PHOTOCHEMICAL REARRANGEMENTS OF 1-ACETYL-1,2-DIHYDROQUINOLINE-2-CARBONITRILES TO THE 3,1-BENZOXAZINES AND CYCLOPROP[*b*]INDOLES

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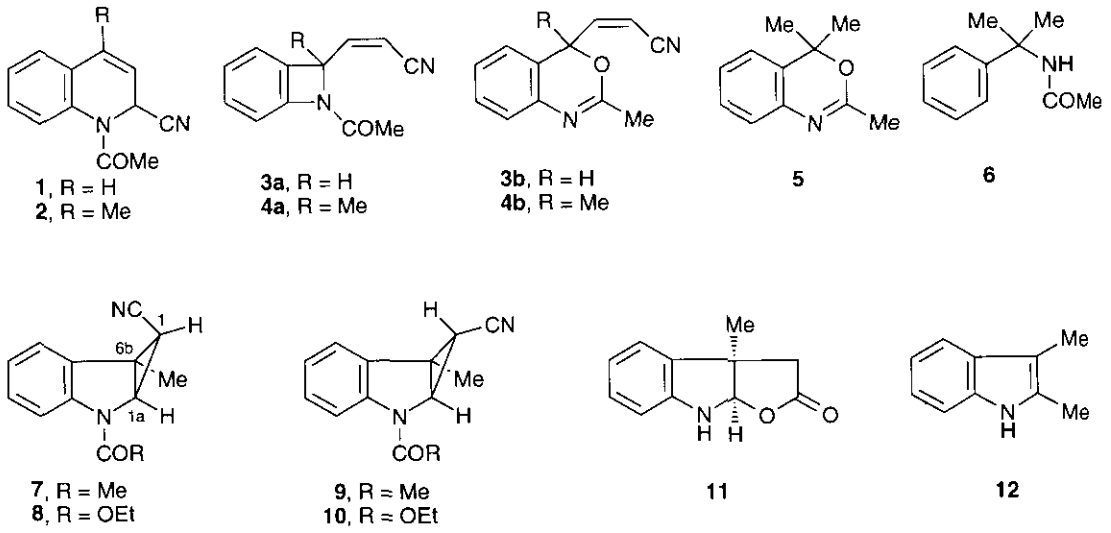
Abstract — Irradiation of 1-acetyl-1,2-dihydroquinoline-2-carbonitrile (**1**) in ether gave the 3,1-benzoxazine (**3b**), while the 4-methyl congener (**2**) in either ether or ethanol gave the 3,1-benzoxazine (**4b**) and the cycloprop[*b*]indole (**7**). A possible mechanism for the formation of these products is also discussed.

Two decades ago we described that irradiation of 1-acetyl-1,2-dihydroquinoline-2-carbonitrile (a Reissert compound) (**1**) in ether gave the benzazete (**3a**), while the 4-methyl congener (**2**) in either ether or ethanol gave the benzazete (**4a**) and the cycloprop[*b*]indole (**7**).[1] The structural assignment of the benzazetes (**3a**) and (**4a**) was based on their IR and ^{1}H-NMR spectroscopic evidence. We now reinvestigated the photochemistry of **1** and **2** and found that the structures of **3a** and **4a** should be revised to the 3,1-benzoxazines (**3b**) and (**4b**), respectively. In this paper we also discuss on the mechanism of the photochemical rearrangements.



