A Macrocyclic Amide from Dehydrochlorination of Indole-3-carbonyl Chloride

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Indolyl-3-ketene **3** was generated from two precursors and was found to form a symmetrical tetramer **4** consisting of a sixteen-membered ring amide. The tetramer was characterized by mass spectrometry, infrared, ^{1}H and ^{13}C-nmr spectroscopy, and single crystal X-ray crystallography.

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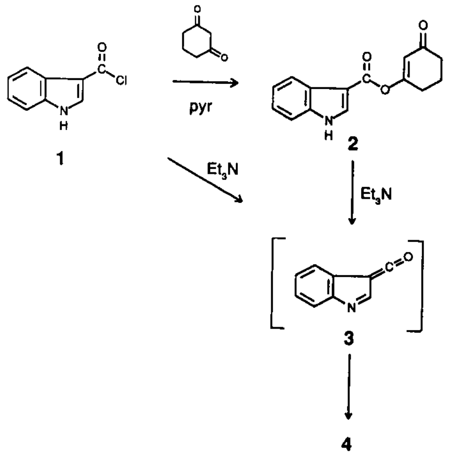
In the accompanying [1] paper we describe competing amine-catalyzed rearrangement pathways followed by the enol ester of cyclohexane-1,3-dione and indole-2-carboxylic acid. We became curious as to whether the corresponding ester of indole-3-carboxylic acid (**2**, Scheme 1) might also undergo rearrangement; if so, spirolactone formation in this case would involve a ring carbon instead of a NH, and a new type of carbon-carbon bond formation would result.

Scheme 1



Enol ester **2** was prepared uneventfully from **1** and cyclohexane-1,3-dione in the presence of pyridine. When an acetonitrile solution of **2** containing triethylamine was allowed to stand overnight, a white solid **4** separated from solution; it was insoluble in aqueous sodium bicarbonate and also in most common solvents. Its mass spectrum (electron impact (EI)) consisted essentially of six ions: m/z 572 (4%), 429 (2%), 286 (33%), 143 (100%), 115 (27%), 88 (3%); the first four of these represent successive multiples of 143 (although a doubly charged m/z 572 could also contribute to the 286 ion). Chemical ionization with ammonia, ^{15}N-ammonia, and ^{2}H-ammonia as reagent gases confirmed a molecular weight of 572 and demonstrated that no exchangeable hydrogens were present. These data suggest a tetrameric structure, $C_{36}H_{20}N_4O_4$, composed of four C_9H_5NO units. Both of the ^{13}C- and ^{1}H-nmr spectra were remarkably simple, the former consisting of nine signals and the latter only four (H-5 and H-6 were not resolved) suggesting a highly symmetrical compound and supporting the idea of four identical subunits. Noteworthy in the ^{1}H-spectrum of **4** was the highly deshielded indole H-2 singlet (δ 9.47, DMSO; δ 9.25, perdeuteriopyridine) relative to the corresponding signal from **2** (δ 8.02, deuteriochloroform).

The apparent C_9H_5NO units suggested ketene **3** as a likely precursor of **4**, and accordingly we treated acid chloride **1** with triethylamine. Indeed, **4** was the only product isolated.

Ketene formation under similar conditions from both pyrrole-2-carbonyl chloride and indole-2-carbonyl chloride has been reported by Boatman and Whitlock [2], and in both cases dimers were isolated and identified. Bergman, *et al.* [3] reported an isomer of **4** ($C_{36}H_{20}N_4O_4$, **5**, Figure 1) from the reaction of indole magnesium bromide with phosgene; nmr data were not reported for **5** but its mass and infrared spectra differed from those of **4**. Of particular interest are two carbonyl absorptions in the infrared spectrum of **5** (1736 and 1644 cm^{-1} -- presumable representing

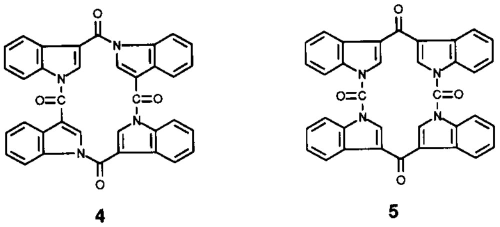

4
5

Figure 1

the ketone and urea carbonyls, respectively); compound **4** produced a single carbonyl absorption (1706 cm^{-1}).

Because of the apparent high degree of symmetry of **4**, and to determine the entire structure, we undertook a single crystal X-ray analysis. Its low solubility severely limited the choices of crystallization solvents, and well-formed crystals were obtained only from dimethylformamide (DMF) and from moist dimethyl sulfoxide-d$_6$ (DMSO; the latter resulting from exposing the nmr sample to humid air; as moisture was absorbed, **4** slowly crystallized).

