2. N. S. Prostakov, A. V. Varlamov, G. A. Vasil'ev, et al., ibid., No. 1, 124-126 (1977).
3. J. T. Plati and W. Wenner, J. Org. Chem., 20, 1412-1424 (1955).
4. N. S. Prostakov, B. Kh. Sisimbina, V. P. Shalimov, et al., Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 22, No. 9, 1062-1066 (1979).
5. N. S. Prostakov, L. A. Gaivoronskaya, and G. Al'varado Urbina, Khim. Geterotsikl. Soedin., No. 8, 1087-1089 (1971).
6. N. S. Prostakov, K. Sudzhi, N. M. Mikhailova, et al., Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 24, No. 11, 1348-1350 (1981).
7. B. N. Halpern. Arch. Int. Pharmacodynam., 68, 339 (1942).

ANTIMICROBIAL PROPERTIES OF CERTAIN HETEROCYCLIC COMPOUNDS AND CHLOROMETHYL β-ARYLAMINOVINYL KETONES

N. G. Prodanchuk, I. V. Megera, and V. K. Patratii

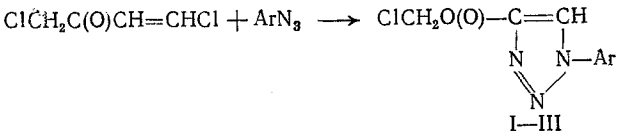
UDC 615.281:547.558.1].012.1

The appearance of microorganisms with medicinal stability hinders the success of therapy by antibiotics. Therefore, a search for new antimicrobial agents is at present an urgent problem [1, 2].

There is information in the literature on the antimicrobial activity of substituted 1,2,4-triazoles [3] and other heterocyclic systems [4]. It was interesting to study the antimicrobial properties of substituted 1,2,3-triazoles, pyrazoles, and isoxazoles.

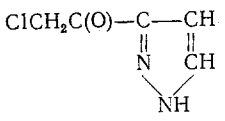
The reactions of β-chlorovinyl ketones were used for the synthesis of these compounds [5-7].

The reaction of chloromethyl β-chlorovinyl ketone with substituted phenyl azides on heating in benzene was used to synthesize 1-aryl-4-chloroacetyl-1,2,3-triazoles (I-III).

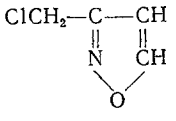


I: Ar = C_6H_5; II: p-$CH_3C_6H_4$; III: p-$CH_3OC_6H_4$.

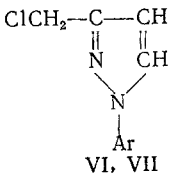
The reaction of chloromethyl β-chlorovinyl ketone with diazomethane and hydroxylamine gave, respectively, chloromethyl 3-pyrazolyl ketone (IV) and 3-chloromethylisoxazole (V), and with phenylhydrazine derivatives, it gave 1-aryl-3-chloromethylpyrazoles (VI, VII).



IV



V



VI, VII

VI: Ar = 4-$O_2NC_6H_4$; VII: 2,4-$(O_2N)_2C_6H_3$.

Compounds I-VII are crystalline, sparingly soluble substances, and compounds I-III have a lachrymating action.

In the IR spectra of compounds I-III there are bands in the 1160-1168 cm^{-1} region characteristic of 1,2,3-triazole rings [8], while for compounds (V-VII) there are bands at 1600,

The Chernovtsy Medicinal Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 2, pp. 173-175, February, 1984. Original article submitted July 25, 1983.

 0091-150X/84/1802-0108$08.50

TABLE 1. Characteristics of Compounds Obtained from Chloromethyl β-Chlorovinyl Ketone

Compound	Yield, %	mp, °C (from alcohol)	Found, %		Empirical formula	Calculated, %	
			Cl	N		Cl	N
I	45	158—160	16,08	19,09	$C_{10}H_8ClN_3O$	15,96	18,96
II	40	180—182	15,25	17,60	$C_{11}H_{10}ClN_3O$	15,04	17,82
III	40	186—188	14,15	16,49	$C_{11}H_{10}ClN_3O_2$	14,08	16,68
VI	65	178—179	15,10	17,90	$C_{10}H_8ClN_3O_2$	14,92	17,68
VII	60	106—108	12,60	19,74	$C_{10}H_7ClN_4O_4$	12,54	19,82
VIII	68	117	18,35	7,32	$C_{10}H_{10}ClNO$	18,16	7,18
IX	70	111—113	15,87	6,38	$C_{11}H_{12}ClNO$	16,90	6,68
X	70	143—144	—	4,21	$C_{10}H_9ClINO$*	—	4,35
XI	70	141—141,5	14,37	11,48	$C_{10}H_9ClN_2O_3$	14,73	11,64
XII	70	142—144	14,68	5,46	$C_{12}H_{12}ClNO_2$	14,91	5,88

*Total halogen, found 50.42%; calculated 50.08%.

