3q, 74965-13-2; **4b**, 74986-04-2; **4c**, 74986-05-3; **4d**, 74986-06-4; **4f**, 74986-07-5; **4i**, 74986-08-6; **4j**, 74986-09-7; **4k**, 74986-10-0; **4l**, 74986-11-1; **4m**, 74986-12-2; **4n**, 74986-13-3; **4o**, 74986-14-4; **4p**, 74986-15-5; **4s**, 66079-76-3; **6b**, 1444-11-7; **6e**, 74986-16-6; **6i**, 74986-17-7; **6l**, 74986-18-8; **7b**, 73529-28-9; **7k**, 74986-19-9; **7m**, 13712-59-9; **7n**, 74986-20-2; **7o**, 74986-21-3; **7r**, 74986-22-4; **7s**, 74986-23-5; **9**, 74986-24-6; **14b**, 131-11-3; **14e**, 20116-65-8; **16b**, 2672-57-3; **16e**, 74986-25-7; **17b**, 23893-69-8; **17i**, 74986-26-8; **21**, 74986-27-9; **22p**, 74965-14-3; **22q**, 74965-15-4; **24**, 635-10-9; DMAD, 762-42-5; dimethyl (*E*)-1-pyrrolyl-2-butenedioate, 66653-26-7.

Preparation and Bromination of a 3a,6-Dihydroindole[1]

Wayland E. Noland

School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Keun Jae Kim

Department of Chemistry, Soongjun University, Taejon, Korea

Chang Kiu Lee,* Sun Kun Bae, and Chi Sun Hahn

Department of Chemistry, Yonsei University, Seoul, Korea

Received November 29, 1979

A 3a,6-dihydroindole was prepared by the Diels–Alder addition of dimethyl acetylenedicarboxylate to dimethyl [*N*-(2,6-dimethylphenyl)pyrrol-2-yl]maleate. Subsequent reaction with bromine gave a 2,3-dibromoindoline which is different from that obtained from the corresponding 3a,7a-dihydroindole.

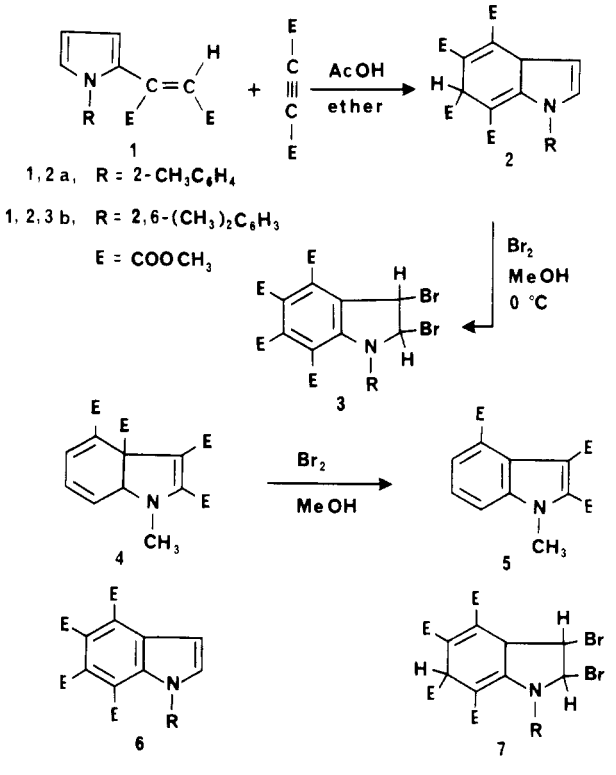
The 3a,6-dihydroindole structure **2** was suggested many years ago for an adduct of 1-methylpyrrole and dimethyl acetylenedicarboxylate (DMAD).[2] The correct structure has subsequently been shown to be **4**.[3] Several reactions have been reported, however, in which indoles are obtained via intermediates of type **2**.[4,5] We now report the isolation of a 3a,6-dihydroindole of this structure.

