RESULTS AND DISCUSSION

Curare-like properties of phosphonium derivatives of crown ethers were confirmed by the results of tests with phrenicodiaphragmatic preparations of rats. Specific data are illustrated in Fig. 1, from which it becomes clear that, begininng at a concentration of 10^{-5} M, compound IV has blocking activity on the neuromuscular transmission. Moreover, studies with the phrenicodiaphragmatic preparation have shown that compound IV is approximately by a factor of ten less active than the known myorelaxant d-tubocurarine.

It was found in experiments with mice that compounds IV, VII, and IX are toxic in the cases of intravenous and intraperitoneal administration. Compound IV proved to be the most active. A visible symptom of the toxic activity of the compounds is paralysis of the respiration, which precedes death of the animal. In the case of intravenous administration of compounds IV, VII, and IX, the animals died during administration or right after it. Slow administration of the compounds to rabbits causes the symptom of "head inclination," which is a characteristic effect of compounds with myorelaxant activity.

The obtained results show that phosphonium derivatives of aza-crown ethers, together with benzo- and dibenzo- crown ethers [1], are members of a new class of physiologically active compounds having curare-like properties.

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SYNTHESIS AND ANTITUMOR ACTIVITY OF PYRROLO[3,2-d]PYRIMIDINES

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We have recently developed a method of synthesis of 5-mercapto-1,2-dihydro-3H-pyrimido-[5,4-e]pyrrolizines [2], starting from N-cyanomethyl-2-pyrrolidone diethyl acetal (I). The method involved condensation of the acetal (I) with CH-acids of the cyanoacetic acid series, the resulting enaminonitriles readily undergoing Thorpe—Ziegler cyclization to the aminopyrrolizines. Cyclization to pyrimidines was effected by using DMF acetal. Another approach to the synthesis of enaminonitriles which are capable of undergoing intramolecular Thorpe—Ziegler condensations was developed, starting with the N-alkylation of 2-(2'-cyano-2'-R-methylenepyrrolidines, -piperidines, and -hexahydroazepines, using ethyl bromoacetate as the alkylating agent. However, the pyrimidine cyclization did not proceed cleanly, the pyrrolo-[3,2-d]pyrimidines being accompanied by polymethylene-pyrrolo[3,4-d]pyrimidines [3].

Continuing this investigation, it was desired to extend the range of compounds examined, and to obtain aminopyrrolizines containing a benzoyl group in the o-position to the NH_2 group. In this connection, it was proposed to examine and compare the method based on the use of the acetal (I) with a method based on the direct alkylation of secondary enaminonitriles.

In the first stage of this study, the effects of different conditions of alkylation of the (dicyanomethylene)pyrrolidine (II) were examined in order to arrive at the optimum method for the synthesis of both tertiary N-functionalized enamines, and the required hydrogenated pyrrolidines bearing CN, COPh, and NH_2 groups in the 2-, 3-, and 4-positions

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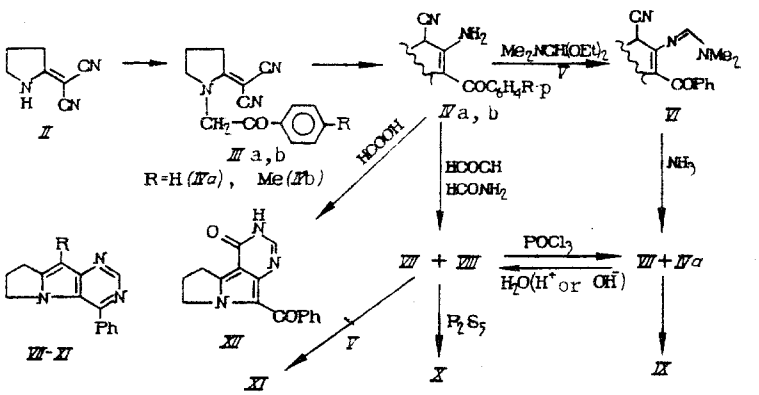
of the pyrrole ring. Alkylation of (II) with phenacyl bromide in the presence of potassium carbonate in DMF and in acetone gave the tertiary enamine, N-phenacyl-2-(dicyanomethylene)-pyrrolidine (IIIa) in yields of 59 and 82% respectively. The phase-transfer catalyzed reaction, with dilute (1.2%) NaOH in the presence of triethylammonium chloride (TEBAC)* also gave 64% of (IIIc). When the concentration of base was increased, the enamine (IIa) underwent intramolecular cyclization to 3-benzoyl-2-amino-1-cyano-5,6-dihydro-7H-pyrrolizine (IVa). Similarly, when MeONa in DMF, or sodium in toluene were used the reaction did not stop at the N-alkylation stage. In the latter case, both the enamine (IIIa) and the bicyclic compound (IVa) were isolated from the reaction mixture. The best method for converting (IIIa) was found to be by stirring (IIIa) with a solution of EtONa in alcohol, the yield of the pyrrolizine (IVa) thus obtained being 97%. The best method for obtaining (IVa) from the secondary dicyanoenamine (II) is therefore by alkylation of the latter with phenacyl bromide in acetone in the presence of potassium, carbonate, followed by Thorpe—Ziegler cyclization in alcohol in the presence of EtONa, the yield over the two steps being ~80%. Similarly, alkylation with p-methylphenacyl bromide in acetone in the presence of potassium carbonate gave the tertiary enaminonitrile (IIIb).

