5.62 (s, 1 H), 4.07 (s, 1 H); IR ($CHCl_3$) 3500–2500 (OH), 1720 (CO) cm^{-1}; MS, m/e (relative intensity) 277 (8.13, $M^+ - 1$), 275 (28.87, $M^+ - 1$), 201 (45.48, $M^+ - OCH_2CO_2H$). Anal. ($C_{15}H_{13}O_3Cl$) C, H, Cl.

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Registry No. 1, 38206-97-2; [1] (phenol), 2432-14-6; 2, 588-22-7; 3, 575-89-3; 3 (phenol), 88-06-2; 4, 588-20-5; 4 (phenol), 59-50-7; 5, 1878-91-7; 5 (phenol), 106-41-2; 6, 94-75-7; 7, 122-88-3; 8, 1878-94-0; 8 (phenol), 540-38-5; 9, 74592-71-5; 9 (phenol), 697-82-5; 10, 5406-14-4; 10 (phenol), 108-68-9; 11, 15267-49-9; 11 (phenol), 1073-72-9; 12, 19545-95-0; 12 (phenol), 88-04-0; 13, 7356-41-4; 13 (phenol), 95-87-4; 14, 25181-66-2; 14 (phenol), 6627-55-0; 15, 19728-23-5; 15 (phenol), 500-99-2; 16, 13335-73-4; 16 (phenol), 95-65-8; 17, 3405-88-7; 17 (thiophenol), 106-54-7; 18, 90296-05-2; 18 (thiophenol), 771-62-0; 19, 2976-74-1; 20, 575-90-6; 20 (phenol), 87-65-0; 21, 3406-76-6; 21 (thiophenol), 106-53-6; 22, 90296-06-3; 23, 84998-84-5; 23 (phenol), 118-79-6; 24, 882-09-7; 24 (phenol), 106-48-9; 25, 21248-54-4; 25 (thiophenol), 3773-14-6; 26, 90296-07-4; 26 (phenol), 5150-42-5; 27, 122-59-8; 27 (phenol), 108-95-2; 28, 1798-04-5; 28 (phenol), 98-54-4; 29, 2298-36-4; 29 (phenol), 123-30-8; 30, 90296-08-5; 30 (phenol), 7463-51-6; 31, 65876-10-0; 31 (phenol), 642-71-7; 32, 1798-11-4; 32 (phenol), 100-02-7; 33, 82513-28-8; 33 (alcohol), 1805-32-9; 34, 90296-09-6; 34 (alcohol), 1777-82-8; 35, 90296-10-9; 35 (alcohol), 60211-57-6; 36, 35513-00-9; 36 (alcohol), 873-76-7; 37, 90296-11-0; 38, 90296-12-1; 38 (alcohol), 90296-27-8; 39, 90296-13-2; 39 (alcohol), 6966-10-5; 40, 82499-60-3; 40 (alcohol), 873-75-6; 41, 90296-14-3; 41 (alcohol), 16308-92-2; 42, 82499-61-4; 43, 90296-15-4; 43 (alcohol), 18282-51-4; 44, 90296-16-5; 44 (alcohol), 2215-78-3; 45, 90296-17-6; 45 (alcohol), 4685-50-1; 46, 90296-18-7; 46 (alcohol), 4170-90-5; 47, 17742-50-6; 47 (thiol), 19552-10-4; 48, 51934-40-8; 48 (alcohol), 589-18-4; 49, 90296-19-8; 49 (alcohol), 27129-87-9; 50, 90296-20-1; 50 (thiol), 90296-28-9; 51, 88920-24-5; 51 (alcohol), 105-13-5; 52, 90296-21-2; 52a, 90296-22-3; 53, 1878-58-6; 53 (phenol), 1470-94-6; 54, 25812-30-0; 55, 90296-23-4; 55 (phenol), 20279-16-7; 56, 6331-61-9; 57, 90296-24-5; 57 (phenol), 2443-58-5; 58, 52160-84-6; 58a, 90296-25-6; 59, 3709-21-5; 59a, 6628-68-8; 60, 90296-26-7; 60 (alcohol), 119-56-2; 61, 41859-67-0; diethyl malonate, 105-53-3; 2-bromoethyl *p*-bromophenyl ether, 18800-30-1; benzyl salicylate, 118-58-1; (2-bromoethyl)benzene, 103-63-9.

