eV) resulted in a peak at 180–185 °C, which gave a fragmentation pattern consistent with **10**: *m/e* (relative intensity) 241 ([M - HCN]$^+$, 5%), 158 (100%), 143 (52%), 129 (80%), 115 (55%), 91 (59%), 83 (58%).

For control samples incubated in the absence of NADP$^+$, less than 0.5% of the initial radioactivity was found in the organic base containing fraction following Sep-Pak chromatography and acid–base partitioning. This compared with 18% for the incubates with NADP$^+$. With subsequent thin-layer chromatography, no zone of radioactivity was detectable. These results confirm that formation of the ^{14}C-labeled organic material is dependent on enzymatic processes utilizing NADPH.

Confirmation of the structure of this product was approached by synthesis of aminonitrile **10**. Following the descriptions given by Leonard and Cook,[8] phencyclidine (3.04 g, 12.5 mmol) was oxidized to the corresponding iminium ion **9** by the addition of the tertiary amine to a solution of mercuric acetate (15.9 g, 50 mmol) in 65 mL of 5% acetic acid which previously had been warmed to 90 °C. After stirring for 2 h at this temperature, the cooled reaction mixture was filtered, and the filtrate was treated with H_2S to precipitate any mercury ions remaining in solution. The filtrate was treated with concentrated $KHCO_3$ until the pH reached 5.5, and then NaCN (3.1 g, 63 mmol) was added. The resulting reaction mixture was stirred overnight at room temperature, and the white precipitate which had separated (2.1 g, 62%) was collected and recrystallized from 2-propanol to yield pure 1-(1-phenylcyclohexyl)-2-cyanopiperidine: mp 85–86 °C; 360-MHz NMR ($CDCl_3$) 2.45–3.45 (m, ring CH_2 protons, 16 H), 3.68 (N-CH, t, J = 7 Hz, 1 H), 4.33 (N-CH, m, 1 H), 5.04 (N-CHCN, m, 1 H), 7.20 (s, Ar H, 5 H) ppm; CIMS (130 °C, isobutane/1.0 torr) *m/e* 242 (MH$^+$ - HCN); GC/EIMS (conditions same as above) *m/e* (relative intensity) 241 ([M - HCN]$^+$, 5%), 158 (100%), 143 (56), 129 (82%), 115 (56%), 91 (54%), 83 (55%); IR (m.o. mull) 2218 (CN) cm^{-1}. Anal. ($C_{18}H_{24}N_2$) C, H, N.

Synthetic **10** cochromatographed with the metabolically derived radioactive adduct of phencyclidine. Isotope dilution analysis (recrystallization to constant specific activity) further confirmed the common identity of the metabolically derived product and synthetic **10**.

Identification of the cyano adduct formed from the coincubation of phencyclidine and NaCN provides indirect evidence for the metabolic formation of iminium ion **9**. We have examined the metabolically dependent covalent binding of 0.1 mM [^{3}H]phencyclidine to rabbit liver microsomal protein as previously described.[4] Under the above incubation conditions, 6 to 8% of the radiolabeled substrate was found covalently bound to protein after 30 min. In the presence of 0.1 mM NaCN, this binding was inhibited by 75%. Concentrations of CN$^-$ as high as 1 mM did not significantly inhibit phencyclidine metabolism by hepatic microsomes. The relative insensitivity of cytochrome P-450 mediated reactions to CN$^-$ has been reported previously.[6] These results lead us to suggest the iminium ion **9** may be undergoing covalent binding to microsomal macromolecules.

Additional studies are in progress to more fully characterize the properties of the iminium ion **9**. Preliminary estimates indicate that 15 to 20% of the initial substrate is trapped as **10**, suggesting that α-C-hydroxylation is a major pathway for phencyclidine metabolism.

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Prostaglandins and Congeners. 29.[1] (16*RS*)-(±)-15-Deoxy-16-hydroxy-16-vinylprostaglandin E_2, an Orally and Transdermally Active Hypotensive Agent of Prolonged Duration

Sir:

The hypotensive action of the 9-ketoprostaglandins has been recognized from the early days of prostaglandin research.[2] However, inasmuch as this effect was no more than transient and obtained only on intravenous administration, it lacked practical application and remained a matter of laboratory interest, albeit an interest enhanced by its favorable mechanism of action and the possibility that clinical hypertension indeed might be a reflection, at least in part, of prostaglandin imbalance.[3] The prospect for the practical exploitation of this property by the development of a prostaglandin analogue with a prolonged hypotensive effect, administrable by a route satisfactory for extended use, and free of significant side-effects has continued as an elusive goal, which to our knowledge has not even been closely approached.[4] In this paper we wish to report substantial progress toward the achievement of this end.

