Structure of Diastereomeric 10-Bromo-10,11-dihydroquinines

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Cinchona Alkaloids, 10-Bromo-10,11-dihydroquinines, New Chiral Center Configuration

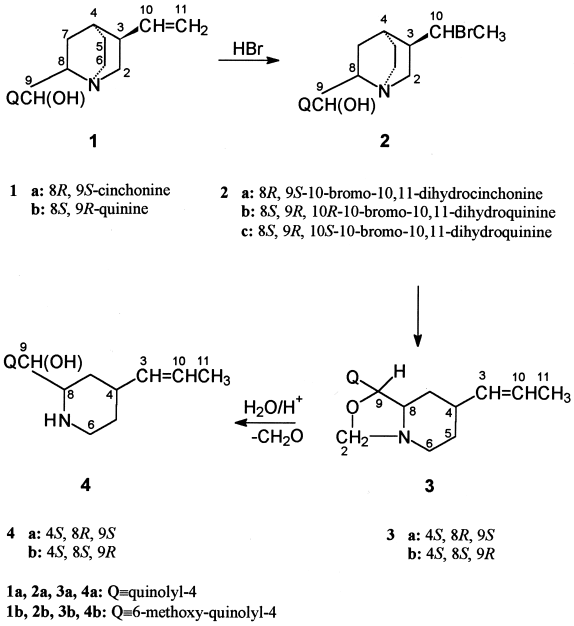
The absolute configurations of new chiral centers in the side chains of diastereomeric 10,11-dihydroquinines, $C_{20}H_{25}BrN_2O_2$, have been determined. Both diastereomers with either 10*R* or 10*S* configuration adopt the conformations in which quinuclidine nitrogen atom points away from the quinoline ring (open conformations). The bulky C3-side chain in the 10*R* diastereomer hinders intermolecular hydrogen bond formation to the quinuclidinic, more basic nitrogen atom. Instead, the hydrogen bond to the quinolinic N atom is formed which is an unusual case for *Cinchona* alkaloid crystal packing. The same bulky C3-substituent in the 10*S* diastereomer does not hinder the common packing mode *via* intermolecular hydrogen bonding to the quinuclidinic N-atom.

Introduction

Hydrobromination of *Cinchona* alkaloid vinyl groups (**1**→**2**, Scheme 1) affords 10-bromo-10,11-dihydro derivatives with an additional stereogenic center at C-10. These derivatives are convenient substrates for new transformations of the parent alkaloids [1–3]. Of particular interest to us is a conversion of the 10-halo derivatives which results in the formal loss of the C-2 carbon atoms in the form of formaldehyde. Nicinquines (**4a**, Scheme 1) are examples of the products lacking the former C-2 atom [4]. These compounds are formed from 10-bromo-10,11-dihydrocinchonines **2a** *via* the intermediate products **3a**, derivatives of 8-oxa-1-azabicyclo[4.3.0]nonane (OABN) [3].

A question arises if formation of the known niquine **4b** [5,6], a 6-methoxy-analogue of nicinquine **4a**, is also preceded by the OABN intermediate **3b**, in other words, whether similar 10-halo derivatives of the other *Cinchona* alkaloids undergo a rearrangement analogous to **2a**→**3a**.

Because of difficulties in the separation of 10-bromo-10,11-dihydrocinchonines, the diastereomeric 10-bromo-10,11-dihydroquinines **2b** and **2c** have been chosen for studying the stereochemistry of their conversion into the possible OABN intermediate **3b**. Podlewski and Suszko [5] found that the **2b**, featuring $[\alpha]_D = -200°$, was converted into the niquine whereas **2c**, showing $[\alpha]_D = -50°$, gave mainly β-isoquinine, a $\Delta^{3,10}$ isomer of quinine.



Scheme 1. Conversion of cinchonine and quinine into products lacking the C2 atom. Rabe's convention for numbering has been used.

