Synthesis of 5-Azaoxindole

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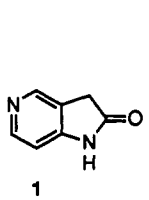
Oxindoles and azaoxindoles together constitute a medicinally important class of heterocyclic compounds.[1] Our interest in the area stems from success of the oxindole derivative tenidap (CP-66,248) as a novel antiinflammatory agent in advanced clinical trials. In a recent program to examine the antiinflammatory properties of azaoxindole analogues of tenidap, a synthetic route to 5-azaoxindole (1) was required. Surprisingly, while three of the four possible unsubstituted azaoxindoles (4-, 6-, and 7-azaoxindole) have been known for some time and can be readily prepared,[2,3] 5-azaoxindole (1) has never been synthesized to our knowledge, although one synthesis has been attempted.[4] In this paper, we report the first preparation of 5-azaoxindole via tribromination of readily available 5-azaindole (2).[4,5] As has been the case in our drug discovery program, we expect the availability of this new compound will make it an attractive intermediate in other areas in which the biological activities of oxindole and azaoxindole derivatives are being exploited.



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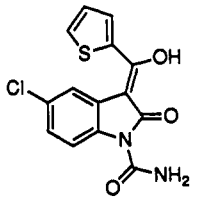

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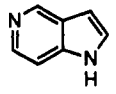

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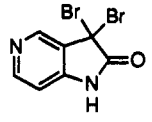

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Our first attempts to prepared 5-azaoxindole (1) followed the procedure described by Marfat[3] for the conversion of 7-azaindole to 7-azaoxindole. Unexpectedly, the treatment of 5-azaindole (2) with 3–4 equiv of pyridinium bromide perbromide (PBPB) in *tert*-butyl alcohol furnished only the hydrobromide of 3-bromo-5-azaindole (3), which precipitated from the reaction mixture and failed to undergo further oxidation to 3,3-dibromo-5-azaoxindole (4), even on heating. During aqueous workup of the reaction mixture, further reaction took place but resulted in the formation of large amounts of dark, intractable material with little, if any, discrete product being formed. We briefly examined the use of different solvent systems both for the oxidation of 2 as well as 3 (isolated following reaction of 2 with 1–2 equiv of PBPB and subsequent basic workup) but achieved little success. While small amounts of 3,3-dibromo-5-azaoxindole (4) were isolated in some attempts, this material proved to be amorphous and unstable at room temperature.

A very satisfactory solution to the problem was achieved by altering the reaction conditions in two ways. First, the reaction was carried out in a mixture of *tert*-butyl alcohol and water using bromine as the oxidant. Secondly, 4 equiv of the latter were used to bring about *tribromination* of 1, thus obviating isolation of the unstable dibromide 4. The initial addition of bromine yields, as expected, the hydrobromide of 3. However, upon slow adjustment of the pH of the mixture to 6.5 to 7, further oxidation to the crystalline tribromide 5 occurs. Precipitating from the reaction mixture, this material is easily isolated (60–90% yield) and is normally sufficiently pure for use in the final hydrogenolysis reaction (H_2/10% Pd/C) yielding 5-azaoxindole (1). Although the tribromide 5 is more stable than the dibromide 4, darkening of 5 occurs on standing at room temperature for a few days. However, this is of little consequence provided the hydrogenation step is carried out within a day or two of the preparation of 5.

This synthesis of 5-azaoxindole is extremely easy to carry out and has allowed the preparation of multigram batches of this new, useful compound. The overall yield of 5-azaoxindole (1) from 2 is typically about 60%.

Experimental Section

3,3,7-Tribromo-5-azaoxindole (5). To a stirred solution of 5-azaindole (2; 1.5 g, 12.7 mmol) in *tert*-butyl alcohol (100 mL) and H_2O (100 mL) at room temperature was added dropwise neat Br_2 (2.6 mL, 50.5 mmol) over a period of 20 min. Following addition of Br_2, the pH of the mixture was approximately 1. By the careful, slow addition of saturated aqueous $NaHCO_3$ solution over 0.5 h, the pH of the mixture was then adjusted to 6.5–7. During this period, precipitation of the yellow product became evident. This material was collected by filtration of the reaction mixture, washed with water, and dried in the air yielding 5 (3.70 g, 79%): mp >250 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.68 (s, 1 H), 8.57 (s, 1 H); IR (KBr disc) 1747, 1613, 1471, 1155 cm^{-1}; HRMS calcd for $C_7H_3{}^{79}Br^{81}Br_2N_2O$ 371.7754 (M^+), found 371.7753. Anal. Calcd for $C_7H_3Br_3N_2O$: C, 22.67; H, 0.82; N, 7.55. Found: C, 23.39; H, 0.97; N, 7.51.

By extraction of the filtrate with EtOAc, more 5 (700 mg, 15%) was obtained; however, this sample was somewhat less pure as determined by TLC. Combined impure fractions from several runs were purified by flash chromatography on silica gel using 10% MeOH/$CHCl_3$ as eluant.