The polyfunctional bicyclic compound (IVa) is a convenient starting material for the preparation of a variety of heterocyclic systems. Attention was however concentrated on developing a method for the preparation of compounds incorporating the pyrrolo[3,2-d]pyrimidine bicycle, since a number of compounds of this type have been found to display high antitumor activity [4]. To this end, (IVa) was reacted with DMF diethyl acetal (V), to give the amide (VI), which was heated with methanolic ammonia in an autoclave. In addition to closure of the pyrimidine ring, cleavage of the amidine moiety to regenerate the amine (IVa) also occurred, such as the authors have reported previously [2] in other cases. Its worthy of particular attention that the pyrimidine cyclization involved the benzoyl group only, the cyano-group being retained. The resulting tricyclic compound incorporated the pyrrolo[3,2-d]pyrimidine system (VII). Comparison of these findings with those reported in [2] shows that the reactivity



R=CN (VII), $CONH_2$ (VIII), H (IX), $CSNH_2$ (X), CON=$CHNMe_2$ (XI).

of the benzoyl group in this reaction is substantially greater than that of the ethoxycarbonyl group; in the latter case, the pyrimidine ring (in pyrrolizine-type compounds) undergoes closure for the most part with the cyano-group. This method is unsuitable for the preparation of (VII), since it affords a mixture of (IVa) and (VII) in a ratio of 65:53 (according to the PMR spectrum). Another approach to the synthesis of (VII) is by treatment of the aminopyrrolizine (IVa) with a mixture of formamide, formic acid, and DMF in a ratio of 7.5:1:2.5. This reaction did not proceed cleanly, giving, in addition to the required cyano-compound (VII), the carboxamide (VIII) as a result of partial hydrolysis of the cyano-group, the proportions of (VII) to (VIII) being 70:30 (by PMR). In spite of this, the method is a good preparative one, since it is unnecessary to separate the products for subsequent work. Treatment of the mixture with $POCl_3$ in DMF gives high yields of the nitrile (VII), while treatment with aqueous acids or bases affords the carboxamide (VIII). On heating (VII) with polyphosphoric acid, elimination of the nitrile group occurs (combined hydrolysis and decarboxylation) to give the pyrimidopyrrolizine (IX). Treatment of the amide (VIII) with

*Sic — Translator. The compound should clearly be triethylbenzylammonium chloride].

TABLE 1. PMR Spectrum ($CDCl_3$) of Isomers (XVIa, b) and (XVIIa, b)

Compound	δ, ppm			
	3-CH_3	4-CH_2	5-CH_2	NCH_2
XVIa	2,07	3,37	3,72	4,87
XVIIa	2,08	3,36	3,72	4,88
XVIb	2,16	3,19	3,91	4,56
XVIIb	2,16	3,13	3,85	4,92

phosphorus pentasulfide results in the smooth formation of the thioamide (X), the structure of which is confirmed by examination of its mass spectrum. The spectrum shows a molecular ion peak ($M^{+\cdot}$ 294), which breaks down mainly by elimination of the thioamide fragment $[M-NH_3]^+$ (277), and $[M-S]^+$ (262). Reaction of the amide (VIII) with (V) gave a high yield of the acylamidine (XI), the mass spectrum of which showed peaks $M^{+\cdot}$ 333, $[M-CH_2-NMe_2]^+$ (290), $[M-N=CHNMe_2]^+$ (262), and $[M-N=CHNMe_2-CO]^+$ (234).