Scheme 1

†This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

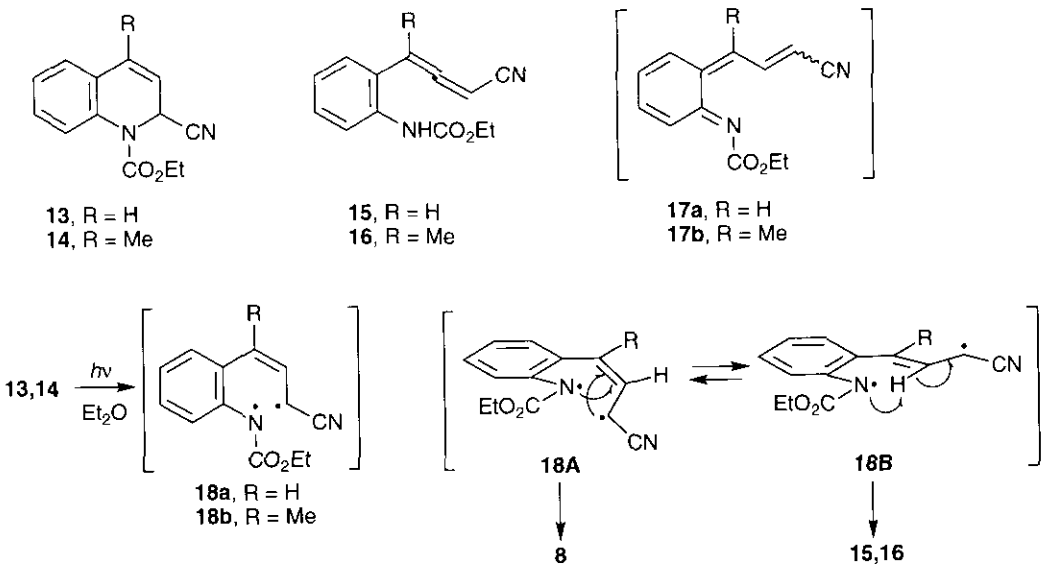
Irradiation of compound (**1**) in ether with a 350 W high-pressure mercury lamp in a Pyrex tube gave **3b** in quantitative yield as a low melting solid which rapidly decomposed on exposure to air. Irradiation of **1** in ethanol gave a complex mixture. On the other hand, irradiation of the 4-methyl congener (**2**) in ether for 5 h gave **4b** as the major product (36% yield) along with a small amount of the cycloprop[*b*]indole (**7**) (9%). Irradiation of **2** in ethanol afforded both **4b** and **7**, whose relative yields depended upon the period of irradiation. Shorter periods of irradiation (1-3 h) gave **4b** as the major product, while only **7** was obtained when the period of irradiation was increased to 10 h.

Comparison of the IR and ^{1}H-NMR spectroscopic data of **3b** and **4b** [a strong absorption at 1640 cm^{-1} in both the IR spectra and methyl singlets at δ 2.16 and 2.25 in the ^{1}H-NMR spectra, respectively] with those of the acetamide (**6**)[2] [a carbonyl absorption at 1650 cm^{-1} in the IR spectrum and a singlet due to the acetyl group at δ 1.94 in the ^{1}H-NMR spectrum] and those of the (4*H*)-3,1-benzoxazine (**5**)[3] [a strong imidate absorption at 1635 cm^{-1} in the IR spectrum and a singlet due to the 2-methyl group at δ 2.11 in the ^{1}H-NMR spectrum] suggested two types of structures, the benzazetes (**3a**) and (**4a**) and the 3,1-benzoxazines (**3b**) and (**4b**). However, the signals appeared at δ 159.1 for **3b** and 158.9 for **4b** in the ^{13}C-NMR spectra would seem to be too high for an acetamide carbonyl carbon (*cf.*, 169.1 for **6**). In comparison, the carbon assigned to the iminyl carbon at the 2-position of the 3,1-benzoxazine (**5**) resonates at δ 160.2, comparable to the values for compounds (**3b**) and (**4b**). More definitive evidence was given by the chemical shift of the signal due to the quaternary carbon at the 4-position of **4b** which resonates at a chemical shift (δ 78.7) similar to that of the corresponding carbon (δ 78.1) of the 3,1-benzoxazine (**5**) but significantly different from that of the benzylic carbon (δ 55.8) of **6**. These data are consistent with the 3,1-benzoxazine structures (**3b**) and (**4b**) rather than the benzazete structures (**3a**) and (**4a**). That *N*-[*o*-(1-methylethenyl)phenyl]hexanamide yields the coresponding 3,1-benzoxazine on irradiation in cyclohexane[4] also supports this assignment. The (*Z*)-stereochemistry about the C-C double bond in **3b** and **4b** was assigned on the basis of the coupling constants (*J* 11.0 Hz for **3b** and 12.1 Hz for **4b**) of the two olefinic protons.[5] All attempts to obtain a crystalline derivative for an X-Ray analysis were unsuccessful. For examples, hydrogenation (PtO_2 in ethanol) and ozonolysis of **3b** and **4b** gave a complex mixture, and when a solution of **4b** and cyclopentadiene in toluene was refluxed, the starting material was recovered unchanged.

