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QUINAZOLINES. 3*. SYNTHESIS OF 6-BROMO-8-CHLORO-SULFONYLQUINAZOLINE-2,4(1H,3H)-DIONE AND ITS INTERACTION WITH NUCLEOPHILIC REAGENTS

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6-Bromo-8-chlorosulfonylquinazoline-2,4(1H,3H)-dione was obtained from 6-bromoquinazoline-2,4(1H,3H)-dione and chlorosulfonic acid in place of the expected 6-bromo-7-chlorosulfonyl-quinazoline-2,4(1H,3H)-dione. Interaction of the product with water, alcohols, ammonia, aliphatic and heterocyclic amines gave 6-bromo-8X-quinazoline-2,4(1H,3H)-diones (X = SO_2OH, SO_2OAlk, $SO_2NR^1R^2$), and, by reduction with $SnCl_2 \cdot 2H_2O$ in hydrochloric acid, 6-bromo-8-mercaptoquinazoline-2,4-dione was obtained.

Keywords: 6-bromo-8-mercaptoquinazoline-2,4(1H,3H)-dione, 6-bromo-8-chlorosulfonylquinazoline-2,4(1H,3H)-dione derivatives, nucleophilic and electrophilic substitution, X-ray crystallographic analysis.

Increased interest in quinazoline derivatives is caused by their high biological activity and broad spectrum of action [2-6]. Recently we have studied the interaction of unsymmetrically substituted 1,3-dialkyl-quinazoline-2,4-diones with chlorosulfonic acid and the behavior of the obtained 6-chlorosulfonyl derivatives in nucleophilic substitution reactions [1]. In continuing these investigations in the present work we have studied the direction of the chlorosulfonation reaction of 6-bromoquinazoline-2,4-dione (**1**), and also the behavior of the obtained chlorosulfonyl derivative **2** in reactions with nucleophilic reagents and under conditions of reduction with $SnCl_2.2H_2O$ in HCl solution.

It should be mentioned that compound **1** does not react with chlorosulfonic acid (CSA) under the chlorosulfonylation conditions of quinazoline-2,4(1H,2H)-diones [1, 7] unsubstituted in the aromatic ring. On increasing the temperature to 130-140°C, in place of the expected 6-bromo-7-chlorosulfonylquinazoline-2,4(1H,2H)-dione, 6-bromo-8-chlorosulfonylquinazoline-2,4(1H,3H)-dione (**2**) was obtained in 70% yield,

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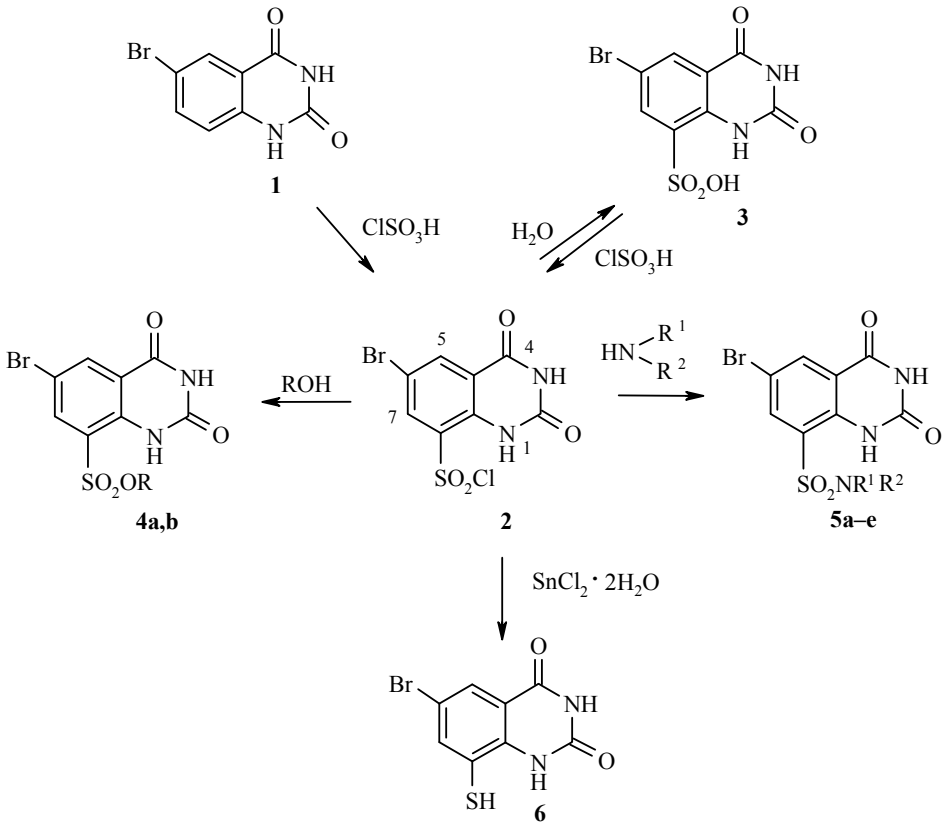
which may probably be explained by the negative inductive (-*I*) and mesomeric (-*M*) effects of the bromine atom, and also by its large size. We were unsuccessful in isolating the sulfonic acid **3** formed as an intermediate, as also in the case of quinazoline-2,4-diones unsubstituted in the aromatic ring [1, 7].



