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1-Ethyl-1*H*-3-nitrobenzopyrano[4,3,2-*cd*]isoindole: a novel heterocyclic ring system bearing an unusually labile deuterium-exchangeable aromatic proton

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Abstract—The ease of deuterium exchange of the aromatic H2 of the novel heterocycle 1-ethyl-1*H*-3-nitrobenzopyrano[4,3,2-*cd*]isoindole was studied by NMR and theoretical calculations.

Xanthones (or xanthen-9*H*-ones) comprise an important class of oxygenated heterocycles, possessing interesting biological activities, not only associated with their tricyclic scaffold, but also depending on the nature and/or position of the different substituents.[1] Among pharmacologically active xanthenone derivatives, a large number of cytotoxic,[2] antituberculotic,[3] antimycobacterial,[4] antimalarial[5] and cardiovascular protective agents[6] have been reported.

We have been involved in the synthesis and antiproliferative activity evaluation of numerous amino substituted xanthenones,[7] as well as the structurally related benzopyrano[4,3,2-*cd*]indazoles.[8] In the course of the continuation of these studies, we were interested in the preparation of bioisosteres of the above mentioned ring systems and we conducted research towards the synthesis of a novel fused xanthenone, namely 1-ethyl-1*H*-3-nitrobenzopyrano[4,3,2-*cd*]isoindole. The only related heterocyclic polycondensed systems reported up to date are pyrroloanthrone (6*H*-anthra[9,1-*bc*]pyrrol-6-one),[9] thiophenanthrone[10] and furanoanthrone,[11] which are the benzoylene derivatives of isoindole, benzo[*c*]thiophene and benzo[*c*]furan, respectively.

We present here an easy synthesis of the title compound as well as an unusual observation concerning the acidity of the H2-aromatic proton of this new heterocyclic ring system. The preparation of the target compound is depicted in Scheme 1. Treatment of 1-methylxanthenone **1**[12] with nitric acid (65%) in sulfuric acid provided, as the main product, the 2-nitroderivative **2**. There exists some controversy concerning the structure of compound **2**, which arises from the fact that nitration at positions 2 (preferentially), 7 or 4 has been reported by Pickert and Frahm, Ref. 12 whereas Recanatini et al. report the preparation of the 4-nitro isomer,[13] using analogous reaction conditions. Therefore, the site of nitration of compound **2** was unambiguously established by ^{1}H and ^{13}C NMR spectroscopy, using both direct and long range heteronuclear correlation experiments (HMBC and HSQC sequences). Structural discrimination resulted from the observation that the 1-methyl group exhibits ^{3}J coupling with two aromatic carbons, namely C2 and C9a. Compound **2** was then treated with NBS in the presence of a catalytic amount of benzoyl peroxide to provide the 1-bromomethyl analogue **3**.[14]

The target derivative **4** resulted from an initial nucleophilic substitution of the bromine atom by ethylamine, followed by spontaneous cyclization of the intermediate 1-(ethylaminomethyl)-2-nitroxanthen-9(9*H*)-one, to provide the benzopyrano[4,3,2-*cd*]isoindole core.[15]

The assignment of the ^{1}H and ^{13}C NMR spectra of compound **4** was performed using the HSQC and HMBC

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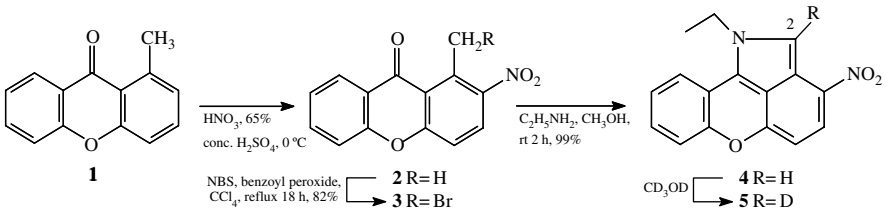


Scheme 1. Synthesis of compound **4** and H–D exchange to compound **5**.

spectra. The aromatic part of the ^{1}H spectrum in $CDCl_3$ is represented by an AX system at 8.14 and 6.17 ppm corresponding to the H4 and H5 resonances, two triplets at 7.28 and 7.21 ppm corresponding to the H9 and H8 protons, two doublets at 7.55 and 7.24 ppm corresponding to H10 and H7 and finally one singlet peak at 7.47 ppm corresponding to the H2 resonance. Solubility studies on **4** led us to the observation that the resonance peak corresponding to H2 was disappearing in CD_3OD–$CDCl_3$ mixtures. This exceptional effect was attributed to a rapid H–D exchange of the aromatic H2 proton.