For some time we have been investigating the synthesis and biology of the 15-deoxy-16-hydroxyprostaglandins and have reported the interesting gastric acid secretion inhibitory properties and bronchodilator properties of certain members of this series.[5] In the course of our further exploration of this important prostaglandin class, we had occasion to prepare the 16-vinyl member, which in addition to blocking metabolic inactivation of the transpositioned 16-hydroxy group would also restore allylic character to this function. This compound was prepared by the conjugate addition procedure as illustrated in Scheme I.

The β-chain (C_{13}–C_{20}) precursor **5** was obtained without difficulty from commercial 1-hepten-3-ol (**1**) via oxidation with pyridinium chlorochromate[6] to 1-hepten-3-one (**2**)

(8) N. Leonard and A. Cook, *J. Am. Chem. Soc.*, **81**, 5627 (1959).

(1) For the previous paper in this series, see Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.
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(4) For earlier attempts, see Shimada, Y.; Okamoto, J.; Inoue, T.; Ohtsuka, Y.; Morii, H.; Wada, M. *Osaka City Med. J.* **1975**, *21*, 71. Johnson, M. R.; Schaaf, T. K.; Constantine, J. W.; Hess, H.-J. *Prostaglandins* **1980**, *20*, 515.
(5) (a) Floyd, M. B.; Schaub, R. E.; Weiss, M. J. *Prostaglandins* **1975**, *10*, 289. (b) The 15-deoxy-16-hydroxy series also has been extensively investigated by a Searle group: Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152.

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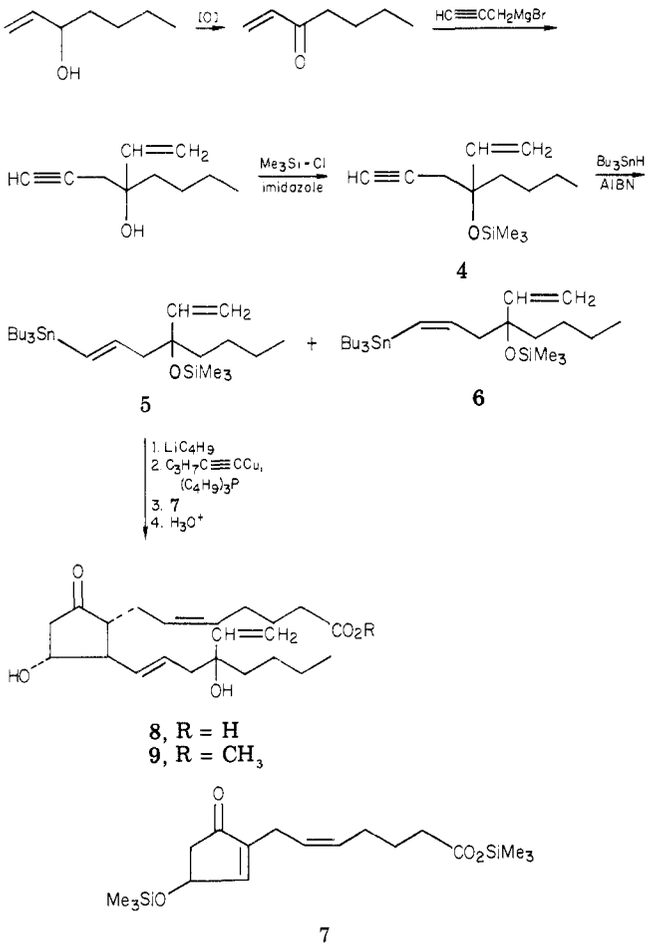
Scheme I



(41% yield). Grignard reaction of enone **2** with propargylmagnesium bromide furnished a 33% yield of (±)-4-hydroxy-4-vinyl-1-octyne (**3**), the hydroxyl group of which was silylated (90% yield) with trimethylchlorosilane and imidazole in DMF.[7] Treatment of protected octyne **4** with tri-*n*-butylstannane in the presence of azoisobutyronitrile (AIBN) at 125 °C provided (±)-(*E*)-1-(tri-*n*-butylstannyl)-4-vinyl-4-[(trimethylsilyl)oxy]-1-octene (**5**) in 83% yield as a colorless liquid.[8] The overall yield of the β-chain precursor **5** from **1** was 10%. In the ^{13}C NMR spectrum of **5**, a few side peaks closely related to the main signals were attributed to the presence of the *Z* isomer **6**. No attempt was made to remove **6**, since the (13*Z*)-15-deoxy-16-hydroxy-16-vinyl-PGE_2 generated from it in the conjugate addition step was easily separated by dry column chromatography of the final product.