Thus, the knowledge of absolute configurations around C-10 of the diastereomers **2b** and **2c** is crucial for understanding the steric course of both reactions: the formation of the supposed **3b** and the reactions concomitant to the **2b**, **2c** → **3b** rearrangement.

The C-10 configurations in 10-halogeno-10,11-dihydro-cinchona derivatives have been determined so far only for single 10-bromo-10,11-dihydro diastereomers of quinidine [7] and epiquinidine [8]. In the current paper the crystal structure and absolute configuration of the new stereogenic center at the C-10 atom for both diastereomers **2b** and **2c** are presented.

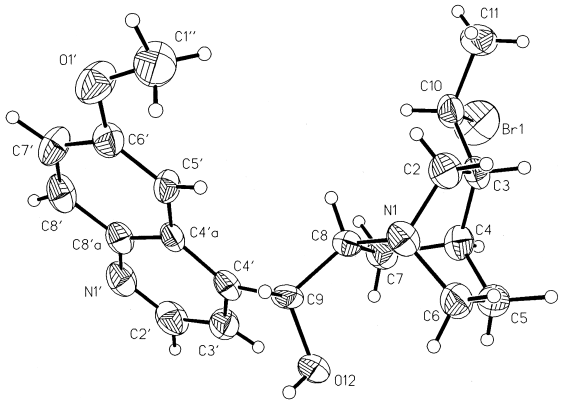
The X-ray diffraction analysis of one of the 10-bromo-10,11-dihydroquinines suffices for finding both the 10*R* or 10*S* configurations since the other stereoisomer must have the opposite arrangement around C-10. However, the alkaloids differ in solubility. Contrary to **2c**, **2b** is very sparingly soluble in $CHCl_3$, DMSO and diethyl ether, and crystallizes from acetone, whereas **2c** crystallizes from benzene, giving a solvate **2c**·$(C_6H_6)_2$. Therefore, we were prompted to seek if any correlation between the crystal structures of both diastereomers and their solubility exists.

Results and Discussion

The asymmetric unit of **2b** contains one molecule of the 10*R* diastereoisomer, whereas the one of **2c** ·$(C_6H_6)_2$ with 10*S* configuration contains one alkaloid molecule and two molecules of benzene. The perspective views of the molecules **2b** and **2c**·$(C_6H_6)_2$ together with the numbering scheme are given in Figs. 1 and 2, respectively.

The molecular conformations are open for both **2b** and **2c**, according to a nomenclature introduced by Svendsen *et al.* [9], but they differ to some extent from those of quinine (**5**, Table 1) [10]. The differences in torsion angles between **2b**, **2c** and **5** are caused by packing requirements.

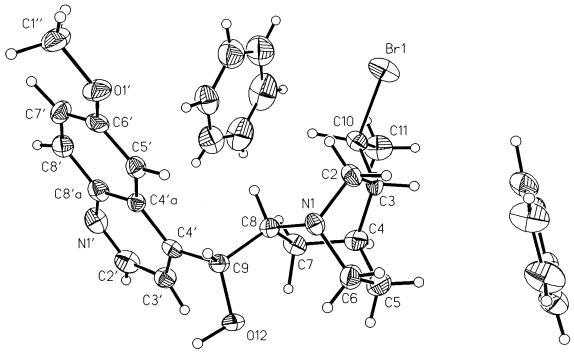
In the open conformation the quinuclidine nitrogen atom is oriented away from the quinoline ring and is accessible to intermolecular hydrogen bond formation. As the potential energy values of the open and closed conformations are almost the same [11,12], probably just the engagement of N1 in the hydrogen bonding favours the open conformation. However, a bulky group at C3 in the quinuclidine moiety can hinder the intermolecular hydrogen bond formation to the quinuclidine nitrogen atom as in the structure of quitenine ethyl ester [13]. Instead, another intermolecular hydrogen bond is formed between the O-H group and the quinolinic N atom. In consequence, a



