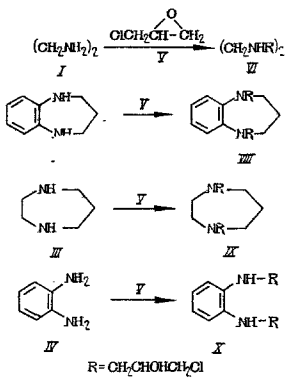
SYNTHESIS AND ANTITUMOR ACTIVITY OF DIAMINES CONTAINING γ-CHLORO-β-HYDROXYPROPYL GROUPS

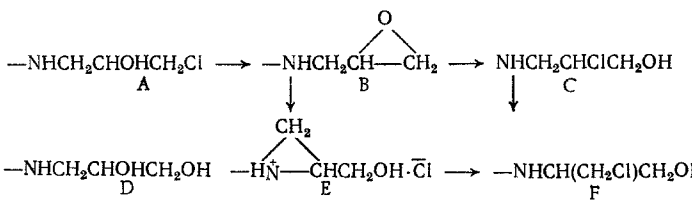
T. A. Andreyanova, S. M. Minakova,
L. F. Linberg, L. M. Alekseeva,
K. F. Turchin, V. A. Chernov,
Yu. N. Sheinker, and T. S. Safonova

UDC 615.273.2: 547.863.1].015.11

In continuation of the search for antitumor drugs [1], with the aim of elucidating structure-activity relationships, compounds have been obtained which carry γ-chloro-β-hydroxypropyl groups on the nitrogen atoms of diamines. These groups are present in the home-produced drug prospidine (N^1N^4-di-(γ-chloro-β-hydroxypropyl)-N^2N^3-dispirotripiperazinium dichloride) [2]. A study has been made of the reactions of ethylenediamine (I), tetrahydrobenzdiazepine (II), hexahydrodiazepine (III), and o-phenylenediamine (IV) with epichlorohydrin (V).



It is known from the litarature [3-5] that amines react with unsymmetrical α-oxides to form a complex of products, consisting of secondary and primary alcohols and epoxides. It has been shown [6-8] that when these reactions are carried out in aqueous alcohol, the principal products are the secondary alcohols A, but depending on the pH of the medium, these may be converted during the course of the reaction into the epoxides B, primary alcohols C, and diols D. For this reason, we reacted (I-IV) with (V) in aqueous alcohol, with the object of obtaining the secondary alcohols A. However, it would be expected from [6-8] that under these conditions a complex mixture of products might be formed, containing in addition to the compounds A the epoxides B and isomeric primary alcohols F. Further, in aqueous solutions compounds of type A may be converted via the epoxides B into the alcohols C, and these, like their isomers F, could give rise to ethyleneimmonium salts (E) [7-8].



It has been found that reaction of (I) with (V) in aqueous ethanol at 28-30°C in fact affords a difficultly-separable mixture of products, from which by repeated recrystallization from benzene was obtained (VI) in 50% yield. Treatment of (VI) with hydrochloric acid gave the dihydrochloride (VII). When (VI) and (VII) were chromatographed on thin layers of bound cellulose, the chromatograms showed a single spot, which was indicative of their purity. Under conditions similar to those used for the synthesis of (VI), compounds (VIII), (IX) and (X) were obtained in yields of 45, 40, and 30% respectively. The elemental compositions of (VI) and (VIII-X)

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 12, pp. 1460-1463, December, 1982. Original article submitted January 25, 1982.

0091-150X/82/1612-0880$07.50

corresponded to the structures A, C, and F. These compounds contained no ionic chlorine, nor was this found when aqueous solutions of (VI) and (VIII-X) were kept for 3-4 h at 18-20°C. These findings cast doubt upon the possibility of the existence of these compounds in form E. The choice between forms A, C, and F was decided in favor of form A in the case of (VI) and (VIII) from their mass and PMR spectra. The presence of the CH_2Cl group in these compounds (isomers A and E) should result in the ejection of the $\cdot CH_2Cl$ fragment (49 m/e) following electron impact. If (VI) and (VIII) contained a primary OH group (forms C and F), their mass spectra would be expected to show fragments arising from the elimination from the molecular ion of the fragments $\cdot CH_2OH$ and $\cdot CH_2O$ (31 and 30 m/e respectively). In addition, removal of the $\cdot CH_2OH$ group (isomers C and F) should give rise to daughter ions containing two atoms of chlorine (ratio of isotopic ions 9 : 6 : 1). It is also important to remember that in the case of structure F, the elimination of the $\cdot CH_2OH$ and $\cdot CH_2Cl$ groups is in practice equally likely, since these processes would give rise to iminium-stabilized ions. However, examination of the mass spectra of (VI) and (VIII) shows that only the radical fragment $\cdot CH_2Cl$ is eliminated. In addition, the spectra do not contain ions with two chlorine atoms, except for fragments formed by the loss of a water molecule, which can be either primary or secondary alcohols. These observations show that (VI) and (VII) contain the $CH_2CHOHCH_2Cl$ group in the side chains, and correspond to structure A.