Stannane **5** was converted to the mixed lithium pentynyl cuprate by lithiation (1 equiv of *n*-BuLi, THF, −35 °C, 1.5 h), followed by addition of 1-pentynylcopper(I) solubilized in tributylphosphine.[9] Conjugate 1,4-addition[10] to protected (±)-cyclopentenone **7**,[11] followed by deblocking, gave (16*RS*)-(±)-15-deoxy-16-hydroxy-16-vinyl-PGE_2 (DHV-PGE_2, **8**) in 50% yield as a colorless oil after dry column chromatography. Diazomethane treatment then provided the methyl ester **9**.[12] Products **8** and **9** each contain two racemates epimeric at C_{16}, and a separation of the two components can be seen on analytical high-pressure liquid chromatography (HPLC) as two sharp peaks of equal intensity. On TLC they appear as two closely overlapping spots, and they can be partially separated with difficulty by preparative HPLC via recycling.[13] The presence of two C-16 epimers also is apparent on inspection of the ^{13}C NMR spectrum, the signals due to C-17 and the C-16 vinylic carbon appearing as paired peaks.

Table I. Comparison of the Intravenous Antihypertensive Effects of *l*-PGE_2 and DHV-PGE_2 in the Conscious, Spontaneously Hypertensive Rat[a]

	l-PGE_2		DHV-PGE_2	
dose, μg/kg	max lowering MABP,[b] mmHg	duration,[c] min	max lowering MABP,[b] mmHg	duration,[c] min
10	60	<5	30	30-45
30	72	<5	55	45-50
100	72	10-20	65	>200
300	70	25-30		
500	50	25-30		

[a] These assays were carried as described for the experiments of Figure 1 except that the compounds, prepared as described for the oral studies, were administered to the lateral caudal vein. [b] MABP = mean arterial blood pressure; mean of two experiments. [c] Duration; determined by return of blood-pressure response to within 10 mmHg of control MABP.

As shown in Figure 1, oral or topical DHV-PGE_2 (1:1 mixture of two C-16 epimeric racemates) produced a rapid, dramatic, and long-lasting lowering of blood pressure in spontaneously hypertensive rats. *l*-PGE_2, at equivalent oral doses or threefold higher topical concentrations, failed to produce a significant effect on blood pressure. On the other hand, when compared by the intravenous route of administration, *l*-PGE_2 was 3–10 times as potent a hypotensive agent as DHV-PGE_2. However, the duration of the hypotensive effect of *l*-PGE_2 was very transient, while the DHV-PGE_2 effect was relatively prolonged (see Table I). In additional topical studies using a petrolatum formulation of DHV-PGE_2 methyl ester (**9**), hypotensive effects were achieved at doses as low as 30 μg/kg, and with doses of 1 mg/kg, a duration of more than 24 h was observed. Preliminary investigations in man have confirmed the hypotensive activity of DHV-PGE_2 methyl ester, administered either orally or topically.[15] Transdermal effects were particularly prolonged. Additional reports concerning this interesting compound and its congeners will appear in due course. At this point we would note that struc-

