^{1}H NMR ($CDCl_3$) δ 4.05 (C-4 hydrogens), 2.04 (C-8 hydrogens), 1.66 (C-3 methyl), 1.60 (C-6 and C-7 methyls), 1.14 and 1.02 (C-1 and C-5 methyls).

Diols 11, 12, 13, 13-d_4 and 14. Analogously to the synthesis of the corresponding monomeric alcohols, as described in the literature,[17] the secondary alcohol **11** and the tertiary alcohols **12–14** were prepared from the corresponding diketones. The crude products were obtained in nearly quantitative yields (95–100%) and were in principle pure enough for the generation of the dications.

Compound 11 (Mixture of Diastereomers). After recrystallization from *n*-hexane (–30 °C) 179 mg (0.47 mmol, 88%) of diol **11** was obtained by starting from 200 mg (0.53 mmol) of ketone **16**: IR 3440 cm^{-1} (br); ^{1}H NMR (CCl_4) in addition to the signals reported above the *endo*-**11** additional peaks for the exoisomer are found at δ 3.90, 1.69, 1.52, and 1.08; mass spectrum, *m/e* 346 ($M^+ - 2H_2O$).

Compound 12. Crystallization from *n*-hexane (–30 °C) afforded 232 mg (0.61 mmol, 71%) of diol **12** from 300 mg (0.86 mmol) of diketone **8**: mp 136–138 °C; IR 3350 cm^{-1} (br); ^{1}H NMR ($CDCl_3$) δ 5.01 (C-3 hydrogens), 2.13 (C-8 hydrogens), 1.59 (C-6 and C-7 methyls), 1.22, 1.07, and 0.95 (C-1, C-4, and C-5 methyls); exact mass calcd *m/e* 346.266 ($M^+ - 2H_2O$), found *m/e* 346.267.

Compound 13. Crystallization from *n*-hexane (–30 °C) afforded 265 mg (0.65 mmol, 81%) of diol **13** from 300 mg (0.8 mmol) of diketone **9**: mp 140–142 °C; IR 3560 cm^{-1} (br); ^{1}H NMR ($CDCl_3$) δ 2.00 (C-8 hydrogens), 1.61 (C-3, C-6, and C-7 methyls), 1.19, 1.09, and 1.02 (C-1, C-4, and C-5 methyls); exact mass calcd *m/e* 374.297 ($M^+ - 2H_2O$), found *m/e* 374.297.

Compound 13-d_4. A 145-mg (0.35 mmol, 90%) sample of crude product **13-d_4** was obtained by starting from 150 mg (0.39 mmol) of labeled diketone **9-d_4**. The ^{1}H NMR ($CDCl_3$) was identical with that for **13** except that it lacked the signal at δ 2.00 (C-8 hydrogens).

Compound 14. From 200 mg (0.53 mmol) of diketone **9** was obtained 265 mg (0.53 mmol, 100%) of crude diol **14**. Diol **14** was crystallized from ethyl acetate (–30 °C): IR 3600 cm^{-1} (br); ^{1}H NMR ($CDCl_3$) δ 2.10 and 2.05 (diastereomeric hydrogens at C-8), 1.63 (C-3 methyl), 1.58 (C-6 and C-7 methyls), 1.34 (C-5 methyl), 1.04 (C-1 methyl and *t*-Bu); exact mass calcd *m/e* 458.391 ($M^+ - 2H_2O$), found *m/e* 458.390.

Generation of Cations. The ionization of the diols with FSO_3H/SO_2ClF to the corresponding dications was performed analogously to the generation of the cations described previously.[17]

Quenching of Cations. After the ^{13}C NMR measurements the samples were in several cases quenched with excess CH_3ONa/CH_3OH. No interpretable ^{1}H NMR spectra were obtained (very broad signals in the δ 1.0–2.5 region) from the unattractive reaction mixtures; however, mass spectra indicated the presence of dimeric products. The mass spectra of the products of the quenching reaction of solutions of **12** and **13** in FSO_3H/SO_2ClF gave M^+ peaks at *m/e* 346 ($C_{26}H_{34}$) and 374 ($C_{28}H_{38}$), respectively, the latter one showing a very low intensity.

Registry No. **6**, 78592-55-9; **7**, 78592-56-0; *meso*-**8**, 78592-57-1; *dl*-**8**, 78655-21-7; *meso*-**9**, 78655-97-7; *dl*-**9**, 78655-22-8; *meso*-**9-d_4**, 78592-58-2; *dl*-**9-d_4**, 78655-23-9; *meso*-**10**, 78655-98-8; *dl*-**10**, 78592-59-3; **11** (isomer 1), 78592-60-6; **11** (isomer 2), 78655-24-0; **12**, 78592-61-7; **13**, 78592-62-8; **13-d_4**, 78592-63-9; **14**, 78609-78-6.

Supplementary Material Available: Spectral data for the alcohols **11–14** in FSO_3H/SO_2ClF at low temperatures (7 pages). Ordering information is given on any current masthead page.