5-Azaoxindole (1). To a solution of 3,3,7-tribromo-5-azaoxindole (5; 6.4 g, 17.3 mmol) in EtOH (1200 mL) was added 10% Pd on charcoal (3.2 g). The mixture was hydrogenated under 3 atm of H_2 for 3 h using a Parr shaker. The catalyst was removed by filtration of the mixture through a pad of Celite and washed well with EtOH. On removal of the solvent, a brown solid remained (predominantly the hydrobromide of 1, 3.5 g). This was dissolved in H_2O, treated with activated charcoal, and filtered through Celite. The pH of the filtrate was adjusted to 7.5 by the addition of saturated aqueous $NaHCO_3$ solution. The mixture was then extracted three times with *n*-BuOH. The combined *n*-BuOH extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a solid. This was triturated with butanone and filtered to collect 5-azaoxindole (1) as a tan solid, 1.60 g (69%). An analytical sample was obtained by re-

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(2) 4- and 6-azaoxindoles: Daisley, R. W.; Hanbali, J. R. *Synth. Commun.* **1981**, *11*, 743 and references cited therein.

(3) 7-Azaoxindole: Marfat, A.; Carta, M. P. *Tetrahedron Lett.* **1987**, *28*, 4027 and references cited therein.

(4) Okuda, S.; Robinson, M. M. *J. Org. Chem.* **1959**, *24*, 1008.

(5) (a) Dormoy, J.-R.; Heymes, A. U.S. Patent 4,425,033. (b) Sakamoto, S.; Condo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823.

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crystallization from MeOH: mp >250 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.77 (br s, 1 H), 8.28 (d, J = 5.4 Hz, 1 H), 8.24 (s, 1 H), 6.83 (d, J = 5.4 Hz, 1 H), 3.53 (s, 2 H); IR (KBr disc) 1712, 1619, 1597, 1488 cm^{-1}; MS m/z (relative percent) 134 (100), 106 (22), 105 (34). Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.28; H, 4.47; N, 20.72.

Unusual, Cofacial Structure of a Sterically Congested Stilbene: (*Z*)-2,2,5,5-Tetramethyl-3,4-diphenyl-3-hexene

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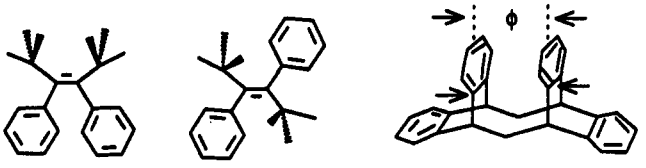
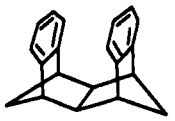
The unusual steric effects and "one-way photoisomerizations" reported in naphthalenes prompted an investigation of the related sterically congested stilbenes, (*Z*)- (1) and (*E*)-2,2,5,5-tetramethyl-3,4-diphenyl-3-hexene (2).[1-3] In order to understand the observed low isomerization barrier and spectra,[2f] a further investigation of 1 and 2 is now reported. X-ray structural analysis, photoelectron (PE) spectroscopy, and theory elaborates the unique structures of 1 and 2 described in the following text.



1 2 3



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The properties of 1 and 2 gave hints to unusual structures.[2f] Both had UV spectra more like toluene than stilbenes (e.g., 2 showed λ = 262, 235 sh, 207 max, ϵ = 1.1 × 10^4). The ^{1}H NMR spectrum of 2 showed an upfield-shifted *tert*-butyl resonance at δ 0.7 and normal aromatic signals, whereas the ^{1}H NMR spectrum of 1 showed upfield shifted aromatic resonances at δ 6.6-6.9 and normal *tert*-butyl signals.

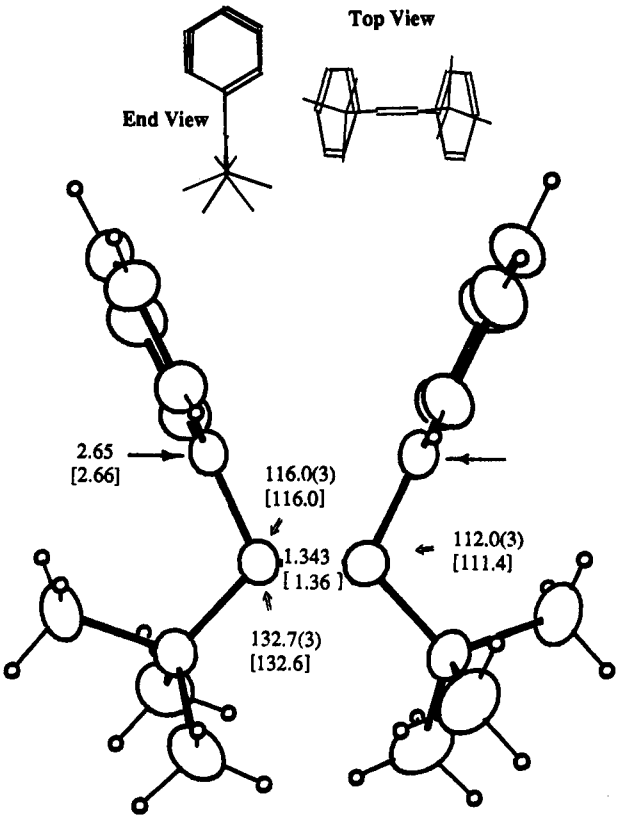

Figure 1. Drawings of X-ray crystal structure of 1. Values in brackets calculated by AM1.