Selected bond length [Å], bond angles and torsion angles [deg.] around C10:

C3-C10	1.512(6)	C11-C10-C3-C2	67.4(6)
C10-Br1	1.976(5)	Br1-C10-C3-C2	–172.4(3)
C3-C10-C11	114.5(5)		
C3-C10-Br1	109.9(3)		
C11-C10-Br1	106.8(4)		

Fig. 1. Displacement ellipsoid representation and the labelling scheme of the 10*R*-bromo-10,11-dihydroquinine (**2b**). The ellipsoids are drawn at 50% probability level, hydrogen atoms are spheres of arbitrary radii.



Selected bond length [Å], bond angles and torsion angles [deg.] around C10:

C3-C10	1.507(6)	C11-C10-C3-C2	178.6(4)
C10-Br1	1.999(4)	Br1-C10-C3-C2	59.3(4)
C3-C10-C11	114.3(3)		
C3-C10-Br1	107.8(3)		
C11-C10-Br1	107.3(3)		

Fig. 2. Displacement ellipsoid representation and the labelling scheme of the10*S*-bromo-10,11-dihydroquinine (**2c** · $(C_6H_6)_2$). The ellipsoids are drawn at 50% probability level, hydrogen atoms are spheres of arbitrary radii.

Table 1. Torsion angles (deg) characterizing the mutual orientation of the quinoline and quinuclidine moieties and the carbinol group.

Torsion angle	**2b**	**2c**	**5**[a]	**6**[b]
N1-C8-C9-C4′	165.0(4)	161.5(3)	147.4	173.5
C7-C8-C9-C4′	−68.0(7)	−71.3(3)	−85.1(2)	167.4
N1-C8-C9-O12	−72.5(6)	−75.7(3)	−89.5(2)	−173.5(1)
C7-C8-C9-O12	54.5(7)	51.5(3)	37.9(2)	−47.6
O12-C9-C4′-C4′a	151.2(5)	154.0(3)	165.7	149.0
O12-C9-C4′-C3′	−24.7(7)	−27.6(4)	−14.3(3)	−32.2(2)
C8-C9-C4′-C3′	97.9(6)	93.8(3)	108.1(3)	−84.9

[a] Quinine [10]; [b] quitenine ethyl ester [13].

closed conformation of quitenine ethyl ester molecule has been found [13], (**6**, Table 1). The closed conformation has been observed also in the cases when the alkaloid molecules do not have any proton donors as in the case of 9-acetylquitenine ethyl ester [14], or *p*-chlorobenzoyl-dihydroquinidine [11].

The structure of **2b** is an apparent exception from the above observation. The conformation of the molecule is open (Table 1) but the bulky substituent at C3 with 10*R* configuration prevents the formation of the intermolecular hydrogen bond to the N1 atom of the quinuclidine moiety. Instead, the O – H···N1′ (quinolinic) hydrogen bond is formed (Table 2, Fig. 3). On the other hand, in the structure of **2c·(C$_6$H$_6$)$_2$** such hindrance from the C(3)-substituent does not operate, the molecular conformation is open and an intermolecular hydrogen bond O – H ··· N1′ (quinuclidinic) is formed (Table 2, Fig. 4). The influence of the steric hindrance by the C3 substituent manifests itself in different conformations of methoxy groups in **2b** and **2c**. In the 10*R* diastereomer **2b**, the methoxy

Table 2. Hydrogen bond data.

