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4-HYDROXY-2-QUINOLONES 155*. BIOREVERSIBLE CHEMICAL MODIFICATION OF CHINOXYCAINE AT THE TERTIARY AMINO GROUP AS A METHOD OF IMPROVING ITS PHARMACEUTICAL ACTIVITY

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There are discussed several variants of the chemical modification of the local anesthetic chinoxicaine at the tertiary amino group, initially in use as the hydrochloride. It was found that a significant improvement in its pharmaceutical properties can be achieved by exchange of the hydrogen chloride for an alternative salt forming acid component.

Keywords: 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides, local anesthetics, prodrug, X-ray structural analysis.

In the process of creating novel drugs their designers try to take into account many very varied factors. None the less complete avoidance of drawbacks is sometimes very complicated and frequently cannot be achieved. In fact, this situation was encountered by us in work on the novel, promising local anesthetic chinoxicaine which is 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid diethylamino-ethylamide (**1**) [2]. In addition to a high specific activity this compound shows clear antiarrhythmic, antimicrobial, antioxidant, and fungicidal effects. It does not show nephrotoxic activity and so can be used safely in patients with urological pathology. In addition, the use of the chinoxicaine did not reveal a single example of lowering of arterial pressure and this usefully distinguishes it from many known anesthetics [3]. Unfortunately, although possessing such a unique set of pharmacological properties, chinoxicaine proved to be not readily soluble in aqueous media (at 20ºC its solubility is only 13.85 g per 100 ml of solvent) and this has created significant problems in preparing an injectable medicinal form. For later stages of introduction of

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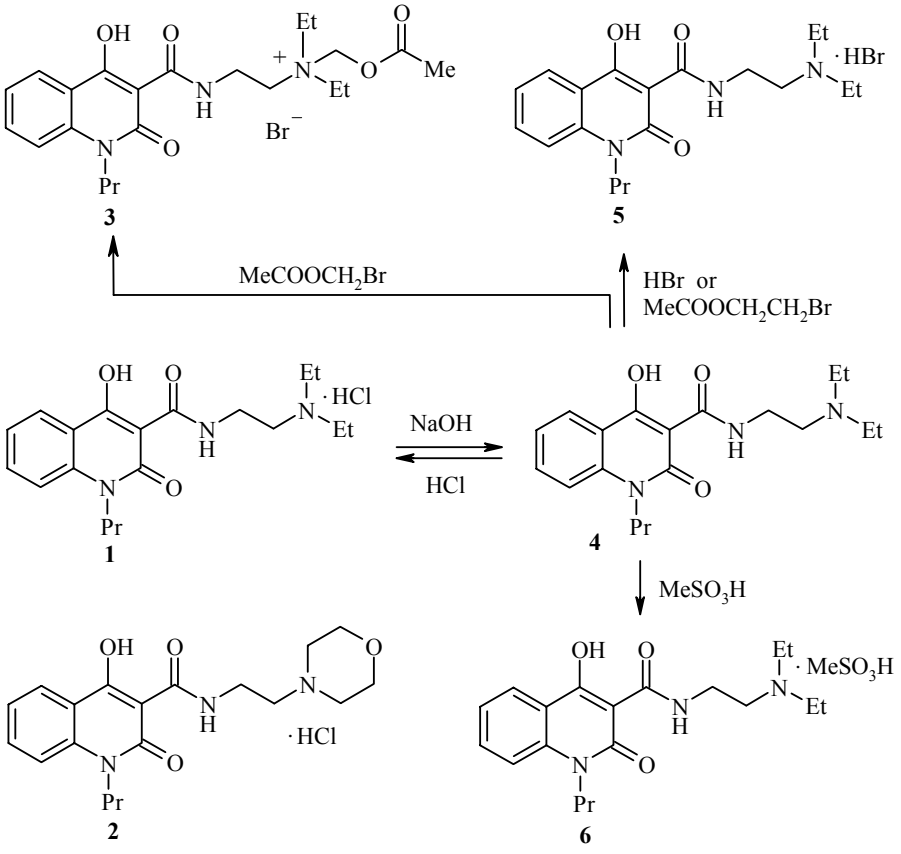
chinoxicaine into medical practice, in fact at the stage of clinical investigation, one serious drawback was revealed. In some patients the preparation caused a short term burning sensation at the point of injection. Although this undesirable effect lasted no more than 1 min subsequent work on the preparation lost all promise overall without its elimination.