[(*E*)-1-[^{123}I]Iodo-1-penten-5-yl]triphenylphosphonium Iodide: Convenient Preparation of a Potentially Useful Myocardial Perfusion Agent

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A rapid iodination method has been developed for the synthesis of the new ^{123}I-labeled phosphonium cation [(*E*)-1-iodo-1-penten-5-yl]triphenylphosphonium iodide by I^+ treatment of the corresponding *trans*-vinylboronic acid. This new model myocardial perfusion agent is obtained after purification in 25–50% yield in <1 h. High myocardial uptake (5 min, 2.38% dose/g) with prolonged retention (3 h, 2.21% dose/g) was observed in rats. In addition, heart/blood ratios were high and continued to increase over a 1-day period (5 min, 17:1; 60 min, 23:1; 3 h, 27:1; 1 day, 158:1). In rats, the liver uptake was moderate (5 min, 1.40% dose/g; 60 min; 0.25% dose/g). Excellent myocardial images were obtained in a dog.

Thallium-201, which is the most widely used cationic radiopharmaceutical for the evaluation of coronary artery disease (CAD) and is a powerful tool for the differentiation of ischemia from irreversible myocardial damage,[1] has the disadvantages of inefficient detection of its low-energy X-rays and redistribution during the imaging period. A myocardial perfusion agent labeled with an isotope having more attractive radionuclidic properties would be an advantage. In addition, nuclear medicine techniques could be of even greater benefit to the cardiologist if agents were available for measuring early indices of myocardial disease as well as regional perfusion.

Several radioiodinated organic cations, including ammonium cations such as *m*-[^{125}I]iodobenzyldimethylammonium,[2,3] [^{131}I]iodomethyltrimethylammonium,[4] and 4-[^{125}I]iodophenyltrimethylammonium,[5] have been used for myocardial imaging in experimental animals. Although encouraging results were observed in these preliminary animal studies, these agents have evidently not been pursued further, and no human studies have been reported.

More recently, interesting in vitro physiological properties of organic phosphonium cations have indicated the potential use of radiolabeled cations for in vivo evaluation of heart disease, which now takes on a new importance. The in vitro cell uptake of a model agent, tetraphenylphosphonium bromide (TPP), has been shown to correlate with the resting transmembrane potential in neuroblastoma-glioma hybrid cells,[6] mouse neuroblastoma,[7] guinea pig brain synaptosomes,[8] and, more importantly, in cardiac membrane vesicles.[9] Woo and colleagues have demon-

(1) Strauss, H. W.; Pitt, B. *Semin. Nucl. Med.* **1977**, *7*, 49.
(2) Counsell, R. E.; Yu, T.; Ranade, V. V.; Buswink, A. A.; Carr, E. A., Jr.; Carroll, M. *J. Nucl. Med.* **1974**, *15*, 991.
(3) Korn, N.; Buswink, A.; Yu, T.; Carr, E. A., Jr.; Carroll, M.; Counsell, R. E. *J. Nucl. Med.* **1977**, *18*, 87.
(4) Huang, C. C.; Friedman, A. M.; Rayudu, G. V. S.; Clark, P.; Fordham, E. W. *J. Nucl. Med.* **1980**, *21*, 679.
(5) Burns, H. D.; Marzilli, L. G.; Dannals, R. F. *J. Nucl. Med.* **1980**, *21*, 875.
(6) Lichtshtein, D.; Kaback, H. R.; Blume, A. J. *Proc. Natl. Acad. Sci.* **1979**, *76*, 650.
(7) Deutsch, C.; Erecinska, M.; Werrlein, R.; Silver, I. A. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2145.
(8) Ramos, S.; Grollman, E. F.; Lazo, P. S.; Dyer, S. A.; Habig, W. H.; Hardegree, M. C.; Kaback, H. R.; Kohn, L. D. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4783.
(9) Reeves, J. P.; Sutko, J. L. *Science* **1980**, *208*, 1461.

