Pharmaceutical Chemistry Journal, Vol. 28, No. 1, 1994

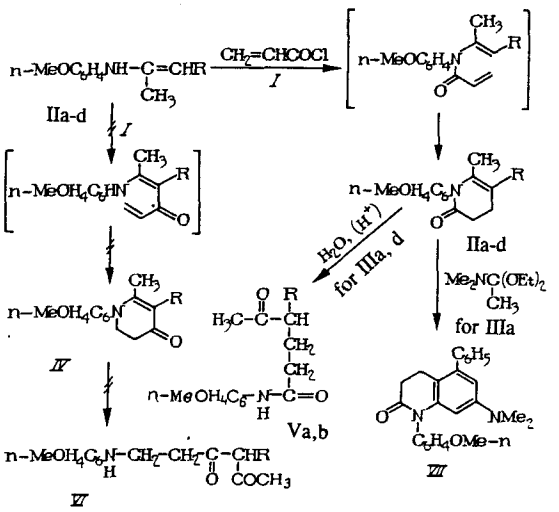
STUDIES OF THE REACTION OF SECONDARY AND TERTIARY ENAMINES WITH ACRYLOYL CHLORIDE. SYNTHESIS OF NEW DERIVATIVES OF CYCLOHEXANE-DIONE-1,3

V. M. Lyubchanskaya, L. S. Sarkisova, L. M. Alekseev, and V. G. Granik

UDC 547.859.07

Interactions of acryloyl chloride (compound I) with enaminocarbonyl compounds containing a secondary amino group are known to take place, reactions involving the secondary amino group, forming hydrogenated pyridone-2 compounds [1]. In the same conditions, tertiary enaminoketones and enaminoesters are converted to dihydroresorcine derivatives [2] or hydrogenated heterocyclic compounds, such as substituted indoles, quinolines, and benzazepines [3]. In the first type of reaction, only N-alkylenaminoketones and enaminoesters are used as secondary enamines [1]. We proposed that reduction of the basicity of the enamino NH group by introduction of an N-aryl substituent could change the direction of the reaction. In addition, it would be of interest to determine the extent to which this reaction is typical only for enaminocarbonyl compounds, or whether it could also involved other enamines.

Starting enamines were N-(p-methoxyphenyl)enaminoketones (compounds IIa, b), an enaminoester (IIc), and a nitroenamine (IId). Acylation of compounds IIa-d with acryloyl chloride was found to occur with involvement of the NH group, resulting in formation of derivatives of N-aryl-3,4-dihydropyridone-2 compounds (IIIa-d).



R = COPh (IIa, IIIa, Va); COMe (IIb, IIIb); COOEt (IIc, IIIc); NO_2 (IId, IIId, Vb)

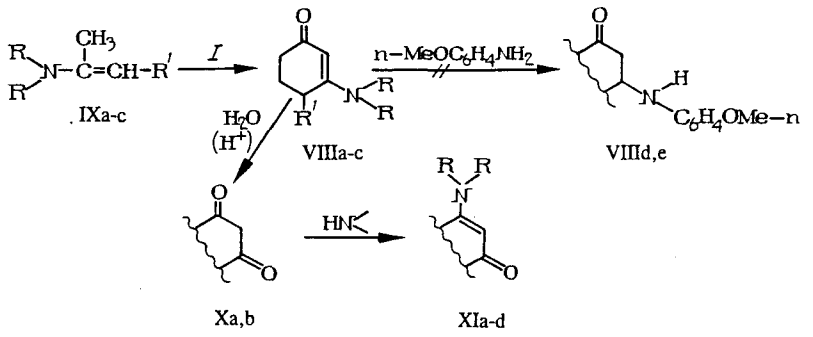
The structure of the products was determined by elemental analysis and mass spectroscopy, and, for pyridines IIIa-d, also by ^1H NMR spectroscopy. Thus, the spectrum of compound IIIa in d_6-DMSO contained the signals (δ, ppm): 1.44 (s, 3H, Me), 2.61 (wide s, 4H, 3,4-CH_2-group), 3.77 (s, 3H, OMe), 7.06 (m, 4H, C_6H_4), 7.81 (m), 7.18 (m) (C_6H_5). In the spectrum of nitropyridone IIId, most signals were weak-shifted (δ, ppm): 2.06 (5, 3H, Me, J = 1.3 Hz), 2.5-3.12 (m, 4H, 3,4-CH_2-group), 3.79 (s, 3H, OMe), and 7.06 (m, 4H, C_6H_4), which was in good agreement with the proposed structures.

