Palladium-Catalyzed Vinylic Substitution Reactions. An Approach to (Aminoalkyl)phencyclidines

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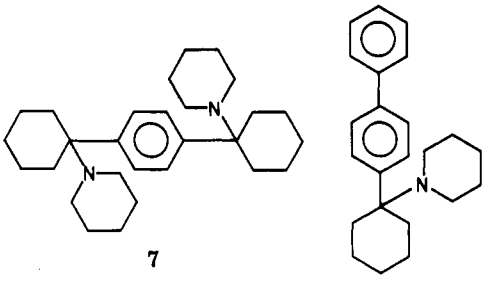
4-Iodophencyclidine (**5**) was reacted with various *N*-alkenylphthalimides in the presence of 1 mol % palladium acetate, triethylamine, and tri-*o*-tolylphosphine in acetonitrile as solvent at 100 °C to give good yields of (*E*)-4-(phthalimidoalkenyl)phencyclidines (**9a–c**). Catalytic hydrogenation of the olefins gave **12a–c**, and cleavage of the phthalimido moiety gave the desired 4-(aminoalkyl)phencyclidines (**2a–c**) which were characterized as their mixed thioureas. Amine **2b** was also synthesized by reduction of the palladium-catalyzed phencyclidine–acrylonitrile adduct. Reaction of acrolein ethylene ketal with **5** in the presence of palladium acetate did not give adduct **15** but rather gave isomerized ketene acetal **17** which underwent further reaction to **16a** or hydrolyzed to **16b** upon workup. Transesterification of **16** with methanol gave methyl ester **18** which was identical with the ester obtained by catalytic reduction of the palladium-catalyzed adduct of **5** and methyl acrylate, **19**. LAH reduction of **19** gave a 4/1 mixture of alcohols **21** and **22**. Mass spectra and ^{13}C NMR spectra are presented for these phencyclidines.

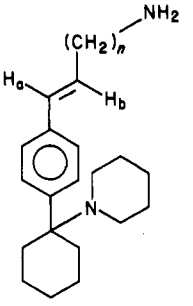
As part of a fluorescence immunoassay for phencyclidine (**1**),[2] we require a number of primary aminoalkyl-substituted phencyclidines **2**. While we recently reported[3] several traditional syntheses for 4-(aminomethyl)phencyclidine (**3**), including a route which would allow specific tritum incorporation, as well as a multistep synthesis for **2a**, which is not amenable to radiolable incorporation, we sought a more efficient approach, amenable to tritium incorporation, for the preparation of **2a–c**. We now find that Heck's[4] palladium-catalyzed vinylic substitution reaction of aryl halides allows us to synthesize **2a–c** in good to excellent overall yields while allowing specific tritium incorporation if desired.

Results and Discussion

4-Bromo- (**4**) and 4-iodophencyclidine (**5**) were reacted with *N*-alkenylphthalimides **6** under standard conditions by using 1 mol % of palladium acetate, 125 mol % of triethylamine, and 2 mol % of tri-*o*-tolylphosphine in dry[5] acetonitrile at 100 °C (Scheme I). 4-Iodophencyclidine was prepared by one of two routes. When large quantities of **5** were required, the Grignard reagent of 1,4-diiodobenzene was reacted with 1-piperidyl-1-cyanocyclohexane[2b] by using the modified procedure reported[3a] for making 4-bromophencyclidine to give **5** in ca. 30% yield along with varying yields of adduct **7** (mp 172–173 °C (EtOH)),[3a] 4-phenylphencyclidine (**8**, (mp 110–111 °C (EtOH)),[6] and **1**. A more convenient approach when smaller quantities



7 **8**



10, $n = 1$
11, $n = 2$

of **5** were required involved metalation of 4-bromophencyclidine with butyllithium in THF at −78 °C followed by reaction of the generated anion with iodine to give, after workup, pure **5** in 55% overall yield.

In all cases, we found that **5** reacted better than **4** in the palladium reactions (i.e., lower reaction temperatures, shorter times, higher yields of product);[4] hence, only those reactions will be reported here. *N*-Vinylphthalimide (**6a**),[4d] which we synthesized by elimination of HBr from *N*-(2-bromoethyl)phthalimide using 1,5-diazabicycloundecene (DBU) in Me_2SO,[7] reacted with **5** to give (*E*)-4-[1-(2-phthalimidoethenyl)]phencyclidine (**9a**) in 40% yield. While it was not obvious at the onset of this work that *N*-(2-propenyl)phthalimide (**6b**)[8] would undergo vinylic substitution[9] or would be stable to the reaction conditions

(1) Visiting Scholar from the East China Engineering Institute, Nanjing, People's Republic of China.

(2) (a) A. Kalir, H. Edery, Z. Pelah, D. Bolderman, and G. Porath, *J. Med. Chem.*, **12**, 473 (1969), and references cited therein; (b) V. H. Maddon, E. F. Godefroi, and R. F. Parcell, *ibid.*, 8, 230 (1965); (c) A. Gabrielevitz, et al., *Life Sci.*, **26**, 89 (1980); (d) A. Kalir, S. Maayani, M. Rehavi, R. Elkavets, I. Pri-Bar, O. Buchman, and M. Sokolovsky, *Eur. J. Med. Chem.*, **13**, 17 (1978); (e) G. A. Brine, E. E. Williams, K. G. Boldt, and F. I. Carroll, *J. Heterocycl. Chem.*, **16**, 1425 (1979); (f) P. Geneste, J. M. Kamenka, and A. Mas, *Bull. Soc. Chem. Fr.*, 609 (1978).

(3) (a) P. Y. Johnson, R. Pan, and J. Q. Wen, *J. Org. Chem.*, **46**, 2049 (1981). (b) Presented in part at the Southeast/Southwest Regional Meeting of the American Chemical Society, New Orleans, LA, Dec 12, 1980, Abstract No. 464.

