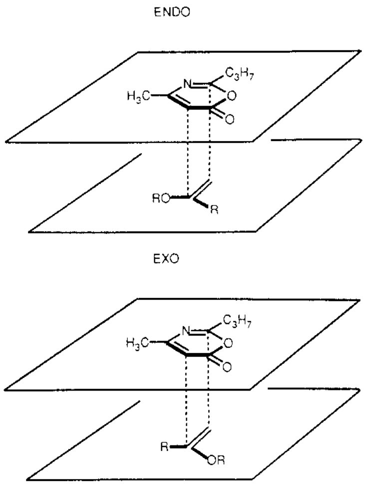

Figure 1.

benzene (2 mL) was treated with glacial acetic acid (2 mL) and was stirred at 24 °C (10 h). The reaction mixture was extracted with benzene (3 × 10 mL), and the combined extracts were washed with water (2 × 10 mL) and saturated aqueous NaCl (1 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 5.0 × 15 cm, 0–100% Et_2O-CH_2Cl_2 gradient elution) afforded **21** (82 mg, 149 mg theoretical, 55%) as a gold oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.87 (s, 1 H, C4-H), 2.85 (t, 4 H, J = 7.5 Hz, C5-H_2 and C7-H_2), 2.70 (t, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 2.49 (s, 3 H, CCH_3), 2.06 (p, 2 H, J = 7.5 Hz, C6-H_2), 1.69 (hextet, 2 H, J = 7.5 Hz, $CH_2CH_2CH_3$), 0.98 (t, 3 H, J = 7.5 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 3066, 2959, 2871, 2847, 1602, 1573, 1457, 1390, 1377, 1123, 856 cm^{-1}; EIMS, m/e (relative intensity) 175 (M^+, 9), 174 (13), 160 (20), 147 (base), 146 (49); CIMS (isobutane), m/e (relative intensity) 176 ($M + H^+$, base), 89 (47); HRMS, m/e 175.1363 ($C_{12}H_{17}N$ requires 175.1361).

3-Methyl-1-propyl-5,6,7,8-tetrahydroisoquinoline (22): gold oil (21 mg, 111 mg theoretical, 19%); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.73 (s, 1 H, C4-H), 2.73 (t, 4 H, J = 8.1 Hz, $CH_2(CH_2)_2CH_2$), 2.71 (t, 2 H, J = 7.4 Hz, $CH_2CH_2CH_3$), 2.48 (s, 3 H, CCH_3), 1.87–1.60 (m, 6 H, $CH_2CH_2CH_2CH_2$ and $CH_2CH_2CH_3$), 1.01 (t, 3 H, J = 7.4 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 2960, 2953, 2869, 1596, 1561, 1451, 1399, 1375, 1088, 860, 789 cm^{-1}; EIMS, m/e (relative intensity) 189 (M^+, 30), 174 (31), 160 (base); CIMS (isobutane), m/e (relative intensity) 190 ($M + H^+$, base); HRMS, m/e 189.1516 ($C_{13}H_{19}N$ requires 189.1518).

3-Methyl-1-propyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine (23): gold oil (70 mg, 120 mg theoretical, 58%); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.83 (s, 1 H, C4-H), 2.82 (m, 6 H, $CH_2CH_2CH_3$ and $CH_2(CH_2)_3CH_2$), 2.54 (s, 3 H, CCH_3), 1.85 (p, 4 H, J = 5.5 Hz, $CH_2CH_2CH_2CH_2CH_2$), 1.67 (m, 4 H, $CH_2CH_2CH_3$ and $(CH_2)_2CH_2(CH_2)_2$), 0.98 (t, 3 H, J = 7.4 Hz, $CH_2CH_2CH_3$); IR (neat) ν_{max} 2958, 2924, 2852, 1595, 1563, 1455, 1390, 976, 830, 788 cm^{-1}; EIMS, m/e (relative intensity) 203 (M^+, 11), 188 (16), 175 (48), 160 (43), 147 (base); CIMS (isobutane), m/e (relative intensity) 204 ($M + H^+$, base); HRMS, m/e 203.1672 ($C_{14}H_{21}N$ requires 203.1674).