An escape from this situation can be sought by different means, e.g. by using a previously revealed "structure – activity" dependence to synthesize a completely new analog of chinoxicaine with improved properties. It would follow, however, that in such a case all of the biological and pharmaceutical investigations would have to be carried out from new and in full amount. Reaching this target would be totally unrealistic as a consequence of the synthesis of just a single material. The speediest successful resolution of such a problem is only possible after studying a series of novel compounds. With this in mind it is more rational and economically convenient to look at another route to improving the pharmaceutical properties of chinoxicaine by its single-minded, bioreversible chemical modification, i.e. the creation of a prodrug based on it.



In addition, the practical realization of such a route is accompanied by specific problems. In particular, an increase in the water solubility in a structural modification of the material generally needs the introduction of additional ionizing groups while the removal of the irritating action upon injection needs the same ionizing groups in the molecule to be masked [4]. In other words, potential methods for removing the complications appearing are mutually exclusive.

The major part of the irritating action of the chinoxicaine is likely associated with the presence in its structure of the 4-OH group which, as is known [5], shows quite marked acidic properties in 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides. It was also noted [6] that the strength of this side effect depends also on the structure of the amide fragment. Hence, for example, although the hydrochloride of 4-hydroxy-2-oxo-

1-propyl-1,2-dihydroquinoline-3-carboxylic acid 2-morpholin-4-ylethylamide (**2**) is inferior to chinoxicaine in specific activity it has virtually no irritant property. The fact also serves as the basis for bringing about a bioreversible chemical modification of chinoxicaine at the tertiary amino group.

One of the obvious solutions to the rebuild of the molecule is simply to use the transformation to quaternary ammonium salts. It should be mentioned straight away that the usual alkyl halides are unsuitable in this case since they form very stable compounds with the tertiary amine drug which hardly undergo metabolism and are excreted from the organism in an unchanged state [4]. More interesting carboxylic acid haloalkyl esters allow transformation of the tertiary amines to quaternary ammonium salts with a labile N^+–C–O group which are able to undergo hydrolytic cleavage liberating the starting drug as the corresponding hydrohalide [4, 7].

The target bromoacetoxymethylate **3** was synthesized by short heating of the 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid diethylaminoethylamide (**4**) with bromomethylacetate in anhydrous acetonitrile. Biological investigation showed that the quaternization in fact led to virtually total elimination of the irritant effect of chinoxicaine **1** by contrast to which a 2% aqueous solution of the bromoacetoxymethylate **3** caused only slight hyperemia of rabbit eye conjunctiva. At the same time (and against expectations) a marked decrease in the water solubility to 8.86 g per 100 ml was noted even though drugs of this type usually show a sharp increase by one or two orders when compared with hydrochlorides [7]. Significantly there is almost a threefold shortening of the duration of the surface anesthesia by the bromoacetoxymethylate **3** and this is evidently due to the low rate of liberation of the starting tertiary amine.

Attempts to optimize this property by exchange of the 2-bromomethyl acetate by 2-bromoethyl were unsuccessful. In the presence of amide **4** this reagent is dehydrobrominated. As a result, in place of the bromoacetoxyethylate the hydrobromide **5** was produced and this was also obtained by neutralization of the tertiary amino group of amide **4** by hydrobromic acid. Salt formation, although not accompanied by a change in the number, nature, and position of the covalent bonds is none the less a discrete form of chemical modification of a drug material widely used in medicinal chemistry hence it follows that the hydrobromide **5** can be considered as a distinctive prodrug of the chinoxicaine **1**. However the change from hydrochloride to hydrobromide did not give a positive result. Indeed, all of the parameters were only inferior. The solubility fell to 3.4 g per 100 ml water, the irritant effect was increased, and the surface anesthesia effect was lower.