(4) (a) J. E. Plevyak, J. E. Dickerson, and R. F. Heck, *J. Org. Chem.* **44**, 4078 (1979); (b) C. B. Ziegler and R. F. Heck, *ibid.*, **43**, 2941 (1978); (c) W. C. Frank, Y. C. Kim, and R. F. Heck, *ibid.*, **43**, 2947 (1978); (d) C. B. Ziegler and R. F. Heck, *ibid.*, **43**, 2949 (1978); (e) T. C. Zebovitz and R. F. Heck, *ibid.*, **42**, 3907 (1977); (f) H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974) and references cited therein.

(5) This is particularly important since palladium catalyzes the decomposition of tertiary amines in the presence of water. S. I. Murahashi and T. Watanabe, *J. Am. Chem. Soc.*, **101**, 7429 (1979).

(6) L. A. Jones, Southeast/Southwest Regional Meeting of the American Chemical Society, New Orleans, LA, Dec 12, 1980, Abstract No. 379.

(7) Conditions similar to those reported for making trienes. C. W. spangler, R. Eichen, S. Silver, and B. Butzlaff, *J. Org. Chem.*, **36**, 1695 (1971).

(8) A. Karim and R. G. Bacon, *J. Chem. Soc., Perkin Trans. 1*, 279 (1973).

(9) Heck and Ziegler reported that olefin **6b** would not react with iodobenzene under their standard $Pd(OAc)_2$ conditions, which did not employ tri-*o*-tolylphosphine as catalyst as we did, when iodobenzenes (as opposed to bromobenzenes) were employed (see ref 4d).

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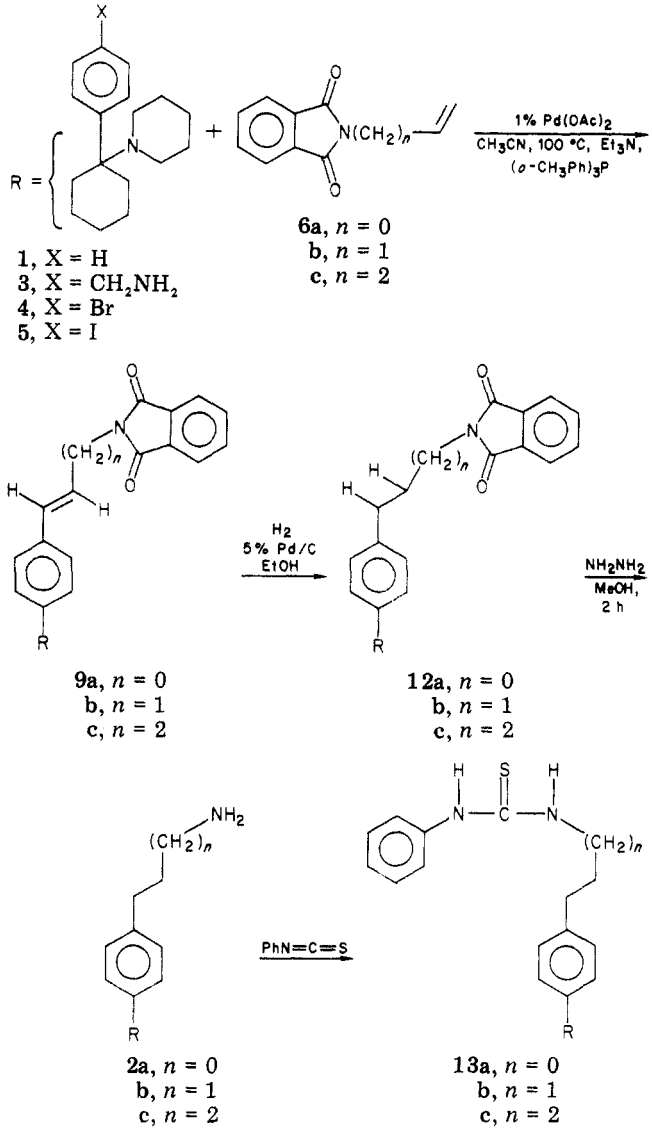
Scheme I

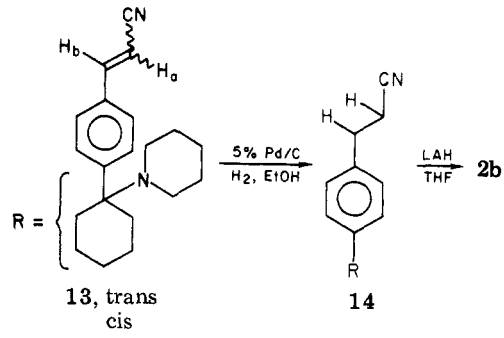


because of its potential to lose phthalimide, giving a π-allylpalladium complex as is the case with allylic acetates,[10] we found this reagent reacted with **5** at 100 °C in the presence of palladium acetate to give (*E*)-4-[1-(3-phthalimido-1-propenyl)]phencyclidine (**9b**) in 83% isolated yield. Similarly, *N*-(3-butenyl)phthalimide (**6c**)[4c] reacted with **5** to give (*E*)-4-[1-(4-phthalimido-1-butenyl)]phencyclidine (**9c**), also in 83% yield.

We found no evidence for either reverse addition[4d] to the olefin or for the formation of the *Z* isomers of **9** in these substitution reactions. In the case of **9b** and **9c**, the stereochemistry about the double bond could best be determined by first cleaving the phthalimide moiety by using 85% hydrazine hydrate in methanol to give unsaturated amines **10** and **11**, respectively. For **10**, inspection of the olefinic protons while the allylic protons were irradiated at δ 3.5 allowed ready determination of the trans coupling constant (J = 15 Hz).