The structure of **7** was determined by a combination of spectroscopic and chemical evidence. The IR spectrum indicated absorptions at 2230 (CN) and 1670 cm^{-1} (an amide group) and the ^{1}H-NMR spectrum showed two doublets due to the C-1 and C-1a protons at δ 1.86 (*J* 5.6 Hz) and 4.15 (*J* 5.6 Hz), respectively, a singlet due to the *N*-acetyl group at δ 2.40, and a singlet ascribable to the 6b-methyl group at δ 1.70. Chemical confirmation for this structure was obtained by cyclopropane ring opening of **7** with base and acid. Thus, treatment of **7** with 5% potassium hydroxide in ethanol at 110 °C gave the furo[2,3-*b*]indol-2-one (**11**)[6] in 63% yield. Refluxing **7** in conc. hydrochloric acid afforded 2,3-dimethylindole (**12**) in 51% yield. The *endo*-stereochemistry of **7** was readily assigned by comparison of the coupling constant of the C-1 proton in the ^{1}H-NMR spectrum with that of the *exo*-isomer (**9**), which was obtained by thermal or photochemical (sensitized) isomerization of **7**. The C-1 proton in **7** which occurred at δ 1.86, showed a large coupling (5.6 Hz) with the C-1a proton, while the corresponding proton of **9** appeared at δ 1.25 with small coupling (1.7 Hz). These values are compatible with those of ethyl *endo*-

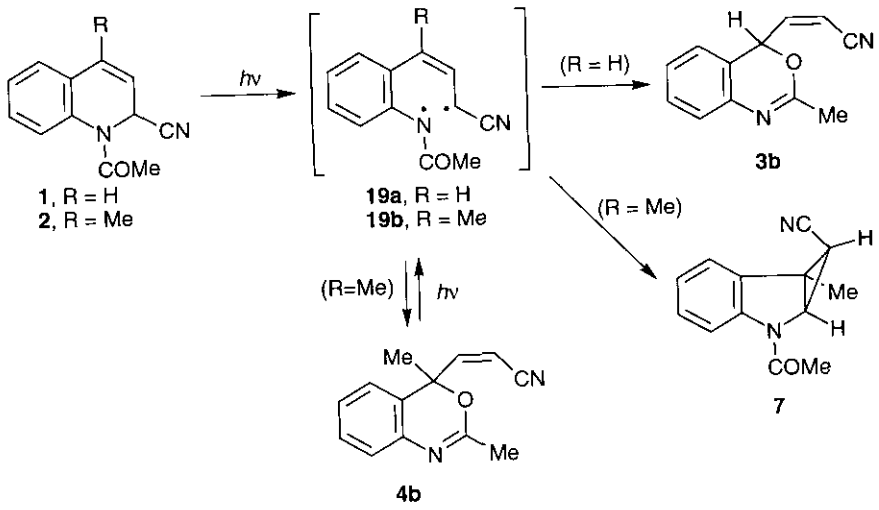
and *exo*-1-cyano-6b-methyl-1,1a,2,6b-tetrahydrocycloprop[*b*]indole-2-carboxylates (**8**) and (**10**) ($J_{1,1a}$ 6 and 2 Hz, respectively).[6]