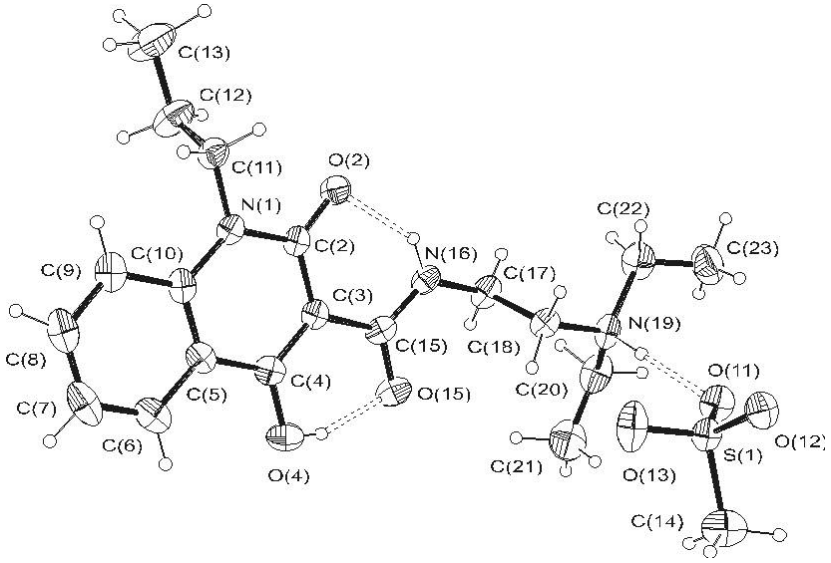


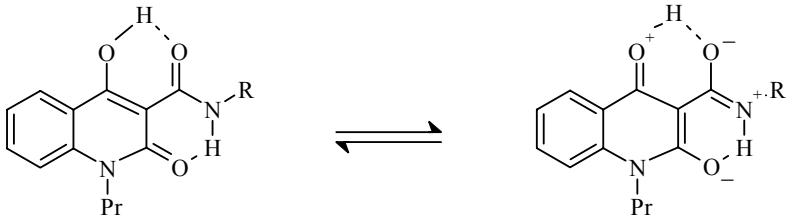
Fig. 1. Structure of the methanesulfonate **6** molecule with atomic numbering. The dotted lines indicate the intra- and intermolecular hydrogen bonds.

Greatest success was achieved by exchange of hydrogen chloride as salt forming reagent for methansulfonic acid which gives the methanesulfonate **6** in virtually quantitative yield with amide **4** in anhydrous ether.

According to the X-ray structural data, in the symmetrically independent part of the unit cell of the synthesized compound there are protonated at atom N(19) molecule of the 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid diethylaminoethylamide and the methanesulfonic acid anion (see Fig. 1 and Tables 1 and 2).

The dihydroquinolone fragment is planar within 0.02 Å. The deviations of atoms C(11) and C(15) from the mean square plane of the dihydropyridine ring are 0.067 and 0.022 Å respectively. A marked deviation of atom C(11) from the ring plane is explained by the presence of an shortened intramolecular contact H(9)···H(11B) of 1.986 Å (sum of van der Waals radii 2.34 Å [8]). The amide fragment is virtually coplanar with the dihydroquinolone (torsional angle C(4)–C(3)–C(15)–O(15) = 4º). Such an orientation is stabilized by two intramolecular hydrogen bonds: O(4)–H(4)···O(15) (H···O 1.74 Å, O–H···O 155º) and N(16)–H(16)···O(2) (H···N 1.91 Å, N···H–O 140º).

The O(4)–C(4) 1.319(3), N(16)–C(15) 1.313(3), and C(2)–C(3) 1.451(3) Å bonds in the compound studied are shortened (mean values 1.331, 1.334, and 1.464 Å respectively [9]) but the O(15)–C(15) 1.264(3) and C(3)–C(4) 1.379(3) Å bonds are lengthened (mean values 1.231 and 1.363 Å respectively). This is likely explained by the existence of a contribution of a zwitterionic resonance structure **6a** to the overall picture.