0022-2623/84/1827-0978$01.50/0

Table I. Distribution of Radioactivity in Female Rat Tissues after Intravenous Administration of [(*E*)-1-[^{123}I]Iodo-1-penten-5-yl]triphenylphosphonium Iodide (4)[a]

time after injection	mean % dose/organ (range)					
	heart	blood	liver	lungs	kidneys	thyroid
5 min	1.49 (1.34–1.66)	1.58 (1.36–1.75)	11.87 (8.06–15.31)	0.89 (0.85–0.98)	13.72 (11.95–17.10)	0.21 (0.18–0.27)
30 min	1.60 (1.51–1.69)	1.59 (1.44–1.84)	5.59 (4.95–5.99)	0.79 (0.73–0.88)	13.11 (10.99–14.91)	0.27 (0.25–0.31)
60 min	1.83 (1.49–2.62)	1.14 (0.92–1.31)	2.64 (1.44–2.35)	0.75 (0.64–0.88)	7.95 (6.15–8.98)	0.28 (0.31–0.36)
3 h	1.54 (1.42–1.74)	0.96 (0.76–1.18)	0.74 (0.69–0.89)	0.61 (0.48–0.85)	4.38 (3.00–5.78)	0.78 (0.58–1.02)
1 day	1.18 (1.08–1.30)	0.20 (0.17–0.24)	0.18 (0.15–0.21)	0.19 (0.17–0.24)	0.79 (0.63–1.06)	1.53 (1.14–2.49)
3 days	0.64 (0.49–0.83)	0.093 (0.07–0.116)	0.13 (0.10–0.22)	0.102 (0.096–0.162)	0.22 (0.18–0.28)	1.45 (1.15–1.95)

[a] Values represent the mean and range for five rats. Radioactive contents of the following tissues were also analyzed: brain, ovaries, spleen, fat, muscle, and large and small intestines.

Table II. Distribution of Radioactivity in Female Rat Tissues after Intravenous Administration of [(*E*)-1-[^{123}I]Iodo-1-penten-5-yl]triphenylphosphonium Iodide (4)[a]

time after injection	mean % dose/g (range)						mean heart/blood
	heart	blood	liver	lungs	kidneys	thyroid	
5 min	2.38 (1.90–3.36)	0.14 (0.11–0.16)	1.40 (0.91–2.04)	0.75 (0.69–0.82)	7.08 (3.99–9.45)	12.7 (10.1–16.1)	17:1
30 min	2.31 (2.09–2.52)	0.15 (0.13–0.18)	0.75 (0.63–0.85)	0.64 (0.57–0.74)	8.91 (6.99–10.4)	16.7 (14.8–19.6)	15:1
60 min	2.59 (2.16–3.49)	0.11 (0.08–0.12)	0.25 (0.21–0.30)	0.65 (0.58–0.78)	5.06 (3.67–6.04)	17.6 (10.0–23.5)	23:1
3 h	2.21 (1.92–2.52)	0.08 (0.07–0.10)	0.09 (0.08–0.10)	0.49 (0.39–0.67)	2.75 (2.11–3.42)	45.8 (35.9–62.6)	27:1
1 day	1.58 (1.39–1.84)	0.01 (0.01–0.02)	0.02 (0.02–0.03)	0.17 (0.14–0.19)	0.46 (0.36–0.59)	116 (64–180)	158:1
3 days	1.00 (0.74–1.42)	0.009 (0.008–0.01)	0.019 (0.01–0.193)	0.91 (0.07–0.14)	0.15 (0.11–0.20)	98 (70–132)	111:1

