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THE CRYSTAL STRUCTURE OF METHYL 4,6-*O*-BENZYLIDENE-2,3-DIDEOXY-2-[2-(METHOXYCARBONYL)PHENYLAMINO]-3-NITRO-β-D-MANNOPYRANOSIDE

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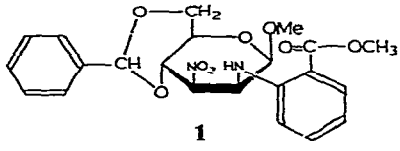
ABSTRACT

The crystal structure of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-[2-(methoxycarbonyl)phenylamino]-3-nitro-β-D-mannopyranoside, $C_{22}H_{24}N_2O_8$, is monoclinic, $P2_1$, with cell dimensions $a = 13.267(4)$, $b = 9.633(4)$, $c = 8.839(3)$ Å, $\beta = 106.26(2)°$, $Z = 2$. The structure was solved by direct methods, and refined to $R(F_{obs}) = 0.056$ for 6959 independent reflections measured with MoKα radiation. The configuration of the molecule was confirmed. The pyranoid conformation is $^4C_1$ with $Q = 0.611$ Å, $\theta = 8.5°$. The dioxolane conformation is close to the ideal chair. The orientation of the anthranilate ring is such that the amine hydrogen atom forms three intramolecular hydrogen-bonds: one major bond to the anthranilate carbonyl oxygen atom, and two minor bonds to the glycosidic oxygen atom and the ring-oxygen atom. The orientation of the anthranilate group is thus fixed such that the angle between the plane of the benzene ring and that of the nitro group is 116°, thereby permitting an intramolecular, C-H···O hydrogen-bond between the benzene ortho C-H and the nitro oxygen atom. This bond is normal to the plane of the nitro group, and is believed to be the source of the color phenomenon that prompted this structure analysis.

INTRODUCTION

Crystals of $C_{22}H_{24}N_2O_8$ (**1**) were obtained from Professor H. H. Baer, University of Ottawa. The crystal structure of this compound is of interest because of the



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yellow color of the crystals and of those of the parent acid, whereas the solutions in chloroform, alcohol, acetone, and dimethyl sulfoxide are colorless. The crystals of the hydrate are also colorless. For the analogous D-glucose derivatives, the crystals and solution are both colorless[1,2].

The crystal-structure analysis was, therefore, undertaken in order to confirm the configuration of **1** and to determine whether the color phenomena could be ascribed to a particular conformation of the molecules in the crystalline state.

EXPERIMENTAL

The crystal data and intensity data given in Table I were obtained from measurements made with a CAD-4 diffractometer at room temperature, using graphite-monochromated MoKα radiation. The cell dimensions were obtained by least-squares fit of 40 reflections, with $30° < 2\theta < 40°$. No corrections were made for absorption or extinction.

The structure was solved by use of the 1978 version of MULTAN[3]. Initial attempts, using all 6959 available data, failed to give a chemically reasonable solution, because the large number of unobserved reflections with $F^2 \geqslant 0$ (2367) in the data resulted in the calculation of an abnormally large scale-factor. The correct solution was obtained by using only the data within the CuKα sphere, *i.e.*, 2631 structure-amplitudes, of which 2356 had $I > 2\sigma(I)$. An E-map with 500 E values > 1.31 provided the positions of 31 of the 32 non-hydrogen atoms in the structure. The remaining atom, C-22, was located on a subsequent E-map. Refinement was by full-matrix least-squares, minimizing $\Sigma_i\omega_i(|F_o| - k|F_c|)^2$, with $\omega_i = \sigma_c^{-2}(F)$, where σ_c was from counting statistics. The non-hydrogen atoms were refined anisotropically by use of the lesser data set. Positions of 17 hydrogen atoms were calculated by using a C–H distance of 1.09 Å and tetrahedral angles, and were refined isotropically. The amine and the six methoxyl hydrogen atoms were located as the seven largest peaks in a difference-Fourier synthesis by using a low-angle, weighting scheme incorporated in the refinement program[4] SHELX-76. Final refinement, using all available data, was by SHELX-76 with $\omega_i = k\sigma_c^{-2}(F)$, where k = 2.53, and with $\omega_i = 0.0$ for $I < 2\sigma(I)$. The maximum, final shift was 0.15σ. The final agreement factors were R(F) = 0.056 and R(ωF) = 0.041 for all 2387 observed reflections, where $R(F) = \Sigma_i||F_o| - |F_c||/\Sigma|F_o|$ and $R(\omega F) = \{\Sigma\omega(|F_o| - k|F_c|)^2/\Sigma\omega|F_o|^2\}^{\frac{1}{2}}$. The atomic-scattering factors used were those of Cromer and Waber[5] for C, N, and O, and of

