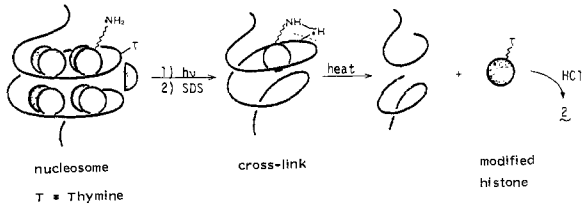
Scheme I. Schematic Representation of the Proposed Mechanism for Photo-Cross-Linking in Nucleosome



peak corresponding to **2** gave a pure product whose chromatographic behaviors,[7a,15] UV spectrum,[7a] and 400-MHz ^{1}H NMR[8] are identical with those of the authentic sample obtained from the model experiment. The contents of thymine–lysine adduct **2** were directly determined by HPLC analysis of the acid hydrolysates of UV-irradiated nucleohistone under various conditions. The amount of **2** in UV-irradiated nucleohistone at pH 10.5 increased proportionally with increasing irradiation time within 40 min, and further irradiation no more increased the yield of **2** significantly (Table I). This may reflect that the lysine ϵ-amino group of intimate association with thymine in DNA is primarily responsible for the formation of **2**.[16] Irradiation at pH 7.5 proceeded less efficiently, and the yield of **2** increased with increasing pH.

In order to confirm whether a similar photo-cross-linking is feasible in irradiation of nuclei, we examined the irradiation of chicken erythrocyte nuceli[17] (0.1 mg/mL) at 0 °C in the same buffer at pH 9.5. After being heated at 70 °C, the photolysate was hydrolyzed (6 N HCl, 110 °C) and then analyzed by amino acid analyzer to reveal again the presence of **2** in the hydrolysate. Control experiments without irradiation or irradiation with light through a Pyrex filter (>280 nm) never produced **2** under the conditions. Thus, we were able to confirm that irradiation of DNA–protein systems in calf thymus nucleohistone or chicken erythrocyte nuclei with 254-nm light followed by acid hydrolysis leads ultimately to the formation of **2**. However, we are not confident whether the adduct formation is resulted solely from the photoreaction of specific DNA–histone systems because of the presence of other proteins in nucleohistone used.[18]

It has previously been reported that UV irradiation of chromatin produces DNA–histone adducts.[4,19] Kunkel and Martinson[20] have observed that a considerable amount of reversal of DNA–histone cross-links occurred in irradiation of calf thymus nuclei with light between 230 and 290 nm, i.e., the histones cross-linked to DNA are released by chemical hydrolysis or upon rechromatography on Sepharose column, while the chemical nature of the reversibility and the sites of binding have been totally unknown.[21] By knowing the chemical reactivity of **3** and by the confirmation of **2** in UV-irradiated DNA–protein systems, it seems probable that the apparent reversibility is due to the cross-links of the lysine ϵ-amino groups to thymine in DNA as outlined in eq 1. Thus, the photoexcited state of thymine N(3) monoanion[7b] in DNA would react with neighboring lysine ϵ-amino groups of histones to result in the formation of DNA–histone adducts which on subsequent heating release free histones containing partially modified lysine residues as illustrated in Scheme I. We have already demonstrated that irradiation of DNA with alkylamines and subsequent heating of the photolysate at an alkaline pH induce DNA strand scission at the sites of reacting thymine.[7b,23] It is therefore highly probable that DNA in UV-irradiated chromatin may suffer strand scission at the sites of reacting thymine upon heating under the slightly alkaline conditions, although the mechanistic details should await further studies using each of the purified histone–DNA adducts.

In conclusion, the present work has demonstrated an important role of thymine–lysine photoreaction in the photo-cross-linking of proteins to DNA. Since the thymine–lysine photoadduct **2** is readily detectable by HPLC and amino acid analyzer, irradiation with 254-nm light may provide a useful means for probing specific interaction sites between thymine and lysine residues in DNA–protein complexes. Furthermore, such type of photo-cross-linking may be relevant to the UV-induced damage on DNA in cells.

