SYNTHESIS, CRYSTAL STRUCTURE AND LIGHT ABSORPTION OF VINYLOGOUS N,N'-DIALKYLINDIGOS

Lutz Fitjer, Ralf Gerke, Wolfgang Lütke, Peter Müller and Isabel Usón

Institut für Organische Chemie der Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany
Institut für Anorganische Chemie der Universität Göttingen, Tammannstrasse 4, D-37077 Göttingen, Germany

Received 10 September 1999; accepted 11 October 1999

Abstract: The base catalyzed N,N'-dialkylation of the vinylogous indigo dye cis-cis-2a proceeds with concomitant isomerization and yields cis-trans-2b,c as minor, and trans-trans-2b,c,d as major products. Upon exposure to light, cis-trans-2b,c isomerizes to trans-trans-2b,c. According to an X-ray analysis, trans-trans-2c and trans-trans-2d are planar. However, due to the different configurations of 2a and 2b-d, the light absorption data of 2a-d cannot be used to quantify the inductive effects of the alkyl groups.

© 1999 Elsevier Science Ltd. All rights reserved.

Introduction

We recently reported on the crystal structure and light absorption of N,N'-dimethylindigo 1b and ascribed the remarkable bathochromic shift of its longest wavelength absorption maximum as compared to 1a ($\lambda_{\text{max}} = 50.5 \text{ nm (CHCl}_3)$) to a Brunings-Corvin effect, i.e. a torsion of the central double bond caused by steric interaction of the methyl and the carbonyl groups. Indeed, according to the crystal structure data, this torsion amounts to 26° and is accompanied by a slight but significant pyramidalization of the carbon atoms of the central double bond, the nitrogen atoms, and the carbon atoms of the carbonyl groups. Whether, and if true, to what extent an inductive effect was operative could not be clarified.

We now report on the synthesis, structure and light absorption of the vinylogous N,N'-dialkylindigos 2b-d in an approach to quantify the inductive effects not only in 1b, but also in 1c and 1d. Our approach was based on the expectation that 2a-d would be both stereochemically identical and planar, so that an eventual bathochromic shift of the longest wavelength absorption maxima of 2b-d as compared to 2a could be ascribed to
pure inductive effects also present in 1b-d. As will be seen from what follows, these expectations were only partially fulfilled.

**Syntheses**

For the synthesis of 2b-d, we first prepared the parent compound 2a by an acid catalyzed condensation of indoxyl (3) with glyoxal as described by Friedländer and Risse.\(^1\) 2a is very sparingly soluble in all organic solvents and \(^1\)H NMR, \(^1\)C NMR and \(^1\)C-\(^1\)H correlation spectra required for a configurational assignment could only be obtained from solutions in dimethyl sulfoxide-\(d_6\). As indicated by the appearance of a single resonance for the vinylic protons (\(\delta = 6.80, s, 2H\)) and the corresponding carbon atoms (\(\delta = 104.31\)), 2a was symmetrical and stereochemically pure. However, at this stage of the investigations, a decision between a cis-cis and a trans-trans configuration could not yet be made.

For the dialkylation of 2a, we followed the protocol of Kuhn and Trischmann\(^6\) for the dimethylation of 1a and reacted 2a with a large excess of the appropriate alkyl iodide in the presence of base. In this way, methyl
and ethyl iodide delivered both a configurationally stable and unstable N,N'-dialkylated product, while isopropyl iodide yielded only a stable one. In all cases, the isomers were separated by chromatography on silica gel in chloroform while being protected from light. During elution of the configurationally unstable isomers, a photoisomerization to the corresponding stable isomers was observed. This isomerization was provoked even by diffuse daylight, could be followed by UV/VIS spectroscopy, and was complete within minutes (Figure 1). Interestingly, acid catalyzed condensation of N-methyl-β-acetyl-indoxyl (4) with glyoxal yielded only the stable isomer of 2b.