A different mode of cyclization, involving the cyano group rather than the benzoyl group, to give the pyrrolo[3,4-d]pyrimidine (XII), was effected by heating (IVa) with formic acid. Both N-formylation and hydrolysis of the cyano-group to carbamoyl occurred, followed by pyrimidine cyclization.

This investigation also included an examination of the synthesis of isomeric aminopyrrolizines with cyano- and benzoyl-groups in positions 2 and 4 of the aromatic pyrrole ring, respectively. First, condensation of the O-methylbutyrolactim (XIII) with α-cyanoacetophenone (XIV) gave 2-(2'cyano-2'-benzoyl)methylenepyrrolidine (XV). Attempts to alkylate this secondary enamine with chloroacetonitrile or bromoacetic ester in the presence of bases (K_2CO_3, EtONa, Na, etc.) were fruitless. It may be that the presence of a strong intramolecular hydrogen bond between the cyclic NH group and the carbonyl oxygen [5] stabilizes the initial state so strongly that deprotonation of (XV), which is necessary for N-alkylation to occur, is highly hindered. For this reason, the required tertiary cyclic enamine (XVI) was obtained in another way, using the 'acetal' method, from N-cyanomethyl-2-pyrrolidone diethyl acetal (I) and the ketone (XIV). Condensation of (I) with (XIV) gave good yields of the tertiary enamine (XVI).

It may be that (XVI) is a mixture of isomers (XVIa, b) relative to the exocyclic double bond [1]. The PMR spectrum (in $CDCl_3$) does in fact show a double set of signals corresponding to structures (XVIa) and (XVIb), their intensities indicating them to be present in approximately equal amounts. Assignment of the signals to the individual structures was carried out by comparing the spectra of (XVIa) and (XVIb) with those of previously-examined mixture of isomers of 1-cyanomethyl-2-(2'-cyano-2'-ethoxycarbonyl)methylenepyrrolidine (XVIIa, b) [1]. The data are shown in Table 1. It is also noteworthy that no interconversion of the isomers occurred under the conditions in which the spectra were obtained ($CDCl_3$, 20°C).

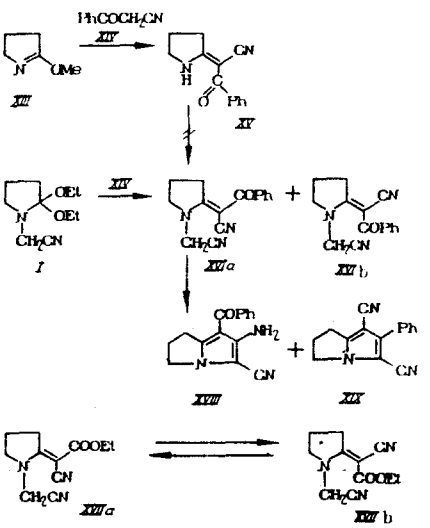


TABLE 2. Physicochemical Data for Compounds Obtained

Compound	mp, °C	Yield, %	Empirical formula	IR spectrum, ν_{max}, cm^{-1}
IIIa	218—20	82	$C_{15}H_{13}N_3O$	2200(CN, 1690(CO)
IIIb	163—4	69	$C_{16}H_{15}N_3O$	2195(CN), 1690(CO)
IVa	189—91	97	$C_{15}H_{13}N_3O$	3410, 3310(NH_2), 2200(CN), 1590(CO)
VI	174—5	64	$C_{18}H_{18}N_4O$	2210(CN), 1630(CO)
VII	220—1	92	$C_{16}H_{12}N_4$	2210(CN)
VIII	260—1 (decomp.)	96	$C_{16}H_{14}N_4O$	3370, 3270, 3140(NH_2), 1660(CO)
IX	135—6	79	$C_{15}H_{13}N_3$	—
X	256—8 (decomp.)	46	$C_{16}H_{14}N_4S$	3250, 3150(NH_2)
XI	189—90	77	$C_{18}H_{19}N_5O$	1620(CO)
XII	>320 (decomp.)	70	$C_{16}H_{13}N_3O_2$	3230(NH), 1680(CO)
XV	147—9	68	$C_{13}H_{12}N_2O$	—
XVI	135—6	60	$C_{15}H_{13}N_3O$	2190(CN), 1630(CO)
XVIII	216—7	41	$C_{15}H_{11}N_3$	2210(CN), 1600(C=C)
XIX	188—9	39	$C_{15}H_{11}N_3O$	3450, 3330, (NH_2), 2190(CN), 1600(CO)