Unsaturated amines **10** and **11** were hydrogenated in 2–4 h at 25° by using 5% palladium on charcoal in ethanol in a Parr apparatus to give amines **2b** and **2c**, respectively, in good yields. Our general approach, however, was to hydrogenate (H_2 or T_2) the phthalimide derivative first and then remove the protecting group. The three- and four-carbon olefins **9b** and **9c** were reduced as described above in 93% and 84% yields, respectively, to give **12b** and **12c**. Reduction of the two-carbon system, enimide **9a**, gave only a 49% yield of **12a** after 3 days.[11] Longer reactions times resulted in extensive hydrogenolysis of the benzylic piperidine group. Cleavage of the phthalimide group with 85% hydrazine in refluxing methanol for several hours gave the desired amines **2a** (91%), **2b** (89%), and **2c** (93%) as viscous oils which could be vacuum distilled to give, after standing, low-melting solids. All three amines reacted readily with phenyl isothiocyanate to give their respective mixed thioureas (**13a–c**) as sharp-melting solids.

Scheme II



Because of our uncertainty at the onset of this project that the three-carbon amine could be made by the *N*-(2-propenyl)phthalimide route, we undertook several other syntheses of **2b**, all involving palladium-catalyzed vinylic substitution reactions as their key step. Reaction of 4-iodophencyclidine with acrylonitrile and palladium acetate under standard conditions (Scheme II) gave, for the first time in our studies, a mixture of *E* (H_a, **13**, Scheme II, δ 5.85, J = 16 Hz) and *Z* (δ 5.40, J = 12 Hz) isomers (5/1 ratio) of vinyl-nitrile adduct **13**. Hydrogenation of the mixture by using 5% palladium on charcoal in ethanol gave nitrile **14** in 86% yield. Further reduction of **14** with LAH in THF gave **2b** in 80% yield.[12] Attempts to make acetal **15** (Scheme III) which we expected to convert to **2b** by reductive amination with sodium cyanoborohydride and ammonium acetate[13] of the freed aldehyde group, by reaction of the ethylene acetal of acrolein with **5** in the presence of palladium acetate resulted in the isolation of esters **16** which were identified by their spectra.

Ester **16a** is believed to have resulted from ketene acetal **17**,[4] which could have resulted directly from the inital adduct by loss of palladium hydride or could have resulted from palladium-assisted isomerization of **15**. We believe that **16b** results both from the facile hydrolysis of **17** during workup and from the reaction of **16a** with the base needed in the workup. The latter reaction would be anchimerically assisted by acylium ion formation as shown in **16c**. Ester **16** was transesterified in refluxing methanol containing toluenesulfonic acid for 20 h to give **18** which was identical with the methyl ester isolated after catalytic reduction of **19**. A small amount (ca. 5%) of cyclohexene **20**, resulting from acid-catalyzed elimination of piperidine, was also isolated from this reaction mixture. Ester **19** was synthesized from the palladium-catalyzed reaction of **5** with methyl acrylate in 68% yield as a mixture (10/1) of *E* (H_a,

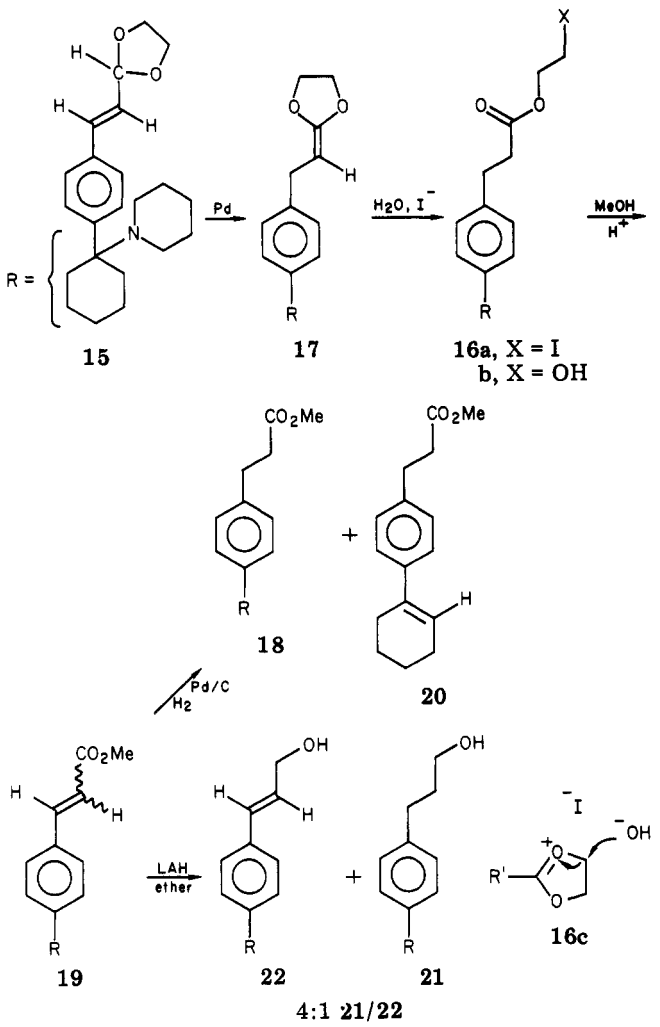
(10) For a recent review of π-allylpalladium complexes, see B. M. Trost, *Acc. Chem. Res.*, **13**, 385 (1980).

(11) Heck also noted the slow, low-yield reduction of β-phenyl-substituted enimids (see ref 4d).

(12) This two-step procedure is required since most catalysts active enough to hydrogenate the cyano group also cause hydrogenolysis of the benzylic piperidine. R. T. Borchardt and D. R. Thakker, *J. Med. Chem.*, 18, 152 (1975).