![Figure 1. Photoisomerization of cis-trans-2b (λ_max 605 nm, left) and cis-trans-2c (λ_max 608 nm, right) to the corresponding trans-trans-configurated isomers in chloroform. In both cases, the first spectrum was registered immediately after elution of the unstable isomer. Afterwards, the probes were subjected for 2.5 (2b) and 1.5 min (2c), respectively, to diffuse daylight until the next spectrum was taken. After registration of the last spectrum, no further change was observed.](image)

The configurationally stable isomers crystallized from ethanol as bronze needles, Fp 285-286 (2b), 259-260 (2c) and 212-214°C (2d), respectively. As in the case of 2a, their 1H NMR, 13C NMR and 1H-13C correlation spectra indicated a symmetrical species. However, this time the resonances for the vinylic protons [δ = 8.03, s, 2H (2b), 8.12, s, 2H (2c), 8.43, s, 2H (2d)] and the corresponding carbon atoms [δ = 111.68 (2b), 111.66 (2c), 113.30 (2d)] were shifted to extremely low field. It thus turned out, that the configuration of 2a was cis-cis, and the configuration of the stable isomers of 2b-c was trans-trans. The configurational assignment of the unstable isomers as cis-trans resulted from the fact that the 1H NMR spectrum of a sample enriched in the unstable isomer of 2b showed two doublets for the vinylic protons [δ = 6.82, d, J = 14 Hz, 1H and 8.08, d, J = 14 Hz, 1H] at chemical shifts nearly identical with those of the corresponding protons in cis-cis-2a and trans-trans-2b, respectively.

Taking into account, that the strength of the nonbonding interactions within a six-membered arrangement follows the order alkyl-hydrogen > oxygen-hydrogen > hydrogen-hydrogen, the preference of 2a and 2b-d for a cis-cis and a trans-trans configuration, respectively, could have been expected. However, the mechanism of the configurational change during the alkylations of 2a is less obvious. As all reactions were performed in the dark, a photochemical isomerization of already alkylated products, as with cis-trans-2b,c, may be excluded. We there-
fore believe that the isomerizations are initiated by a deprotonation of an amino group leading to a resonance stabilized anion with diminished rotational barriers around the formal double bonds and are terminated by a readjustment of the stereochemistry in favour of sterically less demanding trans relationships during the alkylation step.

Crystal Structures

Having established the configurations of 2a and the stable isomers of 2b-d as cis-cis and trans-trans, respectively, we tried to determine their molecular structures next. However, albeit different techniques and a large number of solvents were tested, it was only with trans-trans-2c and trans-trans-2d, that suitable crystals for an X-ray analysis could be obtained: in the case of 2c by diffusion of pentane into a solution in chloroform, and in the case of 2d by diffusion of water into a solution in acetic acid. In the last case, the sample crystallized with two moles of acetic acid.

Figure 2. Crystal structure of trans-trans-2c (left) and trans-trans-2d (right) with 50% probability ellipsoids, and view perpendicular to the crystallographic y-axis of trans-trans-2d (bottom).

Trans-trans-2c crystallizes in the monoclinic space group P2₁/n with half a molecule in the asymmetric unit, the rest of the molecule is generated by the inversion center. Trans-trans-2d crystallizes in the monoclinic space group C2/m with a quarter of 2c and a half molecule of acetic acid in the asymmetric unit. The rest of the molecule and a second molecule of acetic acid are generated by the mirror and the twofold axis. The acetic acid molecules are coordinated to the O atoms of 2c via a hydrogen bond.
On the contrary to what had been found with 1b, all non-hydrogen atoms of trans-trans-2c and trans-trans-2d, with the exception of the methyl-C atoms of the N-alkyl substituents, form a perfect plane. The methyl-C atoms deviate from this plane pairwise in opposite direction and point to the butadiene units. The bond lengths and bond angles of the ring systems match those of 1b closely. As compared to butadiene (1.349 Å),\(^7\) the double bonds in 2c (1.362 Å) and 2d (1.358 Å) are elongated. However, for cross-conjugated systems as in 2c and 2d this would have been expected. Plots of the crystal structures are given in Figure 2.

