The Reaction of Indolizines with Tetracyanoethylene

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Tetracyanoethylene (TCNE) reacts with indolizines (**1a-c**) to give mixtures of 1- and 3-substituted tricyanovinylindolizines, respectively. The isomers are identified by nmr spectroscopy. The occurrence of intramolecular charge-transfer bands in the visible spectra is discussed.

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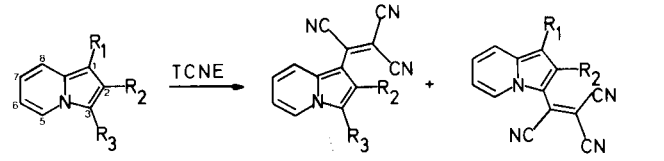
Electrophilic substitution studies on indolizine (**1a**) have demonstrated that the 3-position is the one most easily attacked (1-4). If this position is blocked, the electrophile enters the 1-position. These observations are in accord with the theoretical predictions cited in reference 1, and also with more recent calculations (5-9).

Tetracyanoethylene (TCNE) is known to react with a number of aromatic compounds to give tricyanovinyl derivatives (10-13). Roland and McKusick (12) reported that **3a** is formed when TCNE reacts with indolizine in DMF. Similar products from reaction with TCNE have been reported for other heterocyclic systems with a bridgehead nitrogen (14,15).

3-Tricyanovinylindolizines are potential starting materials for cycl[2.2.3]azines. We have therefore reinvestigated the reaction between indolizine and TCNE and found that, in addition to the red compound **3a**, the orange 1-substituted derivative **2a** is also formed. The **2a**:**3a** ratio varied with the solvent (4:1 in DMF, 3:2 in acetone, and 2:1 in THF). The overall yield (*ca.* 40%) was only slightly affected by change of solvent. In no case could we detect derivatives substituted in the 2-position or in the 6-membered ring. In the reaction between 2-methylindolizine (**1b**) and TCNE, the two isomers **2b** and **3b** were formed, while 1,2-dimethylindolizine (**1c**), as expected, gave only the 3-substituted compound **3c**.



1a $R_1=R_2=R_3=H$ 2a $R_2=R_3=H$ 3a $R_1=R_2=H$

1b $R_1=H$; $R_2=CH_3$; $R_3=H$ 2b $R_2=CH_3$; $R_3=H$ 3b $R_1=H$; $R_2=CH_3$

1c $R_1=R_2=CH_3$; $R_3=H$ 3c $R_1=R_2=CH_3$

The 270 MHz ^{1}H-nmr spectra of **1-3** were all of first order type and chemical shift values and coupling constants could be determined directly. In indolizine, H-5 couples, as reported (16,17), with the other protons in the six-membered ring ($J_{5,6}$ = 7.0, $J_{5,7}$ = 1.1, $J_{5,8}$ = 1.2 Hz) and with H-1 ($J_{1,5} \sim 1$ Hz). The H-5 signal thus appears as a pair of quartets in indolizine, but changes into a pair of triplets in 1-substituted indolizines. On this basis, we have assigned structure **2a** to the orange and **3a** to the red isomer. By the same method we have identified the isomers **2b** and **3b** as the 1- and 3-substituted derivatives, respectively.

The strongly electron withdrawing tricyanovinyl group causes a general downfield shift of the ring protons in **2a,b** and **3a-c** compared to those in the corresponding parent compounds **1a-c**. This shift change is nearly constant for each type of proton except for the protons closest to the tricyanovinyl group which in **2a** (H-2 and H-8) and in **3a** (H-2 and H-5) show a considerable downfield shift ($\Delta\delta$ = 1.15-1.32 ppm) compared to the corresponding protons in **1a**. This is in agreement with the above assignments, which place these neighbouring protons in the deshielding regions (18) of the anisotropic triple-bonds of the tricyanovinyl group. A correspondingly large shift change is not observed for H-8 in **2b** and H-5 in **3b** and **3c**, respectively, probably because the 2-methyl group in these compounds can twist the tricyanovinyl group out of the deshielding region.

