Table I. Conversion of Nitriles to Amides[a]

no.	carbonitrile	carboxamide	crude yield,[b] %	mp, °C found[c]	mp, °C reptd
1	6-cyano[1′,8′]naphthobicyclo[3.2.0]hept-2-ene[f]	6-(aminocarbonyl)[1′,8′]naphthobicyclo[3.2.0]hept-2-ene	71	222–3 (syn) 203–4 (anti)	
2	benzonitrile	benzamide	73	g	133–4[d]
3	1-naphthonitrile	1-naphthamide	57	205–6	204–5[d]
4	undecanenitrile	undecanamide	88	97–8	98–9[e]
5	1-phenyl-1-cyclopropanecarbonitrile	1-phenyl-1-cyclopropanecarboxamide	92	93–5	100–1[e]
6	1-benzocyclobutenecarbonitrile	1-benzocyclobutenecarboxamide	88	143–5[h]	159[i]
7	1-phenyl-1-cyclopentanecarbonitrile	1-phenyl-1-cyclopentanecarboxamide	92	g	111–2[j]
8	9-cyanophenanthrene	9-phenanthrenecarboxamide	87	231–2	232–3[e]
9	(*R*,*S*)-2-phenylbutyronitrile	(*R*,*S*)-2-phenylbutyramide	80	82–3	86[e]
10	2-norbornanecarbonitrile	2-norbornanecarboxamide	74	179–80	183–4[k]
11	9-cyanoanthracene		0		
12	2-chloroacrylonitrile		0		
13	methyl 4-cyanobenzoate	methyl 4-(aminocarboxyl)benzoate	60	200–1	201[l]

[a] All previously reported amides gave satisfactory NMR (^{1}H) and IR data. New compounds gave satisfactory spectroscopic data and elemental analyses. [b] Yields not necessarily optimized. [c] Recrystallized melting point. [d] Weast, R. C., Ed. *Handbook of Chemistry and Physics*, 52nd ed.; CRC Press: Cleveland, OH, 1971–1972. [e] Heilbron, I., Ed. *Dictionary of Organic Compounds*, 4th ed.; Oxford University Press: New York, 1965. [f] Synthesized according to ref 7. [g] Crude mp: **2**, 122–4; **7**, 106–7. [h] Homogeneous by capillary GLC. IR: 3352, 3178, 1656, 1605, 1458, 1420, 1262 cm^{-1}; NMR ($CDCl_3$) δ 3.4 (CH_2, 2 H, m), 4.15 (CH, 1 H, dd), 5.9 (NH_2, 2 H, br s), 7.2 (Ar H, br s, 4 H) ppm. [i] Cava, M. P.; Little, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257. Fraenkel, G.; Asahi, Y.; Mitchell, M. J.; Cava, M. P. *Tetrahedron* **1964**, *20*, 1179. [j] Bavin, P. M. G. *J. Med. Chem.* **1966**, *9*, 52. [k] Exo geometry assumed based upon the amide mp. Aul'chenko, I. S.; Gavrilova, T. F.; Kheifits, L. A. *Zh. Org. Khim.* **1967**, *3*, 1636; *Chem. Abstr.* **1968**, *68*, 29874c. [l] Kattwinkel, P.; Wolffenstein, R. *Ber.* **1904**, *37*, 3223.

Treatment of methyl 4-cyanobenzoate also selectively produced methyl 4-(aminocarbonyl)benzoate in good yield leaving the ester function intact. The modestly hindered 1-naphthocarbonitrile was efficiently transformed to the amide. However, the hindered 9-anthracenecarbonitrile proved highly resistant to this method with only 5% transformation to the amide occurring after a 94-h interval. The highly reactive 2-chloroacrylonitrile polymerized even with brief exposure to the reaction conditions. The active copper catalyzed hydration appears to be the best method for this compound.[6] Experiments with **2′** at reduced concentrations (0.5 mmol **2′** per mmol of nitrile) show that the reaction time remains relatively unchanged. Deliberate addition of a 10-fold stoichiometric excess of water to the reaction mixture showed no dramatic change in reaction time or product yield. Other reactions of **2′** with nitriles are currently being studied.

Experimental Section

Melting points are uncorrected and were determined on a Mel-Temp apparatus. Infrared spectra were determined on a Perkin-Elmer FTIR 1600. Proton NMR spectra were determined on a Varian EM-360L or a Varian VXR 300 spectrometer. GLC analyses were performed on a Hewlett-Packard 5890A capillary gas chromatograph using a 50-m SE-30 column. All nitriles listed in Table I except entry 1[7] are commercially available (Aldrich) and were used as received. The 2-norbornanecarbonitrile was an unspecified mixture of endo and exo isomers but is assumed to be predominantly exo based upon the recovered amide.