4 a R= Me, **b** R= Et; **5 a** $R^1 = R^2 = H$, **b** $R^1 = R^2 = Et$, **c** $R^1 = R^2 = Bu$, **d** $R^1 + R^2 = (CH_2)_5$; **e** $R^1 + R^2 = (CH_2)_2O(CH_2)_2$

Sulfonic acid **3** was obtained by hydrolysis of sulfonyl chloride **2**. On interacting with CSA it was readily converted into the latter in quantitative yield.

As a result of treatment of compound **2** with methanol and ethanol in the presence of triethylamine in acetone at room temperature, the corresponding esters of 6-bromo-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-8-sulfonic acid **4a**,**b** were synthesized.

The reaction of sulfonyl chloride **2** with ammonia, aliphatic, and heterocyclic amines also proceeded smoothly with the formation of the corresponding quinazolinesulfonamides **5a-e**. Heating sulfonyl chloride **2** with a concentrated aqueous solution of ammonia led to 6-bromo-8-sulfamoylquinazoline-2,4-dione (**5a**). On interacting compound **2** with aliphatic amines in the presence of triethylamine at room temperature N,N-dialkyl-amides of 6-bromo-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-8-sulfonic acid **5b**,**c** were obtained, and with piperidine and morpholine the 8-piperidinosulfonyl and 8-morpholinosulfonyl-substituted 6-bromoquinazoline-diones **5d**,**e** were obtained.

8-Mercapto-substituted quinazolinedione **6** was obtained in 70% yield by the reduction of sulfonyl chloride **2** with $SnCl_2 \cdot 2H_2O$ in hydrochloric acid and is of interest for carrying out reactions involving the reactive SH group.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **2-6**

Compound	Empirical formula	Found, %, N / Calculated, %, N	mp, °C*	Yield, %*[2]
2	$C_8H_4BrClN_2O_4S$	8.39 / 8.24	222-224	70
3	$C_8H_5BrN_2O_5S$	9.01 / 8.72	314-316	98
4a	$C_9H_7BrN_2O_5S$	8.56 / 8.35	252-254	77
4b	$C_{10}H_9BrN_2O_5S$	7.82 / 8.02	248-250	74
5a	$C_8H_6BrN_3O_4S$	12.81 / 13.12	350	82
5b	$C_{12}H_{14}BrN_3O_4S$	10.92 / 11.17	254-256	82
5c	$C_{16}H_{22}BrN_3O_4S$	10.01 / 9.72	180	95
5d	$C_{13}H_{14}BrN_3O_4S$	11.14 / 10.82	268-270	96
5e	$C_{12}H_{12}BrN_3O_5S$	10.51 / 10.76	298	97
6	$C_8H_5BrN_2O_2S$	10.52 / 10.25	340-342	70

*Solvent for recrystallization: hexane (compound **2**), water (compound **3**), methanol (compounds **4a, 5c**), ethanol (compounds **4b**, **5a**,**d**, **6**), aqueous ethanol (compounds **5b**,**e**).
*[2]Yield by procedure A.

The composition and structure of the synthesized compounds **2-6** were confirmed by the results of elemental analysis, and also by data of IR, mass spectra, and ^{1}H NMR spectra. The structure of piperidinosulfonyl-substituted **5d** was established with the aid of X-ray crystallographic analysis.