In an attempt to prepare indole compounds such as **6**, we prepared a series of (pyrrol-2-yl)maleate and -fumarate derivatives.[6] Interestingly, of the many (*N*-alkylpyrrol-2-yl)maleates (e.g., alkyl = CH_3, *n*-C_4H_9, *sec*-C_4H_9, *t*-C_4H_9, $C_6H_5CH_2$) and (*N*-arylpyrrol-2-yl)maleates (e.g., aryl = C_6H_5, *p*-BrC_6H_4, *p*-$(CH_3O)C_6H_4$) or -fumarates, only the bulky *N*-(2,6-dimethylphenyl)pyrrole derivative gave the adduct **2b** (Scheme I). Furthermore, compound **2b** was formed only when **1b** and DMAD were refluxed in ether–glacial acetic acid solution (1:1 by volume). Refluxing in benzene or xylene without the acid gave only tar and mostly recovered starting material. Pyrroles having bulkier N substituents such as a α-naphthyl or triphenylmethyl group did not give maleate or fumarate derivatives at all.

Structure **2b** was deduced by spectroscopic methods. The NMR spectrum ($CDCl_3$, Me_4Si) shows four singlets (δ 3.52, 3.63, 3.77, and 3.93), corresponding to the methyl ester groups, and two singlets at δ 1.92 and 2.03, indicating that the 2′- and 6′-methyl groups are nonequivalent. The cyclohexadiene portion of the 3a,6-dihydroindole moiety seems to have a boat[7] conformation; long-range coupling (1.5 Hz) between the 3a-H and 6-H was observed at δ 4.03 and 4.45 while the coupling between the 3-H and 3a-H was almost negligible. An AB quartet centered at δ 6.32 with J = 3.0 Hz is attributed to the olefinic 2-H and 3-H.

When *N*-(2-methylphenyl)pyrrole was refluxed with DMAD in ether–glacial acetic acid (1:1 by volume) solution, compound **2a** was isolated (8%) together with **1a** (both *E* and *Z* isomers).[6] However, attempts to repeat the isolation of **2a** were unsuccessful. Furthermore, compound **2a** could not be prepared from **1a** (both *E* and *Z* isomers)

Scheme I



* To whom correspondence should be addressed at the Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455

(1) Taken in part from the Ph.D. thesis of Chang Kiu Lee, University of Minnesota, Aug 1976; *Diss. Abstr. Int. B* **1977**, *38*, 1210–1211.
(2) Diels, O.; Alder, K.; Winckler, H. *Justus Liebigs Ann. Chem.* **1931**, *490*, 267–276.
(3) Acheson, R. M.; Vernon, J. M. *J. Chem. Soc.* **1962**, 1148–1157.
(4) Hosmane, R. S.; Hiremath, S. P.; Schneller, S. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2450–2453.
(5) Acheson, R. M.; Woollard, J. *J. Chem. Soc., Perkin Trans 1* **1975**, 446–451.

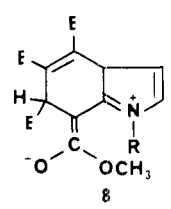
0022-3263/80/1945-4582$01.00/0

and DMAD under reaction conditions similar to those for the preparation of **2b**. Although compound **2a** was obtained only once, its IR, NMR, UV, and mass spectra seem to be consistent with the structure assigned by comparison with the spectra of **2b** (see Experimental Section).

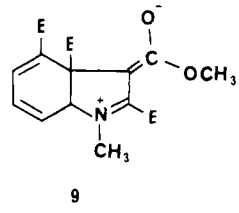
When bromine was added to a suspension of **2b** in methanol at 0 °C, a clear solution formed immediately; however, a white precipitate then formed within 1 min. The spectral data and the elemental analyses of the precipitate seem to be consistent with structure **3**. This is in contrast to the observation that the 3a,7a-dihydroindole ester **4** undergoes elimination of the 3a-ester group in the course of the reaction with bromine to give an aromatized compound, **5**.[3] We have found that aromatization of **4** to **5** by bromine takes place in methanol (95%) better than in any other solvent examined: isopropyl alcohol (67%), *tert*-butyl alcohol (52%), chloroform (13%), tetrahydrofuran (10%), acetonitrile (trace), pyridine (no reaction).