(13) G. L. Grunewald, D. E. Walters, and T. R. Kroboth, *J. Org. Chem.*, **43**, 3478 (1978).

Scheme III



19, Scheme III, δ 6.4, J = 16 Hz) and Z (δ 5.9, J = 12 Hz) isomers. Reduction of ester **19** with LAH in ether at 25 °C gave a (4/1) mixture of alcohols **21** and **22**. The reaction of amines **2** with proteins and use of these haptens to generate phencyclidine antibodies will be presented elsewhere.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. The ^1H NMR spectra were taken on a Varian T-60 or CFT-80 spectrometer and are reported in parts per million downfield from Me_4Si. The ^{13}C NMR spectra were taken on a Varian CFT-20 spectrometer and are reported in parts per million downfield from Me_4Si. The abbreviations (s, singlet; d, doublet; t, triplet; q, quartet) refer to the multiplicity of the absorption in an off-resonance decoupled spectrum. Mass spectra were determined on a Varian MAT-7 spectrometer using the direct-inlet system. Gas chromatography was carried out by using the programmed temperature control on a Varian 1740 instrument equipped with a flame-ionization detector and 2- or 4-ft glass columns packed with SE-30, SE-52, or Carbowax 20 M on Chromosorb P. HPLC separations were performed on a Waters 500 Prep instrument using Prep PAK columns. Microanalyses were performed by Micro-Tech Laboratories. All reactions were executed under dry nitrogen.

1-[1-(4-Iodophenyl)cyclohexyl]piperidine (5). Into a flame-dried Morton flask, equipped with high-torque stirring and set in a darkened hood, containing 2.7 g (0.11 mol) of Mg turnings in 120 mL of ether was added, all at once, 46.2 g (0.14 mol) of 1,4-diiodobenzene in 120 mL of dry benzene. After a mildly exothermic reaction (cooled as needed to maintain gentle reflux) in which all the Mg reacted, the mixture was brought to a vigorous reflux, and 19.2 g (0.1 mol) of 1-piperidyl-1-cyanocyclohexane in 120 mL of ether was added dropwise over 1 h. The mixture was allowed to stir an additional 4 h at reflux, cooled, and quenched with aqueous K_2CO_3 until basic, and the organic layer was separated. The organic layer was washed well with 20% HCl with was neutralized with aqueous Na_2CO_3 and extracted with chloroform which was dried and evaporated to give 14 g of crude material. Recrystallization from EtOH gave 9.5 g (26%) of **5**. The remaining 4 g of material was a mixture of **7**[3a] and **8**.[6]

For **5**: mp 109–110 °C (EtOH); ^1H NMR ($CDCl_3$) δ 1.0–1.7 (m, 12), 1.7–2.1 (m, 4), 2.2–2.4 (m, 4), 7.0 (d, 2, J = 9 Hz), 7.6 (d, 2, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 140.0 (s), 136.5 (d), 129.4 (d), 91.6 (s), 60.7 (s), 46.4 (t), 33.4 (t), 27.0 (t), 26.3 (t), 24.9 (t), 22.3 (t); mass spectrum (70 eV), m/e (relative intensity) 369 (M^+, 50), 368 (25), 326 (100), 312 (15), 217 (25), 166 (20).

Anal. Calcd for $C_{17}H_{24}NI$: C, 55.29; H, 6.55; N, 3.79. Found: C, 55.48; H, 6.54; N, 3.82.

***N*-Alkenylphthalimides 6a–c.** Compounds **6b**[8] and **6c**[4c] were made as described.

N-Vinylphthalimide[4d] was made by reacting excess 1,2-dibromoethane with potassium phthalimide in DMF. The resulting *N*-(2-bromoethyl)phthalimide was dehydrohalogenated in several minutes by treating it with 1,5-diazabicycloundecene in Me_2SO at 25 °C.

General Palladium-Catalyzed Vinyl Substitution Reaction. A mixture of 10 mmol of 4-iodophencyclidine (**5**), 12.5 mmol of *N*-alkenylphthalimide **6**, 12.5 mmol of triethylamine, 0.1 mmol of palladium acetate, and 0.2 mmol of tri-*o*-tolylphosphine[14] in 5 mL of acetonitrile was heated at 100 °C in a syring-cap-stoppered heavy-walled flask. The reaction was heated until aliquots showed (GLC, TLC) no **5**. After cooling, the mixture was extracted with $H_2O/CHCl_3$. Removal of $CHCl_3$ gave compounds **9** in good yields (**9a**, 46%; **9b**, 83%; **9c**, 83%) as amorphous solids.

For (*E*)-4-[1-(2-phthalimidoethenyl)]phencyclidine (**9a**): mp 208–209 °C ($CH_3OH/CHCl_3$); IR ($CHCl_3$) 2960, 1720, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 12), 1.8–2.2 (m, 4), 2.2–2.5 (m, 4), 7.3 (d, 1, J = 14 Hz), 7.35 (AA'BB', 4), 7.4 (d, 1, J = 14 Hz), 7.8 (AA'BB', 4, phthalimido group); ^{13}C NMR ($CDCl_3$) δ 166.4 (s), 139.8 (s), 134.4 (d), 133.5 (s), 131.7 (s), 127.7 (d), 125.3 (d), 123.8 (d), 120.1 (d), 117.1 (d), 60.9 (s), 46.5 (t), 33.6 (t), 27.1 (t), 26.4 (t), 24.9 (t), 22.4 (t); mass spectrum (70 eV), m/e (relative intensity) 414 (M^+, 90), 413 (40), 371 (100), 330 (80), 329 (70), 262 (75).

Anal. Calcd for $C_{27}H_{30}O_2N_2 \cdot 0.5H_2O$: C, 78.12; H, 7.38; N, 6.76. Found: C, 77.70; H, 7.21; N, 6.52.

