was boiled for 5 h (the end of the reaction was determined by chromatography). After filtering off the potash, the mother liquor was evaporated to dryness, and the residue recrystallized from water. This produced 7.8 g compound V.

Compounds VI-XX were synthesized in an analogous manner.

EXPERIMENTAL (BIOLOGICAL)

The antiviral activities of these compounds were studied against the herpes simplex virus (HSV) Type I, strain L_2, in a primary culture of chicken embryo fibroblasts (CEF), as well as in experiments with cases of generalized herpes in mice produced by intranasal inoculation of the animals.

It was determined that compounds VI, VII, X-XII, and XVI-XVIII, XIX inhibit the reproduction of the HSV in the CEF cell culture. Compounds VI and XI at 10 μg/ml reduce the infection titer of the virus by 1.5 log TCD_{50} relative to a control culture: the remaining compounds reduce the infection titer by 1.0-1.25 log TCD_{50} at concentrations from 5 to 10 μg/ml. For compound XI only the chemotherapeutic index was equal to 4; for the other active compounds, it did not exceed 2.

The activities of compounds VI and XI were studied against the generalized herpes cases in mice. Medicinal properties were not established.

LITERATURE CITED

1. V. A. Azimov, V. G. Granik, S. I. Grizik, et al., Khim.-farm. Zh., 19, No. 8, 947 (1985).
2. A. N. Grinev, V. I. Shvedov, and E. K. Panisheva, Zh. Org. Khim., 1, No. 1, 2051 (1965).
3. A. N. Grinev, E. K. Panisheva, A. A. Cherkasova, et al., Khim.-farm. Zh., 21, No. 3, 332 (1987).
4. A. N. Grinev, E. K. Panisheva, I. S. Nikolaeva, et al., Khim.-farm. Zh., 21, No. 5, 575 (1987).
5. E. K. Panisheva, N. I. Mikerova, I. S. Nikolaeva, et al., Khim.-farm. Zh., 22, No. 12, 1455 (1988).
6. N. Z. Tugusheva, Enaminoamides in the Synthesis of Condensed Azoheterocycles [in Russian], Dissertation in Chemistry, Moscow (1989).
7. L. D. Markley, Y. C. Tong, J. K. Dulworth, et al., J. Med. Chem., 29, 427 (1986).
8. E. C. Taylor and A. J. Crovetti, J. Org. Chem., 19, 1633 (1954).

SYNTHESIS AND BIOLOGICAL ACTIVITY OF BENZOYLMETHYLTHIO DERIVATIVES OF PYRIDINE, QUINOLINE, AND ACRIDINE

A. A. Martynovskii, A. A. Brazhko,
V. G. Bulakh, T. V. Panasenko,
B. A. Samura, and E. A. Krasnykh

UDC 615.28:547.835].012.1

A wide range of pharmacological effects has been documented for thio derivatives of pyridine, quinoline, and acridine [6, 8, 9]. In this paper, we continue the search for biologically active compounds among the 2-thiopyridines, 2- and 4-thioquinolines, and 9-thioacridines through the synthesis and biological study of benzoylmethylthio derivatives of these heterocycles.

Hydrobromide salts of the 2-benzoylmethylthio derivatives of pyridine (X-XII) and quinoline (XIII-XV) were produced by alkylation of 2-mercaptopyridine or 2-mercaptoquinoline by substituted α-bromacetophenones in an organic solvent in the presence of alkali, followed by workup of the reaction products in hydrobromic acid. 2-Methyl-4-benzoylmethylthio-6-methoxyquinoline (XVI) was produced as the free base by alkylation of 2-methyl-4-mercapto-6-methoxyquinoline by α-bromacetophenone in DMF in the presence of alkali. The syntheses of methyl-, chloro-, dichloro-, and nitrochloro-9-benzoylmethylthioacridines (XVII-XXVII) were carried out by reacting 9-mercaptoacridines with phenacylbromides in acetone in the presence

Zaporozhski Institute of Medicine. Translated from Khimiko-farmatsevitcheskii Zhurnal, Vol. 25, No. 4, pp. 20-22, April, 1991. Original article submitted May 22, 1990.

