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PARTIALLY HYDROGENATED AROMATIC SUBSTITUTED TETRAZOLO[1,5-*a*]PYRIMIDINES

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By treating 5-aminotetrazole with aromatic α,β-unsaturated ketones or with Mannich base hydrochlorides there have been synthesized aromatic substituted 4,7-dihydrotetrazolo[1,5-a]-pyrimidines. They can be reduced to the corresponding 4,5,6,7-tetrahydro derivatives by the action of $NaBH_4$. The high thermodynamic stability of the 4,7-dihydrotetrazolo[1,5-a]pyrimidines when compared with the 4,5-dihydro isomers has been revealed. Reaction of 5-aminotetrazole both with cyclohexanone as well as with 2-cyclohexylidenecyclohexanone leads to formation of 9,9-pentamethylene-4,5,6,7,8,9-hexahydrotetrazolo[5,1-b]quinazoline, the structure of which was demonstrated using X-ray crystallography.

Keywords: 5-aminotetrazole, dihydrotetrazolo[1,5-*a*]pyrimidines, α,β-unsaturated ketones, tetrahydrotetrazolo[1,5-*a*]pyrimidines, molecular structure, rearrangement, cyclocondensation.

A convenient regioselective method for the synthesis of azolopyrimidines with a nodal nitrogen atom is the cyclocondensation of aminoazoles with unsaturated ketones [1]. However, in the case of non-equivalently substituted tetrazolo[1,5-*a*]pyrimidines, a solution to the question of the position of the substituent in the pyrimidine ring demands consideration of not only the route of formation of the pyrimidine ring but also the possibility of tetrazoloazide tautomeric conversions in the final compounds. The aim of our work is the synthesis of partially hydrogenated aromatic substituted tetrazolo[1,5-*a*]pyrimidines and an investigation of their possible mutual interactions *via* the open azide form.

The dihydro derivatives **3a-l** were obtained by condensation of 5-aminotetrazole (**1**) with Mannich base hydrochlorides **2a-c** or with α,β-unsaturated ketones **2d-l**. The reaction was performed by refluxing solutions of equimolar amounts of the starting materials in isoamyl alcohol (compounds **3a-e**, 3 h) or in DMF (compounds **3f-l**, 20-30 min). By the action of $NaBH_4$ on a suspension of compounds **3d-g,i,j,l** they could be reduced to the tetrahydro derivatives **4** (Scheme 1). Compounds **3f,i,j,l** have been reported by us previously [2]; the characteristics of the compounds obtained for the first time **3a-e,g,h,k** are given in Table 1.

It is known that the dihydro derivatives of azolopyrimidines can exist in the enamine (A) and the imine (B) tautomeric forms [1]. The IR spectra of compounds **3a-e,g,h,k** contain strong absorption bands for the –NH–C=C– fragment in the region 1650-1690 cm^{-1} (Table 1), typical for 1,4-dihydropyrimidine derivatives, and this points to an enamine structure (A) for these substances in the solid phase. The ^1H NMR spectra of compounds **3** contain signals for the protons of the NH group, the aromatic nuclei, the substituent, and the

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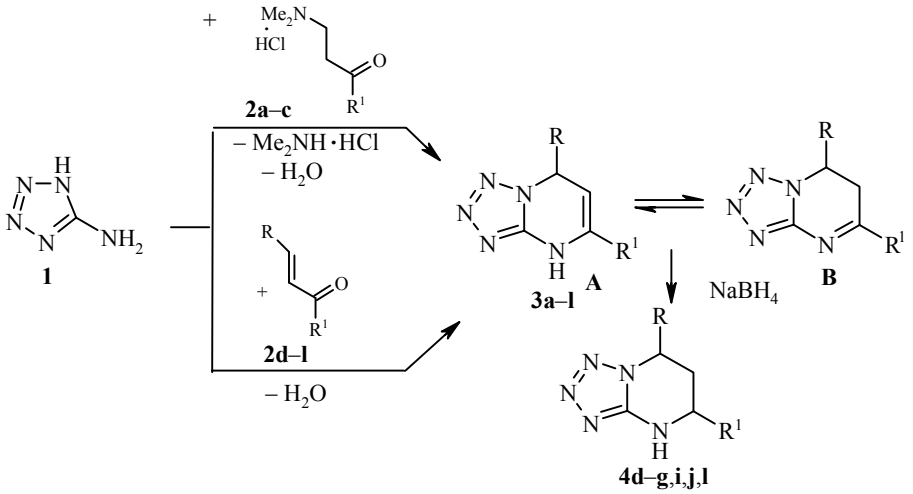
dihydropyrimidine ring (Table 2). The spectra of the dihydro derivatives **3c-l** also characterize them as compounds purely in the dihydro form A. In the case of the dihydrotetrazolopyrimidines **3a,b** there are found the spectra of the tautomers A and B in the integrated ratio of signals of ~95:5 for **3a** and 75:25 for **3b** (Table 2). The relative stabilization of the dihydro form B was observed before for the 2-desaza analogs of compounds **3a,b** (the dihydro derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidine which contain the same substituents R and R^1 [4]).