Structure and Properties of a Stable Isoindole. The Dimethyl Acetylenedicarboxylate–1-(Ethylthio)-2-*n*-propylisoindole Substitution Product

S. Stoney Simons, Jr.,*† Herman L. Ammon,*‡ Ruth Doherty,‡ and David F. Johnson†

Laboratory of Chemistry, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20205, and Department of Chemistry, University of Maryland, College Park, Maryland 20742

Received May 8, 1981

The reactions of 1-(alkylthio)-2-*n*-propylisoindoles with various dienophiles were investigated. Reactions with dimethyl acetylenedicarboxylate (DMAC) yielded stable 1:1 adducts which are dark red, α-substituted isoindoles with a fumarate side chain. The crystalline 1:1 adduct **6**, formed from 1-(ethylthio)-2-*n*-propylisoindole and DMAC was found to exist as a sterically congested, intramolecular charge-transfer complex. This steric crowding undoubtedly contributes to the stability of the isoindole and forces the plane of the fumarate side chain to be approximately perpendicular to the isoindole ring. These structural conclusions were confirmed by an X-ray structure determination of **6**, which also represents the first X-ray structure determination of an isoindole. In addition, these studies unambiguously identify isoindoles as the products of the reaction of *o*-phthalaldehyde and thiols with primary amines. The formation of a fumarate-substituted isoindole is analogous to the reactions of DMAC with pyrrole. However, spectroscopic and X-ray structural data show that the substituted isoindole **6** possesses considerable aromatic character and is not simply a 1,3-butadiene-annulated pyrrole. These results are discussed in terms of the hitherto unresolved questions regarding the structure and reactivity of isoindoles in general.

Questions regarding stability and reactivity have permeated almost all studies of isoindoles. The preparation of the first isoindole in 1951[1] and the unsubstituted, parent isoindole (**1**) in 1972[2] demonstrated that the ring system was stable enough for isolation. However, the questions of whether isoindoles were aromatic, as suggested by their 10-π-electron structure, and why they are so reactive remained unanswered. Because of the relative instability of isoindoles, most attempts to resolve these questions have involved comparisons of isoindole and pyrrole reactivity in Diels–Alder reactions and predictions of the molecular

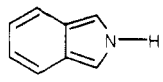
† National Institutes of Health.
‡ University of Maryland.

(1) Wittig, G.; Tenhaeff, H.; Schoch, W.; Koenig, G. *Justus Liebigs Ann. Chem.* **1951**, *572*, 1–22.
(2) Bonnett, R.; Brown, R. F. C. *J. Chem. Soc., Chem. Commun.* **1972**, 393–395.

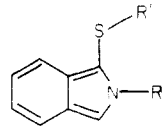
0022-3263/81/1946-4739$01.25/0

geometry and stability from NMR coupling constants or molecular orbital calculations.

Pyrroles generally are said to react with dienophiles to give Michael-type addition products at the α-position,[3-9] especially in the presence of proton donors,[6] but numerous exceptions have been described.[7-9] In contrast, isoindoles usually undergo the normal Diels–Alder reaction to give [4 + 2] cycloaddition products.[2-4,10-12] Several recent studies have concluded, on the basis of vicinal coupling constants in the ^1H NMR spectra and/or molecular orbital calculations, that isoindoles have low levels of resonance stabilization and should exhibit appreciable bond alternation in the six-membered ring.[13-17] Simons and Johnson recently determined that the previously undefined, highly fluorescent products of the reaction of *o*-phthaldehyde (OPTA) and thiols with primary amines[18,19] were the then unknown 1-(alkylthio)- and 1-(arylthio)-2-alkylisoindoles (**2**).[20-24] These isoindoles are considerably more stable



1



2, R = alkyl; R′ = alkyl, aryl
3, R = *n*-propyl; R′ = CH_2CH_2OH
4, R = *n*-propyl; R′ = ethyl

than other monoheterosubstituted isoindoles[21-24] and yield ^1H NMR spectra which show enough deshielding of substituent methylene groups to indicate substantial aromatic ring current in the isoindole molecule.[23] These isoindoles were previously reported to react with dimethyl acetylenedicarboxylate (DMAC) in a manner more typical of pyrroles than isoindoles.[20] Here we describe this reaction in detail and present physical data for these very stable, DMAC–isoindole adducts which indicate the presence of a minimally perturbed isoindole system. We also describe an X-ray structure of one DMAC–isoindole adduct which unambiguously determines the structure of the highly fluorescent isoindoles and also permits conclusions about the structure of the isoindole ring.

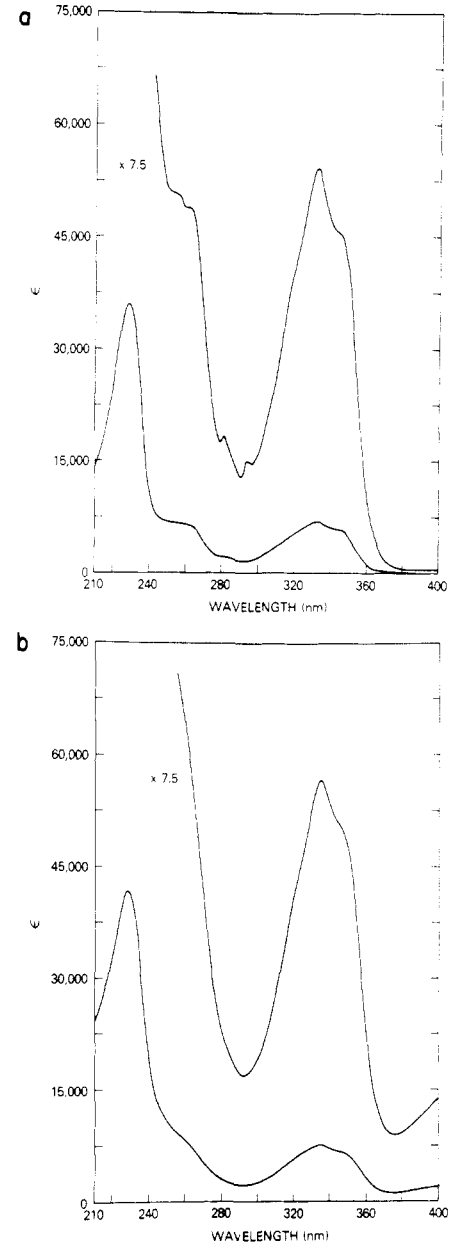


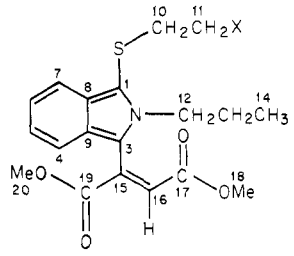
Figure 1. (a) UV spectrum of isoindole **4** in 95% EtOH. (b) UV spectra of the DMAC–isoindole adduct **6** in 95% EtOH.