For (*E*)-4-[1-(3-phthalimido-1-propenyl)]phencyclidine (**9b**): mp 127.5–128.5 °C ($CH_3OH/CHCl_3$); IR ($CHCl_3$) 2970, 1760, 1700, 1380, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.9 (m, 12), 1.9–2.2 (m, 4), 2.2–2.5 (m, 4), 4.45 (d, 2, J = 6 Hz), 6.2 (d (J = 16 Hz) of t (J = 6 Hz), 2), 6.7 (d, 2, J = 16 Hz), 7.3 (AB, 4), 7.8 (AA'BB', 4); ^{13}C ($CDCl_3$) δ 167.8 (s), 139.7 (s), 133.8 (2 carbons, d and s), 133.6 (d), 132.1 (s), 127.5 (d), 125.6 (d), 123.1 (d), 122.1 (d), 61.0 (s), 46.4 (t), 39.6 (t, $=CCH_2N$), 33.4 (t), 26.9 (t), 26.3 (t), 24.8 (t), 22.3 (t); mass spectrum (70 eV), m/e (relative intensity) 428 (M^+, 25), 427 (10), 385 (25), 344 (5), 343 (5), 85 (100).

Anal. Calcd for $C_{28}H_{32}O_2N_2$: C, 78.47; H, 7.53; N, 6.54. Found: C, 77.84; H, 7.52; N, 6.35.

For (*E*)-4-[1-(4-phthalimido-1-butenyl)]phencyclidine (**9c**): mp 159–160 °C ($CH_3OH/CHCl_3$); IR ($CHCl_3$) 2970, 1775, 1710, 1400, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.9 (m, 12), 1.9–2.2 (m, 4), 2.2–2.4 (m, 4), 2.7 (m, 2), 3.9 (t, 2, J = 7 Hz), 6.15 (d (J = 16 Hz) of t (J = 6 Hz), 2), 6.4 (d, 2, J = 16 Hz), 7.3 (AB, 4), 7.3 (AB, 4), 7.8 (AA'BB', 4); ^{13}C NMR ($CDCl_3$) δ 1.68.1 (s), 139.0 (s), 134.7 (s), 133.7 (d), 132.2 (d), 132.0 (s), 127.4 (d), 125.3 (d), 125.1 (d), 123.1 (d), 60.8 (s), 46.3 (t), 37.5 (t), 33.5 (t), 32.1 (t), 26.9 (t), 26.2 (t), 24.8 (t), 22.2 (t); mass spectrum (70 eV), m/e (relative intensity) 442 (M^+, 10), 441 (7), 399 (20), 357 (35), 210 (80), 160 (50), 129 (100).

Anal. Calcd for $C_{29}H_{34}O_2N_2 \cdot 0.5H_2O$: C, 77.12; H, 7.81; N. 6.20. Found: C, 77.15; H, 7.64; N, 6.17.

(14) 4-Bromophencyclidine reactions required tri-*o*-tolylphosphine catalyst; however, 4-iodophencyclidine reactions were found to go equally well with either a triphenylphosphine or tri-*o*-tolylphosphine catalyst. In the case of **5** → **9a** the reaction also went equally well when no catalyst was employed. Other reactions were not run in the absence of catalyst although they may go well under those conditions.

General Hydrogenation Procedure (9 → 12). Alkenylphencyclidines **9** were hydrogenated at 45 psi of H_2 in ethanol by using 5% Pd/C as the catalyst. The reactions were monitored by TLC. After reaction of **9** (**12a**, 3 days; **12b** and **12c**, 2–4 h), the mixture was filtered and the solvent removed. The crude product was taken up in $CHCl_3$ and washed with 5% HCl and water. The $CHCl_3$ was dried and evaporated to give **12** as viscous oils. Trituration with ether gave **12** as solids which were recrystallized from CH_3OH (**12a**, 49%; **12b**, 93%; **12c**, 84%).

For **12a**: mp 109–111 °C (CH_3OH) [lit.[3a] mp 109–111 °C]; mass spectrum (70 eV), *m/e* (relative intensity) 416 (M^+, 40), 415 (15), 373 (80), 331 (100), 242 (20).

For **12b**: mp 121.5–122 °C ($CH_3OH/CHCl_3$); IR ($CHCl_3$) 2960, 1775, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 12), 1.8–2.4 (m, 10), 2.7 (t, 2), 3.8 (t, 2), 7.2 (s, 4), 7.8 (AA′BB′, 4); mass spectrum (70 eV), *m/e* (relative intensity) 430 (M^+, 75), 429 (30), 387 (100), 346 (20), 345 (20), 242 (30), metastable ion at *m/e* 348.5 ($387^2/430 = 348.3$).

Anal. Calcd for $C_{28}H_{34}O_2N_2 \cdot 0.5H_2O$: C, 76.78; H, 8.03; N, 6.38. Found: C, 76.91; H, 8.03; N, 6.09.

For **12c**: mp 135–137 °C ($CH_3OH/CHCl_3$); IR ($CHCl_3$) 2980, 1775, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.4 (m, 24), 2.7 (br t, 2), 3.8 (br t, 2) 7.2 (s, 4), 7.8 (AA′BB′, 4); mass spectrum (70 eV), *m/e* (relative intensity) 444 (M^+, 45), 443 (30), 401 (70), 359 (100).

Anal. Calcd for $C_{29}H_{36}O_2N_2 \cdot 0.5H_2O$: C, 76.78, H, 8.23; N, 6.17. Found: C, 77.02; H, 8.15; N, 6.10.

