4. R. G. Melik-Ogandzhanyan, A. A. Arutyunyan, G. M. Stepanyan, et al., Khim.-farm. Zh., No. 9, 1095 (1989).
5. E. N. Padeiskaya, Methods of Experimental Chemotherapy [in Russian], Moscow (1971), p. 109.
6. G. M. Paronikyan, L. G. Akopyan, G. A. Darbinyan, and É. A. Tumasyan, Genetika, 13, No. 9, 1621-1625 (1977).
7. G. M. Paronikyan, L. G. Akopyan, T. R. Akopyan, and E. G. Paronikyan, Biol. Zh. Armenii, 32, No. 11, 1146-1150 (1979).
8. V. A. Chernov, Methods of Experimental Chemotherapy [in Russian], Moscow (1971), pp. 357-381.
9. R. J. Dubois, C. C. L. Lin, and B. J. Michel, J. Pharm. Sci., 64, 825-829 (1975).
10. J. R. Vaughan and R. L. Osato, J. Am. Chem. Soc., 74, 676-678 (1952).
11. P. F. Wiley and F. A. Mackellar, ibid., 92, 417-418 (1970).

SYNTHESIS, ANTITUMOR, AND ANTIMICROBIAL ACTIVITY OF N-SUBSTITUTED NITROFURYLVINYL(BUTADIENYL)-4-AMINO(HYDRAZINO)QUINOLINES

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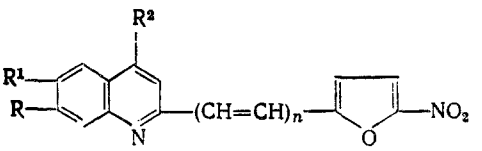
UDC 615.277.3+615.281]: 547.722].011.1

In continuation of searches [2, 4] for physiologically active nitrofurans, some novel N-substituted nitrofurylvinyl(and butadienyl)-4-amino(and hydrazino)quinolines have been obtained.



I—XIX

R = H (I—VII, XV—XVII), Cl (VIII—XIV, XVIII, XIX); R^1 = H (I, VI, VIII—XV, XVIII, XIX), OMe (II—V, VII, XVI, XVII); R^2 = $NHCH_2CH_2OH$ (I—III, IX, X), $NHCH_2CH_2CH_2OH$ (IV, V, XI, XII), $NHN(CH_2CH_2Cl)_2$ (VI, VII, XIV), $NHCH(CH_3)(CH_2)_3NEt_2$ (VIII), NHC_6H_4Cl-3 (XIII), Cl (XV—XIX); n = 1 (I, II, IV, VI—IX, XI, XIII—XVI, XVIII), 2 (III, V, X, XII, XVII, XIX); I—V, VIII—XII·$2H_3PO_4$

The nitrofurylvinylquinolines reported in the literature, with amino-, acetylamino-, chloro-, hydroxy-, ethoxy-, carboxy-, ethoxy-, carboxy- (sic — translator), or carbamoyl groups in the 3-, 4-, or 6-positions, were obtained only by the condensation of 2-methylquinoline or its derivatives with 5-nitrofurfural in acetic anhydride, acetic acid, or mixtures thereof [6, 7]. Attempts to obtain (I)-(XIV) by condensation resulted in the formation of small amounts only of the products of condensation of 5-nitrofurfural with the 2-methylquinoline component having a hydroxyalkylamino-group in the 4-position (I, II, IV, IX, XI).

The starting compounds used for the synthesis of (I-XIV) were the 4-hydroxy derivatives of nitrofurylvinyl(and butadientyl)quinolines, which have for the first time been reacted with thionyl chloride at 65-70°C to give preparative yields of the 4-chloro-compounds (XV-XIX), obtained by us previously by condensation [1, 5].

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 10, pp. 1226-1229, October, 1989. Original article submitted October 24, 1988.

 0091-150X/89/2310-0840$12.50

The conditions for the replacement of the chlorine in the 4-position of nitrofurylvinyl-(and butadienyl)quinolines by the amino- or hydrazino-groups varies with the nucleophile used. For example, the reaction of 4-chloro derivatives of nitrofurylvinyl(and butadienyl)-quinolines with substituted amines takes place in DMF at 140-150°C over 7-10 h. For the reaction to follow the normal course, a slight excess of the amine is required. Compounds (I-V) and (VIII-XII) were isolated as their phosphate salts, which are readily soluble in water, and (XIII) as the free base. The reaction of the 4-chloronitrofurylvinylquinolines succeeded only with dichlorodiethylhydrazine in glycol at 110-112°C (VI, VII, XIV). Under these conditions, hydrazine hydrate and dihydroxydiethylhydrazine failed to react. Compound (XVIII) was found to react with amino-compounds and dichlorodiethylhydrazine to give the mono-derivative.