Results

Reactions of Isoindoles with Dienophiles. The reactions of isoindoles **2** with dienophiles were investigated in order to obtain stable, isolable derivatives. Styrene gave no reaction with the isoindole **3** while 4-phenyl-1,2,4-triazoline-3,5-dione gave a rapid, but incomplete, reaction. Tetracyanoethylene (TCNE) and **3** in tetrahydrofuran at 0 °C afforded several products, none of which could be isolated in solid form. Dimethyl acetylenedicarboxylate (DMAC) gave the best results, reacting readily at 0 °C with **3** in tetrahydrofuran and almost instantaneously in acetonitrile. Even lowering the temperature of the solution of **4** in acetonitrile to −44 °C did not dramatically decrease the rate of the reaction, which was over in 1–2 min. TLC analysis of the reactions of DMAC with **3** or **4** revealed some unreacted isoindole (even after raising the temperature to 40 °C for 50 min) and a major, dark red product. The chemical-ionization mass spectrum of the red product

(3) White, J. D.; Mann, M. E. *Adv. Heterocycl. Chem.* **1969**, *10*, 113–147.
(4) Acheson, R. M.; Elmore, N. F. *Adv. Heterocycl. Chem.* **1978**, *23*, 263–482.
(5) Lee, C. K.; Kim, S. J.; Hahn, C. S. *J. Org. Chem.* **1980**, *45*, 1692–1693.
(6) Noland, W. E.; Lee, C. K. *J. Org. Chem.* **1980**, *45*, 4573–4582.
(7) Mandell, L.; Blanchard, W. A. *J. Am. Chem. Soc.* **1957**, *79*, 6198–6201.
(8) Acheson, R. M.; Vernon, J. M. *J. Chem. Soc.* **1963**, 1008–1011.
(9) Lee, C. K.; Hahn, C. S.; Noland, W. E. *J. Org. Chem.* **1978**, *43*, 3727–3729.
(10) Chacko, E.; Bornstein, J.; Sardella, D. J. *Tetrahedron* **1979**, *35*, 1055–1058.
(11) Kricka, L. J.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 904–908.
(12) Kreher, R.; Hennige, H. *Tetrahedron Lett.* **1973**, 1911–1914.
(13) Palmer, M. H.; Kennedy, S. M. F. *J. Chem. Soc., Perkin Trans. 2* **1976**, 81–89.
(14) Dolby, L. J.; Hanson, G.; Koenig, T. *J. Org. Chem.* **1976**, *41*, 3537–3539.
(15) Rettig, W.; Wirz, J. *Helv. Chim. Acta* **1976**, *59*, 1054–1074.
(16) Chacko, E.; Bornstein, J.; Sardella, D. J. *Tetrahedron Lett.* **1977**, 1095–1098.
(17) Chacko, E.; Bornstein, J.; Sardella, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 8248–8251.
(18) Roth, M. *Anal. Chem.* **1971**, *43*, 880–882.
(19) Benson, J. R.; Hare, P. E. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 619–622.
(20) Simons, S. S., Jr.; Johnson, D. F. *J. Am. Chem. Soc.* **1976**, *98*, 7098–7099.
(21) Simons, S. S., Jr.; Johnson, D. F. *J. Chem. Soc., Chem. Commun.* **1977**, 374–375.
(22) Simons, S. S., Jr.; Johnson, D. F. *Anal. Biochem.* **1977**, *82*, 250–254.
(23) Simons, S. S., Jr.; Johnson, D. F. *J. Org. Chem.* **1978**, *43*, 2886–2891.
(24) Simons, S. S., Jr.; Johnson, D. F. *Anal. Biochem.* **1978**, *90*, 705–725.

from each reaction suggested a 1:1 DMAC–isoindole adduct. On the basis of the intense color of each product, plus their reaction with added 4-phenyl-1,2,4-triazoline-3,5-dione to consume both the adduct and its color,[25] we concluded that the original red 1:1 adducts were the substitution products **5** and **6**. By analogy to the reactions of pyrroles with DMAC,[7,8] the unsaturated side chains in **5** and **6** were assigned the fumarate structure.



5, X = OH
6, X = H

Characterization of the 1:1 DMAC–Isoindole Adducts. The 1:1 adduct **6** derived from the isoindole **4** was isolated as an analytically pure solid.[20] The 1:1 adduct **5** was never obtained pure but its various physical properties were analogous to those observed for the pure adduct **6**.

UV spectroscopy indicated that the structures of **5** and **6** were not as straightforward as expected. *N*-Methylisoindole absorbs at ~324 nm and much more intensely at ~225 nm.[15] The UV spectrum of **4** (Figure 1a) is typical of 1-(alkylthio)-2-alkylisoindoles. Since both 1:1 DMAC–isoindole adducts **6** (Figure 1b) and **5** also retained these characteristic UV spectral features, the dark red color of both adducts could not be due to extended conjugation of the isoindole ring with the fumarate side chain in a planar π system. Instead, the broad, unresolved band at ~461 nm for **6**, and at ~427 nm for **5**, indicates the presence of a charge-transfer (CT) complex. The absorption due to dimethyl fumarate, that should be apparent if **6** is a CT complex, is partially obscured by the isoindole band at ~228 nm (Figure 1a) but is probably visible as the increased absorbance at 210–228 nm (cf. Figure 1b vs. 1a). The invariance of the 461-nm band of **6** at different concentrations [A_{335}/A_{461} = 2.23 ± 0.035 (standard deviation) for 10^{-3}–10^{-5} M solutions in 95% EtOH] established the intramolecular nature of this band.