Scheme 1



2-4 a-c R = H; **d** R = Me; **e,f,j-l** R = Ph; **g** R = *p*-$MeOC_6H_4$; **h** R = *p*-ClC_6H_4; **i** R = *p*-BrC_6H_4; **a,d,f-i** R^1 = Ph; **b,j** R^1 = *p*-$MeOC_6H_4$; **c,l** R^1 = *p*-BrC_6H_4; **e** R^1 = Me; **k** R^1 = *p*-ClC_6H_4

Reduction of the dihydro derivatives **3d-g,i,j,l** leads to the disappearance of the $\nu_{C=C}$ bands in the IR spectra (Table 1). The presence of two chiral centers in the molecules of substances **4d-g,i,j,l** suggests the possible formation of a mixture of diastereomers in them. However, the ^{1}H NMR spectra of these compounds (including the unpurified samples) show them to be single substances, evidence for additional doubling of signals being absent. This fact infers that the reduction of the dihydro derivatives **3** gives only one of the possible steric isomers. The values for the spin-spin coupling $J_{5HA\text{-}HA}$ and $J_{7H\text{-}HA}$ (10.8-11.4 Hz) are typical for a J_{aa} type constant and this points to a diequatorial orientation for the substituents R and R^1 in the predominant conformers of these substances which are, thus, assigned to the *cis*-isomer series. The *cis* structure for compound **4l** was confirmed using the nuclear Overhauser effect. Additional irradiation at the resonance frequency for the 5-H proton leads to an increase in the strength of the signal for the proton at position 7 of the bicycle. In addition, there were also observed increases in the intensity of the signals for the protons of the imino group and the ortho- protons of the p-bromophenyl substituent and this confirms the assignments of signals for the 5-H and 7-H protons made by us on the basis of data in the study [5].

We have previously shown [6] that the reaction of 3-amino-1,2,4-triazole with 2-cyclohexylidenecyclohexanone (**5**) and cyclohexanone (**6**) leads to the formation of the isomeric triazoloquinoxaline system which are 2-desaza analogs of compounds **7** and **8**. By carrying out the condensation of 5-aminotetrazole with ketones **5** and **6** under the same conditions (refluxing in DMF for 1 h) we have observed that the same compound **7** is formed and its structure was confirmed by X-ray analysis.

In our view, the difference in the structure of the dihydropyrimidine fragment in the final products of the reaction of cyclohexanone with 5-aminotetrazole and 3-amino-1,2,4-triazole is connected with the marked ability of tetrazole derivatives to rearrange *via* the open azide form. In the reaction investigated this

TABLE 1. Characteristics of Compounds **3a-e,g,h,j, 4d-f,g,i, 7***

Compound	Empirical formula	Found N, % / Calculated N, %	mp, °C	$\nu_{C=C}$, cm^{-1}	Yield, %
3a	$C_{10}H_9N_5$	35.1 / 35.2	236-238	1665	75
3b	$C_{11}H_{11}N_5O$	30.8 / 30.6	235-243	1665	55
3c	$C_{10}H_8BrN_5$	25.2 / 25.2	246-248	1665	65
3d	$C_{11}H_{11}N_5$	32.9 / 32.8	183-185	1668	45
3e	$C_{11}H_{11}N_5$	33.0 / 32.8	164-166	1690	65
3g	$C_{17}H_{15}N_5O$	23.0 / 22.9	258	1650	46
3h	$C_{16}H_{12}ClN_5$	22.6 / 22.6	244	1660	30
3k	$C_{16}H_{12}ClN_5$	22.9 / 22.6	270	1660	45
4d	$C_{11}H_{13}N_5$	32.5 / 32.5	198-201	—	65
4e	$C_{11}H_{13}N_5$	32.7 / 32.5	166-168	—	30
4f	$C_{16}H_{15}N_5$	25.4 / 25.3	212-214	—	70
4g	$C_{17}H_{17}N_5O$	22.8 / 22.8	178-180	—	10
4i	$C_{16}H_{13}BrN_5$	19.8 / 19.7	219-220	—	65
4j	$C_{17}H_{17}N_5O$	22.7 / 22.8	210-213	—	65
4l	$C_{16}H_{13}BrN_5$	19.9 / 19.7	221-223	—	75
7	$C_{13}H_{19}N_5$	28.5 / 28.5	224-226	1665	49*[2]

