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Hypotensive Phospholipids. Some Stable Analogues of Darmstoff

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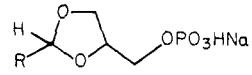
2-Pentadecyl-4-hydroxymethyl-1,3-dioxolane monosodium phosphate (1) has been shown to exhibit bradycardia and hypotension in rats. It is, however, unstable in aqueous solution. In this study, the stable analogues of 1, 2-pentadecyl-5-hydroxymethyltetrahydrofuran monosodium phosphate (7), and 1-hydroxymethyl-3-pentadecylcyclopentane monosodium phosphate (17) were prepared. These substances exhibited cardiovascular effects similar both qualitatively and quantitatively to those elicited by 1 and were stable in solution for about 24 and at least 72 h, respectively.

The mixture of acetal phosphatidic acids known as Darmstoff[1,2] has been shown to consist primarily of the structures shown as 1, where R = $C_{15}H_{31}$ (40%) and R =



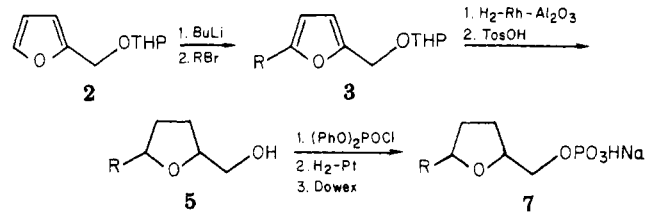
1, R = $C_{15}H_{31}$

$C_{17}H_{33}$ (40%).[3] Some of these materials are reasonably potent stimulators of gastrointestinal smooth muscle[3] and inhibitors of renin.[4] Although it has been claimed that Darmstoff-like activity arises from the presence of prostaglandins as impurities in the preparations,[5-7] observation of identical activities in synthetic materials appears to rule out this possibility. Turcotte[8] has also observed renin inhibition in a series of phosphatidic acids.

All dioxolanes of this type are unstable in neutral aqueous solution. In order to determine whether similar biological effects could be obtained with more stable compounds, we have synthesized the tetrahydrofuran (7) and cyclopentyl (17) analogues of the palmityl phosphatidic acid 1, in which oxygen atoms have been replaced with isosteric methylene groups.

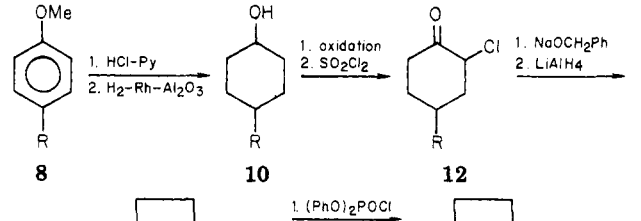
Chemistry. 2-Pentadecyl-4-hydroxymethyl-1,3-dioxolane dihydrogen phosphate ester was prepared by the published procedure[3] and the monosodium salt 1 prepared by reaction with Dowex 50 W-X8 (Na^+ form). The tetrahydrofuran analogue 7 was prepared according to Scheme I. The tetrahydropyranyl (THP) ether of furfuryl alcohol was alkylated in 56% yield by adaptation of a known procedure.[9] Attempts to remove the THP protecting group at this point by dissolving 3 in wet ether and adding a trace of concentrated HCl were unsuccessful. Repeating this procedure with larger amounts of HCl gave only partial hydrolysis as shown by the IR spectrum of the crude product. Using ether–ethanol–HCl mixtures, opening of the furan ring was observed. Failure to find the right conditions for the hydrolysis prompted the reduction of 3 over rhodium on alumina and removal of the THP group at the saturated ether stage. Hydrolysis of the

Scheme I



2 3 5 7

Scheme II



8 10 12 14 17

THP ether was accomplished in quantitative yield following the method described by Corey,[10] which employs 2.8 mmol of *p*-toluenesulfonic acid in methanol for 1 h at 0 °C and 2 h at 23 °C. This gave 5 as a white low-melting wax. Compound 5 was phosphorylated with diphenyl phosphochloridate in anhydrous pyridine, according to the procedure of Brigl and Mueller.[11] The resulting diphenylphosphte ester was reduced in the presence of platinum with ethanol as solvent. Filtration and solvent evaporation gave the furan analogue 6 as a white wax. The material was purified by washing with hexane; the monosodium salt 7 was prepared by a batch reaction with Dowex, followed by lyophilization.