**Light Absorption Data**

As already pointed out, a quantification of the inductive effects in 2b-c and its use to differentiate between the influence of steric and inductive effects to the light absorption of 1b-c was tied to the condition that 2a-c are both stereochemically identical and planar. Unfortunately, the stereochemistry of 2a and 2b-d turned out to be different. Therefore, albeit trans-trans-2c and trans-trans-2d are planar, and trans-trans-2b and cis-cis-2a may be taken as planar, a comparison of the longest wavelength absorption maxima of cis-cis-2a and trans-trans-2b,c,d (Table 1) is hampered by the fact that the influence of their configuration cannot be quantified.\(^8\)

The situation with cis-trans-2b,c is even worse. In these cases the fast isomerization to trans-trans-2b,c indicates a strong steric interaction between the alkyl group and a vinylic proton in the cis-configurated part and hence a nonplanar structure. As the energetically most favourable way to minimize the interactions is a torsion around the central single bond, a hypsochromic shift of the longest wavelength absorption maxima as compared to hypothetically planar species should result. Therefore, the observed hypsochromic shifts as compared to trans-trans-2b,c (Table 1) cannot be attributed to a configurational change alone.

| Table 1. Longest wavelength absorption maxima of 2a-d: (a) in CHCl₃, (b) in DMSO. |
|------------------|------------------|------------------|
|                  | \(\lambda_{\text{max}}\) [nm] (log \(e\)) |
|                  | cis-cis          | cis-trans        | trans-trans      |
|                  | (a)              | (a)              | (a)              |
|                  | (b)              | (b)              | (b)              |
| a                | 597 (--)         | 605 (4.57)       | 626 (4.57)       |
| b                | 593 (4.43)       | 608 (4.60)       | 634 (4.59)       |
| c                |                  | 638 (4.58)       | 638 (4.57)       |
| d                |                  |                  | 642 (4.56)       |

Obviously, the dilemma is twofold: to compare cis-cis-2a and trans-trans-2b,c,d means to compare compounds with different configurations, and to compare cis-trans-2b,c with either cis-cis-2a or trans-trans-2b,c means to compare compounds with different configurations, and nonplanar and planar structures. In no case, the observed shift differences may be attributed to pure inductive effects. Therefore, a quantification of the inductive effects in trans-trans-2b-d, and hence in 1b-d, has to await for a synthesis of trans-trans-2a.
EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 225 spectrophotometer. UV/VIS spectra were obtained with a Cary Instruments spectrometer model 14. 1H NMR, 13C NMR and 13C-1H correlation spectra were measured with a Varian VXR 200 or VXR 500 or a Bruker AMX 300 spectrometer. For standards other than TMS the following chemical shifts were used: δ(H(CHCl3) = 7.24 ppm, δ(H([D2]-DMSO) = 2.49 ppm, δ(CDC13) = 77.00 ppm, δ(C-[D6]-DMSO) = 39.50 ppm. Mass spectra were determined with a Varian MAT 311 A or 701 instrument operated at 70 eV. Rf values are quoted for Macherey & Nagel Polygram SIL G/UV254 plates. Melting points were observed on a Reichert microhotstage and are not corrected.


α,β-Bis(3-oxo-indolinylidene-2)-ethane (2a): To a solution of 3 (20.0 g 150 mmol) in ethanol (350 ml) was added aqueous glyoxal (30% w/w, 14.5 g, 75 mmol) and concentrated hydrochloric acid (10 ml) and the mixture was heated for 1.5 h to reflux. After cooling, the mixture was filtered and the residue was first washed with hot water and then with ethanol until the colour of the filtrate was light-violet. The yield of the remaining 2a amounted to 7.0 g (32%). Blue-violet powder. IR (KBr): C=O 1658 cm⁻¹ (broad). UV/VIS λ [nm] (log ε): DMSO: 593, 331 (4.43, 4.30). 1H-NMR (300 MHz, [D6]-DMSO, [Ds]-DMSO int): δ = 6.80 (s, 2H), 6.91 (t, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 2H), 7.45 (t, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 10.58 (s, 2H). 13C-NMR (125 MHz, [D6]-DMSO, [D6]-DMSO int): δ = 104.31, 111.79, 119.64 (Cτ.), 120.27 (Cτ.), 123.98, 136.00 (Cτ.), 138.34, 151.99, 184.63 (Cq~).