An examination of space-filling models revealed major steric interactions that restrict the rotation of the fumarate side chain to approximately ±30 °C from the perpendicular to the isoindole ring. Such deviations from planarity (i.e., ≥60 °C) result in a dramatic decrease in π-orbital overlap,[26] which would account for the preservation of the isoindole and fumarate chromophores. Further analysis of CPK space-filling models suggested that the restricted rotation of the dimethyl fumarate group should also be reflected in hindered rotation about the N–CH_2 bond of the *n*-propyl side chain. In fact, a variable-temperature ^{1}H NMR spectrum of **6** in acetonitrile-d_3 confirmed the presence of this restricted rotation. At −28 °C the observed pattern is consistent with that of two diasterotopic sets of enantiotopic protons ($J_{CH_2-CH_2}$ = 7 Hz, J_{gem} = 14 Hz). At 73 °C, the triplet expected for free rotation about the N–CH_2 bond is finally observed. With 47 °C taken as the coalescence temperature, the barrier to rotation, ΔG, is calculated as 16 kcal/mol. It should also be mentioned that these NMR spectra also revealed a substantial deshielding of the N–CH_2 and N–C–CH_2 protons and a *shielding* of the S–C–CH_3 protons (δ in starting material − δ in **6** = 0.23 ppm). These phenomena have been observed with simpler isoindoles such as **3** and **4**[23] and are indicative of appreciable aromatic ring current in these isoindoles[23] and the preservation of the isoindole ring system in **6**.

Since **5** and **6** retain the basic 1-(alkylthio)isoindole chromophore which has been found to be intensely fluorescent,[22,24] it was of interest to see if **5** and **6** were also fluorescent. After making the necessary corrections,[24] **5** and **6** were found to be at least 500–900 times less fluorescent than the standard **4**, all in 95% EtOH. Since the effects of substituents on fluorescence intensity are, in general, poorly understood,[27,28] the observed weak fluorescence of **5** and **6** could be due to a substituent effect. A more likely explanation, however, would be energy transfer from the first excited isoindole singlet to the CT complex, which absorbs at the usual isoindole fluorescence λ_{max} of ~433 nm.[24]

X-ray Structure of DMAC–Isoindole Adduct 6. Our above structural conclusions have been confirmed and reinforced by an X-ray structure determination of the adduct **6**. Work on the X-ray crystal structure of the 1:1 DMAC–isoindole adduct **6** spanned more than four years and involved three data sets and two crystal forms. The first two data sets were measured by Dr. James Silverton (National Heart Institute, NIH) on crystals grown from petroleum ether. In studies conducted at the University of Maryland, structure solution and refinement in the monoclinic space group $P2/c$ (Z = 4) revealed a reasonably well-defined isoindole nucleus linked to a two-fold disordered fumarate side arm. Least-squares refinement with individual anisotropic temperature factors for the isoindole nucleus and its nitrogen- and sulfur-linked substituents, with two fumarate units with occupancy factors of 0.4 and 0.6 and with isotropic terms, gave an R ($R = \sum|F_o - F_c|/\sum F_o$) factor of 0.072. Estimated standard deviations of 0.02–0.03 Å for the isoindole bond distances precluded any meaningful insight into the question of bond alternation based on these data. Calculations in space group Pc with two molecules per asymmetric unit, each containing one representation of the disordered fumarate, were unsatisfactory.

A second crystal form was grown from methanol–water, and a third data set was measured at the University of Maryland. The space group was triclinic, $P\bar{1}$ (Z = 2). The structure solution and refinement proceeded normally with a full occupancy fumarate, but the determination was not without problems. Both C15 (the fumarate atom linked to the isoindole) and O2 (one of the carbomethoxy alcohol oxygens) appear to be midpositioned, thus giving rise to abnormal bond lengths around C15 and O2 (see also Discussion). Despite these anomalies, the isoindole nucleus is well-defined. ORTEP drawings of the molecule are given in Figure 2. A complete list of bond lengths and angles is contained in Table I. The nine-atom isoindole nucleus is planar within experimental error, with maximum and average deviations from the least-squares plane of 0.010 and 0.006 Å, respectively. The corresponding values for the eight-atom fumarate side chain (excluding the two methyl groups) are 0.109 and 0.063 Å. The 66.3° angle between these two planes is similar to the value of 60° derived from analysis of the CPK models, which represents the closest approach to coplanarity that can be achieved

(25) Both 1:1 adducts were unreactive when treated with additional DMAC.
(26) Wepster, B. M. In "Progress in Stereochemistry"; Klyne, W., de la Mare, P. B. D., Eds.; Academic Press: New York, 1958; pp 100–156.
(27) Guilbault, G. G. "Practical Fluorescence: Theory, Methods and Techniques"; Marcel Dekker: New York, 1973.
(28) Kanaoka, Y. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 137–147.