6 **6a**

Atom N(1) has a planar trigonal configuration. The substituents at atoms N(1) and N(16) have an *anti*-periplanar conformation (torsional angles N(1)–C(11)–C(12)–C(13) and N(16)–C(17)–C(18)–N(19) 176.2 and 176.3º respectively). The plane of the carbon atoms of the propyl group on the N(1) atom is virtually perpendicular to the mean-square plane of the dihydropyridine ring, the angle between them being 89.1º.

TABLE 1. Individual Bond Lengths (*l*) in the Methanesulfonate **6** Structure

Bond	*l*, Å	Bond	*l*, Å
N(1)–C(2)	1.388(3)	N(1)–C(10)	1.389(3)
N(1)–C(11)	1.459(3)	C(2)–O(2)	1.229(3)
C(2)–C(3)	1.451(3)	C(3)–C(4)	1.379(3)
C(3)–C(15)	1.468(3)	C(4)–O(4)	1.319(3)
C(4)–C(5)	1.442(3)	C(5)–C(10)	1.390(4)
C(5)–C(6)	1.397(3)	C(6)–C(7)	1.366(4)
C(7)–C(8)	1.381(5)	C(8)–C(9)	1.380(4)
C(9)–C(10)	1.406(4)	C(11)–C(12)	1.520(4)
C(12)–C(13)	1.499(5)	C(15)–O(15)	1.264(3)
C(15)–N(16)	1.313(3)	N(16)–C(17)	1.449(3)
C(17)–C(18)	1.506(3)	C(18)–N(19)	1.486(3)
N(19)–C(20)	1.495(3)	N(19)–C(22)	1.540(4)
C(20)–C(21)	1.473(5)	C(22)–C(23)	1.445(5)
S(1)–O(13)	1.430(2)	S(1)–O(12)	1.433(2)
S(1)–O(11)	1.473(2)	S(1)–C(14)	1.760(4)

TABLE 2. Individual Valence Angles (ω) in the Methanesulfonate **6** Structure

Angle	ω, deg	Angle	ω, deg
C(2)–N(1)–C(10)	123.1(2)	C(2)–N(1)–C(11)	116.0(2)
C(10)–N(1)–C(11)	120.8(2)	O(2)–C(2)–N(1)	119.7(2)
O(2)–C(2)–C(3)	123.7(2)	N(1)–C(2)–C(3)	116.6(2)
C(4)–C(3)–C(2)	120.9(2)	C(4)–C(3)–C(15)	118.6(2)
C(2)–C(3)–C(15)	120.4(2)	O(4)–C(4)–C(3)	122.5(2)
O(4)–C(4)–C(5)	117.2(2)	C(3)–C(4)–C(5)	120.3(2)
C(10)–C(5)–C(6)	120.3(2)	C(10)–C(5)–C(4)	118.5(2)
C(6)–C(5)–C(4)	121.2(2)	C(7)–C(6)–C(5)	121.3(3)
C(6)–C(7)–C(8)	118.7(3)	C(9)–C(8)–C(7)	121.4(3)
C(8)–C(9)–C(10)	120.2(3)	N(1)–C(10)–C(5)	120.4(2)
N(1)–C(10)–C(9)	121.6(2)	C(5)–C(10)–C(9)	118.0(2)
N(1)–C(11)–C(12)	111.2(2)	C(13)–C(12)–C(11)	109.8(3)
O(15)–C(15)–N(16)	119.9(2)	O(15)–C(15)–C(3)	119.8(2)
N(16)–C(15)–C(3)	120.3(2)	C(15)–N(16)–C(17)	122.3(2)
N(16)–C(17)–C(18)	110.8(2)	N(19)–C(18)–C(17)	112.3(2)
C(18)–N(19)–C(20)	114.7(2)	C(18)–N(19)–C(22)	109.9(2)
C(20)–N(19)–C(22)	112.8(2)	C(21)–C(20)–N(19)	112.7(2)
C(23)–C(22)–N(19)	113.4(3)	O(13)–S(1)–O(12)	114.3(1)
O(13)–S(1)–O(11)	111.9(1)	$O(12_i)$–S(1)–O(11)	112.3(1)
O(13)–S(1)–C(14)	108.3(2)	O(12)–S(1)–C(14)	104.8(1)
O(11)–S(1)–C(14)	104.5(1)		