Note. The compounds were recrystallized as follows: (IIIa) from acetonitrile, (IIIb, XVIII, X) from alcohol, (IVa, XVIII) from benzene, (VII, XII) from methanol—DMF, (IX, XIX) from 2-propanol, (VIII) from chloroform, and (XI) from dioxane.

Cyclization of the mixed isomers (XVIa, b) was carried out under mild conditions in the presence of EtONa, to give a 1:1 mixture (the ratio of (XVIa) to (XVIb) was 1:1) of the cyanobenzoylpyrrolizine (XVIII) and the dicyanopyrrolizine (XIX). These ratios of the starting isomers and final products of cyclization (Thorpe—Ziegler and Dieckmann respectively) suggest that under these conditions parallel reactions are taking place (XVIIa → XVIII and XVIIb → XIX.* It is noteworthy that the separation of the bicyclic compounds (XVIII) and (XIX) is not easy, and requires the use of column chromatography. At the present time, therefore, it seem that the best method for the synthesis of pyrrolizines bearing adjacent COPh and NH_2 groups is that described above, using the enaminonitrile (II) as starting material, the reaction sequence being (II) → (III) → (IV).

EXPERIMENTAL (CHEMICAL)

IR spectra were obtained on a Perkin—Elmer 599, as pastes in Vaseline grease. Mass spectra were obtained on a Varian MAT-112, and PMR spectra on a Varian XL-200 spectrometer, internal standard TMS. The purity of the products and the progress of the reactions were checked by TLC on Silufol UV-254 plates in the systems $CHCl_3$, $CHCl_3$—methanol (98:2), or benzene—acetone (9:1). Data for the compounds obtained are shown in Table 2. The elemental analyses were in agreement with the calculated values.

1-Phenacyl-2-(2',2'-dicycanomethylene)pyrrolidine (IIIa). A. To a mixture of 1.21 g (9.1 mmole) of the enamine (II) and 3.0 g of K_2CO_3 in 10 ml of DMF was added with stirring 2.0 g (10 mmole) of phenacyl bromide. The mixture was stirred for 5 h at 20°C, then poured into water, and the solid filtered off, washed with water, and dried to give 1.34 g (59%) of (IIIa). B. A mixture of 50 ml of CH_2Cl_2, 50 ml of water, 1.33 g (10 mmole) of (II), 0.6 g (15 mmole) of NaOH, 2.0 g (15 mmole) of phenacyl bromide, and 0.56 g (2.5 mmole) of TEBAC was stirred for 2 h at 20°C. The organic layer was separated, the aqueous layer extracted with dichloromethane, the dichloromethane extracts combined, washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was treated with methanol, and the solid filtered off to give 1.6 g (64%) of (IIIa). C. To a solution of 24.0 g (180 mmole) of (II) in 400 ml of acetone was added 56.0 of K_2CO_3, the mixture stirred for 0.5 h, and a solution of 40.0 g (200 mmole) of phenacyl bromide in 100 ml of acetone added dropwise. The mixture was stirred for 3 h, kept overnight, and the solid filtered off and washed with water to pH 7 and dried to give 37.0 g (92%) of (IIIa).

1-(4-Methylphenacyl)-2-(2',2'-dicyanomethylene)pyrrolidine (IIIb). Obtained as for (IIIa) by method C from (II) and 4-methylphenacyl bromide. The acetone solution was evaporated under reduced pressure to give (IIIb), M^+· 265.