Previously we showed that irradiation of the Reissert compound (**13**) in ether produced the allenic compound (**15**), while the 4-methyl congener (**14**) gave rise to the allenic compound (**16**) and the cycloprop[*b*]indole (**8**).[6,7] Although these transformation reactions had been interpreted in terms of the intermediacy of the azahexatrienes (**17a,b**), the later mechanistic studies[8] revealed that **17a,b** are not intermediates of these transformation reactions. An intriguing alternative would involve diradical intermediates (**18a,b**) which are formed *via* initial cleavage of the N-C bond of **13** and **14**. The diradicals (**18a,b**) in ether may abstract hydrogen atom to form the allenic compounds (**15,16**) or recyclize to give the cycloprop[*b*]indole (**8**). The diradical (**18a**) (R = H) will take preferentially the conformer (**18B**) (R = H) to avoid the steric interaction between the aryl group and cyanomethyl radical, in which the nitrogen radical is in close proximity to the hydrogen atom to be abstracted. On the other hand, in **18b** (R = Me) both the conformers (**18A**) and (**18B**) (R = Me) are present because they are almost energetically equivalent. Therefore, the diradical (**18b**) undergoes either cyclization to form **8** or hydrogen-abstraction to give the allenic compound (**16**). The hydrogen abstraction process seems to be suppressed in ethanol.



Scheme 2

In the present study, regardless of the conformations of the diradicals, the diradicals (**19a,b**) derived from **1** and **2** undergo rapidly ring closure to form the 3,1-benzoxazines (**3b**) and (**4b**). The 3,1-benzoxazine (**4b**) is photochemically unstable and reverts to **19b** which undergoes irreversible isomerization to the cycloprop[*b*]indole (**7**). Indeed, irradiation of isolated **4b** in ether or ethanol gave **7**.



Scheme 3

EXPERIMENTAL

Mps are uncorrected. IR spectra were recorded on a JASCO-IR-A-100 spectrophotometer. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.4 MHz) spectra were measured on a Varian XL-300 spectrometer for solutions in $CDCl_3$. δ-Values quoted are relative to tetramethylsilane, and *J*-values are given in Hz. Irradiation was carried out with an Eikosha 350 W high-pressure mercury lamp. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

1-Acetyl-1,2-dihydroquinoline-2-carbonitrile (**1**). According to the method reported by Popp and his coworkers,[9] **1** was prepared from quinoline, potassium cyanide, and acetyl chloride, mp 97-98 °C (lit.,[9] mp 96-97 °C); IR ν_{max} ($CHCl_3$) cm^{-1}: 1655; ^{1}H-NMR δ: 2.26 (3H, s, COMe), 6.07 (1H, dd, *J* 9.2 and 6.2, 3-H), 6.52 (1H, br d, *J* 5, 2-H), 6.77 (1H, d, *J* 9.3, 4-H), 7.23-7.39 (4H, m, ArH); ^{13}C-NMR δ: 22.1 ($COCH_3$), 40.1 (2-C), 115.7 (C≡N), 121.6, 124.4, 126.76, 126.83, 127.5, 128.7, 129.3, 133.9, 169.5 (C=O).

1-Acetyl-4-methyl-1,2-dihydroquinoline-2-carbonitrile (**2**). According to the method reported by Popp and his coworkers,[9] **2** was prepared in 42% yield from 4-methylquinoline, potassium cyanide, and acetyl chloride, mp 127-128 °C; IR ν_{max} ($CHCl_3$) cm^{-1}: 1650; ^{1}H-NMR δ: 2.16 (3 H, t, *J* 1.3, 4-Me), 2.24 (3H, s, COMe), 5.87 (1H, dq, *J* 6.5 and 1.5, 3-H), 6.43 (1H, br d, *J* 6, 2-H), 7.22-7.46 (4H, m, ArH); ^{13}C-NMR δ: 18.1 (4-Me), 22.0 ($COCH_3$), 40.3 (2-C), 116.1 (C≡N), 118.0, 124.4, 124.5, 126.6, 128.5, 128.6, 133.9, 135.4, 169.2 (C=O). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.47; H, 5.72; N, 12.99.