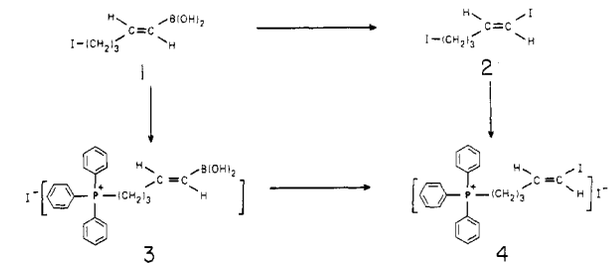
[a] Percent dose per gram values are the mean and range for five rats. Radioactive contents of the following tissues were also analyzed: brain, ovaries, spleen, fat, muscle, and large and small intestines.

strated pronounced and prolonged [^{3}H]TPP myocardial uptake in vivo with very high heart/blood ratios in rats. Excellent myocardial images in a dog have been obtained with a similar agent, the [^{123}I]iodobenzyldimethylphenylammonium cation.[10] Measurement of alterations in the resting myocardial cell potential in relation to the early stages of heart disease with or without accompanying changes in regional perfusion could be very important. The goals of the present studies were to develop a rapid, high-yield synthesis of an ^{123}I-labeled phosphonium cation with the iodine-123 stabilized by attachment as a vinyl iodide[11] and to evaluate this new agent in experimental animals. The results described here represent the initial report of a project directed at developing a variety of structurally modified phosphonium and related cations labeled with γ-emitting radionuclides for evaluation as perfusion agents.

Results

Chemistry. Trivalent phosphorus compounds, such as triphenylphosphine (Ph_3P), are highly nucleophilic and readily displace halogens attached to saturated carbon atoms (R–X) to give the "quaternary" phosphonium cations [(Ph_3P^+–R)X^-]. Vinyl iodides are readily prepared from the corresponding vinyl boronic acids by using I_2[12,13] or ICl.[14,15] An improved method for the conversion of vinyl boronic acids to *trans*-vinyl iodides involves the in situ oxidation of iodide (I^-) to iodonium (I^+) with chloramine-T.[16] We have recently reported[11] the preparation of (*E*)-1,5-diiodo-1-pentene (**2**) from (*E*)-1-borono-5-iodo-1-pentene (**1**) and several other (*E*)-vinyl iodides by this technique.[17] In **1**, the vinylboronic acid group can be iodinated prior to displacement of the primary iodide during fabrication of agents, such as long-chain tellurium fatty acids.[11,17] Alternately, the vinylboronic acid can be attached to a desired organic moiety by displacement of the primary iodide prior to conversion to the (*E*)-vinyl iodide, such as recently reported for boronomalonic esters.[18] These two routes were explored for the synthesis of the model phosphonium cation (*E*)-triphenyl(1-iodo-1-penten-5-yl)phosphonium iodide (**4**), as shown in Scheme I.

Scheme I



The first route (**1** → **2** → **4**) involved the condensation of (*E*)-1,5-diiodo-1-pentene (**2**) with Ph_3P in boiling acetone. Under these conditions, the terminal vinyl iodide is stable.[11,17,18] Nucleophilic attack by Ph_3P displaces only the primary iodide, which becomes the anion associated with the cation product **4**. The condensation of **1** and Ph_3P was also studied for time periods ranging from 30 min to 2 days, which resulted in the formation of **4** in yields ranging from 5 (30 min) to 70% (2 days).