D – H ··· A	D – H (Å)	H ··· A (Å)	D ··· A (Å)	<D – H ··· A (deg)
2b				
O12-H12···N1′[i]	0.67(5)	2.23(5)	2.896(6)	172(5)
C10-H10···N1[ii]	0.89(4)	2.60(4)	3.413(6)	153(4)
C5-H5A···Br[iii]	0.89(4)	2.97(4)	3.816(6)	159(3)
2c · (C$_6$H$_6$)$_2$				
O12-H12A···N1[i]	1.09(5)	1.63(5)	2.728(4)	176(4)
C9-H9A···O12[ii]	0.99(5)	2.40(5)	3.227(5)	140(3)

Symmetry codes: **2b:** [i] −0.5 + *x*, −0.5 + *y*, −*z*; [ii] 0.5 + *x*, −1.5 − *y*, −*z*; [iii] −1 − *x*, 0.5 + *y*, −0.5 − *z*.
2c · (C$_6$H$_6$)$_2$: [i] 3 − *x*, −0.5 − *y*, 2 − *z*; [ii] 3 − *x*, 0.5 + *y*, 2 − *z*.

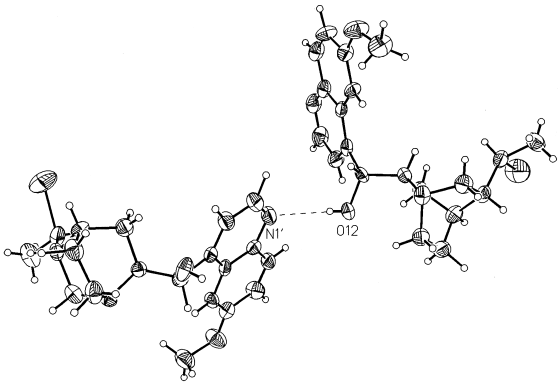


Fig. 3. Intermolecular hydrogen bond to the quinolinic nitrogen atom in the crystal of **2b**.

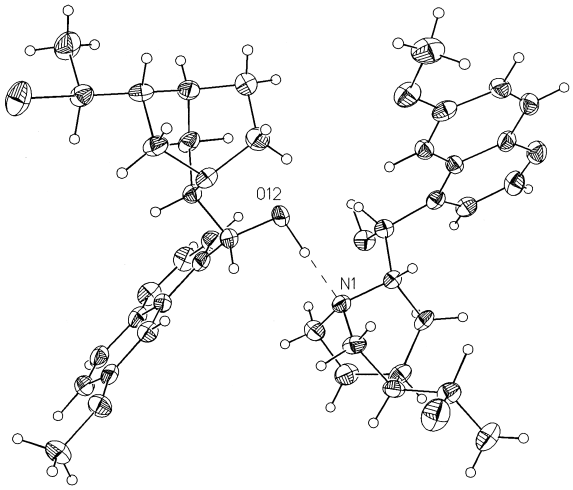


Fig. 4. Intermolecular hydrogen bond to the quinuclidinic nitrogen atom in the crystal of **2c · (C$_6$H$_6$)$_2$** .

group is directed towards the quinuclidine part whereas in the 10*S* epimer **2c**, this group is oriented outside the quinuclidine moiety, as indicated in Fig. 5. The torsion angles describing this orientation are shown in Table 3.

The quinuclidine ring is twisted in all *Cinchona* alkaloids investigated so far, in order to relieve

Table 3. The conformation of methoxy groups in **2b** and **2c · (C$_6$H$_6$)$_2$**, torsion angles (deg).

	2b	**2c · (C$_6$H$_6$)$_2$**
C7′–C6′–O1′–C1″	−174.7(5)	−2.2(5)
C5′–C6′–O1′–C1″	4.0(7)	179.2(3)

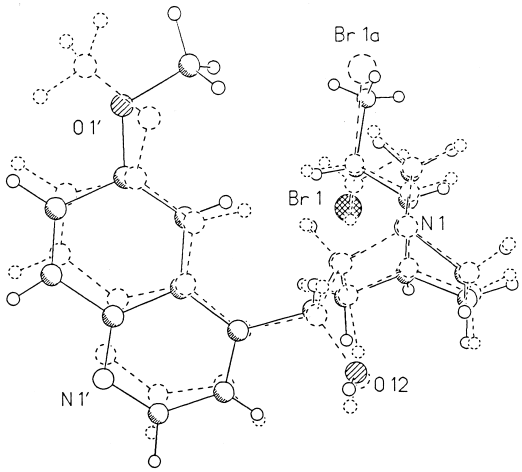


Fig. 5. A superimposition of 10*R* (**2b**) and 10*S* (**2c**) diastereomers. The 10*S* diastereomer is depicted as dashed lines.