TABLE I

CRYSTAL DATA

$C_{22}H_{24}N_2O_8$, m.w. = 444.4, m.p. = 167°
Monoclinic, space group $P2_1$
a = 13.267(4), b = 9.633(4), c = 8.839(3) Å, β = 106.26(2)°
λ_{MoK_α} = 0.71069 Å, V = 1084.5 Å^3, Z = 2
D_m = 1.311 g.cm^{-3}, D_x = 1.361 g.cm^3, μ_{MoK_α} = 1.129 cm^{-1}
Crystal dimensions, 0.48 × 0.26 × 0.24 mm
7312 intensities were measured to $\theta_{max} = 40°$, using $\omega/2\theta$ scans, with scan width $(1.2 + 0.35 \tan\theta)°$.
These gave 6959 symmetry-independent reflections, of which 2387 > 2 σ(I).
R-factor between equivalent reflections = 0.026.

TABLE II

ATOMIC COORDINATES × 10^4, AND EQUIVALENT, ISOTROPIC, TEMPERATURE FACTORS (Å^2) FOR NON-HYDROGEN ATOMS[a]

Atom	*x*	*y*	*z*	B_{eq}
C-1	72(2)	−1746(4)	10126(4)	2.76(8)
C-2	−50(2)	−2090(4)	8392(3)	2.76(8)
C-3	1069(2)	−2126(4)	8157(4)	3.00(8)
C-4	1697(2)	−850(4)	8819(4)	2.67(8)
C-5	1698(2)	−679(4)	10516(4)	2.77(8)
C-6	2408(2)	507(4)	11246(4)	3.32(9)
C-7	−874(4)	−1629(7)	12002(5)	5.09(13)
C-8	3404(2)	71(4)	9497(4)	3.07(8)
C-9	4499(2)	−187(4)	9376(4)	3.44(9)
C-10	5330(3)	420(7)	10407(7)	6.79(17)
C-11	6344(3)	217(8)	10293(8)	7.55(19)
C-12	6516(3)	−583(6)	9143(6)	5.20(13)
C-13	5698(3)	−1203(7)	8119(6)	6.37(15)
C-14	4676(3)	−1017(6)	8221(5)	5.06(12)
C-15	−1619(2)	−1578(4)	6163(3)	2.79(8)
C-16	−1659(3)	−2913(5)	5520(4)	3.61(9)
C-17	−2529(3)	−3370(5)	4372(4)	4.33(11)
C-18	−3372(3)	−2523(6)	3795(5)	4.94(12)
C-19	−3353(3)	−1188(5)	4364(4)	4.25(11)
C-20	−2482(2)	−697(4)	5553(3)	3.06(8)
C-21	−2524(2)	716(4)	6173(4)	3.44(9)
C-22	−3553(5)	2744(7)	6024(7)	6.73(18)
N-2	−752(2)	−1141(4)	7340(3)	3.01(7)
N-3	1003(2)	−2334(4)	6449(3)	4.21(9)
O-1	−902(1)	−1589(3)	10363(2)	3.46(6)
O-4	2749(1)	−1046(3)	8744(2)	3.25(6)
O-5	644(1)	−461(3)	10572(2)	3.04(5)
O-6	3430(1)	190(3)	11088(2)	3.28(6)
O-7	−1878(2)	1233(3)	7275(3)	3.70(6)
O-8	−3397(2)	1397(4)	5403(3)	5.14(8)
O-N3	1030(2)	−1330(4)	5642(3)	5.70(9)
O-N3′	896(3)	−3520(4)	5958(4)	7.27(11)

[a]Estimated standard deviations (given in parentheses) refer to the least-significant digit. $B_{eq} = (\beta_{11}\beta_{22}\beta_{33})^{1/3}(8\pi^2)$, where the temperature-factor expression is: $T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

Stewart and coworkers[6] for H. The final atomic coordinates are given in Tables II and III. The atomic notation, thermal ellipsoids, and principal torsion angles are given in Fig. 1, and the bond lengths and valence angles in Fig. 2*.