General Procedure for Phthalimide Removal (12 → 2 and 9 → 11). Phthalimides **9** or **12** were refluxed in methanol containing 1 equiv of 85% hydrazine hydrate for 2–5 h as needed (TLC). Water was added to the mixture and it was extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with 20% HCl which was made basic with aqueous K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ was dried and evaporated to give **2** or **10** and **11**.

For **2b**: 81% yield; bp 160–170 °C (0.04 mm) (accompanied with some loss of piperidine); IR ($CHCl_3$) 3400–3200 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.7 (m, 14), 1.7–2.1 (m, 6), 2.1–2.4 (m, 4), 2.7 (overlapping br triplets, 4), 7.2 (s, 4); ^{13}C NMR ($CDCl_3$) δ 139.4 (s), 136.8 (s), 127.4 (2 carbons, d), 61.3 (s), 46.4 (t), 41.1 (t), 33.4 (t), 32.5 (t), 27.2 (t), 26.7 (t), 26.2 (t), 24.7 (t), 22.3 (t); mass spectrum (70 eV), *m/e* (relative intensity) 300 (M^+, 55), 299 (20), 257 (85), 242 (25), 215 (40), 198 (100), metastable ions at *m/e* 220.2 ($257^2/300$) and 182.3 ($198^2/215$).

For **2c**: bp 155–165 °C (0.03 mm); IR ($CHCl_3$) 3400–3200 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 16), 1.8–2.2 (m, 6), 2.2–2.4 (m, 4), 2.65 (overlapping br triplets, 4), 7.2 (s, 4); ^{13}C NMR ($CDCl_3$) δ 140.3 (s), 136.7 (s), 127.5 (2 carbons, d), 61.6 (s), 46.5 (t), 42.2 (t), 35.3 (t), 28.6 (t), 26.8 (t), 26.3 (t), 24.8 (t), 22.5 (t); mass spectrum (70 eV), *m/e* (relative intensity) 314 (M^+, 10), 313 (15), 300 (40), 257 (60), 243 (65), 242 (60), 200 (100), 166(50).

For **10**: 82% yield; bp 140–150 °C (0.04 mm); IR ($CHCl_3$) 3400–3200 (NH_2), 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 14), 1.9–2.2 (m, 4), 2.2–2.4 (m, 4), 3.5 (d, 2, *J* = 5 Hz), 6.2 (dd, 1, *J* = 15, 5 Hz; goes to d, *J* = 15 Hz when irradiated at δ 3.5), 6.5 (d, 1, *J* = 15 Hz), 7.2 (AB, 4); ^{13}C NMR ($CDCl_3$) δ 139.1 (s), 134.8 (s), 130.8 (d), 129.1 (d), 127.6 (d), 125.3 (d), 61.1 (s), 46.5 (t), 44.4 (t), 33.5 (t), 27.0 (t), 26.4 (t), 24.9 (t), 22.4.

For **11**: 84% yield; bp 145–150 °C (0.04 mm); IR ($CHCl_3$) 3400–3200 (NH_2), 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 14), 1.8–2.2 (m, 4), 2.2–2.5 (m, 6), 2.75 (br t, 2), 6.1 (dd, 1, *J* = 15, 6 Hz), 6.5 (d, 1, *J* = 15 Hz), 7.3 (br s, 4); ^{13}C NMR ($CDCl_3$) δ 138.2 (s), 135.7 (s), 131.6 (d), 127.5 (d), 127.4 (d), 125.1 (d), 61.5 (s), 46.4 (t), 41.4 (t), 36.7 (t), 33.3 (t), 26.7 (t), 26.2 (t), 24.7 (t), 22.3 (t); mass spectrum (70 eV), *m/e* (relative intensity) 312 (M^+, 70), 311 (35), 269 (100), 242 (20), 228 (20), 200 (30), 199 (30), 198 (30), 166(50), metastable ion at *m/e* 232 ($269^2/312$).

Reaction of 2 with Phenyl Isothiocyanate. Mixed Ureas 13. Amine **2** (1 equiv) was allowed to react neat with a slight excess of phenylisothiocyanate for several hours. The mixture was then triturated with ether and the solid urea recrystallized from the ethanol/hexane.

For **13b**: 69% yield; mp 119–121 °C; IR ($CHCl_3$) 3400, 2970, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 14), 1.8–2.2 (m, 4), 2.2–2.4 (m, 4), 2.7 (t, 2), 3.7 (q, 2, t in D_2O), 6.2 (br s, 1, absent in D_2O), 7.2 (br s, 4), 7.4 (m, 5), 8.2 (br s, 1, absent in D_2O).

Anal. Calcd for $C_{27}H_{37}N_3S \cdot 0.5H_2O$: C, 72.92; H, 8.61; N, 9.50. Found: C, 72.83; H, 8.39; N, 9.06.

For **13c**: 61% yield; mp 80–81 °C; IR ($CHCl_3$) 3400, 2970, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 16), 1.8–2.2 (m, 4), 2.2–2.4 (m, 4), 2.7 (br t, 2), 3.7 (br q, 2, t in D_2O), 6.2 (br s, 1, absent in D_2O), 7.2 (s, 4), 7.4 (m, 5), 7.8 (br s, 1, absent in D_2O).

Anal. Calcd for $C_{28}H_{39}N_3S$: C, 74.78; H, 8.74; N, 9.34. Found: C, 74.51; H, 8.81; M, 9.32.