TsKhLS, S. Ordzhonikidze All-Russian Scientific-Chemicopharmaceutical Institute, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 28, No. 1, pp. 49-53, January, 1994. Original article submitted December 21, 1992.

0091-150X/94/2801-0070$12.50

A more detailed analysis of the interactions of compounds I and II showed, however, that the reaction could occur in two alternative directions, forming isomeric pyridones (III or IV). Actually, acylation of the enamines yielded both N- and C-acyl derivatives, and subsequent heterocyclization must in these cases form different pyridones (III or IV), though these are quite difficult to identify using NMR or mass spectra. Thus, using IIIa and IIId as examples, we studied the hydrolysis of these compounds (as enaminoamides) in acid conditions. The ^{1}H NMR spectra of the hydrolysis products (Va, b) in d_6-DMSO clearly showed that acylation of enamines II involved initial N-acylation* to form pyridone-2 derivatives (IIIa-d). In fact, the spectra of compounds Va, b contained signals from CH_2-group-adjacent methyne protons at 4.88 (5, 1H, CH) and 5.80 (m, 1H, CH), respectively, corresponding to the structures of Va, b rather than to IV (the complete spectral data are presented in the Experimental section).

The structure of V was also supported by the position of ^{1}H NMR signals of aliphatic CH_2 groups in the product obtained by heating pyridone IIIa with the acetal of dimethylacetamide. This formed the quinolone-2 derivative VIII with spectral data (δ, ppm): 2.68 (s, 6H, NMe_2), 3.80 (s, 3H, OMe), 2.58-2.80 (m, 4H, 3,4-CH_2-group), 5.66 and 6.28 (d, both 1H, 6,8-CH, J = 2.5 Hz), 7.12 (m, 4H, C_6H_4), 7.40 (m, 5H, C_6H_5).



NRR = morpholino (VIIIa,c; IXa,c; XIa,c; XIa,b); NMe_2 (VIIIb, IXb, XIb); NHC_6H_4OMe-p (XId); R^1 = COPh (VIIIa, b; IXa, Xa, XIa, b; XId); COOEt (VIIIc, IXc, Xb, XIc)

Transamination of cyclic enaminoketones (VIIIa-c) obtained by reaction of tertiary enaminocarbonyl compounds (IXa-c) with acryloyl chloride I could represent a new variant for synthesis of the N-arylenamines of 4-substituted cyclohexanedione-1,3 compounds (VIIId, e). Transamination of derivatives VIIIa-c could not in fact be obtained in the normal conditions, or in more stringent conditions. We attempted to carry out this reaction by another method: hydrolysis of enamines VIIIa-c to the corresponding cyclohexanediones (Xa, b) followed by interaction with p-anisidine. It was, however, evident that the reaction could now occur at position 1 and at position 3.† We thus carried out the reaction of cyclohexanedione-1,3 compounds Xa, b and p-anisidine and with aliphatic amines (dimethylamine, morpholine), and studied the spectra of the resulting compounds XIa-d,‡ comparing them with previously described enamine of dihydroresorcines VIIIa-c. ^{1}H NMR spectral data of the resulting compounds are shown in Table 1. Comparison of the data shown in Table 1 shows that amination of 4-substituted cyclohexanedione-1,3 compounds Xa, b with both aliphatic and aromatic amines clearly occurs at position 1, forming enaminoketones XIa-d.

Studies on the example of enaminoketone XIa interacting with p-anisidine in acetic acid showed that in this case (unlike those of the isomeric enaminoketones VIII) transamination did occur, although it was quite slow: N-arylenamine XId was obtained with a yield of 28%; we have previously obtained this compound from diketone Xa (see above).

*O-acylation with subsequent sigmatropic regrouping is possible at the first stage for enaminoketones.

†A report [4] appeared when the present studies had been finished, in which the example of the reactions of 4,5-disubstituted derivatives of cyclohexanedione-1,3 was used to show that the reaction with amines occurs at position 1. However, detailed evidence of this supposition was not provided.