Because of the long reaction period required for the synthesis of **4** by the **1** → **2** → **4** sequence, we sought to develop an alternate procedure for **4** labeled with iodine-123 (13.6-h half-life). The pivotal substrate, (*E*)-triphenyl(1-borono-1-penten-5-yl)phosphonium iodide (**3**),

(10) Woo, D. V. *Circulation* **1982**, *66*(4), II-124 (abstract).
(11) Knapp, F. F., Jr.; Goodman, M. M.; Callahan, A. P.; Ferren, L. A.; Kabalka, G. W.; Sastry, K. A. R. *J. Med. Chem.* **1983**, *26*, 1293.
(12) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem.* **1972**, *94*, 7827.
(13) Brown, H. C.; Hamaoka, T.; Ravinkran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786.
(14) Kabalka, G. W.; Gooch, E. E.; Sastry, K. A. R. *J. Nucl. Med.* **1981**, *22*, 908.
(15) Kabalka, G. W.; Gooch, E. E.; Hsu, H. C. *Synth. Commun.* **1981**, *11*, 247.
(16) Kabalka, G. W.; Sastry, K. A. R.; Somayaji, V. *Heterocycles* **1982**, *18*, 157.
(17) Knapp, F. F., Jr.; Srivastava, P. C.; Callahan, A. P.; Cunningham, E. B.; Kabalka, G. W.; Sastry, K. A. R. *J. Med. Chem.* **1984**, *27*, 57.
(18) Srivastava, P. C.; Callahan, A. P.; Cunningham, E. B.; Knapp, F. F., Jr. *J. Med. Chem.* **1983**, *26*, 742.

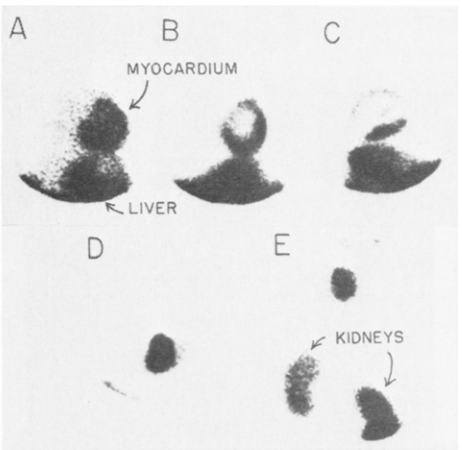


Figure 1. Sequential gamma camera images (500 k counts each) of a male dog after intravenous administration of 850 μCi of [(*E*)-1-[^{123}I]iodo-1-penten-5-yl]triphenylphosphonium iodide (**4**): (A) left anterior oblique, 0–2 min; (B) left anterior oblique, 2–11 min; (C) right anterior oblique, 12–24 min; (D) anterior, 25–38 min; and (E) anterior, 39–43 min.

was prepared by condensation of **1** with Ph_3P. We found that reaction of **3** with I^- and chloramine-T under the usual iodination conditions did not decompose the phosphonium salt. Reaction of **3** with NaI and chloramine-T, followed by treatment with sodium metabisulfite, provided **4** in 49% yield. The product was then treated with excess NaI to ensure the complete incorporation of iodide as the anion in the phosphonium product **4**. The phosphonium compound **4** obtained by this procedure was identical (mp, TLC, NMR, IR, and elemental analysis) to a sample of **4** obtained by the direct condensation of diiodopentene **2** with Ph_3P as described earlier.

Biological Studies. Iodine-125 labeled **4** was prepared in the same manner by reaction of the boronic acid substrate **3** with Na^{125}I and chloramine-T. Evaluation in rats (Tables I and II) demonstrated rapid myocardial extraction, high heart/blood ratios, and significant retention of radioactivity over a 1 day period. An important feature of this new agent is the relatively low liver uptake observed in these studies with subsequent high heart/liver ratios.