The conformational regions of minimum energy for the orientation of the

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TABLE III

ATOMIC COORDINATES × 10^3, ISOTROPIC THERMAL-PARAMETERS, AND BOND DISTANCES FOR THE HYDROGEN ATOMS[a]

Atom	*x*	*y*	*z*	B_{iso}	*C, N, O–H*
H-C-1	46(2)	−247(3)	1081(3)	2.6(6)	0.97(3)
H-C-2	965(2)	−301(3)	818(3)	2.3(6)	0.97(3)
H-C-3	141(2)	−289(3)	866(3)	2.0(6)	0.92(3)
H-C-4	140(2)	1(3)	825(3)	2.7(6)	0.99(3)
H-C-5	198(2)	−143(3)	1111(3)	1.5(5)	0.91(3)
H-C-6	247(2)	62(3)	1236(3)	2.7(6)	0.97(3)
H-C-6′	213(3)	137(4)	1072(4)	4.6(9)	0.98(4)
H-C-7	−152(3)	−156(5)	1209(4)	5.3(9)	0.88(4)
H-C-7′	−42(4)	−97(6)	1257(6)	8.8(1.5)	0.92(6)
C-C-7″	−54(4)	−253(7)	1251(6)	9.0(1.6)	1.02(6)
H-C-8	310(2)	90(3)	897(3)	2.3(6)	0.96(3)
H-C-10	525(4)	83(6)	1122(5)	8.0(1.5)	0.85(4)
H-C-11	697(4)	61(6)	1113(7)	11.4(1.7)	1.02(6)
H-C-12	721(3)	−68(4)	907(4)	5.6(9)	0.95(4)
H-C-13	579(3)	−178(5)	733(4)	7.7(1.1)	0.93(4)
H-C-14	408(3)	−133(5)	741(5)	8.1(1.3)	0.96(4)
H-C-16	−107(3)	−343(4)	586(4)	5.1(8)	0.91(3)
H-C-17	−253(3)	−421(5)	401(4)	5.5(1.0)	0.87(4)
H-C-18	−395(3)	−278(4)	304(4)	5.2(9)	0.90(4)
H-C-19	−395(3)	−52(4)	394(4)	4.7(8)	1.00(4)
H-C-22	−291(4)	337(6)	589(6)	9.7(1.7)	1.08(6)
H-C-22′	−421(4)	313(6)	530(6)	9.2(1.3)	1.00(5)
H-C-22″	−359(3)	256(6)	719(6)	8.5(1.4)	1.06(5)
H-N-2	−79(3)	−47(5)	771(5)	5.1(1.2)	0.73(4)

[a]Isotropic thermal parameters in Å², and bond distances in Å. Estimated standard deviations, in parentheses, refer to the least-significant digit. The temperature expression used is $T = \exp[-(B\sin^2\theta/\lambda^2)]$.

anthranilate group with respect to the pyranoid ring were explored by rotating about the C-2–N-2 bond on a MMS-X graphics system, using standard, van der Waals radii to define the permitted, nonbonded-approach distances.

DISCUSSION

The configuration of the molecule is **1**, as determined by Baer and Kienzle[1]. The pyranoid conformation is $^4C_1$, with a small distortion from the ideal, having Cremer–Pople[7] puckering parameters of Q = 0.611 Å, $\theta = 8.5°$, $\varphi = 339°$. The small distortion, which is towards the $^{\circ}H_5$ conformation ($\varphi = 330°$), corresponds to a diminution in the axial nature of attachment of the anthranilate group and an inequality in the C-1–C-2–C-3–C-4 and C-1–O-5–C-5–C-6 ring torsion-angles (see Fig. 1). The degree of puckering is greater than normal for pyranoses and methyl pyranosides (Q = 0.55–0.58 Å), but the distortion from an ideal chair is no greater