Data were collected from two crystals, one grown from DMF and one grown from DMSO. Both crystals gave the same results for the macrocyclic ring compound and both contained co-crystallized solvent molecules (2 solvent molecules per ring compound). The DMSO molecules were disordered; therefore, the study reported here is that done on the crystal obtained from DMF.

The X-ray study unequivocally indicated a structure with a 16-membered central ring as shown in Figure 1. However, it could not unambiguously distinguish between **4** and **5** or certain other possible 16-membered ring combinations of four of the monomeric units. This is due to the fact that in the solid state the molecule is disordered such that positions 1, 5, 9, and 13, and 3, 7, 11, and 15 (Figure 2) are occupied by either a nitrogen or a carbon atom respectively. The C:N occupancy ratio at each site, as determined by the least-squares refinement, is 1:1. Trying to remove the disorder by expanding the problem to have 2 molecules/asymmetric unit in space group P1 was for two reasons. First, the statistical distribution of the X-ray intensities strongly indicated that the structure was centro-symmetric. Secondly, refinement was actually attempted in space group P1 and not only was the refinement not well behaved but the disorder showed up in both molecules in the cell. One reasonable explanation for the disorder is that the molecule itself possesses an approximate, non-crystallographic, 2-fold axis passing through the center of the 16-membered ring. Rotating the molecular about this pseudo 2-fold axis would result in a molecule having an identical shape and topolgy except that the nitrogen atoms in the big ring would overlap the carbon positions and *vice versa.* There are no strong intermolecular attractions involving these carbon and nitrogen atoms, therefore, as the crystal was forming the molecule was probably as likely to set into either of the pseudo 2-fold orientations. Figure 3 illustrates the three dimensional packing scheme for **4** showing the overall "saddle" shape of the molecule and the different environments around the planar indole rings. A rather unusual feature of this structure is the close, hydrogen-bond like, attraction of the oxygen atoms in both cocyrstallized solvent molecules to the CH moities of the central ring system. One of the oxygen atoms is attracted to C4 and C12 while the other is attracted to C8 and C16 (C--O distances range from 3.14-3.25 Å, O-H distances from 2.19-2.31 Å, and C-H-O angles from 161.7-169.9°).

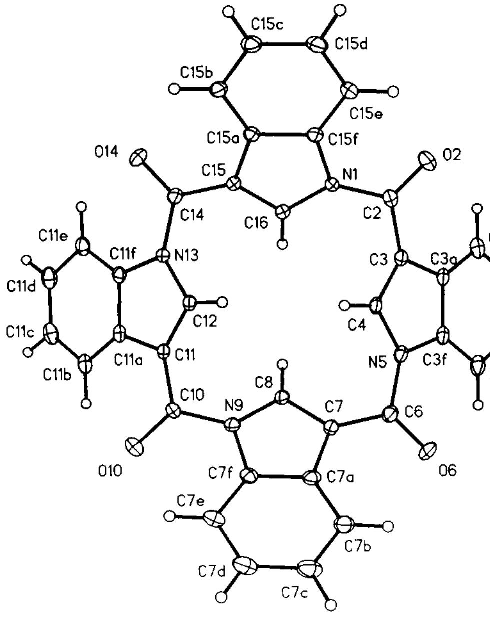


Figure 2. The molecular structure and a numbering scheme for compound **4**.

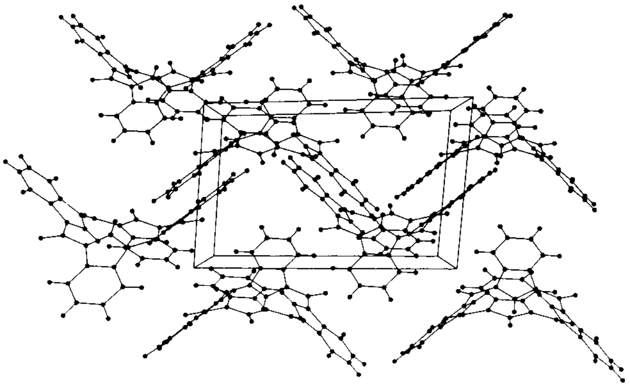


Figure 3. Packing diagram for compound **4**. The figure is drawn looking down the b axis. The solvent molecules have been left out for clarity.