The synthesis of the cyclopentane analogue 17 is shown in Scheme II. Treatment of anisaldehyde with tetradecylmagnesium bromide gave *p*-methoxyphenyltetradecylcarbinol as reported by Hanif.[12] This carbinol or its dehydration product was reduced over palladium on

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Table I. Effect of Phosphatidic Acids on Blood Pressure and Heart Rate in Awake Normotensive Rats[a] (Mean ± SD)

Compd	Dose, mg/100 g	n	Av heart rate/min		Av mean blood pressure (mmHg)	
			Before treatment	2 min after treatment	Before treatment	2 min after treatment
1	1	6	430 ± 50	310 ± 54	125 ± 16	100 ± 13
1	2	2	420	250	125	100
1	4	1	Died in cardiac arrest			
7	1	3	430 ± 40	350 ± 5.8	115 ± 17	100 ± 21
17	1	4	450 ± 57	375 ± 31	130 ± 6.9	120 ± 16

[a] Effects were similar whether drug was administered via the ileac or jugular veins. The results were not affected by administration of propranolol, indicating that the β-adrenergic system is not involved.

carbon at 55 psig to give *p*-pentadecylanisole (**8**). Ether cleavage was accomplished by the method of Prey[13] using pyridine hydrochloride to give *p*-pentadecylphenol (**9**) in 57% overall yield. Alternatively, a Grignard reaction on *p*-benzyloxybenzaldehyde to give *p*-benzyloxyphenyltetradecylcarbinol, followed by hydrogenolysis over 10% palladium on carbon, gave **9** in 77% overall yield. Reduction of **9** over rhodium on alumina followed by a Jones oxidation and treatment with sulfuryl chloride gave the α-chloro ketone **12**. Attempted Favorskii rearrangements on **12** with sodium methoxide and sodium ethoxide in homogeneous medium as well as with sodium benzyloxide in ether were unsuccessful. Ring contraction was finally achieved in yields of 35–45% using base-washed chloro ketone, freshly purified[14] benzyl alcohol, and sodium benzyloxide according to the procedure of Stork and Borowitz.[15] The resulting alkylcyclopentanecarboxylic acid was reduced with lithium aluminum hydride and the primary alcohol phosphorylated in the same manner as described above for **5**.

Pharmacological Data. Rats were fitted with indwelling catheters in the femoral artery and in either the jugular or ileac vein. The catheters were placed to enter the animal on the dorsal side of the neck. Following recovery from the surgery (at least 7 days), blood pressure was measured by connecting a strain gauge to the arterial catheter; drugs were administered via the venous catheter. Blood pressure was measured periodically until each animal exhibited stable blood pressure for at least 1 week; during measurement, the animals were not restrained in any way nor treated with any drug other than the one being tested. Drug solutions were prepared in 0.9% sodium chloride. For determination of stability, drug solutions were stored at 5 °C, and blood pressure measurements were repeated at times indicated. Administration of saline solution in volumes similar to the drug solutions had no effect on heart function or blood pressure.

The effects of administration of the natural substance **1** and analogues **7** and **17** are shown in Table I. It is seen that there is a marked fall both in heart rate and in blood pressure within 2 min after administering the drug and that the effect is relatively transient. Representative chart records for the three substances are also shown in Figure 1; the effect on heart rate is unmistakable, and the reduction persisted for at least 10 min in each experiment. A transient blood pressure effect was also observed. Both **1** and its oleyl analogue have been similarly tested in spontaneously hypertensive rats[16] and exhibited pronounced hypotension and bradycardia, which persisted at least 48 h. Further studies of the effects of these compounds on heart function in normotensive and hypertensive rats, as well as on isolated hearts from both types of animals, are in progress.

Discussion

It is clear from these data that the cardiovascular properties associated with Darmstoff are not limited to the natural substances. It is also of interest that the activity appears to be associated with the intact molecule, for there is an apparent rank order correlation with predicted stability. Whereas solutions of **1** lost all biological effect within 1 h, **7** exhibited about one-half maximal effect after being in solution for 24 h, and **17** was fully active after 72 h.