* Compounds **3f,i,j,l** have been reported by us before [2].
*[2] By method A.

rearrangement relates to the isomeric structures **7** and **8**. The possible realization of such a rearrangement was studied for the tetrahydro derivatives **4d,e,g,i,j,l** in which a close energetic isomer profile might be expected, only differing in the position in the substituents R and R^1.

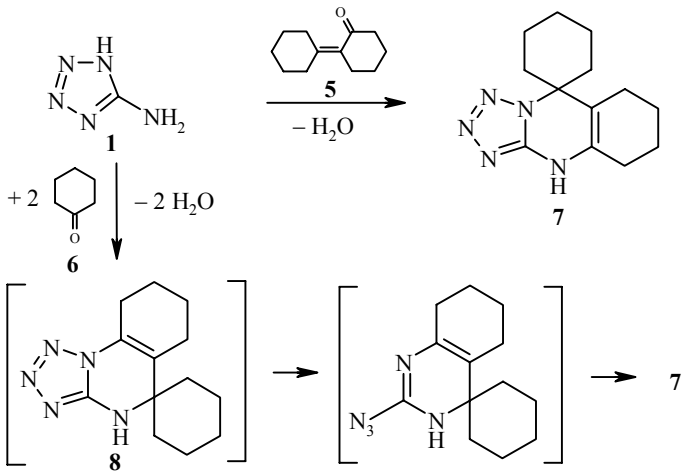


TABLE 2. Proton Chemical Shifts, δ, (Spin-spin Coupling, Hz) for Compounds **3a-l, 4d-g,i,j,l, 7**

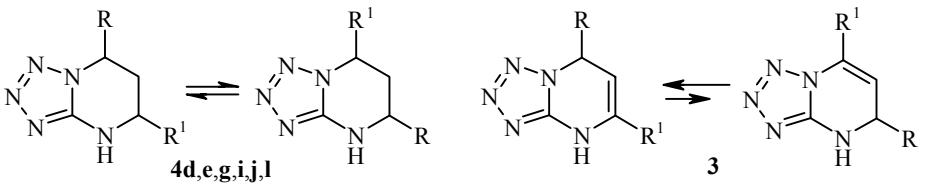
Compound	5-H	7-H	6-H		NH (1H, br. s)	Aromatic protons (m)	CH_3 (3H, s)
			H_A	H_B			
1	2	3	4	5	6	7	8
3a*							
A	—	5.2 (2H, br. s)	5.3 (1H, br. s)		10.2	7.3-8.2	
B	—	4.68 (2H, t)	3.53 (2H, t, 8.0)		10.0	6.9-8.2	
3b*							
A	—	5.1 (3H, br. s, 6-H, 7-H)					3.79
B	—	4.65 (2H, t)	3.49 (2H, t, 8.1)				3.88
3c	—	4.86 (3H, br. s, 6-H, 7-H)			10.0	7.2-7.9	
3d	—	5.51 (1H, m)	5.20 (1H, d, 3.1)		10.2	7.4-7.7	1.63 (d, 6.1)
3e	—	6.36 (1H, br. s)	4.66 (1H, br. s)		10.0	7.2-7.5	1.94
3f	—	6.65 (1H, d)	5.32 (1H, d)		10.6	7.2-7.9	
3g	—	6.54 (1H, d)	5.26 (1H, d)		10.4	6.9-7.8	3.75
3h	—	6.63 (1, d)	5.29 (1, d, 2.9)		10.6	7.3-8.0	
3i	—	6.70 (1H, d)	5.35 (1H, d)		10.7	7.2-8.1	
3j	—	6.58 (1H, d)	5.21 (1H, d, 2.7)		10.5	6.9-7.7	3.35
3k	—	6.61 (1H, d)	5.36 (1H, d, 2.7)		10.6	7.3-7.8	
3l	—	6.60 (1H, d)	5.39 (1H, d, 2.8)		10.8	7.3-8.4	