X-ray analysis of 1, crystallized from methanol, clearly showed (Figure 1) no twisting about the central double bond in contrast to (*Z*)-stilbene.[4-6] Instead, the planes of the phenyl groups are perpendicular to the plane of the central C=C bond. The π-systems of the phenyl rings are cofacial or "face-to-face" to one another and orthogonal to the central π-bond.[7] As has been seen in other cases,[8b] this compression of the phenyl rings did not affect the ring planarity in 1. The dominant distortion is the mutual repulsion of the *tert*-butyl groups to open the *t*-Bu—C=C angle to 132.7° and compress the phenyl rings.

Comparison to related cofacial hydrocarbons, including 3 and 4, reveals 1 to be unique with the (a) absence of a

(1) For a general review of alkene isomerizations, see: Saltiel, J.; Charlton, J. L. In *Rearrangements in the Ground and Excited States*; DeMayo, P., Ed.; Academic: New York, 1980; p 25.

(2) For related papers see: (a) Lenoir, D.; Malwitz, D.; Meyer, B. *Tetrahedron Lett.* **1984**, *25*, 2965. (b) Gano, J. E.; Eizenberg, L. *J. Am. Chem. Soc.* **1973**, *95*, 972. (c) Chapman, O. L.; Gano, J. E.; West, P. R.; Regitz, M.; Maas, G. *J. Am. Chem. Soc.* **1981**, *103*, 7033. (d) Gano, J. E.; Wettach, R. H.; Platz, M. S.; Senthilnathan, V. P. *J. Am. Chem. Soc.* **1982**, *104*, 2326. (e) Mueller, P. H.; Houk, K. N.; Gano, J. E.; Platz, M. S. *Tetrahedron Lett.* **1983**, 485. (f) Lenoir, D.; Gano, J. E.; McTague, J. A. *Tetrahedron Lett.* **1986**, *27*, 5339.

(3) Hamaguchi, H.; Tasumi, M.; Karatsu, T.; Arai, T.; Tokumaru, K. *J. Am. Chem. Soc.* **1986**, *108*, 1698. (b) Arai, T.; Karatsu, T.; Sakuragi, H.; Tokumaru, K. *Tetrahedron Lett.* **1983**, *24*, 2873.

(4) Details of X-ray: Gano, J. E.; Subramaniam, G.; Pinkerton, A. A.; Birnbaum, R. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, submitted for publication.

(5) Partial X-ray structure: Ermer, O. *Z. Naturforsch., Teil B* **1977**, *32*, 837.

(6) MMP2 of 2: Favini, G.; Simonetta, M.; Sottocornola, M.; Todeschini, R. *J. Comput. Chem.* **1982**, *3*, 178.

(7) Although "face-to-face" has been used to describe this relationship, which is clearly not coplanar, the succinct term cofacial is preferred by the current authors.

(8) **Janusenes 3**: (a) Cristol, S. J.; Lewis, D. C. *J. Am. Chem. Soc.* **1967**, *89*, 1476. (b) MacIntyre, W. M.; Tench, A. H. *J. Org. Chem.* **1973**, *38*, 130. **[3,3]Orthocyclophanes 5**: (c) Mataka, S.; Takahashi, K.; Hirota, T.; Takuma, K.; Kobayashi, H.; Tashiro, M. J. *J. Chem. Commun.* **1985**, 983. (d) Mataka, S.; Takahashi, K.; Mimura, T.; Hirota, T.; Takuma, K.; Kobayashi, H.; Tashiro, M. J. *J. Org. Chem.* **1987**, *52*, 2656. **4** (structure in text): (e) Fessner, W.-D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc.* **1987**, *109*, 4626. (f) Prinzbach, H.; Sedelmeier, G.; Krüger, C.; Goddard, R.; Martin, H.-D.; Gleiter, R. *Angew. Chem., int. Ed. Engl.* **1978**, *17*, 271. **Hypostrophenes 6**: (g) Fessner, W.-D.; Sedelmeier, G.; Knothe, L.; Prinzbach, H.; Rihs, G.; Yang, Z.-Z.; Kovac, B.; Heilbronner, E. *Helv. Chim. Acta* **1987**, *70*, 1816.

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