*Confirmation of this suggestion will require separate studies, probably involving isolation of the individual isomers, and cyclization of each of them.

1-Benzoyl-2-amino-3-cyano-4,5-dihydro-6H-pyrrolizine (IVa). A. To a solution of 1.21 g (9.1 mmole) of (II) in 15 ml of DMF was added 4.3 ml of a solution of sodium methoxide obtained from 23.0 g of sodium and 230 ml of methanol. The mixture was evaporated under reduced pressure, and the residue treated with 10 ml of DMF and 2.0 g (10 mmole) of phenacyl bromide in 10 ml of DMF. The mixture was heated on the water bath for 1.5 h, cooled, poured into water, and the solid filtered off, washed with water, and dried to give 0.87 g (38%) of (IVa). B. A mixture of 1.21 g (9.1 mmole) of (II), 20 ml of benzene, 25 ml of 6 N sodium hydroxide, 0.56 g (2.5 mmole) of TEBAC, and 2.0 g (10 mmole) of phenacyl bromide was stirred for 2 h at 20°C. The benzene layer was separated, washed with water, and evaporated under reduced pressure to give 0.99 g (43%) of (IVa). C. In 50 ml of boiling toluene were added 0.46 g (20 mmole) of sodium and 2.66 g (20 mmole) of (II). The mixture was boiled for 0.5 h, 2 ml of ethanol added, and the solvent distilled from the reaction mixture until the temperature reached 110°C (vapor temperature). The mixture was then cooled, and 2 ml of DMF added followed, dropwise, by a solution of 5.0 g (25 mmole) of phenacyl bromide in 30 ml of toluene. The mixture was kept for 1 h at 20°C, then the solid was filtered off, washed with water and 2-propanol, and dried to give 3.6 g of a mixture of (IIIa) and (IVa). Recrystallization of the mixture from acetonitrile gave 1 g (20%) of (IIIa), and the insoluble material was crystallized from benzene to give 1.2 g (44%) of (IVa). D. To a solution of sodium ethoxide obtained from 1 g of sodium and 100 ml of absolute ethanol was added 6.69 g (28 mmole) of (IIIa). The mixture was stirred for 2.5 h at 20°C, then the solid was filtered off, and washed with ethanol to give 6.46 g (97%) of (IVa).

2-(2'-Cyano-2'-benzoylmethylene)pyrrolidine (XV). To a solution of 1.45 g (10 mmole) of α-cyanoacetophenone in 30 ml of toluene was added 1.5 g (15 mmole) of the lactim ether (XIII), and the mixture boiled for 3.5 h. It was then evaporated under reduced pressure, the residue treated with 2-propanol, and the residue filtered off to give 1.5 g of (XV).

1-Cyanomethyl-2-(2'-cyano-2'-benzoylmethylene)pyrrolidine (XVI). A mixture of 12.0 g (60 mmole) of the acetal (I) and 7.2 g (49.6 mmole) of α-cyanoacetophenone in 40 ml of absolute alcohol was boiled for 2 h, kept under vacuum, and the solid filtered off and washed with alcohol to give (XVI).

2-Amino-3-benzoyl-1-cyano-5,6-dihydro-7H-pyrrolizine (XVIII) and 1,3-dicyano-2-phenyl-5,6-dihydro-7H-pyrrolizine (XIX). To a suspension of 0.25 g of (XVI) (0.99 mmole) in 10 ml of absolute ethanol was added at 40°C a solution of 0.1 g of sodium in 5 ml of absolute ethanol. The mixture was kept overnight at room temperature, then the solid was filtered off, applied to a column of silica gel 40/100, and eluted first with benzene to give (XVIII), then with ethyl acetate to give (XIX).

3-Benzoyl-2-(N,N-dimethylaminomethylene)amino-1-cyano-5,6-dihydro-7H-pyrrolizine (VI). A mixture of 2.51 g of the amine (IVa) and 5 ml of the acetal (V) was boiled for 1 h, cooled, and the solid filtered off and washed with alcohol to give (VI), M^+· 306.