TABLE 2 (continued)

1	2	3	4	5	6	7	8
4d	4.63 (1H, m, $J_{5H\text{-}HA}$ = 11.4)	4.55 (1H, m)	1.79 (1H, m)	2.32 (1H, m)	7.8	7.2-7.5	1.54 (d, 6.0)
4e	3.68 (1H, br. s)	5.49 (1H, dd, $J_{5H\text{-}HA}$ = 10.8; $J_{5H\text{-}HB}$ = 3.8)	1.81 (1H, m)	2.34 (1H, m)	7.6	7.2-7.5	1.23 (d, 6.0)
4f	4.78 (1H, dd, $J_{5H\text{-}HA}$ = 11.4; $J_{5H\text{-}HB}$ = 1.7)	5.66 (1H, dd, $J_{5H\text{-}HA}$ = 11.0; $J_{5H\text{-}HB}$ = 4.2)	2.20 (1H, m, $J_{HA\text{-}HB}$ = -12.9)	2.43 (1H, m)	8.0	7.2-7.7	—
4g	4.77 (1H, dd, $J_{5H\text{-}HA}$ = 11.0; $J_{5H\text{-}HB}$ = 1.7)	5.60 (1H, dd, $J_{5H\text{-}HA}$ = 11.2; $J_{5H\text{-}HB}$ = 4.5)	2.21 (1H, m, $J_{HA\text{-}HB}$ = -13.3)	2.40 (1H, m)	8.03	6.8-7.6	3.75
4i	4.77 (1H, dd, $J_{5H\text{-}HA}$ = 10.8; $J_{5H\text{-}HB}$ = 1.2)	5.68 (1H, dd, $J_{5H\text{-}HA}$ = 11.1; $J_{5H\text{-}HB}$ = 4.3)	2.20 (1H, m, $J_{HA\text{-}HB}$ = -13.2)	2.44 (1H, m)	8.06	7.2-7.7	—
4j	4.72 (1H, dd $J_{5H\text{-}HA}$ = 11.3; $J_{5H\text{-}HB}$ = 1.9)	5.64 (1H, dd, $J_{5H\text{-}HA}$ = 11.0; $J_{5H\text{-}HB}$ = 4.4)	2.18 (1H, m, $J_{HA\text{-}HB}$ = -13.2)	2.40 (1H, m)	8.0	6.9-7.5	3.75
4l	4.78 (1H, dd, $J_{5H\text{-}HA}$ = 11.3; $J_{5H\text{-}HB}$ = 2.3)	5.63 (1H, dd, $J_{5H\text{-}HA}$ = 11.1; $J_{5H\text{-}HB}$ = 4.5)	2.20 (1H, m, $J_{HA\text{-}HB}$ = -13.6)	2.45 (1H, m)	8.03	7.2-7.7	—
7	—	—	—	—	9.6	1.2-2.2*[2]	—

* A mixture of tautomeric forms A and B with a B content of 5% in **3a** and 25% in **3b**.
*[2] $(CH_2)_n$.

In fact, after solutions of compounds **4d,e,g,i,j,l** had been allowed to stand for 1 h at 120°C in DMSO-d_6, the ^{1}H NMR spectra of the obtained samples pointed to the formation in solution of a 7: 3 mixture of isomers for **4d+4e** and an approximately 1:1 ratio for **4g+4j** and **4i+4l**.



4d,**e**,**g**,**i**,**j**,**l** **3**

Under these conditions, the ^{1}H NMR spectra of the dihydro derivatives **3d,e,g,i,j,l** remained unchanged and this is connected with the high thermodynamic stability of the 4,7-dihydro structure **3** when compared with their 4,5- dihydro isomers. In our view, the inverse process (rearrangement of **8** to **7**) is realized in the cyclocondensation of 5-aminotetrazole with cyclohexanone.