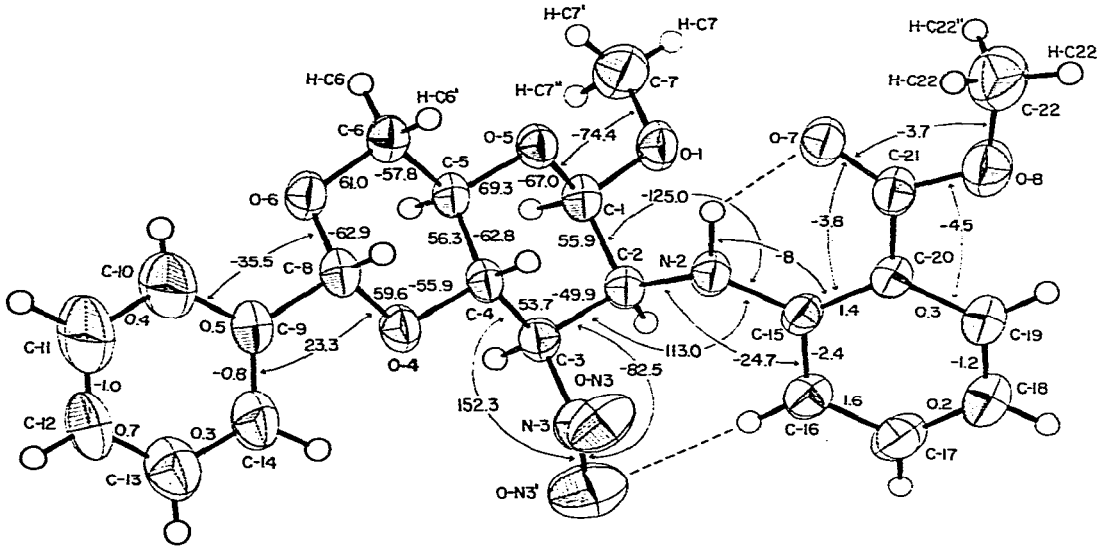

Fig. 1. Atomic notation, thermal ellipsoids[13] at 50% probability, and principal torsion-angles of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-[2-(methoxycarbonyl)phenylamino]-3-nitro-β-D-mannopyranoside. [The ellipsoid of H-N2 is decreased for clarity. Relevant e.s.d. values are: 0.3–0.4° for the internal angles of the sugar and dioxolane rings; 0.7–0.9° and 0.5–0.7° for the internal angles of the benzylidene and anthranilic benzene rings, respectively; 0.3–0.4° for nitro angles; 0.4–0.5° for methoxyl and carboxylate angles; 0.5, 0.5, and 0.3° for angles involving C-8–C-9, N-2–C-15, and C-2–N-2, respectively; 4° for angles involving hydrogen atoms.]

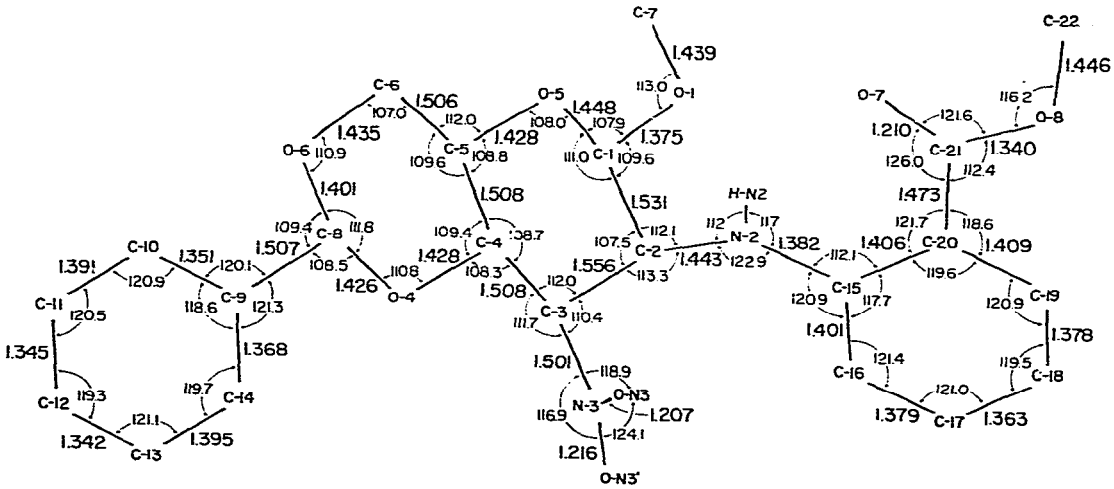

Fig. 2. Bond lengths and valence angles. [E.s.d. values are: C–C (sugar and dioxolane rings), 0.005 Å; C–C (benzylidene benzene ring), 0.006–0.009 Å; C–C (anthranilate group), 0.004–0.006 Å; C–O (methoxyl), 0.006–0.007 Å; C–O (other), 0.004 Å; C–N and N–O, 0.004–0.005 Å. For valence angles having atoms of the following groups as central atoms, the e.s.d. values are: sugar and dioxolane rings, 0.2–0.3°; benzylidene benzene ring, 0.4–0.6°; anthranilate and methoxyl group, 0.3–0.4°; nitrogen atoms, 0.3°.]