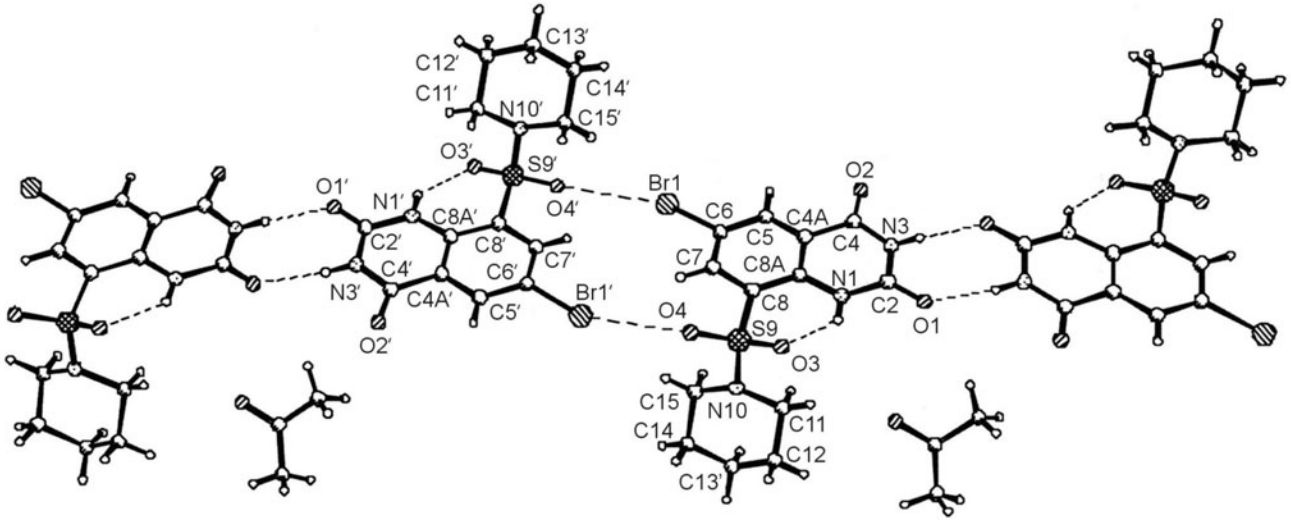


Fig. 1. Numbering of atoms, inter- and intramolecular weak bonds in the crystal structure of compound **5d**.

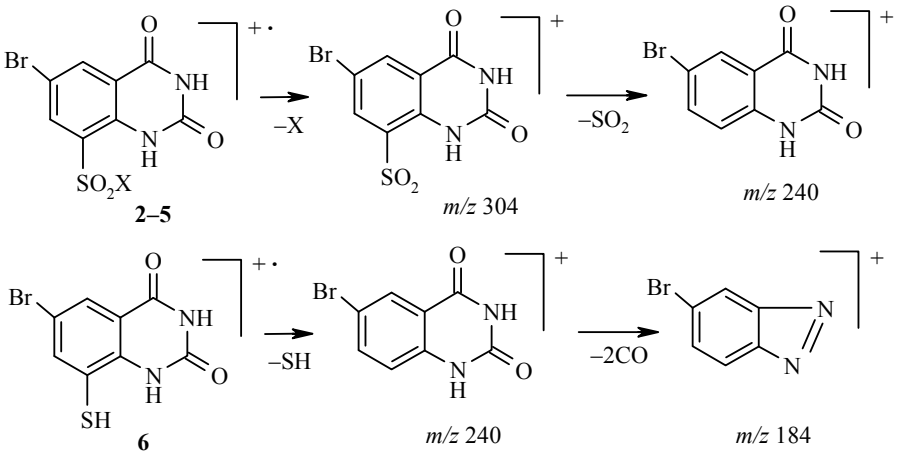
In the IR spectra of compounds **2-5** there were characteristic absorption bands for the stretching asymmetric and symmetric vibrations of the SO_2 group in the region of 1100-1400 cm^{-1}. In the case of sulfonic acid **3** absorption bands were also present for the stretching vibrations of the S–O group (670 cm^{-1}). The presence of absorption bands for the stretching vibrations of an associated SH group (2500 cm^{-1}) and the absence of bands for the asymmetric and symmetric vibrations of the SO_2 group was characteristic of compound **6** (Table 2).

