Table 3. *Details of the weak intramolecular bond forcing coplanarity of the pyrroline and N-phenyl rings*

	Molecule *A*	Molecule *B*
O1···C12	2·866 (4) Å	2·878 (4) Å
O1···H12	2·22	2·11
C12–H12	1·03	1·04
O1–H12–C12	119°	129°
C11–C12–H12	122	115

between pyrroline and the phenyl ring I is caused by the weak interaction between O1 and C12 through H12 (Table 3); also, some π conjugation along the C–N–C–O system can contribute to this effect. The sum of the bond angles around the heteroatom N1 is 359·9° for molecule *A*, 360·0° for molecule *B*, supporting an sp^2 hybridization for this atom; the distances in the pyrroline ring and the planarity of the sequence C11–N1–C2–O1 [torsion angles −0·9 (5)°, molecule *A*; −0·3 (5)°, molecule *B*] indicate a delocalization of the lone pair of the N atom (Argay & Kálmán, 1973). The ethoxycarbonyl group shows planarity at the C6–C7–O2–O3 level; in molecule *B*, C8 is also in this plane; this planarity is in agreement with what is observed in this type of ester (Théobald, Birouk & Robert, 1982). Packing is regulated by normal van der Waals contacts.

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A Neutron Diffraction Study of 2,6-Diaminopyridine* at 20 K

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Abstract. $C_5H_7N_3$, $M_r = 109·14$, orthorhombic, $P2_12_12_1$, $a = 5·397$ (2), $b = 7·337$ (3), $c = 13·597$ (7) Å, $U = 538·4$ (4) Å^3, $Z = 4$, $D_n = 1·35$ Mg m^{-3}, $\lambda = 1·1604$ Å, $\mu = 2·325$ cm^{-1}, $T = 20$ (1) K, final $R(F^2) = 0·093$ for 815 independent reflections. The ring N atom and the two amino N atoms each accept one H bond from a neighboring molecule. Two H atoms of one NH_2 group and one H atom of the other are donors in this three-dimensional network, which differs from the pattern of hydrogen-bonded centrosymmetric dimers commonly occurring in aminopyridine and aminopyrimidine crystals. The exocyclic C–N distances in the title compound are relatively long [1·377 (4) and 1·396 (4) Å], and the amino groups are substantially pyramidalized. Geometry optimization based on *ab initio* molecular-orbital calculations indicates that pyramidalization persists even in the absence of intermolecular interactions.

Introduction. Aminopyrimidine and diaminopyrimidine moieties occur in many biologically important molecules such as cytosine derivatives, folates, and antifolate drugs. Characteristically they associate to form dimers *via* paired N–H···N hydrogen bonds about a center or pseudo-center of inversion, the amino group acting as proton donor and the ring N atom as acceptor (Schwalbe & Cody, 1983). Where the number of amino groups, *m*, exceeds the number of ring N

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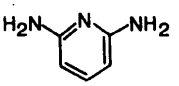
atoms, n, an amino group may develop pyramidalized geometry and also serve as a proton acceptor. This phenomenon has been observed in 2,4,6-triamino-5-chloroquinazoline (Rogan & Williams, 1980) and in 2,4,6-triaminopyrimidine (Schwalbe & Williams, 1982). The present study has the objective of determining precise structural data for the model case of $m = 2$ and $n = 1$. The isomer 2,6-diaminopyridine was chosen because it forms crystals suitable for neutron diffraction.