H–D exchange of aromatic and heteroaromatic substrates displaying different reactivity and selectivity has been previously studied. Neutral D_2O induces only partial deuteration of aromatic compounds activated towards electrophilic substitution, whereas, in the case of weakly activated or deactivated compounds, the addition of concentrated mineral acids, highly reactive Lewis acids, bases, or polymer supported acids is usually required.[16]

In order to study more specifically this exchange reaction, the ^{1}H NMR spectra of compound **4** were recorded in a freshly prepared $CD_3OD/CDCl_3$ (10/90) 0.06 M solution for 14 h every 10 min. The spectra showed the gradual disappearance of the H2 proton resonance peak, and this effect is represented in Figure 1. Moreover, a new broad peak appeared at 4.46 ppm, attributed to the –OD to –OH exchange. The corresponding coupled ^{13}C NMR spectrum also indicated the disappearance of the C2 signal without any changes in other resonances. The reaction product **5** was stable and was isolated by removing the solvent. In the ^{1}H NMR spectrum of **5** in $CDCl_3$ solution, no H2 signal was observable. The ESI-mass spectrum of a CD_3OD solution of the isolated product showed a molecular ion $[M-D]^+$ peak at $m/z = 283.29$ (283.30 calcd for $C_{16}H_{11}N_2O_3D$–D^+), while the corresponding mass spectrum of the starting compound **4** showed 281.25 (281.29 Calcd for $C_{16}H_{12}N_2O_3$–H^+). When the isolated product was redissolved in CH_3OH the initial compound **4** was regenerated quantitatively.

Kinetic measurements for the formation of **5** were based on the ^{1}H NMR spectra recorded. The integral values, ratio of the H2 (7.47 ppm)/H-4 (8.14 ppm) resonance

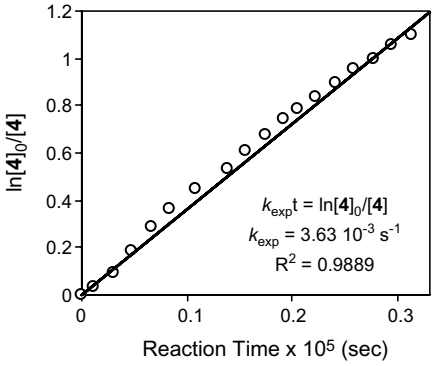


Figure 2. First order kinetics plot for the conversion of compound **4** to **5**.

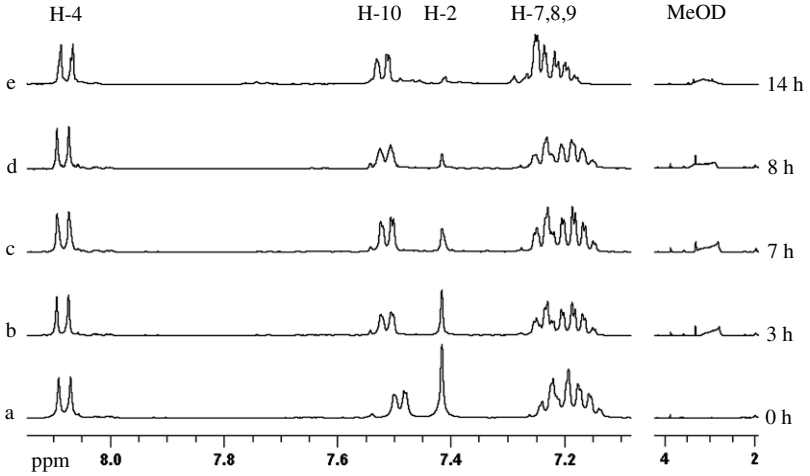
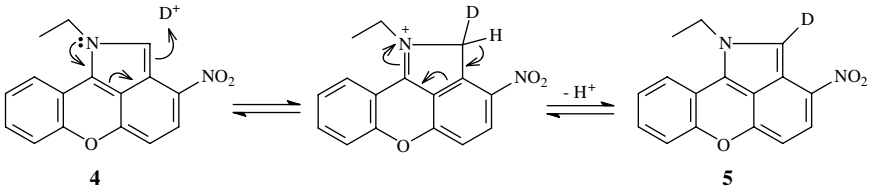


Figure 1. ^{1}H NMR spectra depicting the conversion of **4** into **5**: (a) spectrum recorded in $CDCl_3$ and (b–e) spectra recorded in $CDCl_3/CD_3OD$ (90/10) over 14 h.