TABLE 2. Spectral Characteristics of Compounds **2-6**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)	Mass-spectrum, *m/z*, $[M]^+$ (I_{rel}, %)*
	SO_2(as), SO_2(s), C–S	S–O, NH_2, SH		
2	1375, 1185, 715	—	11.84 (1H, s, H-3); 9.46 (1H, s, H-1); 8.17 (1H, d, $J_{5,7}$ = 2.4, H-5); 8.11 (1H, d, $J_{7,5}$ = 2.4, H-7)	338 (42)
3	1237, 1046, 723	670	11.86 (1H, s, H-3); 9.47 (1H, s, H-1); 8.21 (1H, d, $J_{5,7}$ = 2.3, H-5); 8.18 (1H, d, $J_{7,5}$ = 2.3, H-7)	320 (39)
4a	1370, 1177, 748	—	11.88 (1H, s, H-3); 9.39 (1H, s, H-1); 8.38 (1H, d, $J_{5,7}$ = 2.3, H-5); 8.06 (1H, d, $J_{7,5}$ = 2.3, H-7); 1.52 (3H, s, CH_3)	334 (31)
4b	1371, 1176, 749	—	11.88 (1H, s, H-3); 9.39 (1H, s, H-1); 8.20 (1H, d, $J_{5,7}$ = 2.2, H-5); 8.08 (1H, d, $J_{7,5}$ = 2.2, H-7); 3.15 (2H, q, *J* = 7.1, CH_2); 1.02 (3H, t, *J* = 7.1, CH_3)	348 (33)
5a	1377, 1165, 753	3387	11.84 (1H, s, H-3); 9.46 (1H, s, H-1); 8.17 (1H, d, $J_{5,7}$ = 2.4, H-5); 8.12 (1H, d, $J_{7,5}$ = 2.4, H-7); 8.03 (2H, s, NH_2)	319 (79)
5b	1377, 1157, 752	—	11.89 (1H, s, H-3); 9.49 (1H, s, H-1); 8.38 (1H, d, $J_{5,7}$ = 2.5, H-5); 8.14 (1H, d, $J_{7,5}$ = 2.5, H-7); 3.31 (4H, q, *J* = 7.3, $N(C\underline{H}_2)_2$); 1.12 (6H, t, *J* = 7.3, CH_3)	375 (62)
5c	1377, 1157, 752	—	11.85 (1H, s, H-3); 9.43 (1H, s, H-1); 8.38 (1H, d, $J_{5,7}$ = 2.2, H-5); 8.05 (1H, d, $J_{7,5}$ = 2.2, H-7); 3.18 (4H, m, $N(C\underline{H}_2)_2$); 1.50 (4H, m, $N(CH_2C\underline{H}_2)_2$); 1.21 (4H, m, $N(C_2H_4C\underline{H}_2)_2$); 0.83 (6H, m, $N(C_3H_6C\underline{H}_3)_2$)	431 (6)
5d	1344, 1166, 750	—	11.88 (1H, s, H-3); 9.33 (1H, s, H-1); 8.23 (1H, d, $J_{5,7}$ = 2.4, H-5); 8.03 (1H, d, $J_{7,5}$ = 2.4, H-7); 3.01 (4H, m, $N(C\underline{H}_2)_2$); 1.52 (4H, m, $N(CH_2C\underline{H}_2)_2$); 1.23 (2H, br. s, $N(C_2H_4)_2C\underline{H}_2$)	387 (42)
5e	1337, 1167, 751	—	11.88 (1H, s, H-3); 9.29 (1H, s, H-1); 8.26 (1H, d, $J_{5,7}$ = 2.4, H-5); 8.04 (1H, d, $J_{7,5}$ = 2.4, H-7); 3.59 (4H, m, $O(C\underline{H}_2)_2$); 3.02 (4H, m, $N(C\underline{H}_2)_2$)	389 (65)
6	755	2500	11.60 (1H, s, H-3); 10.57 (1H, s, H-1); 7.98 (1H, d, $J_{5,7}$ = 2.3, H-5); 7.37 (1H, d, $J_{7,5}$ = 2.3, H-7)	272 (41)

* Data for compound **2** are given for ^{35}Cl and ^{79}Br, for compounds **3-6** data are for ^{35}Cl.