In the crystal the molecules of the methanesulfonate **6** form dimers *via* stacking interactions between the dihydroquinolone fragments, the benzene rings being situated over the dihydropyridines. The distance between the ring centroids is 3.54 Å and the mean-square planes of the dihydropyridine and benzene fragments form a dihedral angle of 2.2º.

The cation and anion are mutually bonded by an intermolecular hydrogen bond N(19)–H(19)···O(11) (H···O 1.88 Å, N–H···O 176º).

The results of the investigation have shown that the methanesulfonate **6** shows a marked improve in all of the pharmaceutical properties when compared with the starting hydrochloride **1**. In particular, the local irritation caused by compound **6** was decreased to the level in the bromoacetoxymethylate **3**, i.e. it can be classified as virtually insignificant. The solubility in water is increased by more than six times to 85.72 g per 100 ml of water and this removes the problem of the choice of solvent for preparing an injectable drug form. Finally, positive features were also noted in the appearance of specific activity, i.e. if the overall duration of the local anesthesia remains virtually unchanged the stage of deep anesthesia in increased almost twofold.

Hence there is every reason that a simple and technologically readily performed change of the 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid diethylaminoethylamide to the methanesulfonate can be recommended as a method for improving the pharmaceutical properties of chinoxicaine since it can eliminate all the inherent deficiencies of the hydrochloride.

EXPERIMENTAL

^{1}H NMR spectra for the compounds synthesized were recorded on a Varian MercuryVX-200 instrument (200 MHz) using DMSO-d_6 with TMS as internal standard. Commercial bromomethylacetate, 2-bromoethylacetate, and anhydrous acetonitrile were used from the Aldrich company. 4-Hydroxy-2-oxo-1-propyl-

1,2-dihydroquinoline-3-carboxylic acid diethylaminoethylamide (**4**) was prepared by one of the previously reported methods [2, 10-12].

Bromoacetoxymethylate of 4-Hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid Diethylaminoethylamide (3). A solution of bromomethylacetate (1.84 g, 0.012 mol) in anhydrous acetonitrile (5 ml) was added to a solution of the diethylaminoethylamide **4** (3.45 g, 0.01 mol) in the same solvent (15 ml). A bulky white precipitate was formed upon mixing the reagents. The reaction mixture was stirred for 15-20 min at 50ºC, cooled to room temperature, and diluted with anhydrous ether. The precipitated bromoacetoxymethylate **3** (4.69 g, 94%) was filtered off, washed with water, and dried. Mp 171-173ºC (anhydrous ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.80 (1H, s, OH); 10.53 (1H, t, *J* = 5.7, NH); 8.11 (1H, dd, *J* = 8.1 and *J* = 1.3, H-5); 7.84 (1H, td, *J* = 7.7 and *J* = 1.4, H-7); 7.68 (1H, d, *J* = 8.3, H-8); 7.40 (1H, t, *J* = 7.7, H-6); 5.33 (1H, s, NCH_2O); 4.21 (2H, t, *J* = 7.6, $NC\underline{H}_2CH_2CH_3$); 3.78 (2H, q, *J* = 6.6, $NHC\underline{H}_2CH_2N$); 3.60-3.44 (6H, m, $N(CH_2)_3$); 2.27 (3H, s, $COCH_3$); 1.65 (2H, m, $NCH_2C\underline{H}_2CH_3$); 1.29 (6H, t, *J* = 7.1, $N(CH_2C\underline{H}_3)_2$); 0.98 (3H, t, *J* = 7.3, $NCH_2CH_2C\underline{H}_3$). Found, %: C 53.23; H 6.64; N 8.35. $C_{19}H_{27}N_3O_3 \cdot C_3H_5BrO_2$. Calculated, %: C 53.02, H 6.47; N 8.43.