5,6-Trimethylene-4-phenyl-7-cyanopyrrolo[3,2-d]pyrimidine (VII). A. A solution of 2.0 g of the pyrrolizine (VI) in 20 ml of alcoholic ammonia was heated in an autoclave at 160-170°C for 10 h. The mixture was then evaporated under reduced pressure to give a mixture of 35% of (VII) and 65% of (IVa). B. A mixture of 25.1 g of the amine (IVa), 150 ml of formamide, 50 ml of DMF, and 20 ml of 85% formic acid was boiled for 2 h, and the solid filtered off and washed with methanol to give a mixture of 70% of (VII) and 30% of (VIII). C. To 11.5 g of a mixture of (VII) and (VIII) in 80 ml of acetonitrile were added 6 ml of DMF and 6 ml of $POCl_3$. The mixture was boiled for 2 h, evaporated under reduced pressure, treated with water, and the solid filtered off to give (VII).

5,6-Trimethylene-4-phenyl-7-carbamoylpyrrolo[3,2-d]pyrimidine (VIII). A. A suspension of 10 g of a mixture of (VII) and (VIII) in 150 ml of ethanol and 100 ml of 30% NaOH was boiled for 2 h, kept overnight, and the solid filtered off and washed with water and alcohol to give (VIII). B. To 1.3 g of a mixture of (VII) and (VIII were added 10 g of PPA and 13.75 g of 85% H_3PO_4, and the mixture stirred for 2 h at 110-120°C. The solution was poured on to ice, neutralized with solid KOH to pH 4, extracted with chloroform, and the extract evaporated under reduced pressure to give 1.24 g (89%) of (VIII).

5,6-Trimethylene-4-phenylpyrrolo[3,2-d]pyrimidine (IX). To a solution of PPA, obtained from 60 g of H_3PO_4 and 62.8 g of P_2O_5, was added 4.0 g of (VII). The mixture was stirred for 4 h at 200-210°C, then cooled to 70°C and poured into 300 g of crushed ice. The mixture was neutralized with 8% NaOH to pH 7-8, extracted with chloroform, and the extract evaporated under reduced pressure to give (IX).

TABLE 3. Antitumor Activity and Tolerance of Compounds (VII-XII)

Compound	Lethal dose, mg/kg	Jensen's sarcoma			Carcinoma 755			Lewis pulmonary carcinoma		
		single dose, mg/kg	Y_T, %	C_g	single dose, mg/kg	Y_T, %	C_g	single dose. mg/kg	Y_T, %	MLS, % of control
VII	~400	64—100	0—39	—2,...,—3	53	35	+7	10	0	103
VIII	~400	69—74	34—58*	—12,...,—13	30	73	+16	8	0	104
IX	>400	73	33	+5	54	49	+8	8	0	100
X	>400	69—73	0—21	—2	50	29	—1	270	13	50
XI	270	33—70	0—29	—1,...+1	54	78	—13	7	0	98
XII	>400	65	0	—1	55	54	+9	10	0	99

*Toxic dose.

5,6-Trimethylene-7-thiocarbamoyl-4-phenylpyrrolo[3,2-d]pyrimidine (X). A suspension of 9 g (21.6 mmole) of (VIII) and 9 g (40.5 mmole) of P_2S_5 in 150 ml of xylene was boiled with stirring for 4 h, cooled, and the solid filtered off to give (X).

5,6-Trimethylene-7-(N,N-dimethylaminomethylene)carbamoyl-4-phenylpyrrolo-[3,2-d]pyrimidine (XI). A suspension of 1.2 g of (VIII) in 10 ml of the acetal (V) was boiled for 1 h, cooled, and the solid filtered off and washed with alcohol to give (XI).

5,6-Trimethylene-7-benzoylpyrrolo[3,4-d]pyrimidin-4-one (XII). A solution of 1.5 g of (IVa) in 10 ml of formic acid was boiled for 2 h, cooled, and the solid filtered off and washed with alochol to give (XII).