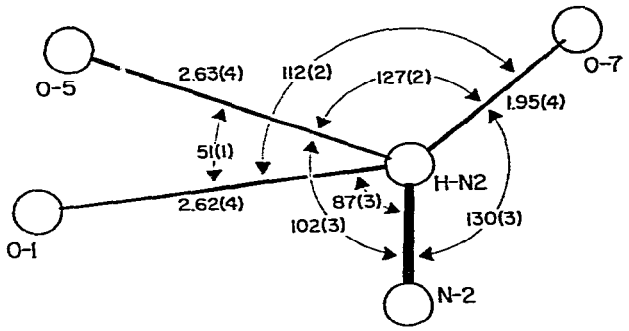

Fig. 3. Projection of the intramolecular, trifurcated, hydrogen-bonding interaction normal to the N···H bond. (Distances and angles are based on an N···H distance of 1.02 Å; e.s.d. values given in parentheses refer to the least-significant digit.)

than that observed in, for example, methyl β-D-xylopyranoside[8], for which $\theta = 8.2°$.

The conformation of the dioxolane ring is closer to the ideal chair than is that of the pyranose ring, with Q = 0.58 Å and $\theta = 3.1°$. The benzene rings are planar, within 0.006 Å, for C-9 to C-14, and within 0.012 Å for C-15 to C-20. Atom C-8 is 0.04 Å out of the plane of C-9 to C-14, and N-2 and C-21 are 0.03 and 0.05 Å, respectively, out of the plane of C-15 to C-20.

The plane of the nitro group is nearly perpendicular to the C-2–C-3 bond, with C-2–C-3–N-3–O-(N3) = +96°. The methoxycarbonyl group is almost coplanar with the benzene ring to which it is attached, with C-15–C-20–C-21–O-7 = −4°.

The methyl anthranilate moiety has an intramolecular N–H···O=C bond (H···O = 1.95 Å) which stabilizes an almost planar, two-ring system, as shown by the torsion angles given in Fig. 1. There are two regions of minimum conformational energy for the orientation of the methyl anthranilate group with respect to the pyranoid ring: with C-3–C-2–N-2–C-15 torsion-angles of ~−180° and ~+100°. In the former, the amine N-H is directed towards the nitro group, as suggested previously to explain the color phenomenon[9]. In the latter, it is towards the methoxyl group on the pyranose ring. The observed conformational angle of +113° is in the second region, but twisted from the minimum orientation, so that the amino hydrogen atom lies almost in the plane of the nitrogen atom to which it is attached and O-7 and O-5. The environment of this hydrogen atom, shown in detail in Fig. 3, suggests a trifurcated, hydrogen-bond interaction with a major component to the carbonyl oxygen atom (O-7), and minor components to the ring-oxygen atom (O-5) and the glycosidic oxygen atom (O-1). This hydrogen-bond interaction locks the orientation of the aglycon at the angle which is 12° away from that of the orientation of minimum conformational energy. A feature of this orientation is that the plane of the anthranilate benzene ring makes an angle of 116° to that of the nitro group. The ortho C–H bond of the anthranilate benzene ring is directed normal to the plane of the nitro group, with a C–H···O–N3′ distance of 2.5 Å. This distance is consistent in direction

and length with the C_α-H···O=$\overline{C}$ bonds reported from neutron-diffraction analyses of amino acids[10].

The bond lengths in the pyranoid ring vary over a normal range, from 1.506(5) to 1.556(5) Å. The difference in the observed bond-lengths in the benzene ring is primarily due to thermal motion. The ring oscillates about the C-8–C-9 bond, leading to an apparent shortening of four of the bonds relative to the two that are parallel to the axis of oscillation. A wagging, thermal motion also shortens those bonds farthest from the link to the rest of the molecule. A similar, but smaller, effect occurs in the anthranilic ring, where the thermal motion is less, due to the partial, double-bond character of N-2–C-15. The C–O bond lengths range from 1.375(4) to 1.448(4) Å, the shortest value being that normal for a β-D-glycosidic C-1–O-1 bond. The bond lengths associated with the methyl anthranilate group and the nitro group have normal values.