1450, 1377, 1150, and 960 cm^{-1}, characteristic of isoxazole and pyrazole rings [9].

In the reaction of chloromethyl β-chlorovinyl ketone with aromatic and cyclic amines, the corresponding chloromethyl β-arylaminovinyl ketones (VIII-XII) and chloromethyl β-dialkylaminovinyl ketones (XIII,XIV) were synthesized.

$ClCH_2COCH{=}CHR$ (VIII—XIV) VIII: $R = NHC_6H_5$; IX: $R = NHC_6H_4CH_3$-p; X: $R = NHC_6H_4I$-p; XI: $R = NHC_6H_4NO_2$-p; XII: $R = NHC_6H_4COCH_3$-p; XIII: $R = N(CH_2CH_2)_2O$; XIV: $R = N(CH_2)_5$.

Compounds XIII and XIX are oily liquids, which cannot be distilled even at reduced pressure, although practically pure substances are obtained from an ether solution after evaporation of ether *in vacuo*. Their IR spectra contain carbonyl group bands at a frequency of 1690 cm^{-1}, an ethylene bond band at 1610 cm^{-1}, and the N—H bond appears at 3260-3214 cm^{-1}.

Data on compounds I-III and VI-XII are listed in Table 1.

The activity of the synthesized compounds toward certain types of bacteria and fungi was determined by the method of serial dilutions in a liquid culture medium. The results of the investigations showed that the antimicrobial activity of compound I-VII is observed mainly for gram-positive bacteria (the minimal suppressing concentrations with respect to *Staphylococcus aureus*, strain 209, are within 15.6-31.2 μg/ml, bactericidal concentrations — 31.2-62.5 μg/ml), and with respect to the *Bacillus anthracid*, strain 297 (minimal suppressing concentrations 15.6-62.5 μg/ml, bactericidal concentrations — 62.5-125 μg/ml). The activity of compounds I-III is influenced by the nature of the substituent in the phenyl ring, which leads not only to an increase in the activity, but also to a broadening of activity spectrum. Chloromethyl β-arylaminovinyl ketones VIII-XIV had a weak antimicrobial effect, and their bacteriostatic action appeared at concentrations of 125-250 μg/ml and the bactericidal action at concentrations of 250-500 μg/ml. Only the introduction of a piperidine residue into the molecule of chloromethyl β-arylaminovinyl ketone leads to some increase in the activity and broadening of the activity spectrum.

EXPERIMENTAL CHEMISTRY

1-Aryl-4-chloroacetyl-1,2,3-triazoles (I-III). These are obtained by one and the same procedure. A mixture of 2.7 g of phenylazide and 2.4 g of chloromethyl β-chlorovinyl ketone in 10 ml of dry benzene is heated for 10 h. To the precipitate 30 ml of dry ether are added. The precipitate is then filtered, washed with alcohol, and dried in air. The yield of compound I is 1.6 g.

Chloromethyl 2-Pyrazolyl Ketone (IV). A 4-g portion of chloromethyl β-chlorovinyl ketone is added, with cooling, to a cold and dry solution of diazomethane, obtained from 8 g of nitrosourea in 100 ml of ether. After a few hours the mixture is filtered, ether is evaporated, and the crystalline substance is treated with 5% sodium carbonate solution. The yield of compound IV is 3 g (75%), mp 119-120°C (from benzene). Found, %: C 24.40, N 19.50. $C_5H_5ClN_2O$. Calculated, %: C 24.52, N 19.37.

3-Chloromethylisoxazole (V) is obtained by the method described in [5].

1-p-Nitrophenyl-3-chloromethylpyrazole (VI). A mixture of 0.2 g of chloromethyl β-chlorovinyl ketone and 0.2 g of p-nitrophenylhydrazine in 10 ml of acetic acid is heated to boiling, and then left to stand for 24 h. An equal amount of water is added, and the precipitate obtained is separated and dried. Compound VII is obtained in a similar way.