Experimental. Sample crystal a black truncated triangular pyramidal fragment approximated by five faces. The planes $(0\bar{1}2)$ and $(\bar{1}\bar{1}\bar{1})$ were 1·50 and 1·13 mm respectively from the vertex at the intersection of $(01\bar{2})$, (012) and $(1\bar{1}0)$. Crystal volume 0·48 mm^3. Neutron diffraction data collected at 20 (1) K in a Displex® model CS-202 closed-cycle He refrigerator* on an automated four-circle diffractometer (Dimmler, Greenlaw, Kelley, Potter, Rankowitz & Stubblefield, 1976; McMullan, Andrews, Koetzle, Reidinger, Thomas & Williams, 1976) at the Brookhaven High Flux Beam Reactor. Data collection by a $\theta/2\theta$ step-scan technique. Lattice parameters from 2θ values of 15 reflections with $40 \le 2\theta \le 101°$. Absorption correction (maximum and minimum transmission factors 0·885 and 0·807) by integration over a Gaussian grid (Busing & Levy, 1957) with mass absorption coefficients for C and N atoms taken from *International Tables for X-ray Crystallography* (1968) and 2·39 m^2 kg^{-1} used for H (Koetzle & McMullan, 1980). Maximum $(\sin\theta)/\lambda = 0{\cdot}668$ Å^{-1}; $-7 \le h \le 7$, $-9 \le k \le 0$, $-18 \le l \le 0$; two intensity monitor reflections remeasured every 50 reflections showed no significant trend; 1813 reflections collected, 815 unique, $R_{int} = 0{\cdot}092$. Integrated intensities obtained from scan profiles, assigned errors from the equation $\sigma^2(F_o^2) = \sigma^2_{count} + (0{\cdot}02F_o^2)^2$. Approximate C- and N-atom positions obtained by direct methods (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) on a preliminary set of X-ray data; H-atom coordinates calculated. Refinement of positions and anisotropic thermal parameters for all atoms and a type I isotropic extinction parameter (Becker & Coppens, 1975) [$g = 1{\cdot}103\ (4) \times 10^{-5}$] against all unique neutron data minimized $\sum w(F_o^2 - k^2F_c^2)^2$ with scattering factors from Koester (1977) and weights $w = 1/\sigma^2(F_o^2)$; $R(F^2) = 0{\cdot}093$, $wR(F^2) = 0{\cdot}086$, $S(F^2) = 1{\cdot}587$, $(\Delta/\sigma)_{max} = 0{\cdot}05$, maximum positive and negative residuals on a difference Fourier synthesis = 2·9 and −2·8% of the height of an N-atom peak, respectively. Computer programs described in the *CRYSNET* manual (Berman, Bernstein, Bernstein, Koetzle & Williams, 1976). Molecular-orbital calculations performed with *GAUSSIAN*80 (Binkley *et al.*, 1980) in the implementation by Chandra Singh & Kollman (1982). Molecular geometry set up and analyzed on the *CHEM-X* system (Davies, 1986).

Discussion. The molecule with its numbering scheme is shown in Fig. 1. Final atomic coordinates and equivalent isotropic thermal parameters are given in Table 1, bond distances and angles in Table 2, and hydrogen-bond geometry in Table 3.*

One would expect the isolated molecule to exhibit a planar ring, symmetrical across a line through N(1) and C(4). In the crystal this symmetry is substantially preserved, with the differences between corresponding distances and angles within the ring barely exceeding 1σ. However, the exocyclic C—N bonds differ by 0·019 (6) Å, presumably due to the different environments of the amino groups.

The ring C—N distances of 1·347 (4) and 1·349 (4) Å agree well with the average heterocyclic C—N distance of 1·344 (10) Å in five unprotonated substituted 2-aminopyridines, as summarized by Nahringbauer & Kvick (1977) and including the study by Kvick, Thomas & Koetzle (1976). Remaining ring-bond distances show less alternation than in the mono-amino compounds, but the lengths are not unusual. However, the exocyclic C—N distances of

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* Lists of structure factors, anisotropic thermal parameters, least-squares planes, and Cartesian coordinates after various degrees of optimization have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44181 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

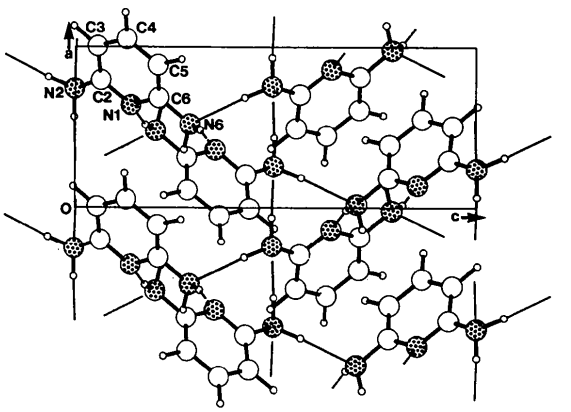

Fig. 1. *PLUTO* (Motherwell & Clegg, 1978) view down **b** of two unit cells showing the atom-numbering scheme. N atoms are stippled and hydrogen bonds drawn as thin lines. Where the H bond is to a molecule translated along **b** from the one shown, the line stops short of the proton acceptor.

Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters* ($\times 10^4$) *with e.s.d.'s in parentheses*

$$U_{eq} = \tfrac{1}{3}\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}(Å^2)
N(1)	6394 (5)	5113 (3)	1437 (2)	65 (10)
C(2)	7956 (6)	5001 (5)	667 (2)	60 (15)
C(3)	10067 (7)	6105 (5)	578 (2)	76 (15)
C(4)	10513 (6)	7372 (5)	1324 (3)	76 (16)
C(5)	8905 (6)	7517 (5)	2121 (3)	74 (15)
C(6)	6851 (6)	6364 (5)	2141 (3)	54 (15)
N(2)	7427 (5)	3675 (4)	−19 (2)	83 (12)
N(6)	5203 (5)	6402 (4)	2932 (2)	86 (12)
H(3)	11317 (15)	5958 (10)	−43 (6)	225 (37)
H(4)	12155 (15)	8195 (11)	1276 (6)	230 (39)
H(5)	9239 (15)	8486 (11)	2716 (5)	216 (37)
H(21)	5652 (15)	3207 (11)	−28 (6)	225 (41)
H(22)	8137 (16)	3876 (12)	−698 (6)	223 (37)
H(61)	4841 (16)	7676 (11)	3187 (5)	204 (36)
H(62)	3631 (16)	5708 (12)	2788 (6)	249 (40)

Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

N(1)–C(2)	1·347 (4)	N(2)–H(21)	1·018 (9)
C(2)–C(3)	1·403 (5)	N(2)–H(22)	1·010 (8)
C(2)–N(2)	1·377 (4)	C(3)–H(3)	1·086 (8)
C(3)–C(4)	1·397 (5)	C(4)–H(4)	1·075 (9)
C(4)–C(5)	1·392 (5)	C(5)–H(5)	1·093 (8)
C(5)–C(6)	1·395 (5)	N(6)–H(61)	1·016 (8)
C(6)–N(1)	1·349 (4)	N(6)–H(62)	1·008 (9)
C(6)–N(6)	1·396 (4)		

C(2)–N(1)–C(6)	118·6 (3)	C(4)–C(5)–H(5)	121·6 (5)
N(1)–C(2)–C(3)	122·7 (3)	C(6)–C(5)–H(5)	120·8 (5)
N(1)–C(2)–N(2)	116·1 (3)	N(1)–C(6)–C(5)	123·0 (3)
C(3)–C(2)–N(2)	121·2 (3)	N(1)–C(6)–N(6)	116·4 (3)
C(2)–C(3)–C(4)	117·5 (3)	C(5)–C(6)–N(6)	120·6 (3)
C(2)–C(3)–H(3)	121·0 (5)	C(2)–N(2)–H(21)	116·3 (5)
C(4)–C(3)–H(3)	121·6 (5)	C(2)–N(2)–H(22)	115·9 (5)
C(3)–C(4)–C(5)	120·6 (3)	H(21)–N(2)–H(22)	113·2 (7)
C(3)–C(4)–H(4)	118·2 (5)	C(6)–N(6)–H(61)	113·9 (5)
C(5)–C(4)–H(4)	121·2 (6)	C(6)–N(6)–H(62)	112·2 (6)
C(4)–C(5)–C(6)	117·6 (3)	H(61)–N(6)–H(62)	111·6 (7)

Table 3. *Geometry of hydrogen bonds in* 2,6-*diaminopyridine*

	N···N (Å)	N–H···N (°)
N(2)–H(21)···N(2^{i})	3·203 (3)	161·2 (7)
N(2)–H(22)···N(6^{ii})	3·067 (4)	165·7 (7)
N(6)–H(61)···N(1^{iii})	2·982 (4)	170·4 (7)

Symmetry code: (i) $-\frac{1}{2}+x$, $\frac{1}{2}-y$, $-z$; (ii) $1\frac{1}{2}-x$, $1-y$, $-\frac{1}{2}+z$; (iii) $1-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$.