(*E*)-4-[1-(2-Cyanoethenyl)]phencyclidine (13). Nitrile **13** was synthesized (*E*/*Z* ratio of 5/1) by reaction of **5** and acrylonitrile according to the general $Pd(OAc)_2$ procedure described above: 69% yield; mp 125.5–126.5 °C (CH_3OH); IR ($CHCl_3$) 2970, 2240, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 12), 1.8–2.2 (m, 4), 2.2–2.4 (m, 4)8 5.8 (d, 1, *J* = 16 Hz), 7.35 (d, 1, *J* = 16 Hz), 7.4 (s, 4) (for (*Z*)-**13** the olefinic protons come at δ 5.4 (*J* = 11 Hz) and 7.15); ^{13}C NMR ($CDCl_3$) δ 150.4 (d), 144.5 (s), 131.2 (s), 128.0 (d), 126.6 (d), 118.4 (s), 95.4 (d), 61.0 (s), 46.5 (t), 33.5 (t), 27.1 (t), 26.3 (t), 24.9 (t), 22.4 (t); mass spectrum (70 eV), *m/e* (relative intensity) 294 (M^+, 40), 293 (20), 251 (100), 166 (20), metastable ion at *m/e* 214.5 ($251^2/294$).

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.89; N, 9.51. Found: C, 81.32; H, 8.90; N, 9.46.

Reduction of 13 to 2 via 14. Olefinic nitrile was hydrogenated in a Parr apparatus as described above to give **14** in 85% yield. Saturated nitrile **14** was further reduced over 4 h by adding it to LAH in THF at reflux to give amine **2b** in nearly quantitative yield.

For **14**: IR ($CHCl_3$) 2225 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 12), 1.8–2.2 (m, 4), 2.2–2.4 (m, 4), 2.7 (t, 2), 3.0 (t, 2), 7.3 (s, 4); ^{13}C NMR ($CDCl_3$) δ 139.0 (s), 135.6 (s), 127.9 (d), 127.4 (d), 119.5 (s), 61.1 (s), 46.6 (t), 33.6 (t), 31.2 (t), 27.0 (t), 26.4 (t), 24.9 (t), 22.4 (t), 19.22.

(*E*)-4-[1-[2-(Carbomethoxy)ethenyl]]phencyclidine (19). Ester **19** was synthesized by reaction of **5** with methyl acrylate in the presence of $Pd(OAc)_2$ as described above: 70% yield; bp 120–130 °C (0.15 mm); IR ($CHCl_3$) 2970, 1705, 1640, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 12), 1.8–2.2 (m, 4), 2.2–2.4 (m, 4), 3.8 (s, 3), 6.5 (d, 1, *J* = 16 Hz), 7.4 (AB, 4, *J* = 8 Hz), 7.75 (d, 1, *J* = 16 Hz) (for cis-**19**, olefinic protons are at δ 5.85 (*J* = 12 Hz) and 6.9); ^{13}C NMR ($CDCl_3$) δ 167.3 (s), 144.5 (d), 142.9 (s), 132.0 (s), 127.7 (d), 127.2 (d), 117.0 (d), 61.1 (s), 51.5 (q), 46.4 (t), 33.3 (t), 26.9 (t), 26.2 (t), 24.8 (t), 22.3; mass spectrum (70 eV), *m/e* (relative intensity) 327 (M^+, 20), 326 (15), 284 (55), 242 (20), 166 (25), 83 (100).

Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.93; H, 8.81; N, 4.32.

4-[1-[2-(Carboxymethyl)ethyl]]phencycline (18). Saturated ester **18** was obtained in good yield by hydrogenation of **19** as described above: bp 115–125 °C (0.1 mm); mp 74–75 °C (EtOH/hexane); IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 12), 1.8–2.2 (m, 4), 2.2–2.4 (m, 4), 2.6 (t, 2), 2.9 (t, 2), 3.7 (s, 3), 7.2 (AB, 4); ^{13}C NMR ($CDCl_3$) δ 173.5 (s), 137.8 (s), 135.4 (s), 127.6 (d), 127.4 (d), 61.3 (s), 51.6 (q), 46.5 (t), 35.6 (t), 33.5 (t), 30.5 (t), 26.9 (t), 26.4 (t), 24.8 (t), 22.4 (t).

Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.41; H, 9.31; N, 4.21.

Reaction of 5 and Acrolein Ethylene Ketal. Isolation of 16. Reaction of **5** and acrolein ethylene ketal in the presence of $Pd(OAc)_2$ as described above gave after workup a mixture of esters **16a** and **16b**. Ester **16a** (ca. 20%) decomposed slowly to **16b** upon standing and rapidly in the presence of base. Ester **16b** was ultimately obtained in 61% yield.

For **16a**: mass spectrum (70 eV), *m/e* 469 (M^+); ^1H NMR ($CDCl_3$) δ 4.2 (OCH_2CH_2I), 3.6 (OCH_2CH_2I). These were readily observable after converting the alcohol (**16b**) to its 3,5-dinitrobenzoyl ester before taking the ^1H NMR spectrum.

For **16b**: IR 3350, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 12), 1.8–2.2 (m, 4) 2.2–2.4 (m, 4), 2.2 (s, 1, absent in D_2O), 2.7 (t, 2), 2.95 (t, 2), 3.8 (t, 2, $CO_2CH_2CH_2OH$), 4.25 ($CO_2CH_2CH_2OH$), 7.2; ^{13}C NMR ($CDCl_3$) δ 66.1 (t) and 60.7 (t) for $CO_2CH_2CH_2OH$; mass spectrum (70 eV), *m/e* 359 (M). Ester **16b** was transesterified to ester **18** by reacting it with refluxing CH_3OH in the presence of toluenesulfonic acids for 20 h.