The high heart/blood ratios observed in the rat tissue distribution studies suggested that the myocardium could be clearly delineated from blood pooled within the cardiac chambers, and this was confirmed by imaging studies in a dog with the ^{123}I-labeled agent (Figure 1). The myocardium was clearly imaged with little interference from blood pool or lung activity for the initial 11-min period after administration (Figure 1A and 1C). In the third sequential image (Figure 1C), only the inferior wall of the myocardium is clearly seen with increased activity in the hepatic region. The heterogeneous distribution of activity in the myocardium in these later images is presumably due to the amount of myocardial muscle tangentially projected toward the camera.[19] In the fourth image (Figure 1D), the large focal mass clearly observed in the liver area is in the expected region of the gallbladder, although gallbladder uptake was not confirmed by laparotomy in this study. In the final image obtained in this sequence (Figure 1E), the camera was positioned for an anterior view to include the kidneys. In addition to the apparent high uptake in the gallbladder and kidneys, low uptake was also observed in the inferior region of the myocardium. Although a region of interest (ROI) analysis was not possible with the camera used in these studies, a steady washout of activity from the myocardium was observed in this dog study, which was in contrast to the prolonged myocardial retention observed in the rat studies.

Discussion

These results demonstrate that the new organic cation (**4**) can be readily iodinated by using the boronic acid substrate (**3**) and that this agent shows high myocardial uptake in rats and dogs. Because of the potential importance of correlating the presence and extent of heart disease with aberrations in myocardial cell membrane potential, these agents should be further explored. Our studies have also shown for the first time that phosphonium cations functionalized on the organic ligand with a vinylboronic acid can be readily converted to the corresponding vinyl iodide substituted phosphonium cations. This is a major advantage, since radiolabeling can be conducted in the final step of the synthesis, as clearly demonstrated by the conversion of the boronic acid **3** to the radioiodinated cation **4**.

Additional studies that will be performed with this new agent include a determination of the myocardial distribution properties in relation to regional perfusion in comparison to radiolabeled microspheres under various flow conditions. The structural versatility of cations such as **4** offers a unique opportunity to study in detail the effects of cation and ligand characteristics on the biological properties of these interesting molecules. In the present studies the phosphonium cation **4** shows high myocardial uptake in rats and in dogs. Since the cation character and lipid solubility are responsible for the high myocardial uptake and since a balance between charge, molecular size, and polar and nonpolar characteristics of the molecule are required for biliary secretion,[20] modification of this type of phosphonium cation could potentially increase myocardial uptake and retention and minimize hepatobiliary secretion.

Experimental Section

Materials. Reagent grade triphenylphosphine (Ph_3P, 99%, mp 79–81 °C) was obtained commercially (Aldrich Chemical Co.), (*E*)-(5-iodo-1-penten-1-yl)boronic acid (**1**) and (*E*)-1,5-diiodo-1-pentene (**2**) were synthesized as reported earlier.[11] All other chemicals and solvents were analytical grade and were used without further purification. Iodine-125 was obtained commercially (New England Nuclear), and iodine-123 was obtained in the generator/iodination ampule kit[21] from the Brookhaven National Laboratory. The melting points (mp) were determined in capillary tubes on a Buchi SP apparatus and are uncorrected. Thin-layer chromatographic analyses (TLC) were performed with 250-μm-thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). Spots on the TLC plates were detected by observation under short-wave UV light or after exposure to iodine vapor. The proton nuclear magnetic resonance spectra (NMR) were obtained at 60 MHz with a Varian 360-L instrument, and the resonances are reported downfield (δ) from the internal tetramethylsilane standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Animal Tissue Distribution Experiments. The distribution of radioactivity was determined in tissues of 10–12 week old female Fischer 344 rats (170–200 g). The animals were allowed food and water ad libitum prior to and during the course of the experiment. The radioiodinated compounds were dissolved in dimethyl sulfoxide and diluted with saline to a final concentration of 1%

(19) Nishiyama, H.; Adolph, R. J.; Deutsch, E.; Sodd, V. J.; Libson, K.; Gerson, M. C.; Saenger, E. L.; Lukes, S. J.; Gabel, M.; Vanderheyden, J. L.; Fortman, D. L. *J. Nucl. Med.* **1982**, *23*, 1102.

(20) Chervu, L. R.; Nunn, A. D.; Loberg, M. D. *Semin. Nucl. Med.* **1982**, *12*, 5.

(21) Richards, P.; Prach, T.; Srivastava, S. C.; Meinken, G. E. *J. Radioanal. Chem.* **1981**, *65*, 47.