1·377 (4) and 1·396 (4) Å are significantly longer than the 1·351 (2) Å found in 2-aminopyridine (Chao, Schempp & Rosenstein, 1975*a*, 1976), which is near to the average value in the five substituted 2-aminopyridines. A single amino group adjacent to a ring N atom in a π-deficient heterocycle is expected to show sp^2 hybridization and to make a significant contribution of p electrons to the π system, thus increasing the bond order and shortening the length of its connection to the ring. The title compound, however, has two such amino groups; and each group experiences less demand for π electrons, less constraint on hybridization, and a longer bond to the ring. In 3-aminopyridine the amino group is more isolated from the heterocyclic N atom, and so less sp^2 character is expected, resulting in a similar lengthening of the C–NH_2 bond to 1·384 (4) Å (Chao, Schempp & Rosenstein, 1975*b*, 1976).

A comparable trend is manifested by the sum of bond angles, $\sum$, at the amino N atom, which should be 360° for perfect sp^2 hybridization and trigonal geometry but which should decrease upon pyramidalization. The title compound is significantly pyramidalized, showing sums of 345 (1)° at N(2) and 338 (1)° at N(6), whereas all mono-2-amino compounds exhibit a sum that is within 1σ of 360°. Substantial pyramidalization also occurs in 3-aminopyridine, where it is 348 (4)°. Chao & Schempp (1977) observed that the exocyclic C–N bond distance is correlated with the non-planarity of the amino group as measured either by $360 - \sum$ or by the dihedral angle between NH_2 and ring planes. The greater length of C(6)–N(6) compared to C(2)–N(2) is in accord with this principle, but both bonds are *ca* 0·02 Å shorter than would be predicted from the graph of Chao & Schempp (1977), which is based on mono-amino compounds.

All five 2-aminopyridines summarized by Nahringbauer & Kvick (1977) form simple centrosymmetric dimers *via* pairs of N(2)–H···N(1) hydrogen bonds, and these dimers pack as discrete units. The title compound is able to dimerize similarly, but it does not; instead, molecules are joined into a three-dimensional network by three N–H···N hydrogen bonds replicated by the 2_1 axes. The N(amino)···N(ring) distance N(6)···N(1) is 2·982 (4) Å, compared to 3·071 Å for the dimer in 2-aminopyridine (Chao, Schempp & Rosenstein, 1975*a*, 1976). Olovsson (1960) predicted that an electron-withdrawing substituent on the proton donor group or an electron-donating substituent on the proton acceptor should lead to a shorter stronger hydrogen bond. Thus, the strongly electron-donating extra amino substituent in the title compound should make N(1) more receptive to a proton donor; this is so even without the hydrogen-bond-strengthening advantage of dimerization (Gold, 1971). In 3-aminopyridine, which also forms single N(3)–H···N(1) bonds, the N···N distance is 3·123 Å. Provided that substituents on the 2-aminopyridine ring exert more effect *ortho* and *para* than *meta*, the above line of reasoning explains why 2-amino-3-nitropyridine (Destro, Pilati & Simonetta, 1975), 2-amino-4-methylpyridine (Kvick & Noordik, 1977) and 2-amino-5-chloropyridine (Kvick & Backéus, 1974; Kvick, Thomas & Koetzle, 1976) have shorter N···N contacts [3·009, 2·996 (2) and 3·058 (3) Å, respectively] than 2-aminopyridine while 2-amino-5-methylpyridine (Nahringbauer & Kvick, 1977) has a longer one [3·113 (2) Å].