General Method for the Hydration of Nitriles. To a 50-mL round-bottom flask equipped with reflux condenser and magnetic stirrer was added 1 mmol of the nitrile, 25 mL of glacial acetic acid, and 1 mmol of mercury(II) acetate. The stirred mixture was refluxed for periods up to 70 h and monitored periodically by TLC on silica gel to determine when the reaction was completed. The warm mixture was then poured into 50 mL of ice and water. The amide generally precipitated within an hour and was isolated by vacuum filtration, washed with copious quantities of water, and then dried overnight under high vacuum.[8] In those experiments in which the amide did not readily crystallize from the diluted reaction mixture, it was subjected to extraction with 6 × 25 mL of CH_2Cl_2, and the organic phases were combined, washed with water, dilute sodium bicarbonate, and saturated brine, and then dried over anhydrous $MgSO_4$. Rotary evaporation of the organic phase produced the crude amide, which was dried overnight in high vacuum.

(7) Plummer, B. F.; Hall, R. A. *Chem. Commun.* **1970**, 44.
(8) For the recovery of mercury salts and their safe disposal, see: Sittig, M. *Metal and Inorganic Waste Reclaiming Encyclopedia*; Park Ridge, NJ, Noyes Data Corp., 1980.

Acknowledgment. We thank the National Science Foundation for the support of this research through an NSF-RUI Grant and we are grateful to NSF for partial support to acquire the Varian EM-360L and Varian VXR 300 NMR spectrometers. We thank the Hewlett-Packard Foundation for the donation of the capillary gas chromatograph and the Keck Foundation for financial support.

Registry No. **1**, 117957-05-8; **1** (carboxamide), 117896-76-1; **2**, 100-47-0; **2** (carboxamide), 55-21-0; **3**, 86-53-3; **3** (carboxamide), 2243-81-4; **4**, 2244-07-7; **4** (carboxamide), 2244-06-6; **5**, 935-44-4; **5** (carboxamide), 6120-96-3; **6**, 117917-37-0; **6** (carboxamide), 117896-77-2; **7**, 77-57-6; **7** (carboxamide), 5296-89-9; **8**, 2510-55-6; **8** (carboxamide), 2510-60-3; **9**, 69350-73-8; **9** (carboxamide), 117957-06-9; **10**, 2234-26-6; **10** (carboxamide), 76649-94-0; **11**, 1210-12-4; **12**, 920-37-6; **13**, 1129-35-7; **13** (carboxamide), 6757-31-9; acetic acid, 64-19-7; mercury(II) acetate, 1600-27-7.

Facile Intramolecular Photoaddition and Oxidative Dimerization of Hapalindole E, a Naturally Occurring Isonitrile-Containing Indole

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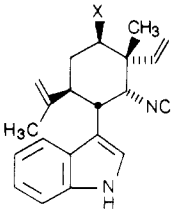
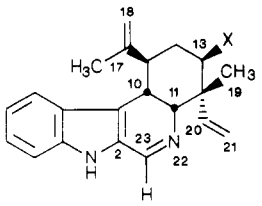
Received September 20, 1988

Recently we have described the isolation and structure elucidation of 20 indoles, the hapalindoles, from the

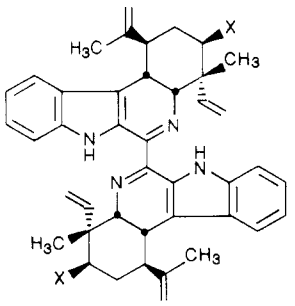
blue-green alga *Hapalosiphon fontinalis*.[1] In an extensive study of the chemical and biological properties of these compounds, some novel chemistry has been discovered, in particular for the tricyclic hapalindoles C (**1**) and E (**2**). For example, these compounds can be directly transformed to 3,4-dihydro-β-carbolines **3** upon acid solvolysis.[2] Another example of unusual chemistry associated with these isonitriles is presented in this paper.