Hydrobromide of 4-Hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid Diethylaminoethylamide (5). A. A solution of 2-bromoethylacetate (2.0 g, 0.012 mol) in anhydrous acetonitrile (5 ml) was added to a solution of the diethylaminoethylamide **4** (3.45 g, 0.01 mol) in the same solvent (15 ml). In contrast to the preceding experiment a precipitate did not form upon mixing the reagents. The reaction mixture was stirred at 50ºC for 1 h and it was then worked up as in the synthesis of compound **3**. Yield 2.98 g (70%); mp 196-198ºC (water). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.84 (1H, s, OH); 10.45 (1H, t, *J* = 5.6, NH); 9.64 (1H, br. s, N^+H); 8.04 (1H, dd, *J* = 8.0 and *J* = 1.3, H-5); 7.80 (1H, td, *J* = 7.8 and *J* = 1.5, H-7); 7.62 (1H, d, *J* = 8.2, H-8); 7.33 (1H, t, *J* = 7.7, H-6); 4.17 (2H, t, *J* =7.4, $NC\underline{H}_2CH_2CH_3$); 3.70 (2H, q, *J* = 6,4, $NHC\underline{H}_2CH_2N$); 3.45-3.13 (6H, m, $N(CH_2)_3$); 1.60 (2H, m, $NCH_2C\underline{H}_2CH_3$); 1.25 (6H, t, *J* = 7.1, $N(CH_2C\underline{H}_3)_2$); 0.94 (3H, t, *J* = 7.2, $NCH_2CH_2C\underline{H}_3$); Found, %: C 53.65; H 6.71; N 9.95. $C_{19}H_{27}N_3O_3 \cdot HBr$. Calculated, %: C 53.53; H 6.62; N 9.86.

B. Concentrated HBr was added to a suspension of the diethylaminoethylamide **4** (3.45 g, 0.01 mol) in hot water (15 ml). The diethylaminoethylamide dissolved and subsequent cooling gave crystalline hydrobromide **5**. For a more complete separation of the final product the reaction mass was held for 4-5 h at 5ºC. The precipitated hydrobromide **5** was filtered off and dried. Yield 4.05 g (95%). A mixed sample with hydrobromide **5** prepared as in method A did not give a depression of melting point. The ^{1}H NMR spectra were identical.

Methanesulfonate of 4-Hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid Diethylaminoethylamide (6). The methanesulfonic acid (0.71 ml, 0.011 mol) was added with vigorous stirring to a solution of compound **4** (3.45 g, 0.01 mol) in anhydrous ether (20 ml) cooled to 5ºC. The precipitated methanesulfonate **6** was filtered off, washed with ether, and dried. Yield 4.37 g (99%); mp 154-156ºC (acetone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.81 (1H, s, OH); 10.48 (1H, t, *J* = 5.8, NH); 9.21 (1H, br. s, N^+H); 8.09 (1H, dd, *J* = 8.2 and *J* = 1.3, H-5); 7.79 (1H, td, *J* = 7.7 and *J* = 1.5, H-7); 7.64 (1H, d, *J* = 8.5, H-8); 7.35 (1H, t, *J* = 7.6, H-6); 4.21 (2H, t, *J* = 7.5, $NC\underline{H}_2CH_2CH_3$); 3.74 (2H, q, *J* = 6.5, $NHC\underline{H}_2CH_2N$); 3.31 (2H, t, *J* = 6.7, $HNCH_2C\underline{H}_2N$); 3.27-3.13 (4H, m, $N(C\underline{H}_2CH_3)_2$); 2.33 (3H, s, SCH_3); 1.65 (2H, m, $NCH_2C\underline{H}_2CH_3$); 1.23 (6H, t, *J* = 7.2, $N(CH_2C\underline{H}_3)_2$); 0.95 (3H, t, *J* = 7.4, $NCH_2CH_2C\underline{H}_3$). Found, %: C 54.46; H 7.13; N 9.46. $C_{19}H_{27}N_3O_3 \cdot CH_4O_3S$. Calculated, %: C 54.40; H 7.08; N 9.52.