The strong absorption bands in the visible spectra of other tricyanovinyl-substituted aromatics, like pyrrole and indole (19), have been attributed to intramolecular charge-transfer transitions. Probably, the corresponding bands in the spectra of tricyanovinyl-substituted indolizines arise from transitions between the indolizine part, acting as a π-donor, and the tricyanovinyl part, acting as a π-acceptor. The two bands observed for **2a**, **2b**, and **3a** in nonpolar solvents overlap more in more polar solvents. For **3b** and **3c**, a single, broad band is observed even in cyclohexane, but this absorption may consist of two overlapping bands.

Deviation from Beer's law due to the formation of self-associated complexes was not observed in the actual concentration range (10^{-4}-10^{-6} mole l^{-1}) which supports the assumption that both bands are due to intramolecular transitions. The bathochromic shift, observed for **2a,b** and **3a-c** when the polarity of the solvent is increased, is consistent with the assumption of transitions for which the excited state is more polar than the ground state (20a). There need be no contradiction between the shift to longer wavelength of the bands of **2b**, **3b**, and **3c** and their nonplanarity, assumed on the basis of their nmr spectral data. It is known (20b) that twisting of the

single bond between the electron-donating and the electron-accepting parts in this kind of composite systems can cause either hypsochromic or bathochromic shifts of a charge-transfer band. Also, alkyl substitution in the electron-donating part of the molecule will affect the position of such bands (21).

In conclusion, we wish to report that attempts to ring-close **3a**, thermally or photochemically, to a cycl[2.2.3]-azine were unsuccessful.

EXPERIMENTAL

The 270 MHz pmr spectra were recorded on a Bruker WH 270 instrument. Deuteriochloroform was used as solvent with TMS as internal reference, and the chemical shifts are reported in δ-values. The concentrations were always less than 0.05*M* in order to avoid, as much as possible, the concentration dependence observed for the indolizine proton shifts (22). Mass spectra and exact mass determinations have been obtained at the Department of Medical Biochemistry, University of Göteborg, with a GEC-AEI 902 mass spectrometer, equipped with an INSTEM Data Mass System. The uv and visible spectra were measured in ethanol (99.5%) or in chloroform with a Cary Model 15 spectrophotometer. The ir spectra were recorded in potassium bromide discs with a Beckman IR 9 spectrophotometer. Silica gel (Merck 60, 0.063-0.20 mm) was used for column chromatography, and analytical and preparative tlc was performed on silica gel (Merck 60, F_{254}, precoated alumina sheets). A cyclohexane-ethyl acetate 3:1 mixture was used as developing solvent, unless otherwise stated. Elementary analyses were carried out by Novo Microanalytical Laboratory, Novo Industry A/S, Denmark, and by Microanalyslaboratoriet, Sveriges Lantbruksuniversitet, Uppsala.

TCNE was of commercial purum quality and was recrystallised from chlorobenzene (23). Indolizine (24), 2-methylindolizine (25), and 1,2-dimethylindolizine (25) were prepared as described in the literature, and they were further purified by vacuum sublimation prior to use.

The Reaction of Indolizine (**1a**) with TCNE.

Compound **1a** (100 mg., 0.85 mmole) was dissolved in 10 ml. of DMF at 50°, and TCNE (110 mg., 0.85 mmole) was then added dropwise with stirring. The solution, which first turned dark-blue on addition of TCNE and then changed to red, was maintained at 50° for 15 minutes and then poured into ice-water. The precipitate was filtered providing 145 mg. of crude product. Two components were separated by chromatography on silica gel using hexane and ethyl acetate as the eluents.

The first component, compound **3a** was purified by tlc on silica gel with ethyl acetate as the eluent yielding 12 mg. (6.5%) of a dark red solid, m.p. 145-146°; pmr: δ 6.87 (C1-H, doublet of doublet, $J_{1,2}$ = 5.1 Hz, $J_{1,5}$ = 0.9 Hz), 7.18 (C6-H, multiplet, $J_{5,6}$ = $J_{6,7}$ = 7.0 Hz, $J_{6,8}$ = 1.1 Hz), 7.47 (C7-H, multiplet, $J_{7,8}$ = 8.6 Hz, $J_{6,7}$ = 7.0 Hz, $J_{5,8}$ = 1.1 Hz), 7.68 (C8-H, multiplet, $J_{7,8}$ = 8.6 Hz, $J_{5,8}$ = $J_{6,8}$ = 1.1 Hz), 8.09 (C2-H, doublet, $J_{1,2}$ = 5.1 Hz), 9.05 (C5-H, multiplet, $J_{5,6}$ = 7.0 Hz, $J_{5,8}$ = 1.1 Hz, $J_{1,5}$ = 0.9 Hz); ir: 2210; uv and visible (chloroform): λ max (ε) 310 (3,300), 327 (3,500), 336 (3,300), 378 (4,300), 507 (25,100), 533 (33,200); ms (50 eV) m/e (relative intensity): 218 (100, M^+), 192 (11, M-CN), 191 (24, M-HCN), 166 (4), 164 (8), 115 (12), 95.5 (8); observed molecular ion: 218.057 ± 0.003; calculated for $C_{13}H_6N_4$: 218.0592.