1: X = H
hapalindole C
2: X = Cl
hapalindole E

3



4: X = H
5: X = Cl

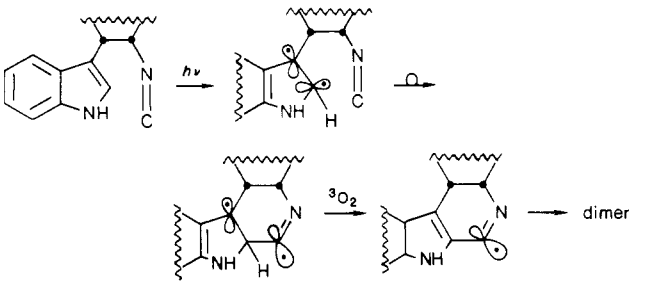
During the course of NMR studies on **1** and **2**, it was noted that both compounds, but **2** in particular, decomposed slowly in $CDCl_3$ in the presence of fluorescent light to yellow, more lipophilic materials. TLC purification of the product from an NMR sample of **2**, for example, yielded a compound **5**, which displayed a similar ^1H NMR spectrum to the starting material, but one where the H-2 signal had disappeared. Moreover, molecular weight was twice that of **2**. The reaction was quite reproducible, generating **5** in up to 50–60% yield. Photodimerization of **1**, however, was slower and gave a lower yield of **4** (15%) under the same conditions.

The structures of the photodimers **4** and **5** were determined by physical methods. The infrared spectrum shows the clear absence of isonitrile absorption (2140 cm^{-1}) and the presence of a new intense band at 1540 cm^{-1}, similar to that seen for the corresponding 3,4-dihydro-β-carbolines **3**. FABMS (fast atom bombardment) analysis generated the molecular formulae, which confirmed the dimeric structures (minus two hydrogen atoms for each compound). Proton and carbon NMR studies (e.g. for **5**) indicated the presence of a symmetrical molecule, which, upon performance of NOE and decoupling experiments, closely matched the ^1H and ^{13}C NMR spectral characteristics for the corresponding dihydro-β-carboline **3**. But, the H-2 resonance was missing, and the C-23 resonance (151.6 ppm, d) found in the monomer was shifted downfield to 156.4 ppm as a singlet, indicating C-23 as the dimerization site.[3]

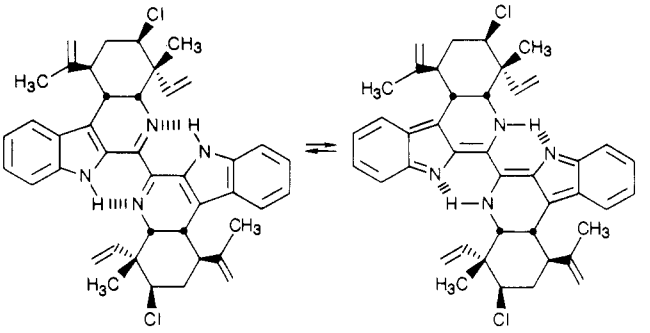
(1) Moore, R. E.; Cheuk, C.; Yang, X. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036.

(2) Bonjouklian, R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1988**, *53*, 5866.

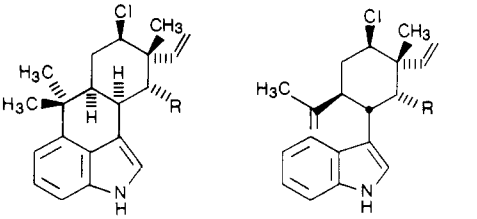
Scheme I



The ultraviolet spectrum of dimer **5** showed maxima at 220 (ε 19 440), 290 (5490), and 326 nm (4840), which were essentially unshifted by acid or base. By comparison, the corresponding dihydro-β-carboline **3** showed UV maxima at 217 (18 600), 235 (11 500), and 323 nm (10 100), which were shifted to 246 (8700), 289 (1700), and 371 nm (16 300) by acid but were unshifted by base. The UV data suggested that the indole NH of one moiety of the dimer was strongly hydrogen bonded to N-22 of the other moiety.



To date we have been able to elucidate the following features of this facile photoprocess. Experimentally, dimer is formed when a dichloromethane solution of the tricyclic hapalindole isonitrile (1 mg/mL in a cork-stoppered 15 × 125 mm Pyrex test tube) is exposed to a horizontal array of GE cool white fluorescent tubes at a distance of 10–15 in. for a period of 3 days. In a number of experiments carried out on other hapalindoles and their derivatives, only hapalindoles C and E (**1** and **2**) were found to undergo this unusual isonitrile addition and oxidative dimerization reaction, although, as previously mentioned, **1** was much less reactive. Hapalindoles A, B, and F and the formamide of E, for example, failed to form photodimers as determined by analytical HPLC, MS and NMR studies.