Registry No. 1, 50-89-5; **2**, 76945-38-5; **3**, 87616-31-7; **4**, 87616-32-8; **5**, 87616-33-9; 2-deoxy-D-ribose, 533-67-5; L-lysine, 56-87-1; L-arginine, 74-79-3.

(15) R_f 0.6 on silica gel TLC (iso-PrOH–30% ammonia–water, 7:1:2).

(16) In fact, addition of NaCl (up to 2 M) to the reaction system considerably retarded the formation of **2** as compared to the control experiment.

(17) Rill, R. L.; Shaw, B. R.; Van Holde, K. E. "Methods in Cell Biology"; Academic Press: New York, 1978; Vol. XVIII, p 76. We are indebted to Professor M. Yanagida, Kyoto University, for providing us the sample.

(18) It is also uncertain whether the histones had a native nucleosome-type conformation under the irradiation conditions.

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(20) Kunkel, G. R.; Martinson, H. G. *Nucleic Acids Res.* **1978**, *5*, 4263.

(21) We also observed that heating (90 °C, 2 h) of the crude DNA–histone adducts isolated by ultracentrifugation with adding SDS in UV-irradiated chicken erythrocyte nuclei releases free histones that are detectable by gel electrophoresis.[22]

(22) Saito, I.; Sugiyama, H.; Matsuura, T. *Nucleic Acids Res.* **1983**, Sp. No 11, 225.

(23) (a) Saito, I.; Sugiyama, H.; Matsuura, T.; Ueda, K.; Komano, T., submitted for publication. (b) Simoncsits, A.; Török, I. *Nucleic Acids Res.* **1982**, *24*, 7957.

Cobalt-Catalyzed Cocyclizations of Isocyanatoalkynes: A Regiocontrolled Entry into 5-Indolizinones. Application to the Total Synthesis of Camptothecin

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Pyridones, particularly those containing bridgehead nitrogen, constitute useful moieties in heterocycle construction of value in alkaloid[1] and drug[2] synthesis. We report the cobalt-catalyzed [2 + 2 + 2] cocyloaddition of the novel 5-isocyanatoalkynes **1** to alkynes, providing a chemo- and regioselective entry into the class of functionalized 2,3-dihydro-5(1*H*)-indolizinones. The method is readily applied to a total synthesis of the antitumor alkaloid camptothecin.[3]

The requisite starting material 5-isocyanato-1-pentyne (**1a**) [bp 85 °C (70 torr)], is available[4] from 5-hexynoic acid via acid chloride formation [$(COCl)_2$, C_6H_6, DMF (catalyst), 25–35 °C, 82%][5] and Curtius rearrangement (NaN_3, CH_3CN, Δ, 1 h, 74%), whereas **1b** [bp 80–85°C (0.2 torr)] is prepared from 3-carbomethoxypropanoyl chloride[6] according to Scheme I.

(1) Pelletier, S. W. "Chemistry of the Alkaloids", Van Nostrand Reinhold: New York, 1970.

(2) Lednicer, D.; Mitscher, L. A. "The Organic Chemistry of Drug Synthesis"; Wiley: New York, 1977 and 1980; Vol. 1 and 2.

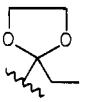
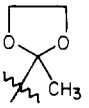
(3) Schultz, A. G. *Chem. Rev.* **1973**, *73*, 385. Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047.