The NMR spectrum ($CDCl_3$, Me_4Si) of **3** shows two singlets of three protons each at δ 1.88 and 2.05 (2′- and 6′-CH_3), four singlets of three protons each at δ 3.55, 3.67, 3.78, and 3.97 ($COOCH_3$), and two doublets of one proton each at δ 3.95 (3-H) and 4.38 (2-H) with J = 2.0 Hz. The latter chemical shift values are typical for protons attached to sp^3-hybridized carbon atoms bearing electron-withdrawing substituents.[8] Three aromatic protons appear as a multiplet centered at δ 7.17.

Since intermediates such as **6** or **7** have not been isolated, it is not known if product **3** is formed by aromatization and subsequent addition of bromine (**2** → **6** → **3**) or by the opposite sequence (**2** → **7** → **3**). However, it is interesting that bromine adds to the C_2–C_3 double bond of the indole. Generally, substitution occurs at C_3 of indole when there is no substituent at that position.[9] The fact that substitution rather than addition of bromine is known to occur on the fully aromatized indole nucleus suggests that the second sequence is the more likely one. When an equimolar amount of bromine was used, the yield of **3** dropped from 82 to 22%; no other crystalline product could be isolated. Other oxidizing agents such as hydrogen peroxide (30%) in methanol or chromium trioxide in pyridine were used, but starting material was recovered in 70–90% yields together with a trace of black gummy residue which could not be characterized. Heating compound **2b** with Pd/C (5%) up to 200 °C gave only tar. The difference in the courses of the reactions of **2b** and **4** with bromine may be due to resonance of the type suggested in structures **8** and **9**. Thus, π electrons on the C_2–C_3 double bond of **2** (**8**) are readily available for the addition of bromine, whereas they are in conjugation with a carbonyl group in **4** (**9**).



8



9

Compound **3** seems to be quite stable to chemical reactions; it was not possible to convert **3** to **6** by using zinc, and attempts to eliminate HBr to prepare a 2- (or 3-) bromoindole derivative by refluxing in MeONa–MeOH or KOH–Me_2SO solution were also unsuccessful.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-18 spectrophotometer. Ultraviolet and visible spectra were recorded on a Shimadzu double-beam spectrophotometer or on a Cary Model 11 spectrophotometer. NMR spectra were recorded on a Varian Associates T-60 spectrometer. Low-resolution mass spectra were obtained by using a Finnigan Model 3300 mass spectrometer. High-resolution mass spectra were obtained on an AEI MS-30 spectrometer at 70 eV and 200 °C by Dr. Roger A. Upham and his associates at the University of Minnesota. Elemental Analyses were performed by the Institute of Physical and Chemical Research, Wako-shi, Saitama-ken, Japan.