According to X-ray data (Figure 1, Table 3) the tetrazole ring in compound **7** is planar. Because of the symmetry of the spiro substituent at atom $C_{(8)}$ relative to the mean plane of the tetrazolopyrimidine fragment, the dihydropyrimidine ring might also be expected to have a planar structure. However, the repulsion between the hydrogen atoms of the methylene groups $C_{(6)}$, $C_{(9)}$, and $C_{(13)}$ (shortened intramolecular contacts $H_{(9A)}\cdots H_{(6A)}$ 2.24 Å, $H_{(9A)}\cdots H_{(6C)}$ 2.06 Å, $H_{(13B)}\cdots H_{(6D)}$ 2.05 Å, and $H_{(13B)}\cdots H_{(6B)}$ 2.23 Å, sum of van der Waal radii 2.32 Å [7]) causes the dihydro ring to change to a strongly flattened sofa type conformation. Atom $C_{(8)}$ deviates from the plane of the remaining atoms in the ring by -0.12 Å. The cyclohexane ring is found in a slightly asymmetric chair conformation. The deviation of atom $C_{(8)}$ from the mean square plane passing through atoms $C_{(9)}$, $C_{(10)}$, $C_{(12)}$, and $C_{(13)}$ is slightly less than that of atom $C_{(11)}$ (-0.58 and 0.76 Å respectively). The cyclohexene fragment is randomized in two equally probable, slightly asymmetric, half chair type conformations. The deviations of atoms $C_{(4)}$ and $C_{(5)}$ from the plane of the remaining ring atoms are 0.24 and -0.39 Å respectively in conformation A and -0.57 and 0.25 Å in conformation B.

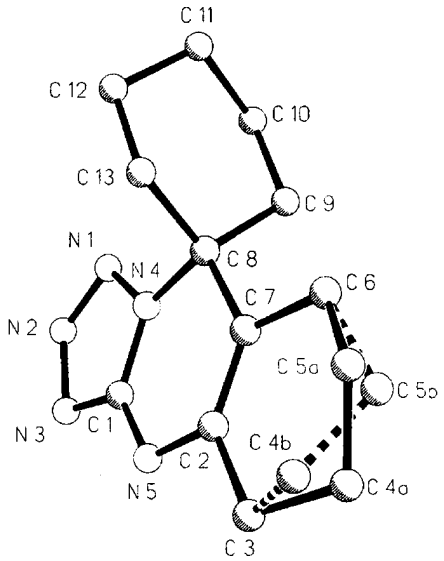


Fig. 1. Partially hydrogenated aromatic substituted tetrazolo[1,5-*a*]pyrimidines.

TABLE 3. Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^3$) for the Non-hydrogen Atoms in the Molecule of **7**

Atom	*x*	*y*	*z*	$U_{(eq)}$
$N_{(1)}$	4120(4)	-42(2)	8417(3)	60(1)
$N_{(2)}$	3466(4)	-713(2)	9052(3)	60(1)
$N_{(3)}$	2077(4)	-345(2)	9550(3)	50(1)
$N_{(4)}$	3151(3)	818(2)	8488(2)	39(1)
$N_{(5)}$	784(4)	1293(2)	9424(3)	51(1)
$C_{(1)}$	1941(4)	604(2)	9178(3)	36(1)
$C_{(2)}$	874(4)	2268(2)	8946(3)	34(1)
$C_{(3)}$	-467(4)	2962(2)	9339(3)	45(1)
$C_{(4A)}$	-199(11)	4063(5)	8984(6)	72(3)
$C_{(5A)}$	533(8)	4226(7)	7839(6)	61(3)
$C_{(4B)}$	-834(8)	3830(5)	8506(7)	46(2)
$C_{(5B)}$	893(7)	4283(5)	8342(7)	41(2)
$C_{(6)}$	2086(5)	3589(3)	7751(3)	60(1)
$C_{(7)}$	2056(4)	2523(2)	8242(3)	34(1)
$C_{(8)}$	3361(4)	1771(2)	7822(3)	32(1)
$C_{(9)}$	5141(4)	2169(3)	7996(3)	42(1)
$C_{(10)}$	6451(4)	1556(3)	7394(3)	51(1)
$C_{(11)}$	5997(4)	1430(3)	6162(3)	54(1)
$C_{(12)}$	4319(4)	927(3)	5998(3)	52(1)
$C_{(13)}$	2985(4)	1540(3)	6574(3)	42(1)

In crystal the molecules form centrosymmetric dimers through the intermolecular hydrogen bonds $N_{(5)}$–H···$N_{(3)}$ (–*x*, –*y*, 2 – *z*): N···H 2.10 Å, N–H···N 157.5°

EXPERIMENTAL

IR spectra for the compounds of types **3**, **4**, and **7** were recorded for KBr tablets on a Specord 75 IR machine and ^{1}H NMR and ^{13}C NMR spectra (DMSO-d_6 solvent) on a Bruker AM 400 spectrometer using TMS as internal standard. The purity of the compounds was monitored using TLC (Silufol UV-254, chloroform, ethyl acetate).