Irradiation of 1. A solution of **1** (150 mg, 0.75 mmol) in ether (20 mL) was irradiated in a Pyrex tube until the starting material had disappeared (6.5 h) (checked by TLC). Evaporation of the solvent gave quantitative yield of (*Z*)-3-[2-methyl-(4*H*)-3,1-benzoxazin-4-yl]propenenitrile (**3b**) which solidified but unstable in the air. IR ν_{max}($CHCl_3$) cm^{-1}: 2230, 1640, 1610; ^{1}H-NMR δ: 2.16 (3 H, s, 2-Me), 5.54 (1 H, dd, *J* 11.0 and 1.0, CH=C*H*CN), 6.23 (1 H, br d, *J* 8.8, 4-H), 6.63 (1 H, dd, *J* 11.0 and 8.8, C*H*=CHCN), 7.00 (3 H, br dt, *J* 7.5, 0.1, ArH), 7.11-7.40 (1 H, m, ArH); ^{13}C-NMR δ: 21.2 (2-Me),

73.8 (4-C), 101.0 (CH=*C*HCN), 114.6 (C≡N), 120.5, 124.0, 124.5, 127.0, 130.0, 137.4, 148.6 (*C*H=CHCN), 159.1 (2-C).

Irradiation of 2. (a) A solution of **2** (300 mg, 1.4 mmol) in ether (40 mL) was irradiated in a Pyrex tube until the starting material had disappeared (5 h) (checked by TLC) and concentrated to give a mixture of two products which was separated by column chromatography on silica gel [hexane-AcOEt (3:1)]. The first fraction gave (*Z*)-3-[2,4-dimethyl-(4*H*)-3,1-benzoxazin-4-yl]propenenitrile (**4b**) (109 mg, 36%) as an oil. IR ν_{max}(CHCl3) cm^{-1}: 2230, 1640, 1610; ^{1}H-NMR δ: 1.87 (3H, s, 4-Me), 2.25 (3H, s, 2-Me), 5.48 (1H, d, *J* 12.1, CH=*CH*CN), 6.56 (1H, d, *J* 12.1, *CH*=CHCN), 7.07-7.34 (4H, m, ArH); ^{13}C-NMR δ: 21.3 (2-Me), 27.7 (4-Me), 78.7 (4-C), 98.3 (CH=*C*HCN), 114.9 (C≡N), 123.0, 124.9, 125.6, 126.9, 129.5, 137.5, 154.0 (*C*H=CHCN), 158.9 (2-C). HRMS (FAB) Calcd for $C_{13}H_{13}N_2O$ [$(M+H)^+$]: 213.1028. Found: 213.1023.

The second fraction gave *endo*-1-cyano-2-acetyl-6b-methyl-1,1a,2,6b-tetrahydrocycloprop[*b*]indole (**7**) (28 mg, 9%) as colourless needles, mp 207-208 °C (from benzene); IR ν_{max}(CHCl3) cm^{-1}: 2230, 1670; ^{1}H-NMR δ: 1.70 (3H, s, 6b-Me), 1.86 (1H, d, *J* 5.6, 1-H), 2.40 (3H, s, COMe), 4.15 (1H, d, *J* 5.6, 1a-H), 7.11-7.49 (3H, m, ArH), 8.20 (1H, d, *J* 8.3, ArH); ^{13}C-NMR δ: 12.4 (1-C), 17.1 (6b-Me), 24.3 ($COCH_3$), 34.5 (6b-C), 49.0 (1a-C), 114.8 (C≡N), 117.1, 123.5, 124.1, 129.3, 129.7, 141.9, 168.5 (C=O). *Anal*. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.65; H, 5.71; N, 13.15.

(b) A solution of **2** (300 mg, 1.4 mmol) in ethanol (40 mL) was irradiated in a Pyrex tube until the starting material had disappeared (5 h). Evaporation of the solvent gave a mixture of two products which was separated by column chromatograpy on silica gel [hexane-AcOEt (3:1)] to give **4b** (90 mg, 30%) and **7** (162 mg, 54%). Prolonged irradiation of the above solution (10 h) resulted in the disappearance of **4b** and an increase of the amount of **7** and polymeric material.