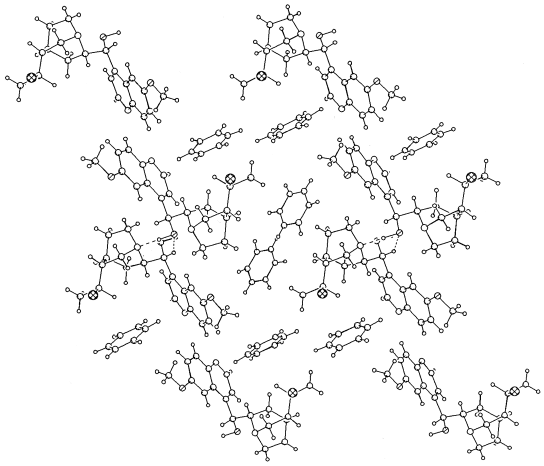


Fig. 6. Packing diagram of **2c · $(C_6H_6)_2$** . The cavities in the crystal structure are filled up with benzene molecules.

some hydrogen-hydrogen eclipsing repulsions. Dijkstra *et al.* [11] have suggested that the handedness of the twist reflects the pseudoenantiomeric relationship between quinines and quinidines. The data in Table 4 indicate contradiction to this conclusion. Probably the packing requirements rather than the above relationship in the alkaloid molecule determine the specific twist of quinuclidine ring. Interestingly, the C9-O-C10 bridge in ethereal isomers of quinidine and cinchonine also gives rise to the twist of quinuclidine moiety and this distortion is opposite to that in the parent alkaloids [15].

Table 4. Conformation of quinuclidine ring in some *Cinchona* alkaloid derivatives, torsion angles (deg.).

	N1–C2–C3–C4	N1–C6–C5–C4	N1–C8–C7–C4
2b	−4.0(6)	−5.0(6)	−11.1(6)
2c · $(C_6H_6)_2$	−4.7(4)	−6.1(6)	−11.9(4)
Quinine [10]	−7.5	−9.0	−13.6
Quitenine ethyl ester [13]	−6.9	−9.9	−12.8
Cinchonidine [16]	+8.4	+8.1	+0.9
Cinchonidinium cation [17]	−13.2(8)	−8.5(8)	−19.5(5)
Quininium [18]			
cation I	−6.3(5)	−2.0(6)	−12.8(5)
cation II	+4.8(5)	+5.3(5)	−3.8(5)

The crystal packing of **2c·$(C_6H_6)_2$** shows that benzene molecules fit best the empty spaces (Fig. 6). No short contacts to benzene molecules have been found. On the other hand, in the packing of **2b** molecules such empty spaces are not formed (Fig. 7).

Although on the grounds of the crystal structures of **2b** and **2c·$(C_6H_6)_2$** we have not found an explanation for the differences in solubility of both diastereomers, the knowledge of the 10*R* and 10*S*

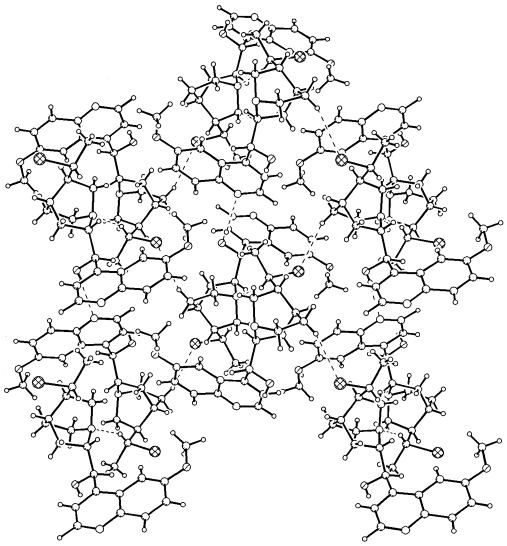


Fig. 7. Packing diagram of **2b**. No cavities in the crystal packing are observed.

absolute configurations in **2b** and **2c**, respectively, provides a firm base for studying their reactivities towards the **2** → **3** rearrangement and the possible asymmetric course of the reaction.