The structures of the products were confirmed by their IR spectra. The spectra of (I-V) and (VIII-XIII) differed from those of the starting materials in showing absorption bands at 1000-1275 cm^{-1} and 3100-3360 cm^{-1} (ν_{C-N}). In addition, the spectra of (I-V) and (IX-XII) showed a narrow, strong band at 3400-5300 cm^{-1} (ν_{OH}). With (VI), (VII), and (XIV), absorption was seen at 3370-3400 cm^{-1} (ν_{C-N}).

Studies of the biological activity of (I-XIV) were preceded by measurement of their acute toxicities, which were highly dependent on the type of substituent in the 4-position of the quinoline ring. The moxt toxic compounds were (VI-VIII) and (XIV), while (I-V) and (IX-XIII) were less toxic. For instance, the LD_{50} of (VIII) was 28 mg/kg, whereas that of (XI) was 440 mg/kg.

The antitumor activity of (I-XIV) was examined in several test systems. The criteria adopted for activity were the percentage inhibition of tumor growth, and the increase in the life span of the tumor-bearing animals. In studies of the antitumor properties it was found that (I-XIV) had a slight effect on the growth of the Jensen sarcoma, sarcoma 45, sarcoma AK, carcinoma NK, and Walker's carcinosarcoma (growth inhibition not greater than 30%). Hepatic alveolar mucous cancer PC-1, Pliss lymphosarcoma, and sarcoma 180 were insensitive to these compounds. Experiments in vitro showed that (I-V) and (VIII-XII) had a powerful inhibitory effect on the Ehrlich ascitic tumor cells (100% death of the tumor cells was seen using 0.01 M solutions of the compounds, but 100% survival with 0.0001 M solutions). These compounds in vitro were as active as the alkylating drug novoembiquin. Tests in vivo showed that the Ehrlich ascitic tumor and lymphatic leukemia L5178 were most sensitive to these compounds. The introduction of a methoxy-group into the 6-position of the quinoline ring, or increasing conjugation by introducing an additional vinylene group, resulted in a drop in activity. Compound (XI) was highly active against Ehrlich's ascitic tumor, prolonging the life span of mice by 82%. Ehrlich's ascitic tumor and lymphatic leukemias L5178 and L5178Y were insensitive to (XIII).

Of the starting 4-chloro-compounds, (XV-XIX) showed slight activity against the Ehrlich ascitic tumor (extending the life span of mice by 40-45%).

The antimicrobial activity of (I-V) and (VII-XIII) in vitro is dependent on the substituent in the quinoline ring, and the length of the conjugated chain. Introduction of an additional —CH=CH— group results in a decrease in activity. The least active compounds against pathogenic microorganisms were those with an aminoethanol group in the 4-position (I-III, IX, X) or a methoxy group in the 6-position (IV, V). The most interesting compound was (XI), which, in addition to antitumor activity, showed antimicrobial properties (the minimum bacteriostatic concentration against Staphylococcus aureau 209-P was 0.31 μg/ml, Streptococcus hemolyticus 295 1.56 μg/ml, Diplococcus pneumoniae 1 0.78 μg/ml, B. anthracoides 0.62 μg/ml, E. coli 675 3.12 μg/ml, and Sh. flexneri 2a 3.12 μg/ml).

Examination of the radiosensitizing properties of (I-V) and (VIII-XII) in comparison with those of azomethine derivatives of nitrofuran and metronidazole showed them to be less active. For example, the sensitizing factor for 5-nitrofurfural oxime was 1.5, metronidazole 1.45-1.5, and (XI) 1.0.

These biological test results show that the antitumor and antimicrobial activity of these compounds is dependent on the length of the conjugated chain, and the type of substituent in the quinoline ring.