Tetramethyl 3a,6-Dihydro-1-(2-methylphenyl)indole-4,5,6,7-tetracarboxylate (2a). Preparation and elemental analyses of **2a** are reported elsewhere,[6] but the spectral data are given here for the purpose of comparison with **2b**: IR (KBr) 1737 (vs), 1708 (s), 1608 (m), 1439 (ms), 1281 (m), 1240 (vs), 1202 (s), 1179 (s), 1017 (ms), 778 (ms) cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 2.47 (br s, $w_{1/2}$ = 16 Hz, 3 H, 2′-CH_3), 3.53 (s, 3 H), 3.67 (s, 3 H), 3.80 (s, 3 H), 3.92 (s, 3 H, all $COOCH_3$), 4.35 (br m, 1 H, 3a-H), 4.60 (s, 1 H, 6-H), 6.25 (d, $J_{3,2}$ = 3 Hz, 1 H, 3-H), 6.62 (d, $J_{2,3}$ = 3 Hz, 1 H, 2-H), 7.28 (m, 4 H, C_6H_4); UV (MeOH) 290 nm (ϵ 6030), 341 (9750); high-resolution mass spectrum, m/e (relative intensity ≥ 7; calcd m/e) 441.1417 (6; $C_{23}H_{23}NO_8$, 441.1422, M), 381.1191 (8; $C_{21}H_{19}NO_6$, 381.1211, M – $HCOOCH_3$), 351.1091 (22; $C_{20}H_{17}NO_5$, 351.1105, M – $HCOOCH_3$ – CH_2O or $^{13}C^{12}C_{19}H_{16}NO_5$, 351.1061, M* – $HCOOCH_3$ – OCH_3), 350.1034 (100; $C_{20}H_{16}NO_5$, 350.1027, M – $HCOOCH_3$ – OCH_3), 338.1385 (16; $C_{20}H_{20}NO_4$, 338.1391, M – $COOCH_3$ – CO_2), 292.0979 (19; $C_{18}H_{14}NO_3$, 292.0972, M – 2 $COOCH_3$ – OCH_3), 205.0879 (7; $C_{15}H_{11}N$, 205.0890, M – 4 $COOCH_3$), 204.0816 (9; $C_{15}H_{10}N$, 204.0812, M – $HCOOCH_3$ – 3 $COOCH_3$).

Tetramethyl 3a,6-Dihydro-1-(2,6-dimethylphenyl)indole-4,5,6,7-tetracarboxylate (2b). A mixture of dimethyl [1-(2,6-dimethylphenyl)pyrrol-2-yl]maleate (**1b**;[6] 0.32 g, 1.02 mmol), DMAD (0.15 g, 1.05 mmol), diethyl ether (anhydrous, 10 mL), and glacial acetic acid (10 mL) was refluxed for 24 h. The solvent was distilled off under vacuum (2 mm) without application of heat, and the residual gummy material was dissolved in warm methanol (10 mL). A few milliliters of ether was added so that the solution became cloudy. After the mixture was cooled in a refrigerator, a yellowish white solid formed, which was recrystallized from methanol to give **2b** as pale yellow prisms: 0.22 g (47%); mp 150–153 °C (lit.[6] 155–157 °C); IR (KBr) 1751 (vs), 1722 (s), 1625 (m), 1560 (ms), 1510 (ms), 1450 (ms), 1291 (ms), 1272 (ms), 1250 (s), 1220 (s), 1185 (ms) cm^{-1}; NMR, see text; UV (MeOH) 278 nm (ϵ 5420, infl), 290 (6600), 343 (9720); high-resolution mass spectrum, m/e (relative intensity ≥ 6; calcd m/e) 455.1548 (6; $C_{24}H_{25}NO_8$, 455.1597, M), 395.1355 (9; $C_{22}H_{21}NO_6$, 395.1368, M – $HCOOCH_3$), 365.1151 (24; $^{13}C^{12}C_{20}H_{18}NO_5$, 365.1218, M* – $HCOOCH_3$ – OCH_3), 364.1117 (100; $C_{21}H_{18}NO_5$, 364.1185, M – $HCOOCH_3$ – OCH_3), 352.1541 (15; $C_{21}H_{22}NO_4$, 352.1548, M – $COOCH_3$ – CO_2), 306.1146 (18; $C_{19}H_{16}NO_3$, 306.1129, M – 2 $COOCH_3$ – OCH_3), 219.1033 (6; $C_{16}H_{13}N$, 219.1047, M – 4 $COOCH_3$), 218.0987 (8; $C_{16}H_{12}N$, 218.0969, M – $HCOOCH_3$ – 3 $COOCH_3$), 204.0837 (6; $C_{15}H_{10}N$, 204.0812, M – 4 $COOCH_3$ – CH_3).