Scheme 2. H–D exchange at C2 of compound **4**.

peaks, were utilized for estimating the concentration variation of compound **4**. The $\ln[\mathbf{4}]_o/[\mathbf{4}]$ plot as a function of time appears as a straight line (Fig. 2) suggesting that the H–D exchange followed first order kinetics. The kinetic expression of the reaction rate can be written as $k_{exp}t = \ln[\mathbf{4}]_o/[\mathbf{4}]$ or $-\mathrm{d}[\mathbf{4}]/\mathrm{d}t = k_{exp}[\mathbf{4}]$ with a pseudo-first-order rate of reaction constant $k_{exp} = 3.63 \times 10^{-3}\ s^{-1}$, as derived from the slope of the plot.

Furthermore, the H–D exchange reaction was spontaneous when the spectrum of a $CD_3OD/CDCl_3$ solution of **4** was recorded in the presence of acetic acid (0.6 mM), or triethylamine (0.6 mM), providing evidence of bifunctional acid–base catalysis, as shown in Scheme 2.

PM3 semi-empirical calculations[17] predict a significant difference between the partial charges of C2 and H2 (calculated to be −0.309 and +0.178, respectively) compared to the other aromatic C–H bonds. Moreover when a methanol molecule was placed in the vicinity of the C2–H2 bond and the nitro group and the energy of the system was further minimized using PM3 calculations, it appeared that the methanol OH group interacts with both the C2–H2 bond and the nitro group. According to the results of these calculations H2 forms a hydrogen bond with the methanol oxygen, the H···OMe distance being 1.8 Å. The structure is further stabilized through the formation of a second hydrogen bond between the methanol hydrogen and a nitro group oxygen.[18] It is interesting to note that in this structure the partial charges on C2 and H2 were calculated to be −0.343 and +0.219, respectively, suggesting that the interaction with methanol increases the C2–H2 polarization enhancing the tendency of H2 to dissociate. The results of the above calculations are supported by the presence of an ion at m/z 313 in the positive-ion ESI-mass spectrum of the undeuterated compound **4** corresponding to an $[MH]^+$–CH_3OH adduct.

In conclusion, we have developed a straightforward method to prepare a novel heterocycle. In this ring system, H–D exchange occurs readily at C2 under mild conditions. The presence of the $-NO_2$ group at C3, probably, facilitates this process by increasing the polarization of the C2–H2 bond through the electron withdrawing effect and by stabilizing the presence of a methanol molecule in the vicinity of C2–H2 through the formation of an $-NO_2\cdots HOCH_3$ hydrogen bond.

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14. 1-Bromomethyl-2-nitro-9*H*-xanthen-9-one **3**. Mp 178–181 °C (ethanol); ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) 5.29 (s, 2H, CH_2Br), 7.41–7.48 (m, 2H, H-5, H-7), 7.53 (d, $J = 8.4$ Hz, 1H, H-4), 7.77 (ddd, $J = 8.7$, 8.1, 1.5 Hz, 1H, H-6), 8.18 (d, $J = 8.4$ Hz, 1H, H-3), 8.29 (dd, $J = 7.9$, 1.5 Hz, 1H, H-8); ^{13}C NMR (50 MHz $CDCl_3$) δ (ppm) 23.28 (CH_2Br), 117.57 (C-5), 119.02 (C-9a), 120.30 (C-4), 122.79 (C-8a), 125.10 (C-7), 127.17 (C-8), 129.83 (C-3), 135.34 (C-6), 136.20 (C-1), 146.47 (C-2), 155.49 (C-4b), 159.65 (C-4a), 177.82 (CO).
15. 1-Ethyl-1*H*-3-nitro-benzopyrano[4,3,2-*c*,*d*]isoindole **4**. Mp 166–169 °C (CH_2Cl_2/ether); ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) 1.62 (t, $J = 7.32$ Hz, 3H, CH_3), 4.45 (q, $J = 7.32$ Hz, 2H, CH_2), 6.16 (d, $J = 8.3$ Hz, 1H, H-5), 7.16–7.31 (m, 3H, H-7, H-8, H-9), 7.46 (s, 1H, H-2), 7.54 (dd, $J = 7.1$, 1.7 Hz, 1H, H-10), 8.13 (d, $J = 8.3$ Hz. 1H, H-4); ^{13}C NMR (50 MHz $CDCl_3$) δ (ppm) 16.40 (CH_3), 45.14 (CH_2), 98.46 (C-5), 114.71 (C-2), 115.78 (C-2a), 118.86 (C-10a), 118.95 (C-7), 119.86 (C-10b), 120.58 (C-10c), 120.81 (C-10), 125.62 (C-9), 128.30 (C-8), 130.50 (C-4),131.48 (C-3), 155.26 (C-6a), 157.94 (C-5a). Anal. Calcd for $C_{16}H_{12}N_2O_3$. Calcd (%) C: 68.57, H: 4.32, N: 9.99. Found (%) C: 68.34, H: 4.23, N: 10.17.
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