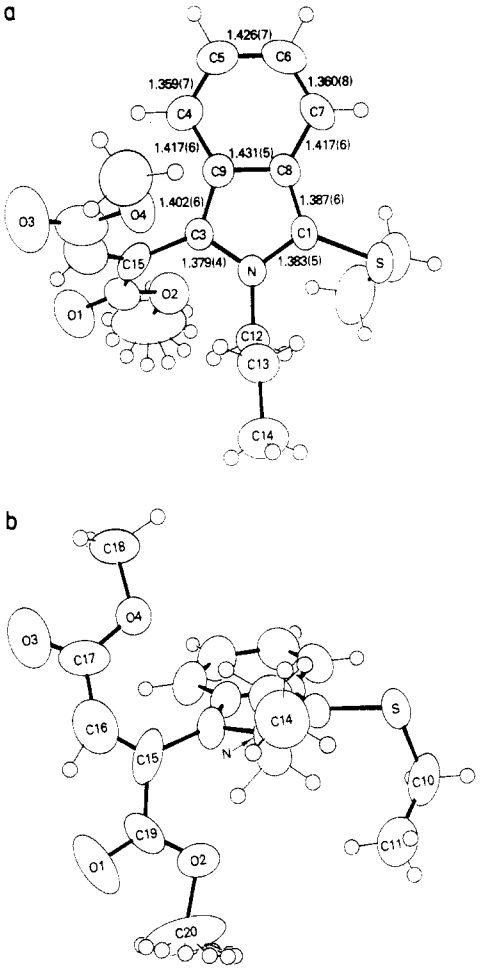


Figure 2. ORTEP drawings with the DMAC–isoindole adduct **6** viewed (a) perpendicular to the isoindole ring and (b) perpendicular to the fumarate side chain. Some bond lengths (Å) and esd's (in parentheses) are shown.

by the planar fumarate and isoindole groups.

Discussion

Reactions of dienophiles with isoindoles generally give [4 + 2] addition products[2-4,10-12] although several examples of the opposite reactivity have been reported.[12,29,30] Here we report another example of the less common reaction of isoindoles to give the α-substitution product (i.e., **3** → **5** and **4** → **6**). However, since other, unisolated products were also formed, we cannot conclude that the normal Diels–Alder addition does not occur at all.

The isolated products **5** and **6** have maintained the isoindole ring system, as determined by the characteristic UV spectra (e.g., Figure 1) and the appreciable aromatic ring current seen in the NMR spectra, and yet are more stable than any other isoindole yet reported.[2,3,23] These two properties probably arise from a combination of steric and electronic factors. The adducts **5** and **6** possess severe steric congestion around the five-membered nitrogen-containing ring, which is the usual site of reaction for isoindoles. Furthermore, possible d orbital overlap of the thioether sulfur atom with the isoindole ring and the existence of an intramolecular CT complex should increase the stability of **5** and **6**.

Table I. Bond Lengths and Angles for the 1:1 Adduct **6**[a]

	Bond Lengths (Å)		
C1-N	1.383 (5)	C12-C13	1.505 (6)
N-C3	1.379 (4)	C13-C14	1.520 (7)
C3-C9	1.402 (6)	C3-C15	1.530 (6)
C9-C4	1.417 (6)	C15-C16	1.262 (8)
C4-C5	1.359 (7)	C15-C19	1.594 (8)
C5-C6	1.426 (7)	C16-C17	1.427 (9)
C6-C7	1.360 (8)	C17-O3	1.211 (8)
C7-C8	1.417 (6)	C17-O4	1.344 (7)
C8-C9	1.431 (5)	O4-C18	1.450 (6)
C1-S	1.742 (4)	C19-O1	1.212 (6)
S-C10	1.817 (6)	C19-O2	1.297 (6)
C10-C11	1.47 (1)	O2-C20	1.573 (8)
N-C12	1.469 (5)		
	Bond Angles (deg)		
C8-C1-N	108.1 (3)	C4-C9-C8	120.0 (4)
S-C1-N	123.2 (3)	S-C10-C11	115.5 (4)
C8-C1-S	128.7 (3)	N-C12-C13	112.5 (4)
C1-N-C3	110.1 (3)	C12-C13-C14	112.0 (4)
C1-N-C12	124.9 (3)	C3-C15-C16	126.2 (5)
C12-N-C3	124.3 (3)	C3-C15-C19	116.5 (4)
N-C3-C9	107.1 (3)	C16-C15-C19	116.6 (5)
N-C3-C15	123.2 (4)	C15-C16-C17	128.4 (6)
C9-C3-C15	129.1 (4)	C16-C17-O3	118.3 (5)
C5-C4-C9	118.6 (4)	C16-C17-O4	120.7 (5)
C4-C5-C6	121.6 (5)	O3-C17-O4	121.0 (5)
C5-C6-C7	121.2 (5)	C15-C19-O1	124.0 (5)
C6-C7-C8	118.8 (4)	C15-C19-O2	112.5 (4)
C1-C8-C7	133.2 (4)	O1-C19-O2	123.4 (5)
C1-C8-C9	107.1 (4)	C19-O2-C20	105.1 (4)
C7-C8-C9	119.7 (4)	C17-O4-C18	114.3 (4)
C3-C9-C4	132.4 (4)	C1-S-C10	101.0 (2)
C3-C9-C8	107.6 (3)		

[a] Estimated standard deviations are given in parentheses.

Table II. Bond Lengths in Isoindoles. Comparison of Calculated and Predicted Values for **1** (from Chacko et al.[17]) vs. Observed Values for **6**

bond	calcd for **1**[a]	predicted for **1**		from X-ray structure of **6**
		localized[b]	delocalized[c]	
C1-N, N-C3	1.384	1.383	1.383	1.383, 1.379
C1-C8, C3-C9	1.370	1.371	1.371	1.387, 1.402
C4-C5, C6-C7	1.357	1.345	1.365	1.359, 1.360
C5-C6	1.448	1.464	1.404	1.426
C4-C9, C7-C8	1.456	1.464	1.425	1.417, 1.417
C8-C9	1.440	1.440	1.393	1.431
av dev[d]	0.019	0.028	0.015	

[a] Bond lengths calculated by Dewar et al.[31] using a modified Pople-type SCF method. [b] Assumed to consist of a pyrrole ring and a carbocyclic ring with polyenic single and double bonds. [c] Assumed to consist of a pyrrole ring and a naphthalenoid carbocyclic ring. [d] Average deviation in bonds of six-membered ring = Σ |actual bond length in **6** − theoretical bond length in **1**|/6.