The NMR spectra of (VI) and its hydrochloride also support this structure. The ^1H NMR spectrum of (VI) (dissolved in deuteropyridine) contains signals for two methylene groups situated between nitrogen atoms, in the form of a singlet at δ = 2.72 ppm. A doublet at δ = 2.85 ppm is assigned to the protons of the α-CH_2 groups. The signal for the protons of the CH_2Cl group is seen at δ = 3.75 ppm (doublet), and of the CHOH group at 4.12 (quintet). The nature of the spectrum therefore excludes structure F, for which signals would be expected for the protons in the α-position to the nitrogen atom, at higher field than those for the CHOH group in structure A. A choice between structures A and C for (VI) was made on the basis of the ^{13}C NMR spectrum of its hydrochloride. In the spectrum of this compound, obtained with partial decoupling from the protons, there are seen four signals: a doublet at δ = 67.3 ppm, a triplet at δ = 51.5 ppm, a triplet at δ = 47.0 ppm, and a triplet at δ = 44.3 ppm, assigned respectively to $C\beta$, the C atoms of the fragment $>NiCH_2CH_2N<$, $C\gamma$, and $C\alpha$. This assignment is confirmed by the ^{13}C NMR spectra of prospidine dihydrochloride, which contains γ-chloro-β-hydroxypropyl groups [9], and NN^3-di-(β,γ-dihydroxypropyl-N^1N^2-dispirotripiperazinium dihydrochloride [10], which contains β,γ-dihydroxypropyl groups. In the spectrum of prospidine dihydrochloride, the signal for $C\beta$ is seen at δ = 65.3 ppm (doublet), and that for C at δ = 46.8 ppm (triplet), and in the spectrum of NN^3-di(β,γ-dihydroxypropyl)-N^2N^2-dispirotripiperazinium dihydrochloride, the signals for $C\beta$ and $C\gamma$ occur at 66.1 (doublet) and 63.1 ppm (triplet), respectively. The presence in the ^{13}C NMR spectrum of (VI) dihydrochloride of a doublet at δ = 67.3 ppm and a triplet at 47.0 ppm confirms structure A.

It has thus been shown by mass and NMR spectroscopy that in the cases of compounds (VI-VIII), reaction of diaminoalkanes (I-IV) with epichlorohydrin affords compounds with γ-chloro-β-hydroxypropyl groups attached to nitrogen.

Biological study of (VI-X) showed (VI-VIII) and (X) to possess low toxicity, and to have low activity against transplanted Jensen's tumor (see Table 1). Compound (IX) was moderately active against the tumor, its inhibition index being 1%.

On comparing these findings with the antitumor activity and toxicity of prospidine, it is seen that (IX) is more toxic (the LD_{50} of (IX) is 65 mg/kg, and of prospidine 1200 mg/kg), and its antitumor activity is lower.

EXPERIMENTAL CHEMICAL SECTION

NMR spectra were obtained on JM 4H-100 (Japan) and Varian XL-100 (USA) instruments, internal standard tetramethylsilane. Mass spectra were obtained on a MAT-12 mass spectrometer at 70 eV, emission current 1.5 mA.

1,5-Bis(γ-chloro-β-hydroxypropylamino)ethane (VI). A mixture of 2 g (0.03 mole) of (I) and 7.07 g (0.07 mole) of (V) in 4 ml of 80% aqueous ethanol was stirred for 3 h at 28-30°C. The solid which separated was filtered off, washed with ater, and dried to give 5.7 g of a white powder, repeated crystallization of which from benzene gave crystals, mp 122-124°C (yield 50%). Chromatography on thin layers of cellulose with binder in the system butanol–pyridine–acetic acid–water (4:1:1:2) showed a single spot, R_f 89 (developed with Dragendorff's reagent). Found, %: C 38.93; H 7.47; Cl 28.6; N 11.42. $C_8H_{18}O_2N_2Cl_2$. Calculated, %: C 39.18; H 7.35; Cl 28.29; N 11.42.