There are peaks in the mass spectra of products **2-6** for the molecular ions and fragments confirming completely the proposed structures. The mass spectra of compounds **2-5**, independent of the nature of substituents at the sulfonyl group, show a single type of fragmentation with cleavage of the SO_2–R bond with the formation of an ion of *m/z* 304, on cleavage of SO_2 from which the ion with *m/z* 240 appears. In the case of compound **6** the fragment with *m/z* 240 is formed directly, then splitting off more CO, what leads to a fragment with *m/z* 184.



In the ^{1}H NMR spectra of compounds **2-6** (Table 2) there were signals characteristic of the quinazolinedione fragment as doublets for the H-5 protons at 8.17-8.38 (^3J = 2.3-2.4) and for H-7 at 7.37-8.18 ppm (^3J = 2.3-2.4 Hz). The signals of the protons of the alkyl substituents R, R^1, and R^2 were displayed at fairly high field (0.83-3.59) and of the protons of NH groups at low field (9.29-11.88 ppm).

According to data of X-ray crystallographic analysis of 6-bromo-8-piperidinosulfonylquinazoline-2,4(1H,3H)-dione (**5d**), in the crystal two molecules are disposed in the independent portion of the unit cell, and also a molecule of acetone (the solvent in which the crystals were grown). In the crystal structure there are intramolecular hydrogen bonds of the N–H···O type with the following parameters: distance N(1)···O(3) 2.731(6), H···O(3) 2.04 Å, angle N(1)–H···O(3) 136° for one molecule and distance N(1')···O(3') 2.714(6), H···O(3') 2.01 Å, angle N(1')–H···O(3') 138° for the other (see Fig. 1). In addition, in the crystal there are intermolecular hydrogen bonds of the N–H···O type and Br···O donor–acceptor interactions thanks to which an unending chain along the *b* axis is formed (see Fig. 1). The parameters of these interactions are the following: distance N(3)···O(1') 2.822(6), H···O(1') 1.97 Å, angle N(3)–H···O(1') 173° and distance N(3')···O(1) 2.864(5), H···O(1) 2.01 Å, angle N(3')-H···O(1) 171°; distance Br(1)···O(4') 3.314(4) and Br(1')···O(4) 3.120(4) Å. The solvated acetone molecule in the crystal is disposed at distances of van der Waals interactions.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer model 2000 Fourier spectrometer, in KBr disks. The ^{1}H NMR spectra were taken on a Unity 400$^+$ spectrometer (400 MHz) in CD_3COOD, internal standard was TMS. The mass spectra were taken on a Kratos MS-30 instrument with direct insertion of sample into the ion source (ionization energy 70 eV). A check on the progress of reactions and the homogeneity of synthesized compounds was effected by TLC on Silufol UV-254 plates in the solvent system benzene–acetone, 5:1, visualization was with a solution of $KMnO_4$ (1 g) in H_2SO_4 (4 ml) and H_2O (96 ml).

6-Bromoquinazoline-2,4(1H,3H)-dione was synthesized by the procedure of [8], mp 324-326°C.

6-Bromo-8-chlorosulfonylquinazoline-2,4(1H,3H)-dione (2). A. Compound **1** (2.41 g, 10 mmol) was added in portions with stirring to chlorosulfonic acid (5.83 g, 50 mmol), cooled to 10-15°C, at such a rate that the temperature of the reaction mixture did not exceed 20°C. The reaction mixture was then heated to 130-140°C, maintained at this temperature for 6 h, and poured onto crushed ice. The obtained solid was filtered off, washed with water, and recrystallized. Product **2** (2.37 g) was obtained.

Compound 2 was also obtained from sulfonic acid **3** by procedure B (see below).

6-Bromo-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-8-sulfonic Acid (3). A mixture of compound **2** (3.39 g, 10 mmol) and water (20 ml) was boiled for 2 h, the solvent was partially distilled, the solid was filtered off, and recrystallized from water. Product **3** (3.13 g) was obtained.

Compound **2** was obtained by treating sulfonic acid **3** with chlorosulfonic acid according to procedure B.

B. Sulfonic acid **3** (3.20 g, 10 mmol) was added in portions to chlorosulfonic acid (2.33 g, 20 mmol), cooled to 0°C, at such a rate that the temperature of the reaction mixture did not exceed 10°C. The reaction mixture was heated to 50-60°C, maintained at this temperature for 2 h, and poured onto crushed ice. The obtained solid was filtered off, washed with water, and recrystallized. Product **2** (3.32 g, 98%) was obtained. Samples of compound **2** obtained by procedures A and B were identical (no depression of melting point for a mixed sample).