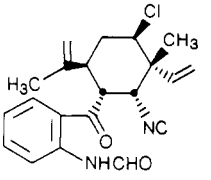
Hap A: R = NC
Hap B: R = NCS

Hap F: R = NCS
Hap E form: R = NHCHO

Furthermore, light and nascent oxygen were required for this photodimerization. Oxygen normally dissolved in the solvent appeared to be the sole source of O_2 in all the reactions described in this work.[4] Use of more polar

(3) See the supplementary material for NMR data comparing **2**, **3**, and **5**.

solvents such as tetrahydrofuran or methanol completely inhibited this photoprocess. If, however, 0.1% rose bengal was added to a methanolic solution of **2**, hapalonamide E (**6**) was formed in high yield after a 1-week period of light



6

exposure; this indicates the presence of singlet oxygen by formation of a typical indole-derived degradation product.[5] Use of *trans*-stilbene, on the other hand, inhibited the photoreaction of hapalindole E in dichloromethane, suggesting that triplet oxygen was the oxidant.[6] In the presence of nascent oxygen, use of radical initiators, such as azobisisobutyronitrile (AIBN) and di-*tert*-butyl peroxide, enhanced formation of the dimer to 80–90% yield during the 3-day standard reaction period. Since the monomeric dihydro-β-carboline **3** failed to photooxidize to the dimer **5** under similar conditions, **3** could be ruled out as a reaction intermediate.

Examples of photochemical oxidative dimerization reactions have been reviewed by Viehe and co-workers.[7] These reactions are characterized by the formation of stable radical species, usually generated under oxidation conditions, which dimerize in synthetically useful yields. If similar radical species are present in our process as shown in Scheme I, the question then arises as to how they are formed in the first place. Imidoyl radicals derived from isonitriles are also well-documented.[8] Our postulated mechanism incorporates both of these features, although initiation of the photochemical process is still a puzzle.

Clearly intramolecular interaction between the isonitrile and the indole is important. The rigidity of the tetracyclic hapalindole A and its failure to undergo this reaction demonstrates that these groups in **1** and **2** must be spatially close. In addition, the comparatively poor production of the photodimer, **4**, of hapalindole C (≈15% in 3 days) also suggests that the equatorial chlorine atom 1,4 to the equatorial indole substituent on the cyclohexane ring of hapalindole E (**2**) plays a subtle but major role in this reaction, perhaps by conformationally freezing the axial isonitrile group into a position of close proximity to the π-system of the indole and thereby lowering even more the energy for this particular intramolecular interaction.

As demonstrated by the facile formation of the monomeric dihydro-β-carboline **3** under acidic conditions, the isonitrile groups of **1** and **2** can readily interact with the C-2 of the indole moiety to form a carbon–carbon bond. Thus, our working hypothesis, as shown in Scheme I, involves photoexcitation of the π-system of the indole of **2**, followed by addition of the isonitrile group to generate a biradical, which then undergoes facile oxidation by triplet oxygen to afford the imidoyl radical, which, in turn, dimerizes to the observed product **5**.

Experimental Section

General Procedures. Analytical TLC was performed on 5 × 10 cm EM silica gel 60 F-254 plates in 2:1 heptane/THF and visualized by UV irradiation or sulfuric acid. Bond-Elut mini silica columns (3 mL) were purchased from Analytichem International, Harbor City, CA.

^{1}H NMR spectra as well as decoupling and NOE experiments were run on a Bruker WM270 instrument. ^{13}C NMR spectra and DEPT experiments were recorded on a Bruker WM250 spectrometer. All chemical shifts are referenced in chloroform-*d* to the residual chloroform signal (7.25 and 77.0 ppm, respectively). IR measurements were determined on a Digilab FTS-14B spectrometer. UV spectra were recorded on a Cary 219 spectrophotometer. FDMS and FABMS experiments were run on MAT 731 and VG-ZAB 3 spectrometers, respectively.