0091-150X/91/2504-0240$12.50

TABLE 1. Properties of Compounds X-XXVII

Compound	Yield, %	mp, °C	Formula
X	69	221—3	$C_{13}H_{11}NOS \cdot HBr$
XI	72	212—4	$C_{13}H_{10}ClNOS \cdot HBr$
XII	75	215—7	$C_{13}H_{10}N_2O_3S \cdot HBr$
XIII	67	165—7	$C_{17}H_{13}NOS \cdot HBr$
XIV	65	147—9	$C_{17}N_{12}N_2O_3S \cdot HBr$
XV	63	87—8	$C_{17}H_{12}BrNOS \cdot HBr$
XVI	71	110—2	$C_{19}H_{17}NO_2S$
XVII	68	156—8	$C_{22}H_{17}NOS$
XVIII	66	149—51	$C_{21}H_{14}ClNOS$
XIX	69	140—2	$C_{21}H_{13}ClBrNOS$
XX	71	133—5	$C_{21}H_{13}ClN_2O_3S$
XXI	83	87—9	$C_{21}H_{14}ClNOS$
XXII	79	189—91	$C_{21}H_{13}ClN_2O_3S$
XXIII	72	145—7	$C_{21}H_{14}ClNOS$
XXIV	77	118—20	$C_{21}H_{13}Cl_2NOS$
XXV	73	217—9	$C_{21}H_{12}Cl_2N_2O_3S$
XXVI	67	230—2	$C_{21}H_{12}ClBrN_2O_3S$
XXVII	74	208—10	$C_{21}H_{13}ClN_2O_3S$

TABLE 2. Antimicrobial Activities of the Compounds Synthesized, Minimum Suppressing Concentrations (μg/ml)

Compound	Staphylococcus aureus	E. coli	Pseudomonas aeruginosa	Bac. anthracoides	Proteus vulgaris	Candida albicans
X	250	—	—	250	—	250
XIV	31,2	—	—	125	125	125
XV	62,5	—	—	125	125	62,5
XIX	62,5	250	250	31,2	—	62,5
XX	62,5	250	250	125	125	31,2
XXI	62,5	250	250	250	—	62,5
XXIII	62,5	—	—	125	—	62,5
XXV	125	250	250	125	—	31,2
Ethacridine lactate	31,2	31,2	250	125	125	62,5

of alkali. When solvents with higher boiling points are used instead of acetone (e.g., dioxane, DMF, DMSO), the corresponding acridone-9's were isolated as reaction products. This was confirmed by elemental analysis and IR spectroscopy. The structures of the products obtained were established by elemental analysis, IR, and mass spectroscopy. The purities of the compounds were confirmed by TLC.

RSH (I—IX)

↓ $BrCH_2COC_6H_4R'$

$RSCH_2COC_6H_4R'$ (X—XXVII)

R = pyridyl-2 (I, X-XII), quinolyl-2 (II, XIII-XV), 2-methyl-6-methoxyquinolyl-4 (III, XVI), 2-methylacridinyl-9 (IV, XVII), 2-chloroacridinyl-9 (V, XVIII-XX), 3-chloroacridinyl-9 (VI, XXI, XXII), 4-chloroacridinyl-9 (VII, XXIII), 2,6-dichloroacridinyl-9 (VIII, XXIV, XXV), 2-chloro-6-nitroacridinyl-9 (IX, XXVI, XXVII); R^1 = H (X, XIII, XVI-XVIII, XXI, XXIII, XXIV), 4-Cl (XI), 4-Br (XV, XIX, XXVI), 4-NO_2 (XII, XIV, XX, XXII, XXV, XXVII).

The IR spectra of the benzoylmethylthio derivatives of pyridine, quinoline, and acridine contain the following characteristic vibrational bands: C=O at 1710-1670 cm^{-1}, C=N at 1640-1625 cm^{-1}, C=C at 1610-1580 cm^{-1}, and $-CH_2-S-$ at 685-675 cm^{-1}. The IR spectra of hydrobromide derivatives of pyridine (X-XII) and quinoline (XIII-XV) contain broad vibrational bands of N^+H in the regions of 3100 and 2500 cm^{-1}.

Fragmentation of the benzoylmethylthiolated heterocycles by electron impact was used to confirm the proposed molecular structures, as well as to verify that the alkylation, when carried in an alkaline medium, takes place at the sulfur atom [4, 5]. The structures of the thio group substituents for these compounds were verified by the presence of the following ions in the mass spectra: $[M-C_6H_4-R^1]^+$, $[M-CO-C_6H_4-R^1]^+$, and $[M-CHCO-C_6H_4-R^1]^+$. Other ions, specific to the arylalkylsulfides, were also obsreved [10]. The syntheses of 2-mercaptopyridine, 2-mercaptoquinoline, and 4-mercapto-2-methyl-6-methoxyquinoline are described in [11]; the synthesis of 9-mercaptoacridine and its methyl-, chloro-, and nitro-substituted analogs is described in [4, 7]. The values found by elemental analysis agree with expected values. The properties of compounds X-XXVII are given in Table 1.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded using KBr pellets on a Model UR-20 spectrometer. Mass spectra were recorded on a Model MAT-311A spectrometer (Varian, USA). Thin-layer chromatography was performed using "Silufol UV-254" plates.