Me_2SO. The solution was filtered through a 0.22-μm Millipore filter, and the sterilized solution was injected via a lateral tail vein into the ether-anesthetized animals. The animals were then anesthetized with ether and killed by cervical fracture at various time intervals. Blood samples were obtained immediately from the beating hearts by cardiac puncture. Organs were excised, rinsed with saline solution, blotted dry, and placed in tared vials and weighed. The radioactive contents of the tissues were determined with an auto-gamma counter. Samples of the injected radioactive solution were also assayed as standards to calculate the percent injected dose per gram of tissue values. The thyroid glands were not weighed directly, but the weights were calculated in the usual manner[22] by multiplying the animal weight by 7.5 mg/100 g. Imaging studies were performed in a male dog (30 kg) with a Phogamma camera equipped with a medium energy collimator. The dog was injected intravenously with a 1% Me_2SO–saline solution (5 mL) of ^{123}I-labeled **4**. Counts (300–500 k) were accumulated at time intervals ranging from 2 to 43 min to obtain a series of sequential images (Figure 1).

(*E*)-Triphenyl(1-borono-1-penten-5-yl)phosphonium Iodide (3). A solution of (*E*)-(5-iodo-1-penten-1-yl)boronic acid (**1**; 1.1 g, 5 mmol) and triphenylphosphine (1.3 g, 5 mmol) in acetone (5 mL) was refluxed for 16 h. The (*E*)-triphenyl(1-borono-1-penten-5-yl)phosphonium iodide (**3**) separated from the reaction solution as a crystalline precipitate and was collected by filtration and washed with acetone to give 1.43 g (57%) of pure **3**: mp 185–187 °C; NMR (Me_2SO-d_6) δ 7.3–8.4 (m, 15 H, triphenyl), 5.3 and 6.3 (2 d, 1 H each, vinyl), 1.68, 2.3, and 3.5 [3 m, 2 H each, $(CH_2)_3$]. Anal. Calcd for $C_{23}H_{25}O_2BIP$: C, 55.01; H, 5.02; B, 2.15; I, 25.27; P, 6.17. Found: C, 54.95, H, 5.03; B, 2.38; I, 25.37; P, 5.96.

(*E*)-Triphenyl(1-iodo-1-penten-5-yl)phosphonium Iodide (4). Method A. A solution of chloramine-T (450 mg, 1.6 mmol) in 15 mL of 50% aqueous tetrahydrofuran (THF) was added to a stirred solution of (**3**; 502 mg, 1 mmol) and NaI (150 mg, 1 mmol) in 50% aqueous THF (15 mL) protected from light. The solution was stirred at room temperature for 30 min in the dark, diluted with $CHCl_3$, and washed with H_2O. The $CHCl_3$ layer was separated and washed thoroughly with 10% aqueous $Na_2S_2O_5$, followed by H_2O. The $CHCl_3$ portion was dried (Na_2SO_4), and the solvent was evaporated under vacuum. The syrupy residue was treated with acetone (10 mL) containing NaI (150 mg, 1 mmol). A crystalline product separated, which was collected by filtration, washed with acetone, and recrystallized from $CHCl_3$–petroleum ether to yield 288 mg (49%) of **4**: mp 199–200 °C; NMR ($CDCl_3$) 7.40–8.26 (m, 15 H, triphenyl), 6.13–6.51 (m, 2 H, vinyl), 3.38–4.09 (m, 2 H, Ph_3PCH_2), 2.7–2.79 (m, 2 H, $CH_2CH{=}CHI$), 1.29–2.24 (m, 2 H $CH_2CH_2CH_2$). Anal. Calcd for $C_{23}H_{23}I_2P$: C, 47.44; H, 4.11; P, 5.10. Found: C, 47.28; H, 3.97; P, 5.30.