X-ray Structural Study. Crystals of methanesulfonate **6** were grown from acetone at 20ºC and are monoclinic with: *a* = 7.607(2), *b* = 11.008(3), *c* = 26.606(9) Å, β = 95.64(2)º, *V* = 2217.3(11) Å^3, M_r = 441.54, *Z* = 4, space group $P2_1/c$, d_{calc} = 1.323 g/cm^3, μ(MoKα) = 0.187 mm^{-1}, *F*(000) = 944. The unit cell parameters and intensities of 4299 reflections (4205 independent with R_{int} = 0.0882) were measured on a CAD4 diffractometer (MoKα radiation, point scintillation detector, graphite monochromator, 2θ/θ scanning to θ_{max} = 26º).

The structure was solved by the direct method using the SHELXS97 program package [13]. The positions of the hydrogen atoms were revealed in electron density difference synthesis and refined isotropically. The structure was refined in F_2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms to $wR_2 = 0.1780$ for 4205 reflections ($R_1 = 0.068$ for 3809 reflections with $F^2 > 2\sigma$ (F^2), $S = 0.984$) using the SHELXL97 program package [14]. The numbering of the atoms in the compound studied and its geometrical structure are shown in Figure 1 as obtained using the ORTEP-3 program [15]. Full crystallographic information has been deposited in the Cambridge Structural Database (deposit No. CCDC 683121). The interatomic distances and valence angles are given in Tables 1 and 2.

REFERENCES

1. I. V. Ukrainets, A. A. Tkach, L. A. Grinevich, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 719 (2009). [*Chem. Heterocycl. Comp.*, **45**, 567 (2009)].
2. I. V. Ukrayinecz and P. A. Bezuhliy, US Pat. 6340692 (2002). http://ep.espacenet.com
3. M. D. Mashkovskii, *Drugs* [in Russian], Vol. 1, OOO Novaya Volna, Izd. S. B. Divov, Moscow (2002), p. 291.
4. S. G. Kuznetsov, S. M. Chigareva, and S. M. Ramsh in: *Summaries in Science and Technology. Organic Chemistry* [in Russian], VINITI, Moscow (1991), p. 19.
5. I. V. Ukrainets, Diss. of Cand. in Pharmaceutical Sci., Kharkiv (1988).
6. O. V. Gorokhova, Diss. of Cand. in Chemic. Sci., Kharkiv (1993).
7. N. D. Vinogradova, S. G. Kuznetsov, and S. M. Chigareva, *Khim. -Farm. Zh.*, **14,** No. 9, 41 (1980).
8. Yu. V. Zefirov and P. M. Zorkii, *Usp. Khim.*, **58**, 713 (1989).
9. H.-B. Burgi and J. D. Dunitz, *Struct. Correl.*, Vol. 2, VCH, Weinheim (1994), p. 741.
10. I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, S. V. Slobodzyan, A. V. Turov, V. P. Georgievskii, A. I. Grizodub, M. G. Levin, G. V. Obolentseva, S. V. Gladchenko, V. I. Krivobok, I. G. Butenko, V. V. Lemeshko, V. I. Padalko, Yu. V. Nikitchenko, T. P. Skubko, A. I. Kobzar', V. N. Sukhinin, and E. G. Litovkina, Russian Pat. 1774624 (1993). http://ep.espacenet.com
11. I. V. Ukrainets, P. O. Bezuhlyi, O. V. Gorokhova, S. G. Taran, and V. I. Triskach, UA Pat. 24967 1998. http://base.ukrpatent.org/searchINV
12. I. V. Romanov and I. V. Ukrainets, Rus. Pat. 2285692 (2006). http://ep.espacenet.com.
13. G. M. Sheldrick, *SHELXS97. Program for the Solution of Crystal Structure*, Univ. of Göttingen, Germany (1997).
14. G. M. Sheldrick, *SHELXL97. Program for the Refinement of Crystal Structure*, Univ. of Göttingen, Germany (1997).
15. L. J. Farrugia, *J, Appl. Crystallogr.*, **30**, 565 (1997).