2-Benzoylmethylthiopyridine Hydrobromide (X). To a solution containing 1.06 g (0.01 mole) 2-mercaptopyridine in 80 ml of dioxane is added 0.01 mole α-bromoacetophenone in 20 ml of dioxane; the resulting mixture is allowed to stand at room temperature for 30 min. The resulting precipitate is removed, washed with water, and dried. The precipitate was treated with 2 ml of 45% hydrobromic acid and 50 ml of ether, and allowed to stand at room temperature

TABLE 3. Acute Toxicities, Diuretic, and Neurotropic Activities of the Compounds Synthesized

Compound	LD_{50}, mg/kg	Diuresis (4 h), relative to the control (%)	Duration of narcotic effect, relative to the control (%)
X	135±13,5	118	79
XIII	185±18,7	129	75
XIV	202±23,5	53	116
XVI	176±14,7	59	105
Hypothiazide	—	220	—
Aminazine	—	—	137

for 2 h. The solid residue was filtered, washed with acetone, and dried. The product was recrystallized from ethanol.

Compounds XI and XII are produced in a manner analogous to that used for compound X.

2-Benzoylmethylthioquinoline Hydrobromide (XIII). To a solution containing 1.61 g (0.01 mole) 2-mercaptoquinoline in 30 ml of ethanol is added 0.56 g (0.01 mole) potassium hydroxide and 2.0 g (0.01 mole) α-bromoacetophenone. The reaction mixture was heated in a boiling water bath for 30 min, cooled, and diluted with water. The oily residue thus formed is extracted into chloroform. The chloroform solution is evaporated over calcium chloride to a dry residue. This residue is treated with 50 ml of ether and 20 ml of 45% hydrobromic aid. The product is separated, washed with acetone, and dried. Yellow needles are obtained upon recrystallization from ethanol.

Compounds XIV and XV are produced in a manner analogous to that used for compound XIII.

2-Methyl-4-benzoylmethylthio-6-methoxyquinoline (XVI). To a solution containing 2.05 g (0.01 mole) of 2-methyl-4-mercapto-6-methoxyquinoline in 30 ml DMF is added 0.56 g (0.01 mole) potassium hydroxide, and 2.0 g (0.01 mol) α-bromoacetophenone. The reaction mixture is boiled for 40 min, cooled, and diluted with water. The precipitate is isolated, washed with water, and dried. Yellow plates are obtained upon recrystallization from ethanol.

3-Chloro-9-(p-nitrobenzoylmethylthio)acridine (XXII). To a solution containing 2.45 g (0.01 mole) of 3-chloro-9-mercaptoacridine in 80 ml acetone is added 0.4 g (0.01 mole) sodium hydroxide in 5 ml water, and 2.44 g (0.01 mole) of p-nitrophenacylbromide. The reaction mixture is heated in a water bath for 5-7 min, cooled, and poured into water. The resulting precipitate is isolated, dried, and recrystallized from ethanol.

Compounds XVII-XXI and XXIII-XVII are produced in a manner analogous to that used for compound XXII.

EXPERIMENTAL (BIOLOGICAL)

Microbiological studies of the substances produced were carried out on 6 strains of pathogenic bacteria and fungi by the method of two-fold serial cultivation on liquid nutrient (aminopeptide) media. An agar culture of microbes (500,000/ml) was injected daily to a liquid nutrient medium containing a known concentration of the compound of interest. The culture flask was thermostatted for 18 h, after which a visual determination of the minimum concentration required for microorganism growth inhibition was made based upon the turbidity of the culture flasks.

Acute toxicities were determined on mice weighing 18-24 g according to the method of Kerber [1]. Compounds were introduced intra-abdominally as 2% suspensions, stabilized with Tween-80. The effects of these compounds on kidney function were studied on rats (Vistar lineage) weighing 130-180 g according to the method given in [2]. Neurotropic activities of these compounds were studied by the method of prolongation of the effects of subnarcotic doses of barbiturates [3]. Compounds were introduced intra-abdominally into the rats at a dose rate of 0.1 (LD_{50}). The results of these studies are presented in Tables 2 and 3.

LD_{50} values for compounds XVII-XXVII fall within the dose range 110-320 mg/kg.