Tetramethyl 2,3-Dibromo-1-(2,6-dimethylphenyl)-indoline-4,5,6,7-tetracarboxylate (3b). Bromine (0.05 g, 0.31 mmol) was added to a suspension of **2b** (0.08 g, 0.17 mmol) in methanol (10 mL) at 0 °C. The mixture became a clear solution immediately, and a white precipitate formed within 1 min. The precipitate was recrystallized from methanol to give **3b** as a white powder: 86 mg (82%); mp 183–184 °C; IR (KBr) 2965, 1750, 1738, 1725, 1615, 1553, 1488, 1445, 1350, 1275, 1213, 1192, 1180, 1120, 800 cm^{-1}; NMR, see text; UV (MeOH) 226 nm (ϵ 15 970, infl), 272 (5670, infl), 279 (6100, infl), 298 (7750), 343 (7560); mass spectrum m/e (relative intensity ≥ 5; M* refers to the ^{81}Br isotopic peak)

(6) Noland, W. E.; Lee, C. K. *J. Org. Chem.*, preceding paper in this issue.
(7) Paschal, J. W.; Rabideau, P. W. *J. Am. Chem. Soc.* **1974**, *96*, 272–274.
(8) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, England, 1969; p 166.
(9) Remers, W. A. In "Indoles. Part One"; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Chapter 1, pp 71–78.

615 (5, M**), 613 (9, M*), 611 (5, M), 524 (40, M** - $HCOOCH_3$ - OCH_3), 522 (100, M* - $HCOOCH_3$ - OCH_3), 520 (39, M - $HCOOCH_3$ - OCH_3), 510 (13), 464 (13), 462 (8), 217 (10), 105 (12), 79 (11).

Anal. Calcd for $C_{24}H_{23}Br_2NO_8$ (mol wt 613.28): C, 47.00; H, 3.78; Br, 26.06; N, 2.28. Found: C, 46.84; H, 3.83; Br, 26.17; N, 2.02.

Acknowledgment. We are grateful to Mr. Thomas Robison for his helpful suggestions in preparing the manuscript. C.K.L. thanks the Korean Science and Engineering Foundation for a research grant.

Registry No. 1b, 74965-13-2; **2a**, 74965-14-3; **2b**, 74965-15-4; **3b**, 74965-16-5; DMAD, 762-42-5.

Synthesis and Some Stereochemical Aspects of [2.2](2,5)Furano(3,6)pyridazinophane and Its *N*-Oxide

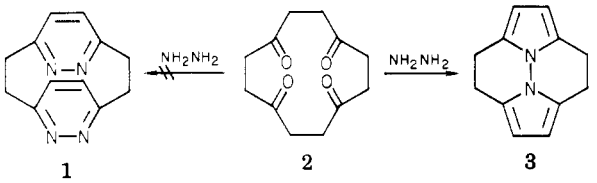
Massimo D. Bezoari and William W. Paudler*

Department of Chemistry, The University of Alabama, University, Alabama 35486

Received June 13, 1980

The synthesis of [2.2](2,5)furano(3,6)pyridazinophane (**6**), the first reported [2.2]pyridazinophane, is described. This comprises only the second known π-excessive/π-deficient [2.2]heterophane. Ultraviolet spectral studies indicate that there is some transannular interaction between the pyridazine and furan rings. A phane containing a 12-membered ring is also formed during the synthesis of the title compound. The chiral *N*-oxide **12** is the first reported *N*-oxide in the para-substituted [2.2]heterophane class.