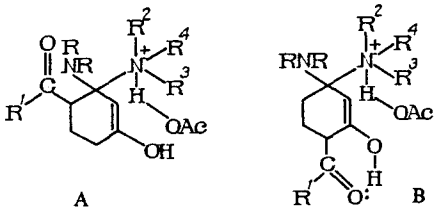
‡XIc was more easily synthesized in a one-step reaction from the β-morpholinocroton ester IVc and acryloyl chloride followed by hydrolysis and reaction with morpholine without purification of intermediates VIIIc and Xb (see Experimental).

TABLE 1. ^{1}H NMR Spectra of Compounds VIIIa-c and XIa-d, δ, ppm (d_6-DMSO)

Compound	2-H	4-H (for VIII), 6-H (for XI)	5,6-CH_2 (for VIII); 4,5-CH_2 (for XI)	COOEt	Morpholino residue	NMe_2	Ph	p-Anisidine residue
VIIIa	5,25	5.02 (m), J_1 = 6.0 Hz, J_2 = 2.2 Hz	1,8—2,5 (m)	—	3,10 (m), 3,51 (m)	—	7,50—8,10 (m)	—
XIa	5,14 (s)	4.42 (q) J_1 = 10 Hz, J_2 = 5 Hz	1,90—2,86 (m)	—	3,31 (m) 3,64 (m)	—	7,47—7,98 (m)	—
VIIIb	5,05 (s)	5.11 (q), J_1 = 6.3 Hz, J_2 = 2 Hz	1,62—2,44 (m)	—	—	2,88 (c)	7,60—8,14 (m)	—
XIb	4,88 (s)	4.32 (q), J_1 = 10 Hz, J_2 = 5.0 Hz	1,8—2,25 (m)	—	—	2,98 (br. (s)	7,28—8,06 (m)	
VIIIc	5,13 (s)	3.92* (asymmetrical quartet)	2,07—2,27 (m)	1,20 (t) 4,15 (m)	3,26 (m) 3,60 (t)	—	—	—
XIc	5,1 (s)	3.25 (q), J_1 = 9.3 Hz, J_2 = 6.3 Hz	2,04—2,68 (m)	1,18 (t) 4,07 (q)	3,31 (m) 3,62 (t)	—	—	—
XId	5,14 (s)	4.50 (q)	1,90—2,82 (m)	—	—	—	7,74—7,94 (m)	3,78 — (s. OMe), 8,90 (s. NH) 7,0 (m, C_6H_4)

*Because of the closeness of the chemical shifts of the protons at C^3, the system of ABKh signals (C^3H_2 and C^4H) has a signal at position 4 in form of an asymmetrical quartet.

The reason for the very different behavior of enamines VIII and XI in the transamination reaction could be as follows: since transamination with aromatic amines occurs in acetic acid, the reactive part is most likely to be the O-protonated form of the enaminoketone (5).* Literature data [6] indicate that the transition states of the transamination reaction may be characterized by structures A (from VIII) and B (from XI):



A B

Destabilization of (A) by spatial factors and stabilization of (B) by an intramolecular hydrogen bond clearly leads to a significant acceleration of the transamination of XI as compared with that of VIII.

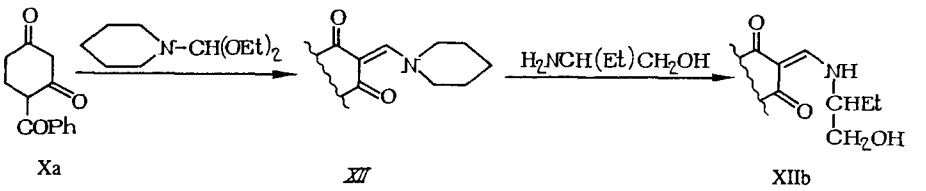
The possibility of synthesizing various enamines from the cyclic asymmetrical diketones X, as described here, is not limited by their use in the preparation of enaminoketones of the XI type. We demonstrated another possible approach using compound Xa as an example. The interaction of compound Xa with the diethylacetal of N-formylpiperidine yielded enaminoketone XIIa, whose structure was unambiguously determined from its ^{1}H NMR spectrum (d_6-DMSO, δ, ppm): 1.62, 3.46, 3.71 (wide signals from the piperidine ring, 1OH), 4.61 (q, 1H, J_1 = 5 Hz, 4-H), 1.78-3.64 (m, 4H, 5,6-CH_2-group), 7.97, 7.55 (m, C_6H_5), and 7.95 (s, 1H, α-CH-enamine). The presence of only one group of signals evidently shows that there is a low energy barrier between the two isomeric forms (Z, E), relative to the enamine double bond [7, 8]. In the case of the secondary enamine XIIb, prepared by transamination of compound XIIa, the spectrum contained two geometrical isomers (δ, ppm) (α-CH): 8.17 and 8.21 (two d, J = 14 Hz) (see Experimental for a description of the spectrum), which is due to stabilization of both forms by intramolecular hydrogen bonds.