This study indicates that benzoylmethylthio derivatives of pyridine are weak antimicrobial agents (see Table 2), whereas the analogous derivatives of quinoline and acridine possess moderate antimicrobial activities against Staphylococcus aureus, Bacillus antracoides, and Candida albicans. The introduction of substituents onto the benzene ring of the phenacyl fragment does not substantially affect the antimicrobial activities of these compounds.

The hydrobromide salts of benzoylmethylthio derivatives of pyridine and quinoline (see Table 3) exhibit very little diuretic activity, and reduce the time period over which a narcotic medication is effective. The introduction of substituents (e.g., bromine atom, nitro group) onto the phenacylthio group's benzene ring in the benzoylmethylthio derivative of quinoline reduces the compound's diuretic activity, and results in a weak neuroleptic activity.

LITERATURE CITED

1. M. L. Belen'kii, Elements of the Quantitative Estimation of Pharmacological Effects [in Russian], 2nd edn., Leningrad (1963), pp. 49-54.
2. E. B. Berkhin, Khim.-farm. Zh., 11, No. 5, 3 (1977).
3. V. V. Gatsura, Methods of Primary Pharmacological Research for Biologically Active Compounds [in Russian], Moscow (1974).
4. P. B. Kurapov, A. A. Matynovskii, N. A. Klyuev, et al., Khim. Geterotsikl. Soedin., No. 11, 1519 (1984).
5. V. P. Maksimets and O. N. Popilin, Khim. Geterotsikl. Soedin., No. 2, 191 (1970).
6. A. A. Martynovskii, A. A. Brazhko, and E. N. Lushchinskaya, Farm. Zh., No. 6, 62 (1986).
7. A. A. Martynovskii, N. N. Malovichko, I. A. Mazur, et al., farm. Zh., No. 1, 33 (1986).
8. A. A. Martynovskii, N. N. Malovichko, I. V. Mel'nik, et al., Khim.-farm. Zh., 23, No. 4, 415 (1989).
9. A. I. Panasenko, A. A. Martynovskii, S. M. Drogovoz, et al., Farmakol. Toksikol., No. 6, 95 (1987).
10. A. A. Polyanova and R. A. Khemel'nitskii, Mass spectrometry in Organic Chemistry [in Russian], Leningrad (1972).
11. A. Albert and G. Barlin, J. Chem. Soc., 7, 2384 (1959).

SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 1-[2-(3,4-DIMETHOXYPHENYL)ETHYL]-4-HYDROXYPIPERIDINE DERIVATIVES

M. Z. Esenalieva, N. M. Kurbat, K. D. Praliev, V. I. Kozlovskii, V. K. Yu, and V. P. Vdovichenko

UDC 615.216.2+615.23]:547.823].012.1

The presence of a carbonyl group in N-substituted α-piperidines clears the way for the production of a number of different compounds with a wide range of pharmacological properties. The 1,4-substituted piperidines have local anesthetic [8], antiarrhythmic (Ropitoin) [9, 11], spasmolytic (Propiverin) [10, 12], and vasodilatory (Infenprodil) [5, 6] properties.

We selected 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidone (I) [7] as the starting material. This compound is reduced by $NaBH_4$ in i-PrOH to yield 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxypiperidine (II), which in turn is reacted with the mixture AcCl–Ac_2O to form 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-acetohydroxypiperidine hydrochloride (III). Compound II can also be reacted with the mixture EtCOCl–$(PtCO)_2O$ or PhCOCl to give the corresponding propionyl (IV) or benzoyl (V) derivatives respectively.

The structures of the compounds synthesized were established by IR spectroscopy. The IR spectrum of compound II is characterized by the –OH group's absorption band in the region of 3600 cm^{-1}; this band is absent in the spectra of the mixed esters III-V. The esters have strong absorption bands at 1730-1746 cm^{-1} corresponding to the mixed ester carbonyl group.

The yields and physical properties of compounds II-V are presented in Table 1.

EXPERIMENTAL (CHEMICAL)

IR spectra of the synthesized compounds were recorded using a Model UR-20 spectrophotometer as dilute solutions in CCl_4 or, in the case of the hydrochlorides, as KCl pellets. The progress of the reactions were monitored using Al_2O_3 plates (degree of activation II-III;

Institute of Chemistry, Academy of Sciences of the Kazakh SSR, Alma-Ata. Grodnenski Institute of Medicine.

Translated from Khimiko-farmatsevitcheskii Zhurnal, Vol. 25, No. 4, pp. 22-24, April, 1991. Original article submitted June 14, 1990.

0091-150X/91/2504-0243$12.50