Table 4. *Energy values from STO-3G molecular-orbital calculations and parameters describing twist and nonplanarity (Dunitz & Winkler, 1975) for the structure after various types of optimization*

Run (see text)	Energy (a.u.)	τ_2	τ_6	χ(C2)	χ(N2)	χ(C6)	χ(N6)
CRYST	−352·28600	−2·1	12·5	2·7	43·3	−2·8	−52·1
CRYST OPT	−352·29296	−5·4	11·6	2·3	58·9	−2·8	−59·0
SYMM OPT	−352·29300	−7·8	7·8	2·9	58·5	−2·9	−58·5
TRANS OPT	−352·29347	−6·4	−7·6	3·0	59·6	3·4	59·4
FLAT OPT	−352·28239	0·0	0·0	0·0	0·0	0·0	0·0

Twist and nonplanarity parameters (°) are defined in terms of torsion angles as follows, where the symbol $\langle x,y \rangle$ means the average of x and y, and all angles are modulo 2π:

$\tau_2 = 0{\cdot}5$ [N(1)–C(2)–N(2)–H(22) + C(3)–C(2)–N(2)–H(21)];
$\tau_6 = 0{\cdot}5$ [N(1)–C(6)–N(6)–H(61) + C(5)–C(6)–N(6)–H(62)];
χ(C2) = ⟨N(1)–C(2)–N(2)–H(21) − C(3)–C(2)–N(2)–H(21), N(1)–C(2)–N(2)–H(22) − C(3)–C(2)–N(2)–H(22)⟩ + π;
χ(N2) = ⟨N(1)–C(2)–N(2)–H(21) − N(1)–C(2)–N(2)–H(22), C(3)–C(2)–N(2)–H(21) − C(3)–C(2)–N(2)–H(22)⟩ + π;
χ(C6) = ⟨N(1)–C(6)–N(6)–H(61) − C(5)–C(6)–N(6)–H(61), N(1)–C(6)–N(6)–H(62) − C(5)–C(6)–N(6)–H(62)⟩ + π;
χ(N6) = ⟨N(1)–C(6)–N(6)–H(62) − N(1)–C(6)–N(6)–H(61), C(5)–C(6)–N(6)–H(62) − C(5)–C(6)–N(6)–H(61)⟩ + π.

The two hydrogen bonds involving the N(2) amino group as donor utilize amino N atoms as proton acceptors. While these are longer than the N(6)–H(61)···N(1) hydrogen bond, as expected, they undoubtedly are of central importance in compensating for loss of the dimer attraction. The second H atom on N(6) is not involved in the hydrogen bonding.

To ascertain whether the observed pyramidalization of the amino groups is caused by these out-of-plane hydrogen-bonding interactions or is intrinsic to the isolated molecule, *ab initio* STO-3G molecular-orbital calculations were carried out with geometry optimization. Total energy values along with parameters assessing nonplanarity at ring C and amino N atoms and twist about the exocyclic C–N bond (Dunitz & Winkler, 1975) are listed in Table 4. After an initial calculation based on the crystallographic conformation (CRYST), geometry optimization (CRYST OPT) significantly reduced the energy, equalized and even enhanced the out-of-plane distortions, but allowed unequal twists about C(2)–N(2) and C(6)–N(6) to persist. A more satisfyingly symmetrical conformation was obtained by intervention to equalize these twists followed by further optimization (SYMM OPT). The small reduction in the total energy from this procedure shows that the energy is relatively insensitive to small twists. Throughout these calculations all four amino H atoms remained on the same side of the ring plane. Reflection of H(61) and H(62) to the opposite side of this plane and optimization (TRANS OPT) led to the lowest energy of all. It is apparent that the completely planar conformation (FLAT OPT) is energetically unfavourable, and the 'natural' state of the isolated molecule has pyramidal amino groups.