During an attempted synthesis of [2.2](3,6)-pyridazinophane (**1**) from the tetraketone **2**, we obtained the unexpected nitrogen-bridged tetrahydroannulene **3**.[1]



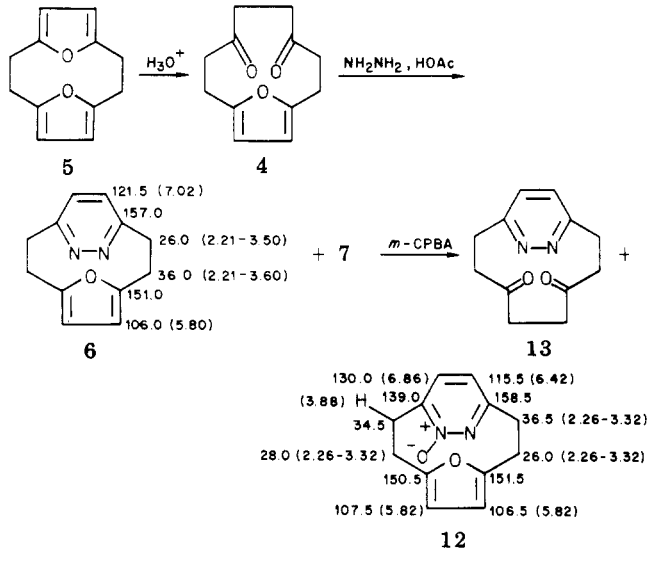
1 2 3

Thus, any potential synthesis of a pyridazinophane demanded a different synthetic approach. The intermediate compound **4** was prepared by hydrolysis of the furanophane **5**[2] in order to ascertain whether a pyridazinophane can be generated from a cyclic diketone. Treatment of the diketone **4** with hydrazine afforded two products, **6** and **7**, in essentially equal yields (Scheme I). An elemental analysis coupled with a mass spectral determination establishes $C_{12}H_{12}N_2O$ as the correct molecular formula for compound **6**, thus identifying it as the expected [2.2]-(2,5)furano(3,6)pyridazinophane. The ^1H NMR spectrum of this compound has singlets at δ 5.80 and 7.02, respectively. These values compare with δ 5.80 for the aromatic protons in 2,5-dimethylfuran (**8**) and δ 7.20 for the similar protons in 3,6-dimethylpyridazine (**9**). Thus, the pyridazine ring protons in the heterophane **6** are shielded with respect to those in 3,6-dimethylpyridazine (**9**), by 0.18 ppm, while the phane structure has no effect on the chemical shift of the ring protons of the furan ring.

We have already reported identical observations for the furanopyridinophane (**10**).[4a] The formation of the heterophane **6** constitutes only the second example of a [2.2]-heterophane containing a π-excessive as well as a π-deficient ring.

Compound **7** has a molecular formula of $C_{24}H_{28}N_4O_2$ as determined by elemental analysis and mass spectrum. This is, to our knowledge, the first reported instance of the formation of a 12-membered ring during the condensation of a 1,4-diketone with hydrazine (as is well-known, this reaction generally affords dihydropyridazines and pyridazines[3]). Interestingly, the yield of the compound can be increased to essentially 100% by appropriate variations of the reaction conditions (see Experimental Section). The infrared spectrum of this compound has no absorption in the N-H region but has a weak band at 1633 cm^{-1}, indicative of the presence of a N=N grouping. The ^1H NMR spectrum shows an AB system for four furan protons centered at δ 5.79, a complex multiplet in the region δ 1.26-3.78, equivalent to 22 protons, and an ABX system with H_x (two olefinic protons) resonating at δ 4.72. The ^{13}C NMR spectrum of this compound shows 12 dif-

Scheme I[a]



[a] Numbers in parentheses are ^1H NMR chemical shifts (δ). The others are ^{13}C NMR chemical shifts (δ).

(1) Paudler, W. W.; Stephan, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 4468.
(2) Haley, J. F.; Keehn, P. M. *Tetrahedron Lett.* **1973**, 4017.
(3) (a) Joule, J. A.; Smith, G. F. "Heterocyclic Chemistry"; Van Nostrand Reinhold Co.: London, 1975. (b) Bradamante, S.; Pagani, G.; Marchesini, A.; Pagnoni, U. M. *Ind. Chim. (Paris)* **1973**, *55*, 962. (c) Tisler, M.; Stanovnik, B. *Adv. Heterocycl. Chem.* **1968**, *9*, 000.

0022-3263/80/1945-4584$01.00/0