(4) All new compounds gave satisfactory spectral and analytical data. For example, **3a**: *m/e* (relative ion current) 249.1362 (M^+, 3.3, calcd for $C_{14}H_{19}NO_3$: 249.1365), 87 (base, 7.7); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, 3 H, *J* = 7.2), 1.62 (s, 3 H), 2.17 (tt, 2 H, *J* = 7.3, 7.7), 2.76 (q, 2 H, *J* = 7.2), 3.04 (t, 2 H, *J* = 7.7), 3.78 (m, 2 H), 4.03 (m, 2 H), 4.15 (t, 2 H, *J* = 7.3), 6.36 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.4, 21.2, 21.6, 26.4, 31.7, 48.8, 64.4, 77.4, 99.1, 108.6, 129.0, 146.2, 150.3, 162.6 ppm; IR (neat) 1647, 1600, 1587 cm^{-1}. **4a**: ^{1}H NMR ($CDCl_3$) δ 1.74 (t, 3 H, *J* = 7.4), 1.79 (s, 3 H), 2.13 (tt, 2 H, *J* = 7.2, 7.7), 2.79 (q, 2 H, *J* = 7.4), 3.01 (t, 2 H, *J* = 7.7), 3.82 (m, 2 H), 4.01 (m, 2 H), 4.10 (t, 2 H, *J* = 7.2), 5.90 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.5, 22.0, 25.0, 27.5, 32.0, 49.0, 64.5, 77.5, 104.0, 110.5, 126.0, 148.0, 153.5, 160.5.

(5) Shamma, M; Smithers D. A.; St. Georgiev, V. *Tetrahedron* **1973**, *29*, 1949.

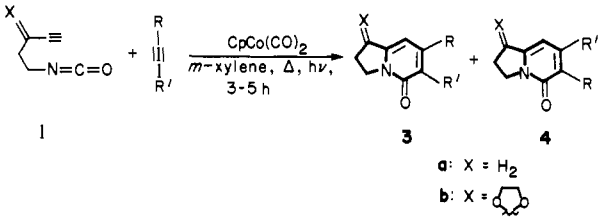
0002-7863/83/1505-6991$01.50/0

Table I. Results of the Cocylization of **1** with Alkynes

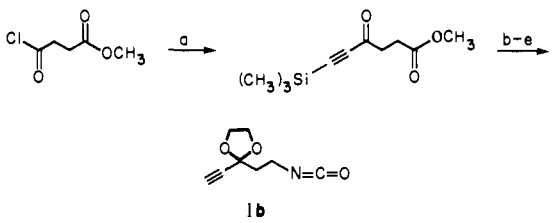
entry	isocyanato-alkyne	R	R'	% yield of **3** (mp, °C)	% yield of **4** (mp, °C)
1	1a	$(CH_3)_3Si$	$(CH_3)_3Si$	72 (117-119)	
2	1a	*n*-Pr	$(CH_3)_3Si$	68 (64-66)	5 (115-120)
3	1a		$(CH_3)_3Si$	76 (150-152)	
4	1a	*t*-Bu	$(CH_3)_3Si$[a]	17 (79-81)	<1
5	1a		Et	41 (oil)	31 (oil)
6	1b	$(CH_3)_3Si$	$(CH_3)_3Si$	68 (134-135)	
7	1b	*n*-Pr	$(CH_3)_3Si$	60 (87-89)	3 (oil)
8	1b	*n*-Pr	$CH_2OSi(t\text{-}Bu)(C_6H_5)_2$	20 (165-167)[b]	18 (oil)
9	1b	CH_3	CO_2Et	14 (108-110; lit.[5] 110-112)	17 (96-97)

[a] Products were isolated in their protodesilylated form after chromatography on silica. [b] Correlated with the aldehyde precursor to **6** (Scheme II).