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Registry No. 2a, 76916-18-2; **2b**, 77415-78-2; **2c**, 77415-79-3; **4**, 2201-33-4; **5**, 77415-80-6; **6a**, 3485-84-5; **6b**, 5428-09-1; **6c**, 52898-32-5; **7**, 76916-13-7; **8**, 77415-81-7; (*E*)-**9a**, 77415-82-8; (*E*)-**9b**, 77415-83-9; (*E*)-**9c**, 77415-84-0; (*E*)-**10**, 77415-85-1; (*E*)-**11**, 77415-86-2; **12a**, 76916-26-2; **12b**, 77415-87-3; **12c**, 77415-88-4; (*E*)-**13**, 77415-89-5; (*Z*)-**13**, 77415-90-8; **13a**, 76916-30-8; **13b**, 77415-91-9; **13c**, 77482-41-8; **14**, 77415-92-0; **16a**, 77482-42-9; **16b**, 77415-93-1; **18**, 77415-94-2; (*E*)-**19**, 77415-95-3; (*Z*)-**19**, 77415-96-4; **20**, 77415-97-5; **21**, 77415-98-6; (*E*)-**22**, 77415-99-7; 1,4-diiodobenzene, 624-38-4; 1-piperidyl-1-cyanocyclohexane, 3867-15-0; *N*-(2-bromoethyl)phthalimide, 574-98-1; palladium acetate, 33571-36-7; phenyl isothiocyanate, 103-72-0; acrylonitrile, 107-13-1; methyl acrylate, 96-33-3; acrolein ethylene ketal, 3984-22-3.

Organic Disulfides and Related Substances. 43. Properties of a Mercaptoalkyl Sulfoxide, a Novel Class of Structure[1]

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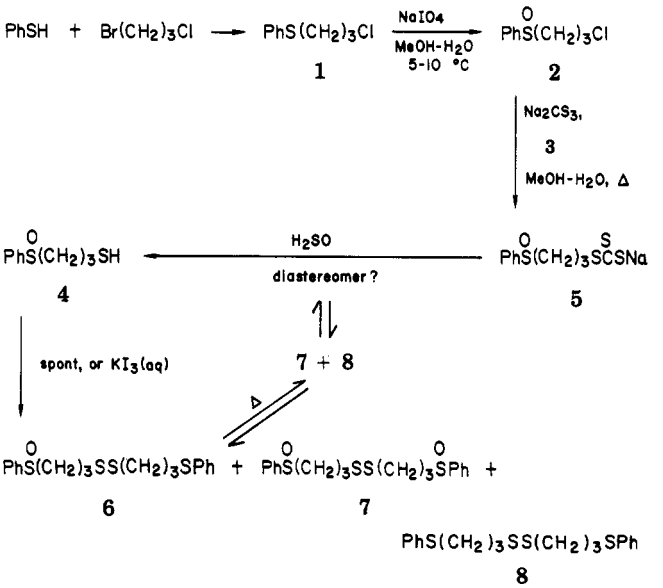
3-Mercaptopropyl phenyl sulfoxide (**4**) was prepared by reaction of 3-chloropropyl phenyl sulfoxide (**2**) with sodium trithiocarbonate (**3**). The mercaptopropyl sulfoxide **4** could be obtained only in a maximum purity of 93% (and yield of 75%) because it underwent rapid oxidation at ~25 °C of the SH function, with reduction of the S(O) function; however, **4** is more stable neat or in chloroform. The thiol **4** could be converted to the 2,4-dinitrophenyl sulfide in 47% yield. Oxidation with iodine gave the corresponding monosulfoxide–disulfide **6**, the disulfoxide–disulfide **7**, and the disulfide–disulfide **8** in respective yields of up to 27%, 38%, and 12%. The intermediary 3-chloropropyl sulfoxide (**2**) was obtained by oxidizing the sulfide with $NaIO_4$ in methanol–water; it (very slowly) disproportionated to the sulfide and sulfone. The chloro sulfoxide **2** reacted far more rapidly than the chloro sulfide **1** with **3**, but use of the chloro sulfide **1** afforded the preferred route to the disulfide–disulfide **8** (26% yield).

Studies on the chemistry of disulfides have led us to an interest in the properties of disulfides containing sulfoxide functions. When an effort to synthesize a sulfoxide–disulfide from a chloroalkyl sulfoxide by using Na_2S_2 gave an unpromising mixture, a mercapto sulfoxide seemed an attractive starting material. Since thiols are well-known to be oxidized to disulfides by sulfoxides (which are reduced thereby to sulfides),[2] our interest in mercapto sulfoxides was stimulated further by curiosity about the compatibility of S(O) and SH functions in the same molecule, a question that seems not to have been addressed heretofore. Mercapto sulfoxides apparently have not been reported previously, although a thiolate salt of one has been invoked as an intermediate.[3] In this paper we report the properties of 3-mercaptopropyl phenyl sulfoxide (**4**), a compound that undergoes redox reactions readily in water or methanol, together with conversion of **4** to the corresponding monosulfoxide–disulfide **6**, disulfoxide–disulfide **7**, and disulfide–disulfide **8**.

For synthesis of the intermediary chloro sulfoxide **2** (Scheme I), oxidation of the known sulfide **1**[4] with ozone[5] was unattractive because large amounts of **2** were desired, and use of SO_2Cl_2–wet silica gel[6] or Me_2SO[7] proved unpromising. Oxidation of **1** with $NaIO_4$ in water or aqueous dioxane[8] gave **2** but also the sulfone. However, use of

Scheme I



$NaIO_4$ in methanol–water with the sulfide **1** gave the pure sulfoxide **2** in 100% yield;[8] the striking improvement effected by methanol warrants special emphasis. It is worth remarking also that the sulfoxide **2** underwent a redox reaction, although slowly, to give the sulfide **1** and the sulfone.

Conversion of the chloride **2** to a thiol derivative first was attempted by using sodium *p*-toluenethiosulfate (*p*-$CH_3C_6H_4SO_2SNa$; 5 days, 70 °C, DMF). The product contained 61% of a thiolsulfonate,[9] but impurities could not be removed. Scheme I shows the route to **4** that proved successful, reaction of the chloro sulfoxide **2** with

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