α,β-Bis(3-oxo-indolinylidene-2)-ethane (2a): To a solution of 3 (20.0 g 150 mmol) in ethanol (350 ml) was added aqueous glyoxal (30% w/w, 14.5 g, 75 mmol) and concentrated hydrochloric acid (10 ml) and the mixture was heated for 1.5 h to reflux. After cooling, the mixture was filtered and the residue was first washed with hot water and then with ethanol until the colour of the filtrate was light-violet. The yield of the remaining 2a amounted to 7.0 g (32%). Blue-violet powder. IR (KBr): C=O 1658 cm⁻¹ (broad). UV/VIS λ [nm] (log ε): DMSO: 593, 331 (4.43, 4.30). 1H-NMR (300 MHz, [D6]-DMSO, [Ds]-DMSO int): δ = 6.80 (s, 2H), 6.91 (t, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 2H), 7.45 (t, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 10.58 (s, 2H). 13C-NMR (125 MHz, [D6]-DMSO, [D6]-DMSO int): δ = 104.31, 111.79, 119.64 (Cτ.), 120.27 (Cτ.), 123.98, 136.00 (Cτ.), 138.34, 151.99, 184.63 (Cq~).

Dialkylation of 2a. General procedure: Protected from light, a mixture of 2a (2.88 g, 10 mmol), DMF (50 ml), barium oxide (10.0 g), water (0.2 ml) and the appropriate alkyl iodide (160 mmol) was stirred under nitrogen for 13 (2b,c) and 19 h (2d), respectively. During this time, the colour of the reaction mixture changed from violet over blue to green-blue. The mixture was diluted with chloroform (25 ml) and filtered, and the residue was washed with chloroform until the filtrate was colourless. The combined filtrates were washed with water, saturated sodium thiosulfate, and water. The solution was dried (Na2SO4) and concentrated on a rotary evaporator to yield the crude N,N'-dialkylated products.

N,N'-Dimethyl-α,β-bis(3-oxo-indolinylidene-2)-ethane (2b): The crude product (2.97 g) was extracted with chloroform (250 ml) and filtered from undissolved material (290 rag). Protected from light, the filtrate was chromatographed on silica gel (0.08-0.20 mm) in chloroform [column 70 x 7.5 cm; Rf 0.16 (trans-trans-2b), 0.06 (trans-cis-2b)] to yield 940 mg (30%) of pure trans-trans-2b and 38 mg (1%) of nearly pure trans-cis-2b. During elution of the latter, several probes were taken and the isomerization to trans-trans-2b documented by UV/VIS spectroscopy, trans-trans-2b: Bronze needles from ethanol, Fp 285-286°C (subl. 250°C). IR (KBr): C=O 1654 cm⁻¹. UV/VIS λ [nm] (log ε): CHCl3: 626, 337 (4.57, 4.58), DMSO: 634, 337 (4.59, 4.58). 1H-NMR (300 MHz, CDC13, CHCl3 int): δ = 3.36 (s, 6H), 6.82-6.90 (m, 4H), 7.43 (t, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 8.03 (s, 2H). 13C-NMR (50 MHz, CDC13, CDC13 int): δ = 28.82 (Cp,~), 108.88, 111.68, 119.54 (Cτ.), 121.56 (Cq~), 124.47, 135.53 (Cτ.), 138.08, 151.62, 185.67 (Cq~). MS m/z 316 (M +, 100), 288 (24), 287 (48), 158 (16). Anal. calcd for C20H16N2O2: C, 75.92; H, 5.10; N, 8.85. Found: C, 75.85; H, 5.17; N, 8.97.

N,N'-Diethyl-α,β-bis(3-oxo-indolinylidene-2)-ethane (2c): The crude product (3.03 g) was dissolved in chloroform (250 ml) and filtered from undissolved material (290 mg). Protected from light, the filtrate was chromatographed on silica gel (0.08-0.20 mm) in chloroform [column 70 x 7.5 cm; Rf 0.16 (trans-trans-2c), 0.09 (trans-cis-2c)] to yield 1.68 g (49%) of trans-trans-2c.