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (Grant CA 42056) and the Alfred P. Sloan Foundation.

Registry No. **1**, 65445-21-8; **3**, 118170-48-2; **5**, 43107-11-5; **6**, 118170-49-3; **7**, 118170-50-6; **8a**, 4231-35-0; **8b**, 75371-82-3; **8c**, 14273-06-4; **9a**, 109-92-2; **9b**, 108-05-4; **9c**, 88-12-0; **9d**, 116-11-0; **9e**, 108-22-5; **9f**, 922-69-0; **9g**, 13735-81-4; **9h**, 7196-01-2; **10a**, 7148-07-4; **10b**, 936-52-7; **11**, 1125-99-1; **12**, 14092-11-6; **15a**, 118170-51-7; **15b**, 118170-57-3; **16**, 5397-28-4; **17**, 118170-52-8; **18**, 6753-29-3; **19**, 118170-53-9; **20**, 118170-54-0; **21**, 118170-55-1; **22**, 94384-37-9; **23**, 118170-56-2; $H_3C(CH_2)_2COCl$, 141-75-3.

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Hydration of Nitriles to Amides Promoted by Mercury(II) Acetate in Acetic Acid

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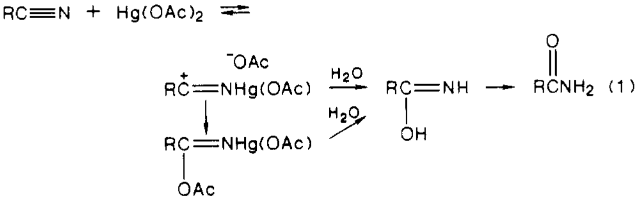
Received July 15, 1988

During a study of the chemical reactivity of 7-chloro-7-cyano-6b,7,8,8a-tetrahydrocyclobut[*a*]acenaphthylene (**1′**),[2] we observed that treatment of **1′** with silver acetate in refluxing acetic acid invariably produced the corresponding amides and rearranged products containing the carbonamide function. To test our hypothesis that silver acetate was acting as a catalyst to transform the nitrile, we subjected benzonitrile to refluxing acetic acid in the presence and absence of silver acetate and with sodium acetate and refluxing acetic acid. Benzamide was formed in 20 h only in the presence of silver acetate. Other nitriles were treated similarly but silver acetate proved to be a poor catalyst for many nitrile hydrations. The fact that mercury salts are often used as catalysts in alkyne chemistry[3] and that mercury(II) acetate (**2′**) is used in oxymercuration reactions of double bonds[4] led us to study the hydration of nitriles in refluxing acetic acid catalyzed by **2′**.

An array of methods is available for the hydration of nitriles to amides.[5] A recent report describes the use of active reduced copper in water at 100 °C in a sealed bottle.[6] The method is effective but requires an inert atmosphere to maintain the activity of the copper catalyst. The catalytic effect of **2′** requires no special precautions and the results are summarized in Table I. Appropriate controls were run in the absence of catalyst and reaction times were extended such that only traces of nitrile could be detected by thin-layer chromatography or GLC. In some cases the reaction was complete in 5 h but most reactions were run at reflux for 70 h. The mechanism in eq 1 is proposed to explain the catalytic effect of mercury(II) acetate and is equally applicable to silver ion catalysis. Because no special precautions are taken to exclude water from the acetic acid, water is probably present at low concentration. Thus, the intermediate that is hydrated could either be the iminium-stabilized carbocation or the imino acetate ester.



(1)

The reaction conditions are moderate and they may be useful in cases where strong acids could be detrimental to other functional groups. The cyclopropyl nitrile was hydrated intact without disruption of the cyclopropyl ring and it exhibited the shortest reaction time to completion.

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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 (^1H) 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.

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.

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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