Cocyclization of **1** with a variety of alkynes in the presence of catalytic η^5-$C_5H_5Co(CO)_2$ (*m*-xylene, Δ, *hν*, 3–5 h) gave the results shown in Table I.[4] The regiochemical assignments were based on comparison of the protodesilylated analogues [CF_3CO_2H, C_6H_6 or $(CH_3)_4N^+F^-\cdot 3H_2O$, DMSO, 1 h, 60–80 °C] with known compounds.[5,9] One notes that good chemo- and regioselectivity[10] is achievable by the use of trimethylsilylated alkynes, the silyl group emerging preferentially α to the amide linkage, even when pitted against *tert*-butyl (entry 4), pointing to the operation of a stereoelectronic effect which appears peculiar for silicon.[11] The thus formed rare silylpyridones[12] are very effective substrates for selective[13] electrophilic 6-halodesilylations[4] (Br_2 or ICl, CH_2Cl_2, 0 °C) to give **3a** [R = *n*-Pr, R′ = Br, 73%, mp 107–109 °C; R = *n*-Pr, R′ = I, 66%, mp 86–87 °C; R = $CH_3CH_2(CO_2C_2H_4)$, R′ = Br, 70%, mp 113–115 °C; R = $CH_3CH_2(CO_2C_2H_4)$, R′ = I, 94%, mp 101–104 °C; R = $(CH_3)_3Si$, R′ = I, 90%, mp 167–168.5 °C] or **3b** [R = *n*-Pr, R′ = I, 93%, mp 114–116 °C; R = $(CH_3)_3Si$, R′ = I, 86%, mp 144–145 °C]. The iodides undergo highly efficient palladium-catalyzed coupling reactions[4] with phenylethyne[14] (**3a**, R = *n*-Pr, R′ = $C_2C_6H_5$, 94%, mp 120–122 °C; **3b**, R = *n*-Pr, R′ = $C_2C_6H_5$, 95%, mp 87–90 °C), methyl acrylate, and styrene[15] (**3b**, R = *n*-Pr, R′ = *trans*-CH=$CHCO_2CH_3$, 97%, mp 139–141 °C; R = $(CH_3)_3Si$, R′ = *t*-CH=$CHCO_2CH_3$, 93%, mp 122–124 °C; R = $(CH_3)_3Si$, R′ =

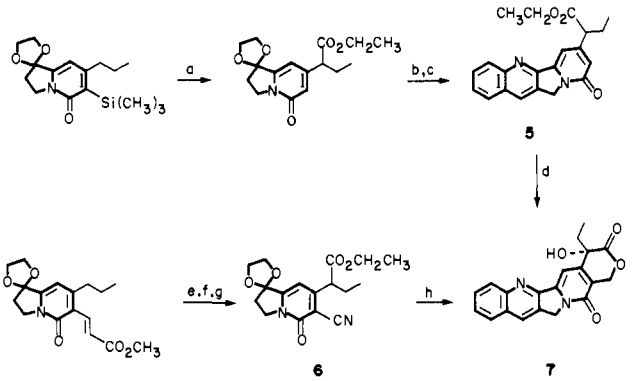


Scheme I[a]



[a] (a)[7] $AlCl_3$, CH_2Cl_2, 0 °C, 83%; (b) $HOCH_2CH_2OH$, TsOH, C_6H_6, Δ, 97%; (c)[8] NaOH, CH_3OH, H_2O, 83%; (d)[5] $(COCl)_2$, C_6H_6, DMF (catalyst), 25-35 °C, 82%; (e) NaN_3, CH_3CN, Δ, 0.5 h, 84%.

Scheme II[a]



[a] (a) $(CH_3CH_2O)_2CO$, KH, toluene, 54%;[17] (b) $(COOH)_2$, CH_3CH_2OH, H_2O, 75%;[5] (c) *N*-(2-aminobenzylidene)-*p*-toluidine,[17,18] TsOH, toluene, 78%; (d) ref 19; (e) OsO_4, $NaIO_4$, 86%, mp 117–118 °C; (f) $NH_2OH\cdot HCl$; SeO_2,[20] 80%, mp 134–135 °C; (g) $(CH_3CH_2O)_2CO$, NaH, toluene, CH_3CH_2OH, 32%; (h) ref 17.