Although the X-ray data do not unambiguously define the structure of **4**, the confirmation of a 16-membered ring like that of **5** allows the elimination of all but one possibility on the basis of symmetry. Thus structure **5**, even if it were considered a likelihood mechanistically, would be ruled out because the two types of carbonyls, urea and ketone, would predict ten, as opposed to nine, signals in the ^{13}C-nmr spectrum as well as two carbonyl stretches in the infrared spectrum. Of all the possible 16-membered

Table 1

Atomic Coordinates (x 10^4) and Equivalent Isotropic Dispalcement Coefficients (Å^{2}x10^3)

	x	y	z	U(eq)
N(1)	3348(4)	2128(2)	5732(2)	30(1)**
C(2)	3103(4)	1125(3)	6096(3)	37(2)
O(2)	3262(4)	556(2)	5592(2)	63(1)
C(3)	2647(4)	852(2)	7087(2)	32(1)**
C(3A)	1861(4)	65(2)	7531(3)	33(1)
C(3B)	1203(4)	-547(3)	7163(3)	45(2)
C(3C)	476(5)	-1231(3)	7786(3)	53(2)
C(3D)	400(5)	-1314(3)	8761(4)	58(2)
C(3E)	1038(5)	-714(3)	9140(3)	47(2)
C(3F)	1783(4)	-10(2)	8498(3)	36(1)
C(4)	3027(4)	1233(2)	7775(2)	36(2)
N(5)	2520(3)	731(2)	8643(2)	32(1)**
C(6)	2833(4)	853(3)	9544(3)	37(2)
O(6)	2968(3)	176(2)	10226(2)	60(1)
C(7)	2989(4)	1829(2)	9577(2)	32(1)**
C(7A)	3777(4)	2089(3)	10233(2)	35(1)
C(7B)	4671(5)	1529(3)	10934(3)	49(2)
C(7C)	5336(5)	2029(3)	11414(3)	58(2)
C(7D)	5156(5)	3038(3)	11206(3)	53(2)
C(7E)	4270(4)	3595(3)	10530(3)	44(2)
C(7F)	3559(4)	3108(3)	10048(2)	33(1)
C(8)	2302(4)	2673(2)	9018(2)	30(1)
N(9)	2632(3)	3463(2)	9287(2)	31(1)**
C(10)	2011(4)	4472(3)	8939(3)	36(2)
O(10)	1879(4)	5062(2)	9417(2)	62(1)
C(11)	1565(4)	4737(2)	7992(2)	30(1)**
C(11A)	501(4)	5557(2)	7622(3)	30(1)
C(11B)	-536(4)	6180(3)	8069(3)	40(2)
C(11C)	-1455(4)	6902(3)	7489(3)	46(2)
C(11D)	-1352(4)	7006(3)	6529(3)	47(2)
C(11E)	-352(4)	6382(3)	6080(3)	40(2)
C(11F)	579(4)	5645(2)	6647(3)	31(1)
C(12)	2264(4)	4345(2)	7260(2)	29(1)
N(13)	1681(3)	4877(2)	6434(2)	29(1)**
C(14)	2249(4)	4729(3)	5512(3)	34(1)
O(14)	2126(3)	5391(2)	4804(2)	54(1)
C(15)	2958(3)	3754(2)	5467(2)	29(1)**
C(15A)	4074(4)	3496(3)	4769(2)	31(1)
C(15B)	4909(4)	4055(3)	4041(2)	37(2)
C(15C)	5955(5)	3564(3)	3499(3)	43(2)
C(15D)	6203(4)	2549(3)	3660(3)	43(2)
C(15E)	5397(4)	1985(3)	4378(3)	38(2)
C(15F)	4328(4)	2471(3)	4936(2)	31(1)
C(16)	2546(4)	2909(2)	6035(2)	31(1)
O(1S)	-92(3)	2734(2)	7600(2)	54(1)
C(2S)	-1097(5)	3441(3)	7520(3)	41(2)
N(3S)	-2086(4)	3649(2)	8196(2)	47(1)
C(4S)	-2112(7)	3035(5)	9117(3)	117(3)
C(5S)	-3220(6)	4496(3)	8035(4)	86(3)
O(6S)	5280(3)	2819(2)	7316(3)	63(1)
C(7S)	6282(5)	2660(3)	6711(3)	49(2)
N(8S)	7274(4)	1870(2)	6776(2)	51(1)
C(9S)	8426(6)	1759(4)	6017(3)	81(3)
C(10S)	7336(6)	1097(4)	7628(4)	95(3)

rings constructed from 1,3-disubstituted indoles consistent with the cyrstallographic results, only the all amide structure **4** would be consistent with a single carbonyl carbon signal in the ^{13}C-nmr spectrum (δ 163.07) and a single $C=O$ stretch in the infrared spectrum (1706 cm^{-1} -- intermediate between the ketone and urea carbonyl signals reported [3] for **5**).

