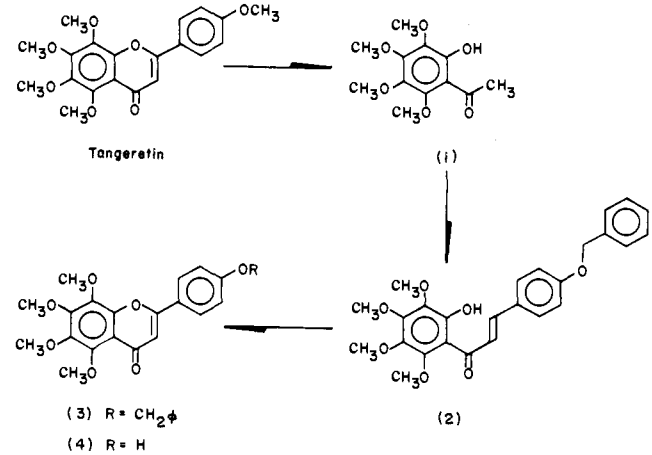
Received March 20, 1972

Many pharmacological properties have been ascribed to various flavonoids. Our current interest has centered in those with fully hydroxylated A rings. Tangeretin (4′,5,6,7,-8-pentamethoxyflavone) has shown marked cytotoxicity against the rapidly developing zebra fish embryo.[1] Nobiletin (3′,4′,5,6,7,8-hexamethoxyflavone) and tangeretin have been described as having fungistatic properties toward *Deuterophoma tracheiphila*, which causes a widespread disease of citrus trees in the Mediterranean.[2]

In another report[3] nobiletin showed antiinflammatory activity which was described as being 46% as effective as hydrocortisone phosphate on a weight basis in the test system used. The capacity of nobiletin and tangeretin to stimulate the enzyme, benzpyrene hydroxylase, which detoxifies carcinogenic hydrocarbons and hydroxylates steroids has been reported by Wattenberg, *et al.*[4]

The present report details the pronounced antiviral effect of 4′-hydroxy-5,6,7,8-tetramethoxyflavone (**4**, 4′-desmethyltangeretin) against type 13 rhinovirus in cell culture. 4′-Hydroxy-5,6,7,8-tetramethoxyflavone (**4**) was prepared in 3 steps starting with 2′-hydroxy-3′,4′,5′,6′-tetramethoxyacetophenone (**1**) prepared by the basic degradation of tangeretin. The condensation of **1** with *p*-benzyloxybenzaldehyde in EtOH and 50% KOH gave a 71% yield of 4-*p*-benzyloxy-2′-hydroxy-3′,4′,5′,6′-tetramethoxychalcone (**2**). Oxidative closure of **2** in *n*-amyl alcohol with SeO_2 gave an 86% yield of 4′-benzyloxy-5,6,7,8-tetramethoxyflavone (**3**).[5] Hydrogenation of **3** in AcOH with 5% Pd/C as catalyst provided 4′-hydroxy-5,6,7,8-tetramethoxyflavone (**4**).



Antiviral Evaluation. 4′-Hydroxy-5,6,7,8-tetramethoxyflavone (**4**) was tested for *in vitro* activity against types 1A, 13, and 56 rhinoviruses grown in continuous-passaged cells of human carcinoma of the nasopharynx (KB). The tests were carried out in disposable plastic microplates using inhibition of virus-induced cytopathogenic effect (CPE), previously described,[6] as the primary criterion for evaluation of antiviral activity. The virus rating (VR) system[6] was used for determining the degree of significance of CPE inhibition. In this VR system, activity of 0.5 or greater was considered indicative of significant antiviral effect. 4′-