N,N'-Diethyl-α,β-bis(3-oxo-indolinylidene-2)-ethane (2c): The crude product (3.03 g) was dissolved in chloroform (200 ml), and, protected from light, chromatographed on silica gel (0.08-0.20 mm) in chloroform [column 70 x 7.5 cm; Rf 0.22 (trans-trans-2c), 0.09 (trans-cis-2c)] to yield 1.68 g (49%) of trans-trans-2c.
During elution of trans-cis-2c, several probes were taken and the isomerization to trans-trans-2c documented by UV/VIS spectroscopy. However, this isomerization was too fast to allow an isolation of trans-cis-2c, trans-trans-2c: Bronze needles from ethanol, Fp 259-260°C. IR (KBr): C=O 1653 cm⁻¹. UV/VIS λmax [nm] (log ε): CHCl₃: 634, 338 (4.58, 4.58), DMSO: 638, 338 (4.57, 4.55). H-NMR (300 MHz, CDC1₃, CHCl₃ int): δ = 1.32 (t, J = 7 Hz, 6H), 3.86 (q, J = 7 Hz, 4H), 6.86 (t, J = 8 Hz, 2H), 6.87 (d, J = 8 Hz, 2H), 7.43 (t, J = 8 Hz, 2H), 7.65 (d, J = 8 Hz, 2H), 8.12 (s, 2H). 13C-NMR (50 MHz, CDC1₃, CDC1₃ int): δ = 12.05 (C₆H₅), 36.98 (C₆H₅), 108.84, 111.66, 119.48 (CH₃), 121.65 (C₆H₅), 124.58, 135.50 (C₆H₅), 136.62, 150.74, 185.88 (C₆H₅). MS m/z 372 (M⁺, 100), 302 (26), 287 (33), 259 (14). Anal. calcd for C₁₂H₁₀NO₂: C, 76.72; H, 5.85; N, 8.11. Found: C, 76.85; H, 5.72; N, 8.24.

trans-cis-2c: UV/VIS λ,ax [nm] (log c): CHCl₃: 608 (4.60); isosbestic point: 619 (4.51).

N,N′-Diisopropyl-γ,β-bis(3-oxo-indolinyliden-2)-ethane (2d): The crude product (1.89 g) was dissolved in chloroform (40 ml), and, protected from light, chromatographed on silica gel (0.08-0.20 mm) in chloroform (column 50 x 5 cm; Re 0.29 (trans-trans-2d)) to yield 850 mg (23%) pure trans-trans-2d: Bronze needles from ethanol, Fp 212-214°C. IR (KBr): C=O 1653 cm⁻¹. UV/VIS λmax [nm] (log c): CHCl₃: 638, 339 (4.56, 4.55), DMSO: 642, 338 (4.56, 4.54). H-NMR (300 MHz, CDC1₃, CHCl₃ int): δ = 1.48 (d, J = 7 Hz, 12H), 4.48 (sept, J = 7 Hz, 2H), 6.85 (t, J = 8 Hz, 2H), 7.11 (d, J = 8 Hz, 2H), 7.40 (t, J = 8 Hz, 2H), 7.66 (d, J = 8 Hz, 2H), 8.43 (s, 2H). 13C-NMR (50 MHz, CDC1₃, CDC1₃ int): δ = 19.54 (Cl), 46.3 (Cl), 111.47, 113.31, 119.24 (CH₃), 122.05 (C₆H₅), 124.61, 135.22 (C₆H₅), 136.51, 151.45, 186.23 (C₆H₅). MS m/z 344 (M⁺, 100), 315 (27), 288 (17). Anal. calcd for C₂₄H₂₄N₂O₂: C, 77.41; H, 6.51; N, 7.52. Found: C, 77.51; H, 6.47; N, 7.25.