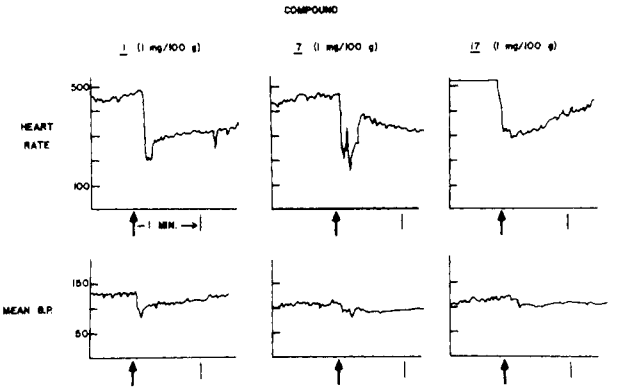

Figure 1. Effects of **1**, **7**, and **17** on heart rate and mean blood pressure in normotensive animals. Compound administered at arrow.

Dioxolane **1** has a longer lasting effect in hypertensive than in normotensive animals.[16] If similar effects are observed for **7** and **17**, these substances may find utility as hypotensive agents.

Experimental Section

Furfuryl alcohol, *p*-anisaldehyde, benzyl alcohol, and diphenyl chlorophosphate were obtained from Aldrich Chemical Co., Milwaukee, Wis. 53233. Pentadecyl bromide was obtained from Fisher Scientific Co., Pittsburgh, Pa. 15219, and myristyl bromide from Sigma Chemical Co., St. Louis, Mo. 63178. Starting materials were purified before use. Analytical reagent grade solvents were used for the most part without further purification. Anhydrous pyridine was dried over KOH and distilled before use. Anhydrous methanol was dried by distillation from magnesium methoxide. Mallinckrodt AR ether was used where the anhydrous state was necessary. Column chromatography was performed on E. Merck silica gel (70–325 mesh) and Woelm neutral alumina (activity grade 1). Thin-layer chromatography was performed on E. Merck silica gel G and alumina plates. IR spectra (cm^{-1}) were determined with a Beckman IR-33 spectrophotometer using NaCl plates and pressed KBr disks. ^1H NMR spectra (δ, ppm) were recorded in $CDCl_3$ [internal $(CH_3)_4Si$] with Varian T-60 and EM-360 spectrometers. All compounds exhibited proton NMR spectra consistent with the structures assigned. Melting points were obtained on a Thomas-Hoover capillary unimelt apparatus and remain uncorrected. Boiling points were determined with noncertified mercury thermometers and pressures with a McLeod gauge. Elemental analyses were performed on a Hewlett-Packard 185B CHN analyzer, University of Kansas, and by Midwest Microlabs, Indianapolis, Ind.

Furfuryl Tetrahydropyranyl Ether (2). Freshly distilled furfuryl alcohol (15.45 g, 0.16 mol) was stirred at 0 °C with 13.67 g (0.163 mol) of dihydropyran. Two drops of concentrated HCl was added and the solution allowed to warm to 25 °C overnight.

Ether (100 mL) was added and the solution washed with 150 mL of 10% NaOH, dried (Na_2CO_3), and evaporated under reduced pressure. The residue was distilled; the fraction coming over at 76–80 °C (1.0–1.5 mmHg) was collected. It represented 21.9 g (75%) of **2** (lit.[17] 124 °C at 24 mm): IR (film) 3130, 1500, 1450, 870, 730 cm^{-1}; ^1H NMR (CCl_4) δ 7.3 (m, 1), 6.2 (m, 2), 4.65 (m, 1), 4.45 (d, 2), 3.5 (m, 2), 1.5 (m, 6). Anal. ($C_{10}H_{14}O_3$) C, H.