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(12) Infrared, magnetic resonance, mass spectral, and microanalytical data support the assigned structures for all new compounds.
(13) In contrast, nonallylic 15-deoxy-16-hydroxy racemates in our hands (also 13-dihydro-15-hydroxy derivatives[14]) have not been separable by chromatographic procedures. However, for one example of such a separation, albeit insufficient and inconsistent, see Pappo, R. et al. In "Chemistry, Biochemistry, and Pharmacological Activity of Prostanoids"; Roberts, S. M.; Scheinmann, F., Eds.; Pergamon Press: New York, 1979; p 17.
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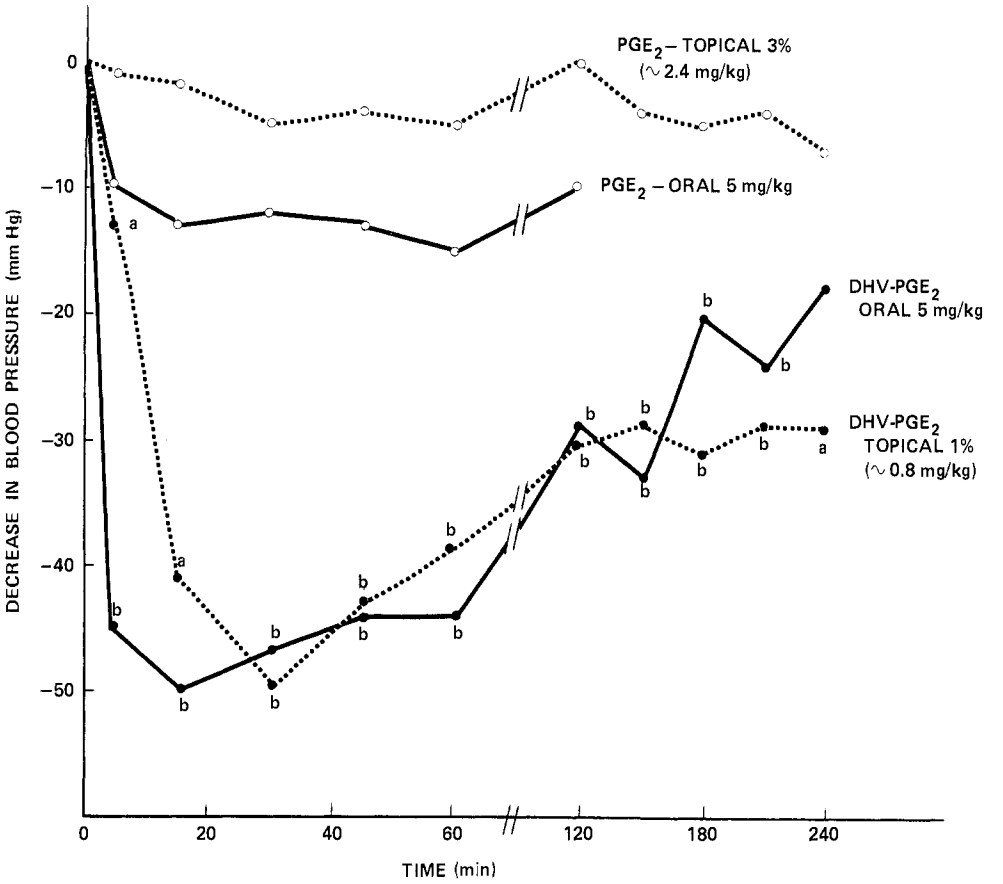

Figure 1. Effect of (16*RS*)-(±)-15-deoxy-16-hydroxy-16-vinylprostaglandin E_2 (DHV-PGE_2) and *l*-PGE_2 on mean arterial blood pressure (MABP). Male, Okamoto, spontaneously hypertensive rats (MABP 179 ± 2 mmHg) weighing approximately 300 ± 20 g (Taconic Farms, Germantown, NY) were restrained in a supine position. The iliac artery was cannulated and connected by means of a small nylon catheter to a pressure recording device for monitoring blood pressure according to the procedure of Chan and Poorvin.[21] Following a stabilization period, DHV-PGE_2 or *l*-PGE_2 was administered orally by gavage or topically. For oral studies, sodium salts of the prostaglandins were prepared by dissolving the acids in 0.1 mL of absolute ethanol, adding appropriate equivalents of 0.6 M $NaHCO_3$, and diluting with saline. For topical studies, rats were shaved with an electric clipper, and the abdomen was depilated using a standard mixture of barium sulfide and gum acacia on the evening before testing. The prostaglandins were dissolved and diluted to an appropriate concentration with absolute ethanol, and 0.1-mL aliquots of these solutions were added to 0.9 g of Aquatain cream base. These formulations were applied to a circular area of approximately 3.5-cm diameter on the abdominal surface. Appropriate vehicle controls were conducted for both oral and topical formulations. Statistical comparisons were made using Student's *t* test with levels of significant difference between treatment and control designated as *a* ($p < 0.05$) or *b* ($p < 0.01$); *n* values were as follows: PGE_2 topical (2), PGE_2 oral (3), DHV-PGE_2 oral (4), DHV-PGE_2 topical (3).

ture–activity studies indicate the unique effect of the 16-hydroxy-16-vinyl moiety.[16] For example, both (16*RS*)-(±)-15-deoxy-16-hydroxy-PGE_2[5a] and its 16-methyl derivative[20] failed to produce a hypotensive response when tested in the spontaneously hypertensive rat at a dose of 5 mg/kg by the oral route.

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(16) DHV-PGE_2 in animal models is also one of the most potent bronchodilators that we have seen. Thus, in the Konzett assay (guinea pig, iv administration) it is 4–5 times as potent as *l*-PGE_2 as an inhibitor of bronchoconstrictions induced by serotonin or histamine.[17] Surprisingly, on the other hand, it is relatively ineffective as an inhibitor of gastric acid secretion as measured by the dog fistula assay[18] (oral administration).[19] This latter property is in sharp contrast to the very potent activity observed for the corresponding 16-methyl-PGE_1 and PGE_2 derivatives.[5b,18,19]

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