*The essence of this point is not altered if the reaction also involves the C-protonated form which, after attachment of the amine, can undergo enolization.

TABLE 2. Properties of Compounds IIIa-d, Va, b, VII, Xa, b, XIa-d, and XIIa, b

Compound	Melting temperature, °C	Yield, %	Elemental formula	Mass, M^+
IIIa	130—2	85,6	$C_{20}H_{19}NO_3$	321
IIIb	118—20	58,4	$C_{15}H_{17}NO_3$	
IIIc	131—3	45,0	$C_{16}H_{19}NO_4$	
IIId	151—3	71,3	$C_{13}H_{14}N_2O_4$	262
Va	122	68,0	$C_{20}H_{21}NO_4$	339
Vb	108—10	75,0	$C_{13}H_{16}N_2O_5$	280
VII	156—8	34,9	$C_{24}H_{24}N_2O_2$	372
Xa	156—9	68,4	$C_{13}H_{12}O_3$	216
Xb	Oil	62,2	$C_9H_{12}O_4$	184
XIa	165—7	77,3	$C_{17}H_{19}NO_3$	285
XIb	91—4	26,7	$C_{15}H_{17}NO_2$	243
XIc	78—80	49,0	$C_{13}H_{19}NO_4$	
XId	155—7	52,6 46,7 28,0	$C_{20}H_{19}NO_3$	321
XIIa	147—9	85,9	$C_{19}H_{21}NO_3$	311
XIIb	128—30	83,3	$C_{18}H_{21}NO_4$	315

Notes. Compounds IIIa, d, Va, VII, and XIa were recrystallized from alcohol, IIIb from CCl_4, IIIc from acetone, Vb from $CHCl_3$, Xa from dichloroethane, XIb-d and XIIa from ethyl acetate, and XIIb from a mixture of alcohol and hexane.



Xa XII XIIb

Thus, these studies have demonstrated the synthesis of a number of new enaminoketones, which might be of use in a variety of syntheses for heterocyclic compounds, and, in particular, for the synthesis of indoles and benzofurans using Nenicescu reactions, which have already been used to prepare a large group of biologically active compounds, including therapeutic agents [9-11].

EXPERIMENTAL

^{1}H NMR spectra were taken on a Varian X-linked-200 spectrometer, using TMS as the internal standard, and d_6-DMSO as the solvent. Mass spectra were obtained on a Varian (FRG) chromato-mass-spectrometer with direct sample injection into the ion flow. Reactions and individual substances were monitored chromatographically on Silufol UV-254 plates in a benzene–methanol (9:1) system, with visualization in UV light. The properties of compounds are shown in Tables 1 and 2. Experimentally determined elemental analyses corresponded to calculated values.

1-(p-Methoxyphenyl)-5-benzoyl-6-methyl-3,4-dihydropyridone-2 (IIIa). A solution of 11.75 g (44 mmoles) of enamine IIa and 4.0 g (44 mmoles) of acryloyl chloride I in 170 ml of dry benzene was boiled for 3 h. Triethylamine (4.4 g, 44 mmoles) was added dropwise, and boiling was continued for another 30 min. The reaction was filtered hot and the filtrate was evaporated. The residue was taken up in ether, and crystals were filtered, washed with ether, and dried. the yield was 12.1 g of compound IIIa. Compounds IIIb, c were prepared by the same method.

2,6-Dioxo-3-nitro-6-(p-methoxyphenylamino)hexane (Vb). A mixture of 1.31 g (5 mmoles) of compound IIId, 0.86 g (5 mmoles) of p-toluenesulfonic acid, and 5 ml of acetic acid was stirred for 4 h at 20°C. The resulting solution was diluted with 100 ml of water, and the precipitate was filtered, washed with water, and dried. The yield was 1.05 g of compound Vb.