5-Pentadecylfurfuryl Tetrahydropyranyl Ether (3). Dry THF (30 mL) was placed in a 200-mL three-neck round-bottom flask equipped with a magnetic stirring bar, a dropping funnel, a rubber septum, and a cold-finger condenser. The air was swept out of the flask with dry N_2 and a light flow was maintained throughout the reaction. Butyllithium in hexane (38.6 mL of a 2.2 M solution, 0.063 mol) was introduced with a syringe. The solution was stirred and cooled to −78 °C and then 11.5 g (0.063 mol) of **2** was added over a period of 10 min. The reaction mixture was stirred at this temperature for 3 h, at which time 18.4 g (0.063 mol) of pentadecyl bromide in 20 mL of dry tetrahydrofuran was added over a period of 15 min. The reaction mixture was allowed to warm to 25 °C overnight. The mixture was poured onto 200 g of ice and extracted with ether (3 × 200 mL). The combined ether extracts were washed with H_2O and saturated NaCl, dried (Na_2CO_3), and evaporated. The resulting residue was distilled. The fraction boiling at 205 °C (100–150 μm) was collected and gave 13.9 g (56%) of **3**: IR (film) 3110, 1555, 885, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.2 (d, 1), 5.9 (d, 1), 4.6 (m, 1), 4.5 (d, 2), 3.7 (m, 2), 2.5 (m, 2), 1.65 (m, 6), 1.3 (s, 26), 0.9 (m, 3). Anal. ($C_{25}H_{44}O_3$) C, H.

5-Pentadecyltetrahydrofurfuryl Alcohol (5). Compound **3** (8.93 g, 0.023 mol) was dissolved in 50 mL of tetrahydrofuran–ethanol (1:1) and placed on a Parr shaker with 0.8 g of 5% $Rh–Al_2O_3$ at 50 psig for 20 h. Filtration through Celite and evaporation under reduced pressure left 9.1 g of a heavy oil: IR (film) 1460, 1120, 1025 cm^{-1}.

A solution of this oil (9.1 g, 0.023 mol) in 250 mL of methanol containing 0.003 M *p*-toluenesulfonic acid was stirred at 25 °C for 2 h. The methanol was evaporated and replaced with hexane. The resulting solution was washed with 5% NaOH, dried ($MgSO_4$), and filtered. Evaporation under reduced pressure left 7.1 g (100) of **5** as a white low-melting wax: IR (film) 3450, 1460, 1050, 700 cm^{-1}. Anal. ($C_{20}H_{40}O_2$) C, H.

2-Pentadecyl-5-hydroxymethyltetrahydrofuran Dihydrogen Phosphate Ester (6). Alcohol **5** (3.85 g, 0.012 mol) was added to 5 mL of dry pyridine in a 25-mL round-bottom flask. The flask was closed with a rubber septum, flushed with argon, and cooled in an ice–salt bath. Diphenyl chlorophosphate (4.3 g, 0.016 mol) in 5 mL of dry pyridine was added with a syringe over 5 min. The flask was again flushed with argon and placed in the refrigerator at 5 °C. After 24 h the flask was removed and allowed to warm to 25 °C. Ice (0.5 g) was added and after 30 min the contents were poured into 300 mL of ice water. The solution was extracted with $CHCl_3$ (2 × 250 mL), and the combined extracts were washed with 3 N HCl (55 mL) and H_2O (2 × 100 mL). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated under reduced pressure to give the diphenyl phosphate ester: IR 1590, 1490, 1460, 1280, 1180, 750, 680 cm^{-1}. The diphenyl phosphate ester was dissolved in 50 mL of absolute ethanol and placed in a Parr bottle with 0.2 g of prereduced PtO_2. After reduction at 50 psig for 24 h, the catalyst was removed by filtration and the solvent evaporated under reduced pressure. The residue was washed with hexane and dried under a stream of N_2 to give 2.5 g (52 %) of **6**: IR (film) 1465, 1200, 1030 cm^{-1}. Anal. ($C_{20}H_{41}PO_5$) C, H.

2-Pentadecyl-5-hydroxymethyltetrahydrofuran Monosodium Phosphate (7). Compound **6** (1.34 g, 0.003 mol) was dissolved in 30 mL of H_2O and 3 mL of wet Dowex 50 W-X8 (Na^+) (1.9 mequiv/mL) was added. This suspension was stirred for 1 h and filtered. The filtrate was lyophilized to give a fine white powder which was washed with 50 mL of dry acetone and dried with the aid of an oil pump: mp 83–88 °C; IR (Nujol) 2400, 1180, 1035 cm^{-1}. Anal. ($C_{20}H_{40}PO_5Na$) C, H.