N,N′-Dimethyl-γ,β-bis(3-oxo-indolinyliden-2)-ethane (2b) from N-methyl-O-acetyl-indoxyl (4): To a warm solution of 4 (1.0 g, 5.3 mmol) and aqueous glyoxal (1.11 g, 30% w/w, 5.2 mmol) in ethanol (15 ml) was added conc HCI (1.5 ml), causing an instantaneous colour change from colourless over green-blue to deep-blue. The mixture was held for 5 min at 70°C and then cooled. The precipitate was suction-filtered, washed with a small amount of cold ethanol and dried to yield 425 mg (51%) of pure trans-trans-2b as bronze needles, Fp 284-286°C. The ¹H and ¹³C NMR data were identical with those of authentic material.

Crystal structure analyses: trans-trans-2c: C₂₂H₂₀N₂O₂, Mr = 344.40, crystal size: 0.40 × 0.30 × 0.05 mm³, monoclinic, space group P2₁/n, a = 10.1634(2), b = 6.5592(2), c = 12.8535(3) Å, β = 100.451(1)°, V = 842.65(4) Å³, Z = 2, ρcalc = 1.357 Mg m⁻³, F(000) = 364, λ = 0.71073 Å, T = 133 K, µ(MoKα) = 0.088 mm⁻¹. Total number of reflections measured 19270, unique 1030 (R(int) = 0.0765). Data/restraints/parameters: 1030/0/120, data collection range: 2.36 < 0 < 21.97°. Final R indices: R₁ = 0.0625, wR₂ = (Σw(Fo² - Fc²)²/Σw(Fo²))¹/² = 0.1621 on data with I>2σ(I) and R₁ = 0.0709, wR₂ = 0.1713 on all data; goodness of fit S = [Σw(Fo² - Fc²)²/(n-p)]¹/² = 1.156; extinction coefficient 0.0111; largest difference peak and hole: 0.301 and -0.283 e·Å⁻³. trans-trans-2d: C₂₄H₂₄N₂O₄, + 2 C₂H₄O, Mr = 372.47 + 2·60.02, crystal size: 0.70 × 0.50 × 0.10 mm³, monoclinic, space group C2/m, a = 8.0279(2), b = 6.6746(1), c = 11.4342(2) Å, β = 101.586(1)°, V = 1273.12(2) Å³, Z = 2, ρcalc = 1.285 Mg m⁻³, F(000) = 524, λ = 0.71073 Å, T = 133 K, µ(MoKα) = 0.091 mm⁻¹. Total number of reflections measured 14705, unique 1194 (R(int) = 0.0879). Data/restraints/parameters: 1194/1/111, data collection range: 1.82 < 0 ≤ 24.71°. Final R indices: R₁ = 0.0509, wR₂ = 0.1230 on data with I>2σ(I) and R₁ = 0.0598, wR₂ = 0.1529 on all data; goodness of fit S = 1.144; extinction coefficient 0.004; largest difference peak and hole: 0.314 and -0.205 e·Å⁻³. The crystals were mounted on a glass fiber in a rapidly cooled perfluoropolyether. Diffraction data were collected on a Stoe-Siemens-Huber four-circle-diffractometer coupled to a Siemens CCD area-detector at 133(2) K, with graphite-monochromated MoKα radiation (λ = 0.71073 Å), performing φ- and ω-scans. The structures were solved by direct methods using the program SHELXS-97 and refined against F² on all data by full-matrix least squares with SHELXL-97. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as...
supplementary publication no. CCDC 133686 and CCDC 133687, respectively. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: Code + (44) 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk).

REFERENCES AND NOTES

Dedicated to Professor Martin Klessinger on the occasion of his 65th birthday

8. The only hint that the influence of the configuration on the longest wavelength absorption maxima of 2b-d might be small is the fact that the three stereoisomeric muconic acid methyl esters 5 absorb at nearly identical wavelengths: $\lambda_{max}$ [nm] (EtOH): 265 (trans-trans), 266 (cis-trans), 265 (cis-cis): Elvidge, J. A., Linstead, R. F., Sims, P., Orkin, B. A. J. Chem. Soc. 1950, 2235-2241.

\[
\begin{align*}
\text{trans-trans-5} & \quad \text{cis-trans-5} \\
\text{cis-cis-5}
\end{align*}
\]