2,4,4-Trimethyl-(4*H*)-3,1-benzoxazine (**5**). According to the method reported by Capozzi and his coworkers,[3a] **5** was prepared in 47% yield from *N*-[*o*-(1-methylethenyl)phenyl]acetamide as a colorless oil; IR ν_{max}(CHCl3) cm^{-1}: 1635 and 1610; ^{1}H-NMR δ: 1.61 (6H, s, 2x4-Me), 2.11 (3H, s, 2-Me), 7.04-7.28 (4H, m, ArH); ^{13}C-NMR δ: 21.9 (2-Me), 28.7 (2x4-Me), 78.1 (4-C), 122.2, 124.0, 126.3, 128.4, 130.4, 137.9, 160.2 (2-C).

***N*-(1-Methyl-1-phenylethyl)acetamide** (**6**). According to the method reported by Ritter and Minieri,[2] **6** was obtained in 1.5% yield from α-methylstyrene and acetonitrile as colorless plates, mp 102-103 °C (from petroleum ether) (lit.,[2] 96-97 °C); IR ν_{max}(CHCl3) cm^{-1}: 1650; ^{1}H-NMR δ: 1.67 (6H, s, 2xMe), 1.94 (3H, s, COMe), 7.16-7.50 (5H, m, ArH); ^{13}C-NMR δ: 24.2 ($COCH_3$), 29.0 (2xMe), 55.8 (quaternary C), 124.7, 126.5, 128.3, 146.8, 169.1 (C=O). *Anal*. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.63; H, 8.63; N, 8.14.

3a-Methyl-3,3a,8,8a-tetrahydrofuro[2,3-*b*]indol-2-one (**11**). A solution of **7** (50 mg, 0.25 mmol) in ethanol (1 mL) containing 5% aqueous potassium hydroxide (1 mL) was heated at 110 °C for 3 d. After cooling, the mixture was neutralized with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane-EtOAc (3:1)] to give **11** (25 mg, 63%) as colorless needles, mp 101-102 °C (from hexane-ether) (lit.,[6] mp 101-102 °C).

2,3-Dimethylindole (**12**). Compound (**7**) (100 mg, 0.5 mmol) in conc. hydrochloric acid (1 mL) was refluxed for 1.5 h. After cooling, the mixture was diluted with water and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentarated. The residue was chromatographed on silica gel [hexane-EtOAc (20:1)] to give **12** (37 mg, 51%), mp 100-101 °C (from petroleum ether) (lit.,[10] mp 104-106 °C).

Thermal Isomerization of 7. A solution of **7** (500 mg, 2.5 mmol) in decalin (20 mL) was refluxed for 18 h and concentrated *in vacuo* to give a 1:1 mixture of **7** and **9**, which was separated by chromatography on silica gel [hexane-AcOEt, (5:1)] to give **7** (249 mg, 50%) and the *exo*-1-cyano-2-acetyl-6b-methyl-1,1a,2,6b-tetrahydrocycloprop[*b*]indole (**9**) (164 mg, 33%). The *exo*-isomer had mp 180-181 °C (from benzene-petroleum benzin); IR ν_{max} ($CHCl_3$) cm^{-1}: 2230, 1670; ^{1}H-NMR δ: 1.25 (1H, d, *J* 1.7, 1-H), 1.85 (3H, s, 6b-Me), 2.45 (3H, s, COMe), 4.21 (1H, br d, *J* 1.7, 1a-H), 7.09-7.40 (3H, m, ArH), 8.14 (1H, d, *J* 8.1, ArH); ^{13}C-NMR δ: 14.1 (1-C), 14.5 (6b-Me), 24.3 ($COCH_3$), 32.9 (6b-C), 50.0 (1a-C), 117.55 (C≡N), 117.63, 123.1, 124.1, 129.0, 132.3, 140.9, 168.6 (C=O). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.49; H, 5.69; N, 13.24.

Photochemical Isomerization of 7. After a solution of **7** (100 mg, 0.5 mmol) in acetone (20 mL) was irradiated in a Pyrex tube for 5 h, the mixture was concentrated to give a 1:1 mixture of **7** and **9**.

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