TABLE 1. Toxicity and Antitumor Activity (Jensen's sarcoma) of Derivatives of Diazepine, Ethylenediamine, and o-Phenylenediamine when Administered per os

Compound	LD_{50}, mg/kg	Dose, mg/kg	No. of doses	Inhibition index, %	Change in body wt. of animals, g	
					test	control
VI	1000	150	5	0	−6	−13
		87	7	+38	+12	+9
VII	1000	81	6	+38	+7	−10
VIII	750	130	7	+32	−5	−5
IX	65*	7	7	+71	+8	+20
		5	7	+32	+7	−8
X	900	125	6	+36	+7	−7
Prospidine	1200*	150	10	+94	+10	0
		60	9	+51	+1	+1

* Intraperitoneal administration.

1,2-Bis-(γ-chloro-β-hydroxypropylamino)ethane Dihydrochloride (VII). This was obtained by dissolving (VI) in hydrochloric acid with heating, followed by cooling, isolation of the resulting solid, and washing of the latter with ether. MP 180-182°C. Chromatography as above gave a single spot. Found, %: C 30.26; H 6.17; N 8.34; Cl_{tot} 44.85; Cl^- 21.29. $C_8H_{18}C_2N_2O_2 \cdot 2HCl$. Calculated, %: C 30.18; H 6.28; N 8.81; Cl_{tot} 44.65; Cl^- 22.33.

N^1N^5-Bis-(γ-chloro-β-hydroxypropyl-1,2,4,5-tetrahydro-1,5-benzdiazepine (VIII). A mixture of 1 g (0.0067 mole) of (II), 3 g (0.032 mole) of (V), and 5 ml of 80% of aqueous ethanol was stirred for 5 h at 28-30°C. The solvent was extracted with boiling light petroleum, and the extract was filtered and cooled. The oily product which separated was separated from the light petroleum, and the thick oil was again extracted with boiling light petroleum, and the solution treated as above. Extraction of the oily product was repeated several times to give 0.99 g (45%) of (VIII) as an oil. Found, %: C 54.23; H 6.94; Cl 21.03; N 8.28. $C_{15}H_{22}N_2Cl_2O_2$. Calculated, %: C 54.05; H 6.60; Cl 21.32; N 8.40.

N^1N^4-Bis-(γ-chloro-β-hydroxypropyl)hexahydro-1,4-diazepine (IX). A mixture of 0.8 g (0.008 mole) of (III), 4.45 g (0.048 mole) of (V), and 1 ml of ethanol was stirred for 5 h at 28-30C. The solvent was removed in vacuo, and the residue recrystallized repeatedly from anhydrous alcohol to give 0.91 g (40%) of (IX), mp 45-50°C. Found, %: C 45.79; H 7.60; Cl 24.99. $C_{11}H_{22}N_2O_2Cl_2$. Calculated, %: C 46.31; H 7.72; Cl 24.91.

N^1N^2-Bis-(γ-chloro-β-hydroxypropyl)-1,2-phenylenediamine (X). A mixture of 5.4 g (0.05 mole) of (IV), 28.3 g (0.3 mole) of (V), and 20 ml of alcohol was stirred for 5 h at 78°C. The solvent was removed in vacuo, and the resulting oil was purified by repeated reprecipitation from benzene with light petroleum to give 4.29 g (30%) of (X). Found, %: C 49.38; H 6.04; Cl 24.55. $C_{12}H_{18}N_2O_2Cl_2$. Calculated, %: C 49.14; H 6.14; Cl 24.23.

EXPERIMENTAL BIOLOGICAL SECTION

The compounds were tested on rats with transplanted Jensen's tumors. Compounds (VI-VIII) and (X) were administered per os on the fifth day following transplantation of the tumors, once daily for 6-7 days. Prospidine and (IX) were administered intraperitoneally. The animals were killed on the day following the last dose, and the index of inhibition of tumor growth determined. The effects of the compounds on the animals were measured by calculating their LD_{50} values. Results were treated statistically (see Table 1).

LITERATURE CITED

1. G. G. Dvorantseva, L. M. Alekseeva, T. N. Ul'yanova, et al., in: Current Problems in the Experimental Chemotherapy of Tumors [in Russian], Chernogolovka (1980), Vol. 1, p. 30.
2. M. I. Dorokhova, V. A. Chernov, S. M. Minakova, et al., Khim.-farm. Zh., No. 2, 36 (1976).
3. L. Pakett, Fundamentals of the Modern Chemistry of Heterocyclic Compounds [in Russian], Moscow (1971), p. 9.
4. R. E. Parker and N. S. Jgaac, Chem. Rev., 59, 737 (1959).
5. R. Fuchs et al., J. Am. Chem. Soc., 76, 1631 (1954).