5-Phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine (3a). A mixture of 5-aminotetrazole **1** (0.85 g, 10 mmol) and β-dimethylaminopropiophenone hydrochloride **2a** (2.13 g, 10 mmol) in isoamyl alcohol (25 ml) was refluxed for 3 h and cooled. Filtration gave compound **3a** (1.5 g, 75%); mp 236-238°C (isoamyl alcohol).

Compounds **3a-e** were prepared similarly.

5,7-Diphenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine (3f). A solution of 5-aminotetrazole (0.85 g, 10 mmol) and the α,β-unsaturated ketone **2f** (2.07 g, 10 mmol) in DMF (1 ml) was refluxed for 30 min, cooled, mixed with benzene (30 ml), and filtered to give compound **3f** (2.2 g, 80%); mp 232-233°C (benzene–DMF, 3:1).

Compounds **3g-j** were prepared similarly.

5,7-Diphenyltetrahydrotetrazolo[1,5-*a*]pyrimidine (4f). A suspension of compound **3f** (2.75 g, 10 mmol) in absolute methanol (5 ml) was treated portionwise with $NaBH_4$ (1.0 g). At the end of the reaction, water (200 ml) was added and compound **4f** (1.94 g, 71%) was filtered off; mp 212-214°C (methanol).

Compounds **4d,e,g,i** were prepared similarly.

9,9-Pentamethylene-4,5,6,7,8,9-hexahydrotetrazolo[5,1-*b*]quinazoline (7). A. A solution of 5-aminotetrazole **1** (0.85 g, 10 mmol) and 2-cyclohexylidenecyclohexanone (1.78 g, 10 mmol) in DMF (0.5 ml) was refluxed for 30 min, mixed with benzene (30 ml), and filtered to give **7** (1.21 g, 49%); mp 224-226°C

(isopropanol). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 149.8 (3a-C); 128.2 (4a-C), 106.4 (8a-C), 62.8 (9-C), 33.8 (10-C), 26.0 (5-C), 24.1 (8-C), 23.0, 22.7 (6-C + 7-C), 21.6, 21.4 (11-C + 12-C). Mass spectrum, *m/z* (I_{rel}, %): 245 (M^+, 15), 202 (100), 174 (15), 133 (10).

B. A solution of 5-aminotetrazole **1** (0.85 g, 10 mmol) and cyclohexanone (1.96 g, 20 mmol) in DMF (0.5 ml) was refluxed for 45 min, mixed with benzene (30 ml), and filtered to give compound **7** (1.65 g, 67%).

X-ray structural investigation. Crystals of compound **7** are monoclinic, $C_{13}H_{19}N_5$, at 20°C a = 8.040 (2), b = 13.092 (3), c = 11.896 (2) Å; β = 91.88 (3)°; V = 1251.5 (4) Å^3; M_r = 245.33; Z = 4; space group $P2_1/c$; d_{calc} = 1.302 g/cm^3; λMoKα= 0.083 mm^{-1}; F(000) = 528. The unit cell parameters and intensities of 3419 reflections (3189 independent, R_{int} = 0.09) were measured on a Siemens P3/PC automatic, four circle diffractometer (MoKα, graphite monochromator, 2θ/θ scanning, $2\theta_{max}$ = 60°).

The structure was solved by a direct method using the SHELXTL PLUS [8] program package. The positions of the hydrogen atoms were calculated geometrically and refined using the "riding" model with fixed U_{iso} = 1.2 U_{eq} of the non hydrogen atom bound to the given hydrogen atom. The randomized fragment was refined with an applied restriction of the C–C bond length of 1.54 (1) Å. F^2 refinement by full matrix least squares analysis in the anisotropic approximation for non hydrogen atoms was carried out to wR_2 = 0.125 (R_1 = 0.082 for 991 reflections with $F > 4\sigma$ (F), S = 1.28). The coordinates of the non hydrogen atoms are given in Table 3.

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