TABLE 1. Physicochemical Properties of (I-XIV)

Compound	Yield, %	mp, °C (decomp.)	Empirical formula
I	48,0	80—2	$C_{17}H_{15}N_3O_4 \cdot 2H_3PO_4$
II	59,8	106—9	$C_{18}H_{17}N_3O_5 \cdot 2H_3PO_4$
III	63,1	94—7	$C_{20}H_{19}N_3O_5 \cdot 2H_3PO_4$
IV	56,2	83—6	$C_{19}H_{19}N_3O_5 \cdot 2H_3PO_4$
V	61,2	98—101	$C_{21}H_{22}N_3O_5 \cdot 2H_3PO_4$
VI	49,7	263—5	$C_{19}H_{18}Cl_2N_4O_3$
VII	61,3	277—9	$C_{20}H_{20}Cl_2N_4O_4$
VIII	64,6	135—7	$C_{24}H_{29}ClN_4O_3 \cdot 2H_3PO_4$
IX	62,7	102—4	$C_{17}H_{14}ClN_3O_4 \cdot 2H_3PO_4$
X	61,9	103—5	$C_{19}H_{16}ClN_3O_4 \cdot 2H_3PO_4$
XI	59,8	99—103	$C_{18}H_{16}ClN_3O_4 \cdot 2H_3PO_4$
XII	63,9	96—9	$C_{20}H_{18}ClN_3O_4 \cdot 2H_3PO_4$
XIII	67,2	283—5	$C_{21}H_{15}Cl_2N_3O_3$
XIV	61,3	277—9	$C_{20}H_{20}Cl_2N_4O_4$

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a Specord-75 (C. Zeiss, East Germany) in thin layers (in Vaseline grease, Nujol, and hexachlorobutadiene). The properties of the compounds obtained are shown in Table 1. The elemental analyses were in agreement with the calculated values.

2-[2-(5-Nitro-2-furyl)vinyl]-4-(1-diethylamino-4-methylbutylamino)-7-chloroquinoline Diphosphate (VIII). To a mixture of 3.35 g (0.01 mole) of (XVIII) and 2.37 g (0.015 mole) of 1-diethylamino-4-aminopentane was added 15 ml of DMF. The mixture was stirred for 7-8 h at 140-145°C, cooled, and extracted with 300 ml of chloroform. The chloroform solution was washed with water until neutral, dried over anhydrous potassium carbonate, the solvent removed under reduced pressure, the residue dissolved in 250 ml of acetone, and the resulting solution of the free base passed through alumina, washed with acetone, and eluted with sufficient acetone (~300 ml). The acetone soluton was treated with 1% H_3PO_4 to pH 3.0-3.6, and the solid filtered off, washed with acetone, and dried in a vacuum desiccator over anhydrous calcium chloride.

Compounds (I-V) and (IX-XII) were obtained similarly.

2-[2-(5-Nitro-2-furyl)vinyl]-4-(3-chloroanilino)-7-chloroquinoline (XIII). A mixture of 3.35 g (0.01 mole) of (XVIII), 1.27 g (0.01 mole) of 3-chloroaniline, and 15 ml of DMF was stirred for 10 h at 140-145°C, cooled, and the solid filtered off and recrystallized from DMF.

2-[2-(5-Nitro-2-furyl)vinyl]-4-[N,N-di-(2-chloroethyl)hydrazino]quinoline (VI). A mixture of 1.93 g (0.01 mole) of N,N-di-(2-chloroethyl)hydrazine hydrochloride, 3 g (0.01 mole) of (XV), and 90 ml of glycol was heated at 100-110°C for 2-3 h, cooled, 10 ml of 2% sodium bicarbonate added, and the solid filtered off, washed with water followed by alcohol, and recrystallized from aqueous DMF. If no solid separated following addition of sodium bicarbonate, the mixture was poured into crushed ice, thoroughly stirred, and the solid filtered off and washed with alcohol. Compounds (VII) and (XIV) were obtained similarly.

2-[2-(5-Nitro-2-furyl)vinyl]-4-chloroquinoline (XV). A mixture of 53.6 g (0.2 mole) of 2-[2-(5-nitro-2-furyl)vinyl]-4-hydroxyquinoline and 89.6 g (0.8 mole) of thionyl chloride was kept at 65-70°C for 20-30 min. It was then cooled, the solid filtered off, washed on the filter with chloroform, and recrystallized from DMF to give 59.1 g (98.5% of theory) of (XV).

Obtained similarly were (XVI), (XVII), (XVIII), and (XIX), in yields of 96.4, 78.6, 97.8, and 82%, respectively.