The unusual stability of **6** has allowed us to obtain the first X-ray structure determination of an isoindole, which in turn permits several conclusions. First, we now have definitive proof that the fluorescent adducts of the OPTA reaction have the previously assigned isoindole structure **2**.[20-24] Second, the major product of **4** plus DMAC is established as a substitution product with a fumarate side chain. In this respect, the isoindole **4** (and by analogy the isoindole **3**) reacts just like pyrroles.[3-6] Third, the fumarate side chain in **6** is almost perpendicular to the isoindole ring and cannot be conjugated with the isoindole ring.[26] This supports the conclusions drawn from space-filling models and the UV spectra (Figure 1) and explains why the isoindole ring of **6** is electronically equivalent to that of the monosubstituted isoindole **4**. Fourth, there is some ab-

(29) Veber, D. F.; Lwowski, W. *J. Am. Chem. Soc* **1964**, *86*, 4152–4158.
(30) Kreher, R.; Schmitt, D.; Herd, K. J. *Tetrahedron Lett.* **1980**, *21*, 3471–3474.
(31) Dewar, M. J. S.; Harget, A. J.; Trinajstic, N.; Worley, S. D. *Tetrahedron* **1970**, *26*, 4505–4516.

solute bond alternation in the isoindole ring of **6** (Figure 2a) but much less than would be expected if isoindoles are simply 1,3-annulated pyrroles (Table II). This result is in contrast to various predictions.[13-17] In fact, the observed values are much closer to those predicted by Chacko et al.[17] for a delocalized isoindole than to the values predicted for a localized isoindole (Table II). These structural data thus indicate that at least the isoindole **6**, and probably isoindoles in general, possess substantial aromatic character, which confirms our conclusions based on ^{1}H NMR spectral data (see Results and ref 23). Furthermore, since isoindoles are not simply 1,3-butadiene annulated pyrroles, some other explanation for the reactivity of isoindoles must be found.

Finally, the crystal structure of **6** represents one of the few X-ray structures that is available for a CT complex. We expected that intramolecular charge transfer in **6** would involve donation of an electron from the highest occupied orbital of the π-excessive isoindole to the lowest unoccupied orbital of the π-deficient fumarate via a nonbonded C=O···C3 (or N) interaction. The X-ray structure of **6** (Figure 2) does not support this proposal even though the same dark red color in the solutions and crystals of **6** attest to the presence of a CT complex in the solid state. The most likely candidates for an isoindole–fumarate interaction involve C3 and the two carbomethoxy alcohol oxygens, O2 and O4. The C3···O2 and C3···O4 distances of 2.78 and 2.85 Å, respectively, are smaller than the usual oxygen–aromatic ring van der Waals contact of 3.1 Å (1.4 + 1.7 Å). The σ antibonding orbitals of the alcohol oxygens[32] are approximately coplanar with O2–C3–O4 and are thus well positioned for overlap with the p–π bonding orbital of C3 (Figure 2b). While this interaction (π–σ^*) might be predicted to be of too high energy to account for the observed CT band, the "chelation" of the C3 p–π orbital by the antibonding orbitals of both O2 and O4 may reduce the energy differences.

It appears that the CT complex **6** is not an isolated phenomenon and that isoindoles in general, like indoles,[33] may readily form CT complexes.[34] The highly colored products of 1-(alkyl(and aryl)thio)-2-alkylisoindoles and iodine[23] are almost certainly due to CT complex formation, and the reported dark blue 1:1 adduct of 1-phenylisoindole and 1,4-naphthoquinone of unknown structure[29] is probably the substitution product analogous to **5** and **6**, giving another intramolecular CT complex.

Experimental Section

DMAC was obtained from Eastman. All other chemicals were used as previously described.[23] Silica gel and neutral alumina TLC plates were purchased from Analtech. Melting points were determined on a Fisher-Johns hot-stage melting point apparatus and are corrected. Perkin-Elmer 237B grating infrared and Carey 14 spectrophotometers were used to record IR and UV spectra, respectively. ^{1}H NMR spectra were acquired at 60 MHz (Varian A-60). Low-resolution, chemical-ionization mass spectra were obtained on a Finnigan 1015D spectrometer by Mr. Noel Whittaker of the Laboratory of Chemistry, NIAMDD. Analyses were performed by the Microanalytical Section of the Laboratory of Chemistry, NIAMDD.

1:1 Isoindole–DMAC Adduct 6. Equimolar amounts (2.98 mmol) of *o*-phthalaldehyde (400 mg), ethanethiol (0.221 mL), and *n*-propylamine (0.245 mL) were mixed in the stated order in acetonitrile to give the isoindole **4**. Additional acetonitrile (1.8 mL) was added and the solution cooled to −44 °C in a liquid N_2/acetonitrile slurry bath. Stirring was omitted at this point to avoid the crystallization of presumably the isoindole **4**. An equimolar amount of DMAC (0.367 mL, 2.98 mmol) was added to give a dark red solution after 1–2 min. Removal of solvent under reduced pressure gave a red-black liquid. Extraction of crude **6** with petroleum ether yielded a gum, from which more **6** could be obtained after treatment with benzene and removal of a white solid. The crude **6** was chromatographed (benzene on 1000-μm neutral alumina preparative TLC plates) to give 551 mg (51% yield) of impure product. Recrystallization from petroleum ether and preparative TLC ($CHCl_3$ on a 2000-μm silica gel plate) of the supernatant material followed by recrystallization from petroleum ether gave a total of 319 mg (30% yield) of solid product **6** (mp 69.3–73.3 °C). During all of these and subsequent manipulations, it appeared that a lower R_f, yellow compound was continuously being formed at a slow rate. The analytical sample was obtained after recrystallization from petroleum ether: mp 73.3–73.8 °C; IR (Nujol) 3050, 1718 (br), 1625, 1612, 1250, 1160, 1020, 755 cm^{-1}; UV (95% EtOH) 228 nm (ϵ 4.23 × 10^4), 335 (7.58 × 10^3), 461 (3.40 × 10^3); ^{1}H NMR (60 MHz, CD_3CN) 7.67 (m, 1 H, C7), 7.3–6.8 (m, ~3 H, C4–C6), 7.18 (s, ~1 H, C16), 4.26 (temperature-dependent m, 2 H, C12), 3.73 (s, 3 H, COOMe), 3.47 (s, 3 H, COOMe), 2.72 (q, J = 7 Hz, 2 H, C10), 1.73 (tq, $J' \simeq J''$ 7 Hz, 2 H, C13), 1.12 (t, J = 7 Hz, 3 H, C11), 0.82 ppm (t, J'' = 7 Hz, 3 H, C14); chemical-ionization mass spectrum (with isobutane), m/e (relative intensity) 362 (MH$^+$, 100). Anal. Calcd for $C_{19}H_{23}NO_4S$ (mol wt 361.44): C, 63.13; H, 6.41; N, 3.88; S, 8.87. Found: C, 63.49; H, 6.21; N, 3.73; S, 8.59.