Chloromethyl β-arylaminovinyl ketones (VIII-XII) are prepared by one and the same procedure. A 2.7-g portion of chloromethyl β-chlorovinyl ketone and 3.6 g of aniline in 50 ml of alcohol are mixed together. A colored precipitate is separated after 3-4 h. The yield of compound VIII is 2.7 g.

Chloromethyl β-Morpholino- and Piperidinovinyl Ketones (XIII, XIV). A 1.6-g portion of piperidine is added to a solution of 1.35 g of chloromethyl β-chlorovinyl ketone in 50 ml of ether. Piperidine hydrochloride precipitate is filtered, washed a few times with ether, and then the filtrate is evaporated *in vacuo* to yield an oily compound XIV in the residue. Compound XIII is obtained in a similar way.

LITERATURE CITED

1. S. D. Voropaeva, Antibiotiki, No. 5, 415-418 (1969).
2. I. I. Sidorchuk and E. I. Tishchenko, VNIIMI Nov. Lek. Prep. Ekspress Inform., No. 2, 21-25 (1979).
3. H. Nesvadba and H. Reishagen, Swiss Patent No. 617931 (1980); Ref. Zh. Khim., No. 23086 (1980).
4. I. I. Sidorchuk and M. I. Shevchuk, Fiziol. Akt. Veshchestva, No. 3, 52 (1971).
5. N. K. Kochetkov, A. N. Nesmeyanov, and N. A. Semenov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 87 (1952).
6. A. N. Nesmeyanov and N. K. Kochetkov, Dokl. Akad. Nauk SSSR, 77, 65 (1951).
7. A. N. Nesmeyanov, N. K. Kochetkov, and M. I. Rybinskaya, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 350 (1950).
8. G. R. Harvey, J. Org. Chem., 31, 1587 (1966).
9. Physical Methods in Chemistry of Heterocyclic Compounds [in Russian] (A. R. Katritskii, ed.), Moscow-Leningrad (1966).

SYNTHESIS AND ANTIVIRAL ACTIVITY OF SILVER AND COBALT SALTS OF p-AMINOBENZOSULFAMIDE DERIVATIVES

A. E. Mil'grom, A. S. Chegolya, L. N. Andrianova, O. I. Pesnya, E. I. Boreko, and L. K. Zaporozhets

UDC 615.281.8:[546.57+546.73].012.1

The silver and cobalt salts of some p-aminobenzosulfamide derivatives exhibit antimicrobial activity [1, 2] and are used in medicine. For example, a 15% colloidal dispersion of the silver salt of norsulfazole is used for the treatment of wounds [3]; the ointment dermazine, which contains micronized silver sulfadiazine, was recommended at the 1981 Moscow symposium "Clinical Value of Dermazine Preparations" for disinfecting and preventing infection in burns. The preparation was presented at the exhibition Medicine-81.

However, there are no reports of antiviral activity in this type of compound, and we have therefore studied the biological action of a series of silver and cobalt salts of p-aminobenzosulfamide derivatives (Ia-d and IIa-h).

$$p\text{-}H_2NC_6H_4SO_2NNaR + Me(NO_3)_n \longrightarrow \underset{\text{Ia-d, IIa-h}}{(p\text{-}H_2NC_6H_4SO_2\bar{N}R)_nMe^{n+}} + NaNO_3$$

Ia: R = 2.4-dimethyl-6-pyrimidinyl; Ib: R = 5-ethyl-1,3,4-thia-2-diazolyl; Ic: R = 3-methoxy-pyridazinyl; Id: R = acetyl; Ia-d: Me = Ag(1+), n = 1; IIa: R = 4-thiazolyl; IIb: R = 2-methoxy-6-pyrimidinyl; IIc: 2,4-dimethyl-6-pyrimidinyl; IId: R = 5-ethyl-1,3,4-thia-2-diazolyl; IIe: R = 3-methoxy-6-pyridazinyl; IIf: R = 3-methoxy-2-pyridinyl; IIg: R = 2,4-dimethoxy-6-pyrimidinyl; IIh: R = acetyl; IIa-h: Me=Co(2+), n = 2.

All-Union Scientific-Research Institute of Synthetic Fibers, Kalinin. Belorussian Scientific-Research Institute of Epidemiology and Microbiology, Minsk.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 2, pp. 175-178, February, 1984. Original article submitted May 16, 1983.

0091-150X/84/1802-0110$08.50