The ^1H NMR spectrum (d_6-DMSO, δ, ppm) was: 2.31 (s, $COCH_3$), 2.39 (s, 4H, CH_2-group), 3.70 (s, OCH_3), 5.80 (s, CH), 7.15 (m, C_6H_4), 9.84 (NH). Compound Va was prepared by the same method, and its ^1H spectral data (d_6-DMSO, δ, ppm) were: 2.15 (s, $COCH_2$), 2.15 (m, 4H, CH_2-group), 3.70 (OCH_3), 4.88 (t, CH), 7.14 (m, C_6H_4), 7.56-8.08 (m, C_6H_5), 9.73 (NH).

1-(p-Methoxyphenyl)-2-oxo-5-phenyl-7-dimethylamino-1,2,3,4-tetrahydroquinoline (VII). A mixture of 3.21 g (10 mmoles) of pyridine IIIa and 16.1 g (100 mmoles) of the diethyl acetal of dimethylacetamide was boiled for 1 day. The reaction was diluted with 100 ml of water and the precipitate was filtered, washed with water, dried, and recrystallized from alcohol with activated charcoal. The yield was 1.3 g of compound VII.

4-Benzoylcyclohexanedione-1,3 (Xa). A solution of 25.5 g (105 mmoles) of 3-dimethylamino-4-benzoylcyclohexane-2-one (VIIIb) mixed with 150 ml of acetic acid and 250 ml of water was boiled for 3 h, diluted with 2 liters of water, and kept for 20 h at 4°C. The resulting precipitate was filtered, washed with water, and dried. The yield was 15.5 g of compound Xa. The ^1H NMR spectral data (d_6-DMSO, δ, ppm) were: 2.12 (m, 6-CH_2), 2.40 (m, 5-CH_2), 4.54 (q, 4-H, J_1 = 5.5 Hz, J_2 = 9 Hz), 5.28 (s, 2-H), 7.49-8.0 (C_6H_5), 11.35 (3-OH).

4-Ethoxycarbonylcyclohexanedione-1,3 (Xb). A solution of 25.3 g (100 mmoles) of compound VIIIc mixed with 50 ml of acetic acid and 50 ml of water was boiled for 1 h, and diluted with 200 ml of water; the resulting oil was extracted with ethyl acetate, washed with water, dried over $MgSO_4$, and evaporated. The clear oil was dried over KOH in a desiccator. The yield was 11.6 g of compound Xb in the form of colorless oily crystals.

3-Morpholino-6-benzoylcyclohexen-2-one (XIa). A solution of 9.5 g (44 mmoles) of compound Xa and 3.8 g (44 mmoles) of morpholine in 300 ml of dry benzene containing catalytic quantities of p-toluenesulfonic acid was boiled in a Dine–Stark apparatus for 1.5 h. The benzene was evaporated and the residue was recrystallized from alcohol. The yield was 9.7 g of compound XIa.

3-Dimethylamino-6-benzoylcyclohexen-2-one (XIb). Dimethylamine was passed into a boiling solution of 2.16 g (10 mmoles) of compound Xa in 250 ml of dry benzene containing catalytic quantities of p-toluenesulfonic acid until the initial TLC spot disappeared (1-1.5 h). The benzene was evaporated and the residue was dissolved in chloroform, and chromatographed on a column containing silica gel, eluted with a mixture of chloroform and alcohol (8:2). Fractions containing the main product were evaporated and the resulting oil was taken up in ethyl acetate, filtered, washed with ether, and dried. The yield was 0.65 g of compound XIb.

3-Morpholino-6-ethoxycarbonylcyclohexen-2-one (XIc). a) A solution of 16.2 g (180 mmoles) of acryloyl chloride I in 100 ml of dry benzene was added dropwise over 3 h, with mixing, to a boiling solution of 36.1 g (180 mmoles) of morpholinocrotonic ester (IXc) in 300 ml of dry benzene. Triethylamine (18 g, 180 mmoles) was added dropwise to the boiling reaction, and boiling was continued for 30 min. The reaction mix was filtered hot, and the precipitate was washed on the filter with 100 ml of hot benzene, and the filtrate was evaporated. The residue was dissolved in a mixture of 400 ml of acetic acid and 400 ml of water and boiled for 2 h. The residue was dissolved in 300 ml of benzene, and the solution was supplemented with 15.6 g (180 mmoles) of morpholine and catalytic quantities of p-toluenesulfonic acid. The reaction was boiled in a Dine–Stark apparatus for 2 h. The solution was evaporated and the residue was recrystallized from ethyl acetate. The yield was 23.3 g of compound XIc.

b) Compound XIc was prepared by the same method as compound XIb, from diketone Xb. A mixture of samples from this method and from method (a) did not show depression of the melting temperature.