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(8) Warren, C. K.; Weedon, B. C. L. *J. Chem. Soc.* **1958**, 3972.
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(11) See also: Brien, D. J.; Naiman, A.; Vollhardt, K. P. C. *J. Chem. Soc., Chem. Commun.* **1982**, 133, and the references therein.
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(13) 2-Pyridones are normally brominated to mixtures of 3- and 5-bromo derivatives: Tee, O. S.; Paventi, M. *J. Am. Chem. Soc.* **1982**, *104*, 4142. Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, *6*, 229.
(14) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. Austin, W.; Bilow, N.; Kelleghan, W.; Lau, K. S. *J. Org. Chem.* **1981**, *46*, 2280. Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.
(15) Heck, R. F. *Org. React.* **1982**, *27*, 345.

t-CH=CHC$_6$H$_5$, 69%, mp 99–102 °C).

To demonstrate the utility of these transformations in natural product construction two formal total syntheses of camptothecin (**7**), a molecule of renewed recent interest,[16,17] were executed[4] as in Scheme II in respectable yield[21] through the intermediacy of the two key intermediates **5** and **6**.

The present work offers a uniquely versatile way to assemble annulated pyridones with extensive control of their substitution pattern,[13] by using a transition metal as a template on which to simultaneously generate three new bonds. This approach should surpass the flexibility attained by conventional Diels–Alder routes.[22]

Finally, we note that another catalyst reported to catalyze the formation of 2-pyridones from alkynes and isocyanates, bis(η^4-cyclooctadiene)nickel,[23] is unsuccessful in our systems and very likely operates through an alternative mechanism.[11]

Acknowledgment. This work was supported by the NSF (CHE 82-00049). K.P.C.V. is a Camille and Henry Dreyfus Teacher-Scholar (1978–1983). We thank Professors Büchi and Danishefsky for providing us with comparison data and Harold Helson for technical help.

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(20) Sosnovsky, G.; Krogh, J. A.; Umhoefer, S. G. *Synthesis* **1979**, 722.

(21) For example, **5** is made by us starting from 3-carbomethoxypropanoyl chloride in 9 steps, 9% yield, superior to the Danishefsky route[19] (11 steps, 1.2%) and Quick's synthesis[19] (10 steps, 9%) both from 3-aminopropanal diethylacetal, and the Kende approach[19] from furfural dimethylacetal (13 steps, 2.7%), but inferior to Büchi's strategy[19] from methyl 2,2-dimethoxyethanoate (6 steps, 18%).

(22) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A.-M; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428.

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Iminium Ion and Acyliminium Ion Initiated Cyclizations of Vinylsilanes. Regiocontrolled Construction of Unsaturated Azacyclics

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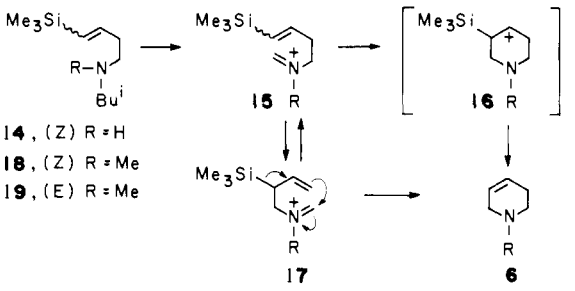
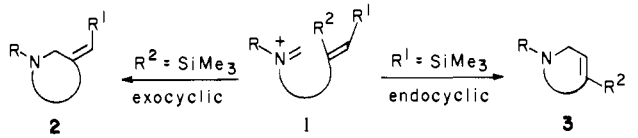
Vinylsilanes are rapidly becoming important terminators for cationic cyclizations.[2] We have described[2a,b] a general stereocontrolled synthesis of alkylidene azacyclics by the intramolecular reaction of vinylsilanes with iminium ions (**1** → **2**). During the course of these studies, we became interested in whether these weakly reactive cyclization components would also participate in