Methyl and Ethyl Esters of 6-Bromo-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-8-sulfonic Acid (4a,b) (General Method). A mixture of methanol or ethanol (10 mmol) and triethylamine (1.01 g, 10 mmol) in acetone (15 ml) was added dropwise to a solution of compound **2** (3.39 g, 10 mmol) in acetone (50 ml). The reaction mixture was stirred at room temperature for 3 h, the acetone was then distilled off, and water (100 ml) added to the residue. The obtained solid product **4** was filtered off and recrystallized.

6-Bromo-8-sulfamoylquinazoline-2,4(1H,3H)-dione (5a). A mixture of compound **2** (3.39 g, 10 mmol) and concentrated ammonia solution (100 ml) was boiled with stirring for 2 h and then left at room temperature for 16 h. The precipitated solid was filtered off and recrystallized. Product **5a** (2.61 g) was obtained.

N,N-Diethyl- and N,N-Dibutylamides of 6-Bromo-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-8-sulfonic Acid (5b,c) (General Method). Diethyl- or dibutylamine (10 mmol) and triethylamine (1.01 g, 10 mmol) in acetone (15 ml) was added dropwise to a solution of compound **2** (3.39 g, 10 mmol) in acetone (50 ml). The reaction mixture was stirred at room temperature for 2 h, the acetone was then distilled off, and water (100 ml) was added to the residue. The obtained solid product **5** was filtered off and recrystallized.

6-Bromo-8-piperidinosulfonyl- and 6-Bromo-8-morpholinosulfonylquinazoline-2,4(1H,3H)-diones (5d,e) were synthesized analogously to dialkylamides **5b**,**c** using piperidine or morpholine (10 mmol) in place of dialkylamine.

6-Bromo-8-mercaptoquinazoline-2,4(1H,3H)-dione (6). Stannous chloride ($SnCl_2 \cdot 2H_2O$) (9 g, 40 mmol) was added in portions to a solution of compound **2** (3.39 g. 10 mmol). The reaction mixture was heated to 50°C and maintained at this temperature for 4 h with vigorous stirring. The obtained solid was filtered off, washed with water, and recrystallized. Product **6** (1.90 g) was obtained.

X-ray Structural Investigation of Compound 5d. Crystals of 6-bromo-8-piperidinosulfonyl-quinazoline-2,4(1H,3H)-dione **5d** were obtained from a solution in acetone by slow removal of solvent at room temperature. Parameters of the crystal unit cell were determined and refined on a Stoe Stadi-4 diffractometer (t = 298 K, graphite monochromator). Crystals were triclinic: a = 10.040(2), b = 10.869(2), c = 15.793(3) Å, α = 83.22(3), β = 87.34(3), γ = 86.96(3), V = 1707.5(6) Å^3. M_r = 834.56, Z = 2, space group $P\bar{1}$, d_{calc} = 1.623 g/cm^3, μ = 4.678, $F(000)$ = 848. A three-dimensional set of 5056 reflections (4414 independent) for these crystals was obtained on the same diffractometer with $\omega/2\theta$ scanning using CuKα radiation with a crystal of size 0.2×0.2×0.3 mm ($2.82 \le \theta \le 60.0^o$; region of indices h, k, l: $-11 \le h \le 11$, $-12 \le k \le 12$, $0 \le l \le 17$. Corrections to absorption were introduced by the Psi-scan method.

The structure was solved by the direct method within the framework of the SHELXS-97 set of programs. Calculations on the refinement of structures were carried out according to the SHELXL-97 program [9]. All non-hydrogen atoms were refined by the least squares method (on F^2) in a full-matrix anisotropic approximation to $R_1 = 0.0665$, $wR_2 = 0.1840$ for 4414 reflections ($S = 1.060$). The positions of hydrogen atoms were established geometrically and refined with fixed parameters of the isotropic displacement $U_{iso} = nU_{eq}$, where $n = 1.2$ for methylene groups and the aromatic ring, and U_{eq} is the equivalent isotropic parameter of the displacement of the corresponding carbon atoms.

The data of the X-ray crystallographic analysis as CIF have been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 740189).

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