Valence angles of note are O-5–C-1–O-1 = 107.9(2)° and C-1–C-2–C-3 = 107.5(3)°. The former is characteristic for a β-pyranoside[11], but the latter is unusually small for a pyranoid ring. Both benzene rings show a closing of the valence angle at their point of junction, *i.e.*, C-10–C-9–C-14 = 118.6(4)° and C-16–C-15–C-20 = 117.7(3)°.

Explanation of the color phenomena

Several features of the crystal structure can be examined in seeking an explanation of the yellow color that prompted this analysis. (1) There is no evidence for π-bond conjugation between the nitro group and benzene-ring chromophores, as these groups are separated by normal, single bonds. (2) There is no evidence of distortion, or strain, in the molecule that could affect the π-orbital levels of the chromophores. The conformations of both the six-membered pyranoid and the dioxolane ring are normal chairs, and the benzene rings and nitro group are not significantly distorted

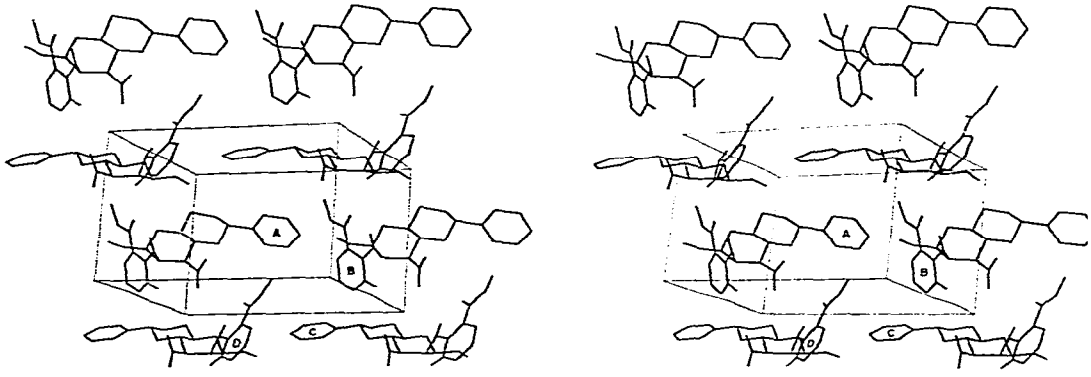

Fig. 4. Stereoview of the crystal structure, showing the staggered packing of the benzene rings. [Angles between planes of the rings are: A and C, 74.7°; B and D, 141.3°; A and B, 43.3°; and A and D, 101.6°. Only those hydrogen atoms involved in hydrogen bonds (H-N-2, H-C-16) have been included. The *a* axis runs from right to left; *b*, from bottom to top; and *c*, from front to back. The origin is at 0.0, 0.0, 0.5.]

from planarity. (3) In the crystal, stacking arrangements of the nitro and benzene rings that could lead to a charge-transfer spectrum are not observed. The molecules pack in a common, herring-bone arrangement (similar to that of solid benzene), as shown in Fig. 4.

We are left with the conclusion that the color is a consequence of the orientation of the nitro and anthranilate groups, which permits the formation of a hydrogen bond between an ortho C–H bond and a nitro oxygen atom. We postulate that this C–H···O interaction disrupts the degeneracy of the nitro p-orbitals, lessening the π delocalization; this decreases the energy separation of the bonding and anti-bonding orbitals, corresponding to a bathochromic shift in the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, sufficiently to bring them into the visible region. In a protonic solution, or in the hydrated crystal, the specific, hydrogen-bond environment of the N–H bond can be disrupted in favor of an energetically more favorable hydrogen-bonding arrangement that includes a water or solvent molecule; this releases the constraint on the orientation of the anthranilate groups, and removes the particular C–H to NO_2 interaction. Similarly, in the D-glucose configuration, where the anthranilate group is equatorial, the conformation leading to the color phenomena does not occur. The analogous D-glucose compound melts at a temperature that is 58° higher, suggesting that intermolecular, rather than intramolecular, hydrogen-bonding occurs in the crystalline state.

Yellowness of nitro compounds is generally associated with molecules in which the nitro group is bonded directly to an aromatic ring. Where the crystal structures are known[12], short C–H···O distances are frequently reported, and the nitro and benzene planes are often nearly orthogonal, as in structure **1**. To the best of our knowledge, compound **1** is, however, the only example of colored crystals where the nitro and benzene groups are separated by unconjugated, single, C–C bonds.

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