1:1 Isoindole–DMAC Adduct 5. The preparation of **5** from the isoindole **3** and DMAC was very similar to the above preparation of **6**. The reaction to yield **5** was faster at 0 °C in acetonitrile than in tetrahydrofuran. Two preparative thin-layer chromatographies (BuOAc on silica gel) afforded a 33% yield of a fairly pure (by TLC) oil that would not crystallize: UV (95% EtOH) 226 nm (ϵ 2.7 × 10^4), 333 (4.4 × 10^3), 427 (2.0 × 10^3); ^{1}H NMR (60 MHz, external Me_4Si, $CDCl_3$) 7.9–7.0 (m, ~5 H, C4–C7 plus a singlet at 7.26 for C16), ~4.33 (m, ~2 H, C12), 4.0–3.5 (m for C11 and C11 OH with two COOMe singlets at 3.83 and 3.57, ~9 H), 2.92 (t, J = 6 Hz, ~2 H, C10), 1.18 (possible tq, $J' \simeq J'' \simeq$ 7 Hz, ~2 H, C13), 0.92 ppm (t, J'' = 7 Hz, ~3 H, C14); chemical-ionization mass spectrum (with isobutane) m/e (relative intensity) 378 (MH$^+$, 100).

X-ray Structure Determination of 1:1 Isoindole–DMAC Adduct 6. Slow crystallization of **6** from petroleum ether (bp 40–60 °C) or methanol–water yielded dark red (almost red-black) blocks. For the petroleum either specimens, the Laue symmetry, systematic absences ($h0l$ absent for l odd), and crystal density were consistent with the monoclinic space groups $P2/c$ or Pc, with Z = 4. Data sets 1 and 2 were measured at the National Heart Institute on a Nonius CAD-4 diffractometer with Cu radiation. The refined cell constants were a = 14.431 (1) Å, b = 8.934 (1) Å, c = 15.510 (1) Å, β = 101.20 (1)°. These crystals showed a disordered fumarate and no further data will be reported for them.

X-ray data for the methanol–water crystals of **6** were obtained at the University of Maryland. Preliminary X-ray oscillation and Weissenberg photographs (Ni-filtered Cu radiation) were taken, and all final measurements were made on a Picker FACS-I diffractometer with monochromatized Cu radiation (highly oriented graphite crystal, Cu Kα λ = 1.5418 Å. A 0.15 × 0.20 × 0.30 mm crystal was mounted and aligned to place b^* approximately parallel to the instrument's ϕ axis. The cell parameters were determined by the method of least-squares from the Bragg angles of 13 automatically centered reflections. The crystal data were as follows: $C_{19}H_{23}NO_4S$; mol wt 361.44; triclinic, $P\bar{1}$; a = 9.663 (4) Å, b = 11.444 (5) Å, c = 8.935 (3) Å, α = 95.31 (4)°, β = 94.04 (3)°, γ = 83.83 (2)°; d_{calcd} = 1.23 g cm^{-3} for Z = 2. The intensity data (third set) were collected with the θ–2θ scan method, with a 2θ speed of 2° min^{-1}, a scan range calculated from (1.8 + 0.3 tan θ)°, and two 10-s background measurements. Four standard reflection intervals were used to monitor and later to correct for intensity variations (the derived scale factors ranged from 1.0 to 1.030). There were 2880 unique reflections in a total of 3236 measured to a 2θ maximum of 120°; 2416 of the unique data were more than three standard deviations above background.

(32) Jorgensen, W. L.; Salem, L. "The Organic Chemist's Book of Orbitals"; Academic Press: New York, 1973; pp 70, 106, 168.
(33) Cipiciani, A.; Santini, S.; Savelli, G. *J. Chem. Soc., Faraday Trans 1*, **1979**, 497–502.
(34) The isoindole **3** and tetracyanoethylene in tetrahydrofuran at 0 °C give a transient green color before changing to a dark red solution. This green color is most likely due to an intermolecular CT complex.[33]

The structure was solved with direct methods; an E map revealed maxima for the 25 C, N, O, and S atoms. The structure refinement was by the method of full-matrix least-squares with anisotropic temperature factors for C, N, O, and S and isotropic terms for H. Several H atoms were fixed at precalculated positions, and the three atoms in one methyl group were described by an appropriately located circle of 12 0.25-weight atoms. The function minimized was $\sum w(F_o - F_c)^2$, where $w = 1/\sigma(F_o)^2$. Only those data for which I_c was greater than $3\sigma(I_o)$ were included in the refinement. The final R and R_w ($[\sum w(F_o - F_c)^2/w\sum F_o^2]^{1/2}$) factors were 0.082 and 0.068, respectively. Sattering factors for C, N, O, and S were calculated from the analytical expressions of Cromer and Mann[35] and the H values were interpolated from the data of Stewart et al.[36] A final difference electron map contained two ca. 0.65 e Å^{-3} maxima near C15. Earlier attempts to fit a split-atom model to this region were unsuccessful.