***p*-Pentadecylanisole (8).** *p*-Methoxyphenyltetradecylcarbinol (22.0 g, 0.068 mol) was dissolved in 150 mL of ethyl acetate and placed in a Parr bottle along with 2.5 g of 10% Pd/C. The reduction was allowed to run at 55 psig for 24 h. The catalyst was removed by filtration (Celite) and the solvent removed under reduced pressure with the aid of a steam bath. The residue was distilled and the desired product was collected at 184 °C (1 mm) in 80% yield: melting point just above room temperature; IR (film) 1610, 1510, 1465, 1240, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0 (Ar, 4), 3.75 (s, 3), 1.3 (s, 28), 0.9 (m, 3). Anal. ($C_{22}H_{38}O$) C, H.

***p*-Pentadecylphenol (9).** A solution of **8** (8.92 g, 0.028 mol) in 50 mL of dry pyridine was heated at reflux and a strong stream of HCl gas was passed into the stirred reaction mixture. Refluxing ceased after 20 min and with continued heating began again. After 4.5 h the solution was allowed to cool and 50 mL of H_2O was added. Et_2O (100 mL) was added, the phases were separated, and the water layer was extracted with ether (2 × 100 mL). The combined ether extracts were washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure leaving an off-white solid, which was recrystallized from hexane to give 7.7 g (89%) of **9**: mp 71.4–73 °C; IR (film) 3390, 1410, 1460, 1250, 800, 700 cm^{-1}; ^1H NMR (CCl_4) 6.8 (Ar, 4), 2.45 (t, 2), 1.25 (s, 26), 0.9 (m, 3). Anal. ($C_{21}H_{36}O$) C, H.

4-Pentadecylcyclohexanol (10). A solution of **9** (22.3 g, 0.073 mol) in 150 mL of absolute ethanol was reduced with 5.0 g of 5% $Rh–Al_2O_3$ at 55 psig for 72 h. The catalyst was removed by filtration and washed with 50 mL of ethanol. Solvent evaporation left 21.4 g which was distilled [bp 140–155 °C (20 μm)] to give 17.4 g (77%) of **10**: mp 49–56 °C; IR (film) 3315, 1465, 1030, 935, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.9 (m, 1), 2.8 (s, 1), 1.5–0.9 (m, 40). Anal. ($C_{21}H_{42}O$) C, H.

4-Pentadecylcyclohexanone (11). To a solution of **10** (12.3 g, 0.039 mol) in 400 mL of acetone was added Jones reagent (23 mL of concentrated H_2SO_4, 26.72 g of CrO_3, and H_2O to a volume of 100 mL) until an orange color developed which lasted 20 min. 2-Propanol was added until the solution turned green. The reaction mixture was then filtered; the filtrate was treated with Na_2CO_3 to neutral pH and filtered, and the acetone was removed under reduced pressure. The residue was treated with 50 mL of H_2O and extracted with ether (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated leaving 12.0 g (98%) of **11**. Distillation [bp 165 °C (400 μm)] yielded an analytical sample: mp 45.5–47 °C; IR (film) 1717, 1460, 1153, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3 (m, 4), 1.3–0.8 (m, 36). Anal. ($C_{21}H_{40}O$) C, H.

2-Chloro-4-pentadecylcyclohexanone (12). In a three-neck flask equipped with a condenser, N_2 inlet tube, and a rubber septum were placed 3.00 g (0.01 mol) of **11** and 50 mL of CCl_4. Freshly distilled sulfuryl chloride (1.31 g, 0.01 mol) was added in one portion. The solution was stirred magnetically and heated at reflux. After 6 h the reaction mixture was allowed to cool to 25 °C and evaporated under reduced pressure to a yellow oil which was dissolved in ether, washed with dilute $NaHCO_3$, and dried ($MgSO_4$). Evaporation of the ether left a pale yellow oil which solidified just below 25 °C and showed only one spot on TLC (silica, ethyl acetate–hexane, 1:1): IR (film) 1730, 1460, 790, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.4 (t, 1), 2.6–0.8 (m, 38). Anal. ($C_{21}H_{39}ClO$) C, H.