EXPERIMENTAL (PHARMACOLOGY)

The acute toxicities of the compounds were determined in mongrel white mice weighing 18-22 g, in a single intraperitoneal dose. Each dose was tested on at least six mice, which were kept under observation for 21 days. The acute toxicities were assessed quantitatively by their LD_{50} values, calculated by the method of Litchfield and Wilcoxon, supplemented by calculation of the confidence limits using the nomogram developed by Z. Roth, for $P \geq 0.05$.

The antitumor activity of (I-XIX) was examined in mongrel white rats weighing 80-140 g, and mice weighing 18-22 g. The rats were implanted with Walker carcinosarcoma, Jensen sar-

coma, sarcoma 45, hepatic alveolar cancer PC-1, and Pliss lymphosarcoma. The mice were implanted subcutaneously with sarcoma 180 and carcinoma NK. Treatment of the animals with the rapidly developing Walker carcinoma, sarcoma 180, and carcinoma NK commenced after 24 h, and animals with the Jensen sarcoma, PC-1 tumor, and Pliss lymphosarcoma 6 days following implantation of the tumor. Ten animals were taken both for the tests and the control. In addition, the antitumor activity against the Ehrlich ascitic tumor, lymphatic leukemia L5178 and L5178Y, and sarcoma 37 was examined by the method of Lukevits et al. [3].

Antimicrobial activity was assessed by the method of Sukhova et al. [5].

The radiosensitizing activity was assessed using the chromosomal aberration method (bridges and fragments). The activity was assessed from the numbers of cells with chromosomal aberrations in cells of the NK/L ascitic tumor in mice following treatment with the nitrofuran compounds and irradiation on the 7th-8th day of development of the tumor, when a high degree of hypoxia therein had been reached.

LITERATURE CITED

1. S. A. Giller, M. Yu. Lidak, N. N. Sukhova, and K. K. Venter, Khim. Geterotsikl. Soedin., No. 2, 253-255 (1976).
2. A. A. Zidermane, I. M. Kravchenko, A. Zh. Dauvarte, et al., Farmakol. Toksikol., No. 6, 711-714 (1970).
3. É. Lukevits, T. V. Lapina, N. M. Sukhova, et al., Khim.-farm. Zh., 15, No. 11, 53-56 (1981).
4. N. M. Sukhova, K. K. Medne, and M. Yu. Lidak, ibid., 4, No. 9, 21-22 (1970).
5. N. M. Sukhova, M. Yu. Lidak, L. V. Kruzmetra, and A. Ya. Zile, ibid., 16, No. 12, 55-58 (1982).
6. K. Kiura, T. Oohashi, I. Okada, et al., Yakugaku Zasshi, 83, No. 12, 1129-1131 (1963).
7. K. Miura, M. Ikeda, T. Oohashi, et al., ibid., 85, No. 4, 289-298 (1965).

SYNTHESIS, AND CYTOSTATIC AND TUBERCULOSTATIC ACTIVITY OF UNSYMMETRICAL AZINES OF N-ARYLACETYLFORMAMIDOXIMES

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UDC 615.277.3.012.1

Some aldehyde and ketone azines are known to possess biological activity of various types [4]. For example, furfural azine displays antitumor activity [8]. It has been reported [4] that N-arylacetylformamidoximes and their derivatives can inhibit significantly the growth of experimental tumors in animals. Tuberculostatic activity has been found in N-arylacetylformamidoxime thiosemicarbazones [7]. In order to examine their biological activity, a number of unsymmetrical azines of N-acrylacetylformamidoximes have been prepared. It was assumed that the introduction of aldehyde residues, including that of p-N,N-bis-(2-chloroethyl)aminobenzaldehyde, into amidoximes via an azine bridge might enhance their cytostatic activity, and enable compounds to be obtained showing antitubercular activity.

The aldehyde components used to obtain the unsymmetrical N-arylacetylformamidoxime azines were benzaldehyde, p-N,N-bis-(2-chloroethyl)aminobenzaldehyde, some other benzaldehydes, furfural, and 5-nitrofurfural. The hydrazone components were the N-arylacetylformamidoxime hydrazones (Ia-i), the synthesis of which has been reported [6, 7] (see scheme at top of following page).

The azines (II-L) were normally obtained quite easily by brief heating of the hydrazone (I) with the appropriate aldehyde in alcohol, but occasionally the symmetrical azines were also formed, and in some cases only the symmetrical azine could be isolated. As already

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 10, pp. 1229-1232, October, 1989. Original article submitted October 18, 1988.

0091-150X/89/2310-0843$12.50