Anal. Calcd. for $C_{13}H_6N_4$: C, 71.5; H, 2.8; N, 25.7. Found: C, 71.4; H, 2.8; N, 25.6.

1-Tricyanovinylindolizine (**2a**).

The second component from the above reaction, compound **2a**, was purified by tlc on silica gel with ethyl acetate as the eluent yielding 49.5 mg. (27%) of a red solid, m.p. 227-228°; pmr: δ 7.14 (C6-H, multiplet, $J_{5,6}$ = $J_{6,7}$ = 7.0 Hz, $J_{6,8}$ = 1.1 Hz), 7.46 (C3-H, doublet, $J_{2,3}$ = 3.7 Hz), 7.53 (C7-H, multiplet, $J_{7,8}$ = 9.0 Hz, $J_{6,7}$ = 7.0 Hz, $J_{5,7}$ = 1.1 Hz), 7.94 (C2-H, doublet, $J_{2,3}$ = 3.7 Hz), 8.20 (C5-H, multiplet, $J_{5,6}$ = 7.0 Hz, $J_{5,7}$ = $J_{5,8}$ = 1.1 Hz), 8.56 (C8-H, doublet, $J_{7,8}$ = 9.0 Hz); ir: 2210; uv and visible (ethanol): λ max (ε) 216 (14,800), 238 (6,500), 278 (3,600), 340 (1,300), 491 (41,500); ms (50 eV) m/e (relative intensity): 218 (100, M^+), 192 (8, M-CN), 191 (27, M-HCN), 166 (7, M-2CN), 164 (10, M-2HCN), 142 (90), 115 (14), 95.5 (6); observed molecular ion: 218.058 ± 0.003; calculated for $C_{13}H_6N_4$: 218.0592.

Anal. Calcd. for $C_{13}H_6N_4$: C, 71.5; H, 2.8; N, 25.7. Found: C, 71.6; H, 2.6; N, 25.3.

The Reaction of 2-Methylindolizine (**1b**) with TCNE.

Compound **1b** (150 mg., 1.15 mmoles) was dissolved in 15 ml. of acetone at 5° and TCNE (150 mg., 1.17 mmoles) was then added dropwise with stirring. The solution was maintained at 5° for 10 minutes and then the solvent was removed under reduced pressure. Two components were separated by chromatography on silica gel using hexane and ethyl acetate as the eluents.

The first component, compound **3b** was purified by tlc on silica gel with dichloromethane as the eluent yielding 28 mg. (10%) of a violet solid, m.p. 169-170°; pmr: δ 2.55 (C2-CH_3, doublet, J_{1,CH_3} = 0.8 Hz), 6.67 (C1-H, doublet, J_{1,CH_3} = 0.8 Hz), 7.13 (C6-H, multiplet, $J_{5,6}$ = $J_{6,7}$ = 7.0 Hz, $J_{6,8}$ = 1.5 Hz), 7.39 (C7-H, multiplet, $J_{7,8}$ = 8.6 Hz, $J_{6,7}$ = 7.0 Hz, $J_{5,7}$ = 1.1 Hz), 7.56 (C8-H, multiplet, $J_{7,8}$ = 8.6 Hz, $J_{6,8}$ = 1.5 Hz, $J_{5,8}$ = 1.1 Hz), 8.16 (C5-H, multiplet, $J_{5,6}$ = 7.0 Hz, $J_{5,7}$ = $J_{5,8}$ = 1.1 Hz); ir: 2210; uv and visible (ethanol): λ max (ε) 232 (17,000), 300 (5,100), 331 (3,500), 393 (6,400), 535 (19,200); ms (50 eV) m/e (relative intensity): 232 (60, M^+), 206 (16, M-CN), 205 (100, M-HCN), 204 (75), 180 (5), 179 (20), 178 (9); observed molecular ion: 232.077 ± 0.003; calculated for $C_{14}H_8N_4$: 232.075.