3-(p-Methoxyphenylamino)-6-benzoylcyclohexen-2-one (XId). a) A solution of 2.16 g (10 mmoles) of compound Xa and 1.23 g (10 mmoles) of p-anisidine in 250 ml of dry benzene was boiled in a Dine–Stark apparatus for 15 h. The solution was evaporated to a volume of 50 ml, cooled, and the precipitate was filtered, washed with benzene and petroleum ether, and recrystallized from benzene. The yield was 1.5 g of compound XId.

b) A mixture of 1.43 g (5 mmoles) of compound XIa and 0.65 g of p-anisidine in 25 ml of acetic acid was boiled for 6 h. The reaction was diluted with water, and the precipitate was filtered, washed with water, dried, and recrystallized from ethyl acetate. The yield was 0.45 g of compound XId. A mixed sample containing material from methods (a) and (b) did not show depression of the melting temperature.

2-Piperidonemethylene-4-benzoylcyclohexanedione-1,3 (XIIa). A mixture of 3.4 g (16 mmoles) of compound Xa and 6.0 g (32 mmoles) of the diethyl acetal of N-formylpiperidine in 60 ml of benzene was boiled for 2 h. The benzene was evaporated, and the residue was recrystallized from ethyl acetate. The yield was 4.2 g of compound XIIa.

2-(α-Hydroxymethylpropylaminomethylene)-4-benzoylcyclohexanedione-1,3 (XIIb). A solution of 2.5 g (8 mmoles of compound XIIa, 6.9 g (80 mmoles) of 2-aminobutanol, and 1.4 g (8 mmoles) of p-toluenesulfonic acid in 60 ml of

dimethylformamide was mixed for 4 h at 20°C. The solvent was evaporated and the residue was recrystallized from a mixture of hexane and ethanol. The yield was 2.0 g of compound XIIb. The ^1H NMR spectral data ($CDCl_3$, δ, ppm) were: 0.95 (q, CH_2CH_3), 0.92 (q, CH_2CH_3), 1.6-3.26 (m, 5,6-CH_2-group), 3.26-3.64 (m, CH_2OH), 4.44 (m, 4-H), 8.21 (d), 8.17 (d) (J = 14 Hz), 8.0 (m), 7.33 (m) (C_6H_5) 10.89 (2 wide m, NH).

REFERENCES

1. P. W. Hickmott and G. Sheppard, J. Chem. Soc. (C), No. 11, 2113 (1971).
2. P. W. Hickmott and G. Sheppard, J. Chem. Soc. Perkin Trans., **1**, No. 8, 1038 (1972).
3. V. G. Granik, A. M. Zhidkova, R. G. Glushkov, et al., Khim. Geterotsikl. Soedin., No. 10, 1348 (1977).
4. J. Edafiogho, C. N. Hinko, H. Chang, et al., J. Med. Chem., **35**, No. 15, 2798 (1992).
5. L. V. Ershov and V. G. Granik, Khim. Geterotsikl. Soedin., No. 5, 656 (1985).
6. V. G. Granik, A. M. Zhidkova, I. S. Zhivotovskaya, et al., Zh. Obshch. Khim., **16**, No. 11, 2421 (1981).
7. J. Shvo and Shanan-Atidi, J. Am. Chem. Soc., **91**, 6684-6689 (1969).
8. N. P. Kostyuchenko, V. G. Granik, A. M. Zhidkova, et al., Khim. Geterotsikl. Soedin., No. 9, 1212 (1974).
9. V. M. Lyubchanskaya, G. A. Bogdanova, I. S. Nikolaeva, et al., Khim.-farm. Zh., No. 3, 34 (1990).
10. M. D. Mashkovskii, Therapeutic Agents [in Russian], Vol. 1, Moscow (1977), p. 418.
11. International Application WO 90/08135, published July 26, 1990.