3-Pentadecylcyclopentanecarboxylic Acid (13). Sodium (0.72 g, 0.031 g-atom) was added to 17.4 mL of freshly purified benzyl alcohol[14] in a 50-mL three-neck flask equipped with a magnetic stirring bar, cold finger condenser, argon inlet tube, and rubber septum. An ice water bath was used to cool the solution to 5 °C, at which time 3.3 g (0.01 mol) of **12** in a pear-shaped flask was melted, taken up in a warm syringe, and added dropwise over 10 min to the sodium benzyloxide solution. The flask and syringe were rinsed with 2 mL of warm benzyl alcohol and this washing was also added through the rubber septum. The ice bath was removed and the resulting reaction mixture stirred at 25 °C for 1 h and 15 min. After this time, the solution was viscous. Water (40 mL) was added and the solution heated at reflux for 2 h. Stirring and an argon atmosphere above the solution were maintained throughout. The solution was allowed to cool to 25 °C and washed with ether (4 × 50 mL). The solution was acidified with 3 N HCl and extracted with ether (3 × 50 mL). The latter three extracts were combined, dried ($MgSO_4$), and evaporated. A small flask containing the residue was evacuated with an oil pump overnight, resulting in 1.45 g (45%) of a brown semisolid. This residue was chromatographed (column: 3.0 × 45 cm, 135 g of silica, slurry packed with benzene). Initial development with 1 L of benzene eluted unhydrolyzed ester and nonpolar impurities. The benzene was followed by 2 L of $CHCl_3$ (225-mL fractions were

collected). Fractions 3–8 contained 1.1 g (35%) of **13**: mp 46–48 °C; IR (film) 2690, 1700, 1470, 1298, 940, 710 cm^{-1}. Anal. ($C_{21}H_{40}O_2$) C, H.

1-Hydroxymethyl-3-pentadecylcyclopentane (14). $LiAlH_4$ (0.70 g, 0.018 mol) was added to 26.5 mL of dry ether in a 50-mL three-neck flask equipped with a reflux condenser, a gas inlet tube, and a rubber septum. A positive pressure of argon was maintained throughout the reaction. The $LiAlH_4$ solution was stirred magnetically at 25 °C and 1.97 g (0.006 mol) of **13** in 10 mL of ether was added dropwise over 10 min. After stirring overnight, 1.6 mL of ethyl acetate was added, followed by 1 mL of H_2O and then 25 mL of 10% H_2SO_4. The resulting clear solution was extracted with ether (3 × 40 mL). The combined extracts were washed with 10% NaOH, followed by H_2O, and dried (Na_2SO_4). Evaporation of the Et_2O gave 1.68 g (89%) of **14** as a low-melting solid: IR (film) 3350, 1460, 1020, 700 cm^{-1}. Anal. ($C_{21}H_{42}O$) C, H.

1-Hydroxymethyl-3-pentadecylcyclopentane Diphenyl Phosphate Ester (15). A solution of **14** (1.0 g, 0.003 mol) in 3 mL of dry pyridine was placed in a 25-mL flask. The flask contained a stirring bar and was stoppered with a rubber septum. The solution was cooled to 5 °C (ice bath) and 1.5 mL (0.007 mol) of freshly distilled diphenyl chlorophosphate in 3 mL of pyridine was added with a syringe. The resulting reaction mixture was stirred 15 min and kept at 5 °C overnight. Ice water (5 mL) was added and the solution stirred. After 30 min it was poured onto 60 g of ice and extracted with $CHCl_3$ (3 × 60 mL). The combined extracts were washed, first with dilute HCl and then with H_2O. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was streaked on preparative TLC plates (20 × 20 cm × 1.5 mm, Al_2O_3) and developed with hexane. The bands remaining at the origin were removed with ether and streaked on additional alumina plates. These were developed with benzene to give a single band, R_f 0.5. Elution with ether gave 1.0 g (58%) of pure **15**: mp 34–35 °C; IR (film) 3080, 1600, 1480, 1470, 1280, 1185, 1030, 760, 680 cm^{-1}. Anal. ($C_{33}H_{51}PO_4$) C, H.