The crystallographic computations were performed on a UNIVAC 1108 in the University of Maryland's Computer Science Center with the X-RAY 76[37] package of programs.

Acknowledgment. We thank Dr. Ruth S. McDiarmid (NIAMDD) for helpful discussions and Ms. Joan V. Todd for the preparation of this manuscript. This work was supported, in part, by NIH Contract 263-MD-012893 to H.L.A. and through the facilities of the University of Maryland's Computer Science Center.

Registry No. **3**, 61214-21-9; **4**, 61214-22-0; **5**, 61214-24-2; **6**, 61214-25-3; *o*-phthalaldehyde, 643-79-8; ethanethiol, 75-08-1; *n*-propylamine, 107-10-8; DMAC, 762-42-5.

Supplementary Material Available: The visible spectrum of the adduct **6** (Figure 3), pictures of the CPK space-filling models of **6** (Figure 4), the temperature-dependent ^{1}H NMR spectra of the NCH_2Et methylene protons of **6** (Figure 5), and a list of the atomic fractional coordinates and temperature factors for the X-ray structure of **6** (Table III) are given (6 pages). Ordering information is given on any current masthead page.

(35) Cromer, D. T.; Mann, J. B. *Acta Crystallogr. Sect. B* **1968**, *B31*, 418-422.
(36) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175-3187.
(37) Stewart, J. M.; Machin, P. A.; Dickinson, C.; Ammon, H. L.; Heck, H.; Flack, H. Technical Report 446; Computer Science Center, University of Maryland: College Park, MD, 1976.

Absolute Configurations of the *cis*- and *trans*-13-Methyltetrahydroprotoberberines. Total Synthesis of (+)-Thalictricavine, (+)-Canadine, (±)-, (-)-, and (+)-Thalictrifoline, and (±)-, (-)-, and (+)-Cavidine

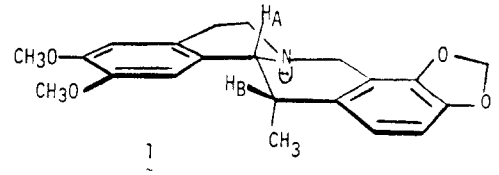
Kinuko Iwasa, Yash Pal Gupta, and Mark Cushman*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

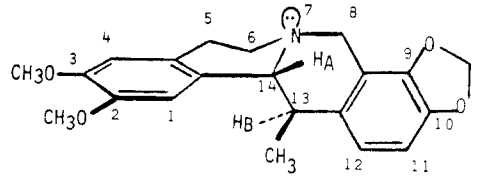
Received May 29, 1981

The tetrahydroprotoberberine alkaloids (+)-thalictricavine [(+)-**6**] and (+)-canadine [(+)-**23**] have been synthesized from an optically resolved (+)-13-carboxy-7,8,13,14-tetrahydro-9-oxoprotoberberine [(+)-**26**]. This establishes the absolute configuration of (+)-thalictricavine as 13*S*,14*R*. (+)-Thalictrifoline [(+)-**2**] and (+)-cavidine [(+)-**1**] have also been prepared from a common intermediate, (+)-**32**, whose absolute configuration was established by correlation with (+)-**26**. This determines the absolute configuration of (+)-thalictrifoline as 13*R*,14*R*, of (+)-corydalic acid methyl ester (**22**) as 3*R*,4*R*, and of the protopine (+)-corycavine (**20**) as 13*R*.

The 13-methyltetrahydroprotoberberine alkaloids are a group of metabolites which occur in various species of *Corydalis*. Compounds in which protons H_A and H_B are cis [e.g., cavidine (**1**)] are referred to as cis diastereomers,



1



2

while in the trans isomers [e.g., thalictrifoline (**2**)] these protons are trans. As portrayed in structures **1** and **2**, the cis isomers exist in the *trans*-quinolizidine conformation, while the trans diastereomers exist in the *cis*-quinolizidine conformation in solution in order to avoid a nonbonded interaction between the C-13 methyl group and the C-1 hydrogen atom.[1]

The absolute configurations of the tetrahydroprotoberberines which lack substituents in the B and C rings were determined by the conversion of (-)-*N*-norlaudanosine (**3**) to *N*-(β-carboxyethyl)-L-aspartic acid (**4**) of known absolute configuration and (-)-norcoralydine (**5**), which therefore must have the 14*S* configuration.[2] The tetrahydroprotoberberines related to compound **5** which are

(1) (a) Bersch, H. W. *Arch. Pharm. (Weinheim, Ger.)* **1958**, *291*, 595. (b) Jeffs, P. W. *Experientia* **1965**, *21*, 690. (c) Yu, C. K.; MacLean, D. B.; Rodrigo, R. G. A.; Manske, R. H. F. *Can. J. Chem.* **1970**, *48*, 3673. (d) Govindachari, T. R.; Nagarajan, K.; Charubala, R.; Pai, B. R.; Subramanian, P. S. *Indian J. Chem.* **1970**, *8*, 769. (e) Takao, N.; Iwasa, K.; Kamigauchi, M.; Sugiura, M. *Chem. Pharm. Bull.* **1977**, *25*, 1426. (f) Takao, N.; Iwasa, K. *Ibid.* **1976**, *24*, 3185.
(2) Corrodi, H.; Hardegger, E. *Helv. Chim. Acta* **1956**, *39*, 889.

0022-3263/81/1946-4744$01.25/0