Experimental Section

10R-Bromo-10,11-dihydroquinine (**2b**)

20 g of quinine dihydrobromide (**1b**·2HBr·$3H_2O$), three times crystallised prior to use, was dissolved in 100 ml of 62% aqueous hydrobromic acid, placed in two 60 ml vials, sealed and kept for 9 h at 40 °C. After cooling, the reaction mixture was poured onto ice and partially neutralised with sodium carbonate. The still acidic mixture was made alkaline (with ~20% NaOH) while being vigorously shaken with 1350 ml of diethyl ether [5]. The ethereal extract was dried over anhydrous potassium carbonate only for a few minutes to avoid precipitation of the alkaloids on K_2CO_3. The extract was then immediately decanted and left overnight for crystallisation. 3.07 grams of the first fraction precipitated. The mother liquor was concentrated to 400 ml to give 2.33 g of the second fraction. Distilling off further 200 ml of ether provided 3.76 g of the third fraction, and removal of the solvent gave 1.86 g of a solid residue.

The first fraction was crystallised twice from acetone giving pyramidal, colourless crystals of **2b** suitable for X-ray analysis. M.p. (capillary method): solid shrinks and darkens at 155–160 °C, decomposes and melts at 166–167 °C (lit. [5]: 166–167 °C); $[\alpha]_D = -213.7°$ (c = 1.015, chloroform: ethanol/2:1 v/v), lit. [5]: $[\alpha]_D = -200°$, the same solvent).

10S-Bromo-10,11-dihydroquinine (**2c·(C$_6$H$_6$)$_2$**)

The above mentioned third fraction was crystallized from benzene. M.p. (capillary method): solid shrinks, decomposes and melts at 142.5–144 °C (lit. [5]: 160–162 °C, dec.). $[\alpha]_D = -52°$ (c = 1.039; chloroform: ethanol ½:1 v/v), (lit. [5]: $[\alpha]_D = -50°$, the same solvent).

100 mg of the recrystallized **2c** was dissolved at room temp. in 40 ml of benzene and left for 4 d to deposit colourless crystals in the form of prisms suitable for X-ray diffraction analysis.

X-ray analysis of **2b** and **2c·(C$_6$H$_6$)$_2$**

X-ray diffraction data were collected on a KUMA KM4CCD $\varkappa$-geometry diffractometer with CCD detector [19], using graphite-filtered Mo-K_α radiation (λ = 0.71073 Å). The unit cell parameters were calculated from the least-squares fit of the most intense reflections from the whole experiment [20]. We used 3205 reflections for **2b** and 4840 reflections for **2c·(C$_6$H$_6$)$_2$**, the θ angles ranging from 3.58° to 25.00°. Relevant crystallographic data together with data collection and structure refinement details are listed in Table 5. For **2b** the measurement was performed in four separate runs (132 frames each), for **2c·(C$_6$H$_6$)$_2$** in four runs (132 frames each) and two additional runs (125 frames each). For both, **2b** and **2c·(C$_6$H$_6$)$_2$** the ω width of each frame was 0.75°. The θ, $\varkappa$ and ϕ angles for the runs were chosen in such a way as to cover the appropriate part of the Ewald sphere. Two reference frames were measured after every 50 frames of experiment; neither the geometry nor the intensity of the reflections in these frames changed during the data collection. Intensity data were corrected for Lorentz and polarizatioin effects [20] and for absorption [21]. Both structures were solved with the SHELXS-97 program [22]. Full-matrix least squares refinement was carried out with the SHELXL-97 program [23]. Scattering factors incorporated in SHELXL-97 were used. The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma^2(F_o)^2 + (0.0342P)^2]$ for **2b** and $w^{-1} = [\sigma^2(F_o)^2 + (0.0674P)^2 + 0.15P]$ for **2c·(C$_6$H$_6$)$_2$**, where $P = (F_o^2 + 2F_c^2)/3$. Empirical extinction corrections were also applied according to the formula $F_c' = kF_c[1 + 0.001 \cdot x \cdot F_c^2 \cdot \lambda^3/\sin 2\Theta]^{-1/4}$ [23]. The final values for x are given in Table 5.