1-Hydroxymethyl-3-pentadecylcyclopentane Dihydrogen Phosphate (16). Diphenyl phosphate ester **15** (0.5 g, 0.0009 mol) was dissolved in 25 mL of absolute ethanol and reduced over 400 mg of PtO_2 at 55 psig for 60 h. Filtration and solvent evaporation left a quantitative yield of **16** as a low-melting wax: IR (film) 1465, 1170, 1010 cm^{-1}. Anal. ($C_{21}H_{43}PO_4$) C, H.

1-Hydroxymethyl-3-pentadecylcyclopentane Monosodium Phosphate (17). To a solution of **16** (0.36 g, 0.0009 mol) in 15 mL of H_2O was added freshly washed Dowex 50 W-X8 (3 mL, wet). The resulting mixture was stirred 1 h. Filtration and lyophilization gave a quantitative yield of the monosodium salt **17**: mp 57–61 °C. Anal. ($C_{21}H_{42}PO_4Na$) C, H.

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References and Notes

(1) W. Vogt, *Arch. Exp. Pathol. Pharmakol.*, **206**, 1 (1949).
(2) W. Vogt, *Biochem. Pharmacol.*, **12**, 415 (1963).
(3) R. D. Bunag and E. J. Walaszek, *Eur. J. Pharmacol.*, **23**, 191 (1973).
(4) R. A. Wiley, D. D. Sumner, and E. J. Walaszek, *Lipids*, **5**, 803 (1970).
(5) N. H. Andersen, *Arch. Intern. Med.*, **133**, 30 (1974).
(6) E. W. Horton in "Recent Advances in Pharmacology", 4th ed, J. M. Robson and R. S. Stacey, Ed., Churchill, Ltd., London, 1968, pp 185–212.
(7) "Fundamentals of Biochemical Pharmacology", Z. M. Bacq, Ed., Pergamon Press, New York, N.Y., 1971, p 334.
(8) J. G. Turcotte, C. Yu, H. Lee, S. K. Pavanaram, S. Sen, and R. S. Smeby, *J. Med. Chem.*, **18**, 1184 (1975).
(9) G. Buchi and A. Wuest, *J. Org. Chem.*, **31**, 977 (1966).
(10) E. J. Corey, *J. Am. Chem. Soc.*, **91**, 4218 (1969).
(11) P. Brigl and H. Mueller, *Ber.*, **72**, 2121 (1939).
(12) M. Hanif, J. Rehman, M. Ahmad, T. Ahmad, S. A. Khan, and M. K. Bhatty, *Pap. J. Sci. Ind. Res.*, **11**, 258 (1968).
(13) V. Prey, *Ber.*, **74**, 1219 (1941).
(14) E. Katchalski, *Methods Enzymol.*, **3**, 540 (1957).
(15) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **82**, 4307 (1960).
(16) R. D. Bunag and E. J. Walaszek, personal communication.
(17) G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.*, **69**, 2246 (1947).

Preparation and Biological Actions of Some Symmetrically N,N-Disubstituted Dopamines

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The title compounds have been synthesized and evaluated for emetic effects in the dog, actions on the cardioaccelerator nerve in the cat, pecking in pigeons, and for behavioral effects following both peripheral and direct intracerebral injection into the nucleus accumbens and caudate-putamen of the rat. Generally, in the series studied, the *N,N*-diethyl and *N,N*-di-*n*-propyl congeners of dopamine displayed notably high degrees of activity. However, the test compounds exerted differing effects on peripheral and central dopamine receptors and in the area postrema. Differentiations of the activities of the different homologues within the brain were also shown.

Prior communications have described dopaminergic[1,2] and α-adrenergic effects[3] of *N,N*-dimethyldopamine (**1**). Ginos et al.[4] have demonstrated dopaminergic activities in a series of unsymmetrically N,N-disubstituted dopamines, but they found *N,N*-dimethyldopamine to be inert as a dopaminergic agonist in their assay systems. The dopaminergic activity of 2-amino-5,6-dihydroxytetralin and aporphine derivatives is modified qualitatively and quantitatively by N-alkylation, where ethyl or *n*-propyl substitution confers the maximal increase in activity.[5-8]

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