Conversion of Hapalindole E (2) to Dimer 5. Hapalindole E (**2**) (8 mg, 0.023 mmol) was dissolved in 8 mL of dichloromethane and placed in a cork-stoppered 15 × 125 mm Pyrex test tube. No attempt was made to exclude molecular oxygen. The test tube was placed 10–15 in. from a horizontal array of GE Westinghouse F40 CW 4-ft fluorescent lamps (part of our blue-green algal cultivation facility) and left for 3 days at ambient temperature. After that time, the yellow solution was concentrated at reduced pressure, and the crude product was passed through a Bond-Elut silica cartridge equilibrated in 6:1 heptane/THF. The photodimer **5** was eluted first (4.5 mg) followed by the starting material (1.5 mg, R_f 0.5) and <1.0 mg of polar oxidation product. **5**: R_f 0.79; IR (KBr) ν_{max} 3360, 1540 cm^{-1}; UV (MeOH) λ_{max} 220 nm (ε 19440), 290 (5490), 326 (4840); ^{1}H NMR ($CDCl_3$) δ 10.80 (s, NH), 7.58 (d, H-4), 7.07 (dd, H-5), 7.26 (dd, H-6), 7.36 (d, H-7), 3.41 (br dd, H-10), 3.88 d, H-11), 4.66 (dd, H-13), 2.21 and 2.07 (dt, H-14), 2.21 (td, H-15), 1.66 (s, 3H-17), 4.65 and 4.60 (2 s, H-18), 1.53 (s, 3 H-19), 6.29 (dd, H-20), 5.65 and 5.60 (dd, H-21); ^{13}C NMR ($CDCl_3$) δ 156.40 (s, C-23), 146.92 (d, C-20), 146.04 (s, C-16), 136.78 (s, C-8), 126.78 (s, C-9), 125.35 (s, C-2), 124.74 (d, C-6), 122.22 (s, C-3), 120.81 (d, C-5), 120.01 (d, C-4), 114.48 (t, C-21), 113.37 (t, C-17), 112.11 (d, C-7), 71.35 (d, C-11), 62.78 (d, C-13), 46.78 (s, C-12), 45.71 (d, C-15), 36.81 (t, C-14), 32.97 (d, C-10), 21.06 (q, C-18), 18.30 (q, C-19); FDMS, *m/z* (relative intensity) 674, 676, 677, 678 (8:5:2:1); high-resolution FABMS 675.3018 (calcd for $C_{42}H_{45}N_4Cl_2$, mmu error −0.3).

Conversion of Hapalindole C (1) to Dimer 4. Via the same procedure described above, **1** (7 mg, 0.023 mmol) afforded 1.5 mg of the photodimer **4** as well as 4.0 mg of recovered starting material and <1.0 mg of polar oxidation products (unidentified). **4**: R_f 0.85; IR (KBr) 3330 cm^{-1}; ^{1}H NMR δ 10.87 (s, NH), 7.52 (d, H-4), 6.95 (dd, H-5), 7.13 (dd, H-6) 7.23 (d, H-7), 3.28 (dd, H-10), 3.57 (d, H-11), 1.93, 1.75, 1.50 (3 m, H-13, H-14, H-15), 1.56 (s, 3 H-17), 4.52 and 4.59 (2 s, H-18), 1.27 (s, 3 H-19), 6.27 (dd, H-20), 5.37 (dd, H-21); FDMS, *m/z* 607 (M + 1)$^+$.

Oxidation of Hapalindole E (2) to Hapalonamide E (6). Hap E, **2** (5.6 mg), in 5.6 mL of MeOH containing 0.1% rose bengal was exposed to fluorescent lighting for 6 days. Spectral analysis of the crude reaction indicated that it was essentially one product, hapalonamide E, **6**: FDMS, *m/z* 370/372 (M$^+$); IR (CH_2Cl_2) ν_{max} 3400, 2145, 1700, 1665, 1266 cm^{-1}; UV (MeOH) λ_{max} 230, 262, 324 nm (relative intensities 1.2/0.5/0.2); ^{1}H NMR ($CDCl_3$) δ 8.82 (br d, H-7), 8.47 (d, H-2), 7.74 (br d, H-4), 7.65 (t, H-6), 6.02 (dd, H-20), 5.37 (d, *E* H-21), 5.30 (d, *Z* H-21), 4.81 and 4.74 (br s, 2 H-17), 4.33 (dd, H-13), 3.88 (d, H-11), 3.06 (td, H-15), 2.41 (dt, eq H-14), 1.88 (q, ax H-14), 1.60 (br s, 3 H-18), 1.42 (s, 3 H-19).

Acknowledgment. We would like to thank Professor Leo Paquette (consultant) and Drs. Ho-Shen Lin and Herb Kirst for helpful discussions and Dr. Doug Dorman, Mike Heathman, and other members of the Lilly Physical Chemistry Research Department for their assistance. This research was supported in part by the National Science Foundation (Grant No. CHE83-03996).

Supplementary Material Available: Tables of spectral data for compounds **2**, **3**, and **5** (4 pages). Ordering information is given on any current masthead page.

(4) At room temperature, the concentration of $^3O_2$ in typical organic solvents is 10^3–10^4 M. Thus, sufficient oxygen is probably available since the concentration of **2** is 3×10^3 M.

(5) (a) Moore, R. E.; Yang, X. G.; Patterson, G. M. L. *J. Org. Chem.* **1987**, *52*, 3773. (b) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2196.

(6) Turro, N. J. *Modern Molecular Photochemistry*; Benjamin/Cummings Publishing Co. Inc.: Menlo Park, CA, 1978; p 353.

(7) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917.

(8) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971; p 84.