Scheme I

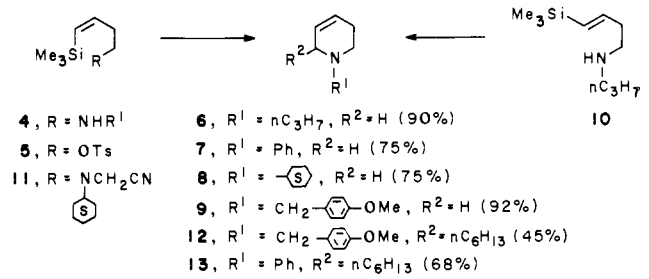


ring closures that are endocyclic[3] with respect to the vinylsilane terminator (**1** → **3**). In this communication, we report that such



cyclizations do occur readily and provide a useful new method for the regiocontrolled assembly of unsaturated azacyclic systems.

We initially explored cyclizations to form tetrahydropyridines. The starting (*Z*)-4-(trimethylsilyl)-3-butenamines (**4**)[4] were prepared by aminolysis (excess amine, 25–80 °C) of readily available tosylate **5**.[4,5] Reactions of **4** with excess paraformaldehyde occured in refluxing acetonitrile in the presence of 0.95 equiv of camphorsulfonic acid to give 1,2,5,6-tetrahydropyridines **6–9**[4] in excellent yields. Alternatively, a (cyanomethyl)amine[6]



could be employed and the cyclization (e.g., **11** → **8**, 56%) accomplished by treatment with silver trifluoroacetate (1 equiv, 100 °C). The stereochemistry of the vinylsilane terminator was not critical, since the (*E*)-vinylsilane **10**[4,7,8] was converted to **6** in 73% yield when treated under similar conditions with paraformaldehyde and acid. Other aldehydes could also be employed. For example, amines **4** (R^1 = Ph and *p*-methoxybenzyl) were cleanly cyclized at 120 °C with heptanal (3 equiv) and camphorsulfonic acid (0.95 equiv) to yield the 2-substituted tetrahydropyridines **12**[4] and **13**.[4]

The 1,2,5,6-tetrahydropyridine ring is found in several natural products and numerous pharmacologically active materials.[9] This

(1) NIH Postdoctoral Fellow, 1981–1983.

(2) (a) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851–1853. (b) Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297–5300. (c) Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Smith-Strickland, S. M.; Saunders, J. O. *Ibid.* **1981**, *46*, 2400–2402. (d) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529–6530. (e) Mikami, K.; Kishi, N.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 795–798. (f) Nakamura, E.; Fukuzaki, K.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 499–501.

(3) Cf.: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(4) Yields refer to material purified by chromatography on silica gel. All compounds reported were homogeneous by TLC analysis and showed 250-MHz ^{1}H NMR, IR, and mass spectra consistent with the assigned structures. The molecular composition of key compounds was determined by high-resolution mass spectrometry or combustion analysis.

(5) Available on a large scale from the tetrahydropyranyl ether of 3-butyn-1-ol by silylation (BuMgBr, Me_2SiCl), semihydrogenation (*i*-Bu_2AlH, H_2O), deprotection (MeOH, pyridinium tosylate), and tosylation (TsCl, pyridine) using standard reaction conditions.

(6) Prepared from the reaction of **4** (R = cyclohexyl) with paraformaldehyde, KCN, and acid; cf.: Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2741–2744 and references cited therein.

(7) Prepared analogously to **4** from (*E*)-4-(trimethylsilyl)-3-butenol, which was readily prepared from the corresponding *Z* stereoisomer[4] by bromine atom equilibration.

(8) Cf.: Zweifel, G.; On, H. P. *Synthesis* **1980**, 803–805.

(9) (a) For reviews, see: Pinder, A. R. In "The Alkaloids"; Grundon, M. F., Ed.; Chemical Society: London, 1982; Vol. 12, Chapter 2, pp 29–35, and earlier volumes of this series. Coutts, R. T.; Scott, J. R. *Can. J. Pharm. Sci.* **1971**, *6*, 78–84. (b) 1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine has recently been reported to induce Parkinson's disease in monkeys: *Science (Washington, D.C.)* **1983**, 705.

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