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Structures of Lorazepam* Isopropyl Alcohol Solvate (I) and Isoamyl Alcohol Solvate (II)

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Abstract. (I): $C_{15}H_{10}Cl_2N_2O_2.0{\cdot}5C_3H_8O$, $M_r = 351{\cdot}21$, triclinic, $P\bar{1}$, $a = 16{\cdot}563$ (7), $b = 10{\cdot}558$ (3), $c = 10{\cdot}297$ (4) Å, $\alpha = 113{\cdot}20$ (2), $\beta = 90{\cdot}58$ (3), $\gamma = 90{\cdot}98$ (3)°, $V = 1655$ (1) Å^3, $Z = 4$, $D_x = 1{\cdot}41$ g cm^{-3}, $\mu = 4{\cdot}2$ cm^{-1}, λ(Mo $K\alpha$) = 0·71069 Å, $F(000) = 724$, $T = 291$ K, $R = 0{\cdot}050$ for 4679 observed reflections. (II): $C_{15}H_{10}Cl_2N_2O_2.C_5H_{12}O$, $M_r = 409{\cdot}31$, triclinic, $P\bar{1}$, $a = 12{\cdot}923$ (7), $b = 10{\cdot}271$ (5), $c = 8{\cdot}687$ (3) Å, $\alpha = 69{\cdot}91$ (3), $\beta = 72{\cdot}68$ (3), $\gamma = 85{\cdot}33$ (4)°, $V = 1033{\cdot}5$ (8) Å^3, $Z = 2$, $D_x = 1{\cdot}315$ g cm^{-3}, $\mu = 3{\cdot}5$ cm^{-1}, λ(Mo $K\alpha$) = 0·71069 Å, $F(000) = 428$, $T = 291$ K, $R = 0{\cdot}068$ for 2809 observed reflections. In common with several other benzodiazepines the seven-membered ring is in a boat conformation in both molecules (I) and (II). The angle between the benzene ring of the 1,4-benzodiazepine system and the aromatic 5-substituent is 84·6 (5) and 82·6 (5)° for the two independent molecules of (I), and 85·5 (5)° in (II). The two solvates differ in the number of hydrogen bonds between lorazepam and the solvent.

Introduction. Bandoli & Clemente (1976) published the molecular and electronic structure of lorazepam. They found a formulation in which one ethanol molecule is present for two lorazepam molecules. Several structural studies of benzodiazepines have been published since then (Gilli, Bertolasi, Sacerdoti & Borea, 1977, 1978*a*, *b*; Chananont, Hamor & Martin, 1980, 1981; Butcher, Hamor & Martin, 1983; Butcher & Hamor, 1985) but only one of them has shown a solvate molecule (Chananont, Hamor & Martin, 1980). In our study on the polymorphism of lorazepam we have recrystallized the molecule from five solvents (Rambaud, Maury, Pauvert, Delarbre & Lasserre, 1987) and have found five different solvates. In this paper we present the structural study of two of these: the isopropyl alcohol solvate (I) and the isoamyl alcohol solvate (II).

Experimental. (I): obtained by recrystallization from isopropyl alcohol at room temperature, colourless prismatic crystal 0·16 × 0·21 × 0·29 mm. Lattice parameters refined using 15 reflections in the range $5 \le 2\theta \le 25°$. No absorption correction. Syntex $P2_1$ diffractometer, graphite-monochromatized Mo $K\alpha$ radiation. 7608 independent reflections with $(\sin\theta)/\lambda \le 0{\cdot}649$ Å^{-1}, 4679 with $I \ge 2{\cdot}5\sigma(I)$. Index range h −21/21, k−13/12, l 0/13. Standard reflection $(5\bar{1}\bar{2})$ checked every 50 reflections. No significant deviation. Structure solved by direct methods using *SHELX*84 (Sheldrick, 1984). H atoms of lorazepam from difference Fourier synthesis. H atoms of isopropyl alcohol included in the calculation in theoretical positions, their coordinates were not refined. Anisotropic least-squares refinement on F with *SHELX*76 (Sheldrick, 1976). H isotropic with common refined temperature factor ($B_{eq} = 4{\cdot}75$ Å^2). The atoms of isopropyl alcohol, principally C(*S*), show some tendency towards disorder and a difference Fourier synthesis showed a strong peak, with a residual electron density 1·2 e Å^{-3},

* Lorazepam: 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one.

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