All non-hydrogen atoms were refined anisotropically. The hydrogen atoms in the methyl group in **2c·(C$_6$H$_6$)$_2$** were calculated in idealized positions and refined using a riding model. The other hydrogen atoms were found in difference maps and their positional and isotropic displacement parameters were refined for both **2b** and **2c·(C$_6$H$_6$)$_2$**.

The absolute configuration for **2b** and **2c** was assigned according to the previous determination of the absolute configuration of the naturally occuring quinine as 8*S* and 9*R* [24 and references therein]. The absolute configuration of 10*R* in **2b** and 10*S* in **2c·(C$_6$H$_6$)$_2$** was defined in consistency with the alkaloid molecule configuration. The absolute structure parameters for **2b** and **2c·(C$_6$H$_6$)$_2$**, given in Table 5, confirm the correctness of the C10 configuration assignments.

Additional crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 178045 and 178046. Copies of the data can be obtained, free of charge, on application to CCDC, 12

Table 5. Crystal data and structure refinement for **2b** and **2c · $(C_6H_6)_2$.**

	2b	**2c · $(C_6H_6)_2$**
Empirical formula	$C_{20}H_{25}BrN_2O_2$	$C_{20}H_{25}BrN_2O_2 \times 2(C_6H_6)$
Formula weight	405.33	561.55
Temperature	293(2) K	130(1) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
Unit cell dimensions	a = 10.521(2) Å	a = 14.196(1) Å
	b = 11.378(2) Å	b = 7.297(1) Å, β = 105.49(1)°
	c = 15.390(3) Å	c = 14.464(1) Å
Volume	1842.3(6) Å^3	1443.9(2) Å^3
Z	4	2
Calculated density	1.461 Mg/m^3	1.292 Mg/m^3
Absorption coefficient	2.247 mm^{-1}	1.454 mm^{-1}
F(000)	840	588
Crystal size	0.1 × 0.2 × 0.4 mm	0.08 × 0.2 × 0.4 mm
Theta range for data collection	3.58° to 25.00°	3.57° to 25.00°
Index ranges	$-12 \le h \le 11$, $-11 \le k \le 13$, $-18 \le l \le 17$	$-16 \le h \le 14$, $-8 \le k \le 8$, $-17 \le l \le 16$
Reflections collected / unique	9466 / 3205 [R(int) = 0.0594]	10091 / 4840 [R(int) = 0.0469]
Completeness to 2Θ = 50°	99.6%	99.5%
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	3205 / 0 / 327	4840 / 1 / 474
Goodness-of-fit on F^2	0.938	1.054
Final R indices [I > 2σ(I)]	$R1$ = 0.0437, $wR2$ = 0.0722	$R1$ = 0.0446, $wR2$ = 0.1051
R Indices (all data)	$R1$ = 0.0885, $wR2$ = 0.0798	$R1$ = 0.0527, $wR2$ = 0.1115
Absolute structure parameter	−0.005(11)	0.044(10)
Extinction coefficient	0.0037(8)	0.0051(18)
Largest diff. peak and hole	0.330 and −0.301 e·Å^{-3}	0.524 and −0.537 e·Å^{-3}

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