Anal. Calcd. for $C_{14}H_8N_4$: C, 72.4; H, 3.5; N, 24.1. Found: C, 72.2; H, 3.5; N, 23.6.

2-Methyl-1-tricyanovinylindolizine (**2b**).

The second component from the above reaction, compound **2b** was purified by tlc on silica gel with ethyl acetate as the eluent yielding 57 mg. (21%) of a red solid, m.p. 206-207°; pmr: δ 2.50 (C2-CH_3, doublet, $J_{CH_3,3}$ = 0.9 Hz), 7.04 (C6-H, multiplet, $J_{5,6}$ = $J_{6,7}$ = 6.8 Hz, $J_{6,8}$ = 1.3 Hz), 7.31 (C3-H, doublet, $J_{CH_3,3}$ = 0.9 Hz), 7.49 (C7-H, multiplet, $J_{7,8}$ = 9.0 Hz, $J_{6,7}$ = 6.8 Hz, $J_{5,7}$ = 1.1 Hz), 7.58 (C8-H, doublet, $J_{7,8}$ = 9.0 Hz), 8.10 (C5-H, multiplet, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = $J_{5,8}$ = 1.1 Hz); ir: 2200, 2215; uv and visible (ethanol): λ max (ε) 218 (17,900), 242 (8,700), 278 (3,900), 285 (3,800), 362 (1,600), 515 (17,700); ms (50 eV) m/e (relative intensity): 232 (74, M^+), 206 (15, M-CN), 205 (100, M-HCN), 204 (81), 180 (4), 179 (22), 178 (14); observed molecular ion: 232.074 ± 0.003; calculated for $C_{14}H_8N_4$: 232.075.

Anal. Calcd. for $C_{14}H_8N_4$: C, 72.4; H, 3.5; N, 24.1. Found: C, 72.1; H, 3.5; N, 23.9.

1,2-Dimethyl-3-tricyanovinylindolizine (**3c**).

Compound **3c** was obtained from **1c** (100 mg., 0.7 mmole) and TCNE (100 mg., 0.8 mmole) in the same manner as described for **2b**. A violet solid (42 mg., 24%) was obtained by chromatography, m.p. 187-188°; pmr: δ 2.29 (C1-CH_3 or C2-CH_3,

singlet), 2.47 (C1-CH_3 or C2-CH_3, singlet), 7.15 (C6-H, multiplet, $J_{5,6}$ = $J_{6,7}$ = 7.0 Hz, $J_{6,8}$ = 1.5 Hz), 7.43 (C7-H, multiplet, $J_{7,8}$ = 8.8 Hz, $J_{6,7}$ = 7.0 Hz, $J_{5,7}$ = 1.1 Hz), 7.56 (C8-H, multiplet, $J_{7,8}$ = 8.8 Hz, $J_{6,8}$ = 1.5 Hz, $J_{5,8}$ = 1.1 Hz), 8.16 (C5-H, multiplet, $J_{5,6}$ = 7.0 Hz, $J_{5,7}$ = $J_{5,8}$ = 1.1 Hz); ir: 2210; uv and visible (ethanol): λ max (ε) 205 (18,300), 215 (17,000), 243 (12,200), 280 (6,100), 307 (3,400), 344 (3,800), 397 (5,500), 555 (16,700), ms (50 eV) m/e (relative intensity): 246 (100, M^+), 245 (70, M-H), 231 (11, M-CH_3), 220 (16, M-CN), 219 (95), 218 (76), 217 (32), 204 (59), 192 (24); observed molecular ion: 246.089 ± 0.003; calculated for $C_{15}H_{10}N_4$: 246.0905.

Anal. Calcd. for $C_{15}H_{10}N_4$: C, 73.2; H, 4.1; N, 22.7. Found: C, 73.0; H, 3.9; N, 22.3.

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