EXPERIMENTAL

Mass spectra were obtained from a Finnigan model 4510 gas chromatograph-mass spectrometer. Electron ionization spectra were collected at 70 eV and a source block temperature 150°. Infrared spectra were recorded from potassium bromide pellets on a Perkin Elmer Model 3600 spectrophotometer. The nmr spectra were obtained using a General Electric QE-300 NMR spectrometer. Mention of a proprietary product does not imply endorsement by the U. S. Department of Agriculture.

Tetramer **4**.

Indole-3-carboxylic acid (220 mg), oxalyl chloride (300 μl), dichloromethane (2 ml) and *N,N*-dimethylformamide (3 μl) were combined at room temperature. As the acid dissolved, gas was evolved and a voluminous white solid separated. After 1 hour, the dichloromethane and excess oxalyl chloride were stripped *in vacuo*, then toluene (2 ml) was added and stripped to ensure removal of oxalyl chloride. The residual acid chloride was dissolved in dry tetrahydrofuran (2 ml), and triethylamine (250 μl) was added dropwise. A rapid reaction was accompanied by separation of a white solid. After standing 4.5 hours at room temperature, water was added and the mixture was extracted 3 times with a mixture of ether and tetrahydrofuran (**4** is insoluble in ether alone). The combined organic extracts were washed successively with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and saturated sodium chloride, then were dried (magnesium sulfate) and concentrated *in vacuo*. Ether was added to the white residue, and the mixture was filtered and the insoluble **4** was collected and rinsed with additional ether to give 146 mg crude **4**. Recrystallization from *N,N*-dimethylformamide gave 88 mg of **4** as small rods, mp >300°; ^{1}H-nmr (DMSO-d$_6$): numbering based on monomeric indole unit, δ 9.47 (s, 1H, H-2), 8.41 (dd, 1H, J = 6.9 and 1.5 Hz, H-7 or H-4), 8.18 (dd, 1H, J = 6.5 and 1.5 Hz, H-7 or H-4), 7.55 (m, 2H, H-5 and H-6); ^{13}C-nmr (DMSO-d$_6$): δ 163.07, 137.64, 135.67, 128.11, 125.80, 124.92, 120.83, 115.40, 112.46; ir (potassium bromide): 3454 (br), 3059 (w), 1706 (s), 1539 (s), 1451 (s), 1376 (s), 1200 (s), 1021 (s), 840 (s), 768 (s), 758 (m), 744 (s); ms: in text.

Single-Crystal X-ray Diffraction Analysis of Compound **4**.

$C_{36}H_{20}N_4O_4 \cdot 2[(CH_3)_2NCHO]$, F.W. = 718.8, triclinic space group P1, a = 9.247(1), b = 24.342(2), c = 14.751(2) Å, α = 75.53(1), β = 82.70(1), γ = 79.57(1)°, V = 1856.0(4) Å^3, Z = 2, ρ calc = 1.286 mg mm^{-3}, λ (CuKα) = 1.54184 Å, μ = 0.68 mm^{-1}, F (000) = 752, T = 245°K.

A clear colorless 0.12 x 0.18 x 0.42 mm crystal, in the shape of a rod, was used for data collection on an automated Siemens R3m/V diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 25 centered reflections within $31 \leq 2 \leq 76°$. The data collection range of *hkl* was: $0 \leq h \leq 9$, $14 \leq k \leq 15$, $-15 \leq l \leq 15$, with $[(\sin \theta)/\lambda]$ max = 0.54. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±2.5% during the data collection. A set of 5106 reflections was collected in the

$\theta/2\ \theta$ scan mode, with scan width [2 θ ($K_{\alpha 1}$) -0.5] *το* [2 θ ($K_{\alpha 2}$) +0.5]° and ω scan rate (a function of count rate) from 10.2°/min to 29.3°/min. There were 4596 unique reflections, and 3870 were observed with $F_o > 3\sigma(F_o)$. The structure was solved and refined with the aid of the SHELXTL system of programs [4]. The full-matrix least-squares refinement varied 491 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms, H atoms included using riding model [coordinate shifts of C applied to attached H atoms, C-H distance set to 0.95 Å, H angles idealized]. Tables of atomic coordinates and bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre [5]. Final residual were R = 0.059 and wR = 0.070 with final difference Fourier excursions of 0.39 and 0.38 $_e$Å^{-3}.

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