Method B. A solution of (*E*)-1,5-diiodo-1-pentene (**2**; 644 mg, 2 mmol) and triphenylphosphine (525 mg, 2 mmol) in acetone (4 mL) was refluxed for 18 h. The crystalline (*E*)-triphenyl-1-iodo-1-penten-5-yl)phosphonium iodide (**4**) was collected by filtration and washed with acetone to give 779 mg (67%) of pure **4**, mp 199–200 °C. Compound **4** obtained by method B was identical (mp, TLC, and NMR) with a sample of **4** prepared by method A.

(*E*)-Triphenyl(1-[^{123}I]iodo-1-penten-5-yl)phosphonium Iodide ([^{123}I]4). A solution of (*E*)-triphenyl(1-borono-1-penten-5-yl)phosphonium iodide (**3**; 12.5 mg, 25 μmol) and $Na^{123}I$ (6.0 mCi, 3.8 mg, 25 μmol) in 50% aqueous THF (3 mL) was treated with chloramine-T (7 mg, 25 μmol) for 30 min in the dark. The solution was partitioned between $CHCl_3$ (15 mL) and H_2O (15 mL). The $CHCl_3$ layer was washed with 10% aqueous $Na_2S_2O_5$ followed by H_2O, dried (Na_2SO_4), and evaporated under vacuum. The syrupy residue was treated with acetone (5 mL) containing NaI (150 mg), and the acetone was evaporated. The residue was partitioned between H_2O (5 mL) and $CHCl_3$ (5 mL). The $CHCl_3$ portion was evaporated and purified by silica gel column chromatography by elution with $CHCl_3$, followed by 30% acetone in $CHCl_3$, to yield 1.2 mCi (~25%) of [^{123}I]4 with a specific activity of 194 mCi/mmol. The [^{123}I]4 cochromatographed with a cold authentic sample of **4**. Iodine-125-labeled **4** was similarly prepared in 40% yield with a specific activity of 1180 mCi/mmol.

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(22) Remington, R. E.; Remington, I. W.; Welsch, S. S. *Anat. Rec.* **1937**, *67*, 367.

Isomeric *N*-Methyl-7-deazaguanines: Synthesis, Structural Assignment, and Inhibitory Activity on Xanthine Oxidase[1]

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The *N*-methyl isomers of 2-amino-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one[1] (**2a**) have been synthesized regiospecifically and their structures assigned. The 3-methyl compound **3** was obtained by alkylation of the parent chromophore **2a** with dimethyl sulfate, and the 1-methyl isomer **5b** was obtained by condensation of ethyl 2-cyano-4,4-diethoxybutyrate with *N*-methylguanidine and subsequent cyclization. Methylation of 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**7b**), however, with methyl iodide in the presence of 50% NaOH, by phase-transfer techniques, followed by the replacement of halide by hydroxyl, yielded the 7-methyl compound **2b**. The *N*-methyl isomers of **2a** were all found to be inhibitors of xanthine oxidase from cow's milk. While the 3-methyl isomer **3** exhibits a K_i of 40 μM, the 7- and 1-isomers show K_i values of 4.5 and 3 μM, respectively.

Syntheses of methylated nucleobases are undertaken in our laboratory in order to study biological and pharmacological activity. Furthermore, they help to evaluate routes for the regioselective synthesis of methylated derivatives of naturally occuring nucleosides, such as 7-deazaguanosine (**1a**)[2] and the recently discovered cadeguomycin (**1b**).[3] *N*-Methyl derivatives of guanine can serve as potent inhibitors and regiospecific probes of nu-

(1) The numbering for 7-deazapurines and pyrrolo[2,3-*d*]pyrimidines is different; only the latter are numbered in agreement with the IUPAC rules.

(2) Seela, F.; Hasselmann, D. *Chem. Ber.* **1981**, *114*, 3395.

(3) Wu, R. T.; Okabe, T.; Namikoshi, M.; Okuda, S.; Nishimura, T.; Tanaka, N. *J. Antibiotics* **1982**, *35*, 279.

0022-2623/84/1827-0981$01.50/0