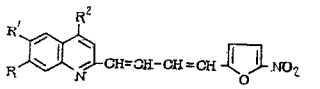
6. G. P. Kofman, I. B. Vasil'eva, and M. S. Pevzner, Khim. Geterotsikl. Soedin., No. 9, 1281 (1976).
7. V. A. Mikhailov, V. A. Chernov, M. I. Dorokhova, et al., Khim.-farm. Zh., No. 6, 9 (1972).
8. U. Ross, Biological Alkylating Agents [in Russian], Moscow (1964), p. 120.
9. G. G. Dvorantseva, A. I. Lutsenko, G. N. Ul'yanova, et al., Dokl. Akad. Nauk SSSR, Ser. Khim., 245, No. 6, 1410 (1979).
10. G. G. Dvorantseva, L. M. Alekseeva, G. N. Ul'yanova, et al., in: Current Problems in the Experimental Chemotherapy of Tumors [in Russian], Chernogolovka (1980), Vol. 1, p. 148.

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW NITROFURYLBUTADIENYLQUINOLINES

N. M. Sukhova, M. Yu. Lidak, L. V. Kruzmetra, and A. Ya. Zile

UDC 615.281 : 547.863.1].012

In continuation of studies [1] on the synthesis and examination of new pharmacologically active quinoline derivatives, we have synthesized and investigated the antimicrobial properties of some new substituted 2-[4'-(5"-nitrofur-2"-yl)-1',3'-butadienyl]quinolines.



I. $R = R_1 = R_2 = H$; II: $R = H$, $R_1 = CH_3O$, $R_2 = Cl$; III: $R = R_2 = Cl$, $R_1 = H$;
IV: $R = R_1 = H$, $R_2 = COOH$; V: $R = Cl$, $R_1 = H$, $R_2 = COOH$;
VI: $R = Cl$, $R_1 = H$, $R_2 = COOCH_3$; VII: $R = R_1 = H$, $R_2 = COOC_2H_5$;
VIII: $R = Cl$, $R_1 = H$, $R_2 = COOC_2H_5$.

In the present investigation, we have studied known methods for the synthesis of compounds (I-VIII). When 2-methylquinoline was condensed with β-(5-nitrofur-2-yl)acrolein by heating in acetic acid for 3 h [2], resinification of the reaction mixture occurred, and when the reactants were heated in acetic anhydride for 1 h at 100°C [3] or for 20-30 min at 130-135°C [4], (I) was isolated in low yield. It was found that the condensation of 2-methylquinoline and its substituted derivatives with β-(5-nitro-2-furyl)acrolein could be successfully effected by brief heating of the reactants at 130-135°C in acetic anhydride, followed by keeping the reaction mixture at room temperature. From its IR spectra and melting point, the (I) obtained was identical with that described in the literature [3]. This method enabled (I-VIII) to be obtained in 30-75% yields (Table 1). Under our conditions, the reaction also proceeded in mixtures of acetic anhydride and acetic acid, but slight resinification occurred.

It has previously been shown that in the case of 2- and 4-[2'-(5"-nitro-2"-furyl)vinyl]quinoline [4] the use of anhydrous zinc chloride as condensing agent increased the yields of the desired products. This effect was also noted in the preparation of (I-III) and (VI-VIII) (Table 1). The reaction was successful only when the substituted 2-methyl-quinoline melted below 130°C, otherwise resinification of the β-(5-nitro-2-furyl-acrolein occurred.

The IR spectra of (I-VIII) showed strong absorption bands. Bands at 1612-1646 cm^{-1} were assigned to $-C=C-$ stretching vibrations, in agreement with the literature values [5]. Table 1 shows the frequencies of the symmetrical and antisymmetrical vibrations of the nitro-group.

The compounds obtained (I-VIII) were light to dark-orange crystalline solids which were soluble in DMF, sparingly soluble in alcohol, and insoluble in water.

EXPERIMENTAL BIOLOGICAL SECTION

The antimicrobial activity of (I) and (III-V) was studied by twofold serial dilution in a liquid nutrient medium on a spectrum of eight strains of microorganisms.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 12, pp. 1463-1466, December, 1982. Original article submitted March 16, 1982.

0091-150X/82/1612-0883$07.50