EXPERIMENTAL (BIOLOGICAL)

The antitumor activity of compounds (VII-XII) was examined in 92 noninbred rats (initial body weight 120-140 g) with Jensen's sarcoma, and 168 BDE_1 hybrid mice (initial body weight 18-20 g) with mammary carcinoma 755 and Lewis pulmonary carcinoma. The compounds were administered in 10% polyvinylpyrrolidone solution, intraperitoneally (ip) daily for seven days, commencing 72-96 h after transplantation of the tumor. The animals were killed with ether 24-48 h following the last dose of the compound. The growth inhibition coefficient for the tumor (Y_i, %) and the body weight change coefficient of the treated animals during treatment as compared with the controls (C_g) were determined. Positive values of C_g indicated greater, and negative values smaller, increments in weight in the test animals as compared with the controls [6]. Additionally, in the animals with the Lewis pulmonary carcinoma the mean lifespan (MLS, as % of the controls) was measured. Tolerance of the test compounds was also assessed by the magnitude of the single dose required to cause death on i/p administration to intact, noninbred mice.

The test compounds were of low toxicity. For example, a single i/p dose of (IX), (X), or (XII) in doses of up to 400 mg/kg did not result in the deaths of the animals, although in the case of cyano-compound (VII) and the amide (VIII) this dose proved toxic. Only the acylamidine (XI) caused the deaths of mice in single doses of 270 mg/kg and above.

Data for the antitumor activity and tolerance of the test compounds on repeated administration in the optimum doses are shown in Table 3.

Except for (X) and (XII), all the test compounds slightly inhibited the growth of Jensen's sarcoma in rats. Their activity against adenocarcinoma 755 of the mammary gland in mice was greater, the most active being the carbamoyl compound (VIII) and its N,N-dimethylaminomethylene derivative (XI), which inhibited the growth of these tumors by 73 and 78% respectively. The compounds were without effect on Lewis pulmonary carcinoma.

These pyrrolo[3,2-d]pyrimidines therefore show slight or moderate effects on tumor growth, the greatest antitumor and toxic effects being found with the carbamoyl derivatives.

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SEARCH FOR α-ADRENOBLOCKERS AMONG β(γ)-DIALKYLAMINOALKYL DERIVATIVES OF HYDROXYSTYRYLISOXAZOLES

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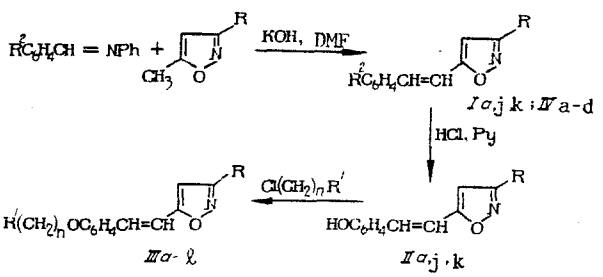
This article describes the search for α-adrenoblockers among β(γ)-dialkylaminoalkyl derivatives of 5-[2(4)-hydroxystyryl]isoxazoles (III). The basis for such a search were data [1] on the high hypotensive activity of structurally related 5-(aryloxymethyl)isoxazoles, which, as we assumed, is connected with the α-adrenoblocking activity of these compounds.

For the synthesis of the key intermediates, methoxystyrylisoxazoles (I), we used in the scheme that we have developed, in addition to the Wittig—Horner reaction used earlier [9, 10], also the so-called "anil method" [8], which made it possible to realize the condensation methylisoxazoles with anils of methoxybenzaldehydes. Then in the usual way were prepared from I hydroxystyrylisoxazoles (II), from which by alkylation with β(γ)-chloroalkylamines in the presence of NaH [1] were prepared β(γ)-dialkylaminoalkyl derivatives of 5-[2(4)-hydroxystyryl]isoxazoles IIIa-ℓ.



R = Me (Ia, k, IIa, k, IIIa-i, k, ℓ, IVa, c), Ph (Ij, IIj, IIIj, IVb, d); R^1 = NEt_2 (IIIa, j, ℓ), NMe_2 (IIIb, i, k), piperidino (IIIc), morpholino (IIId), hexamethyleneimino (IIIe), 4-methylpiperazino (IIIg), 4-(furanyl-2)piperazino (IIIh); R^2 = OMe (Ia, j, k), H (IVa, b), NMe_2 (IVc, d); n = 2 (IIIa-h, j-ℓ), 3 (IIIi); substituent at the ortho position of the benzene ring (Ia, j, IIa, j. IIIa-j) or at the para position (Ik, IIk, IIIk, ℓ, IVd, e).

Compositions and structures of IIIa-ℓ were confirmed by elemental analyses and by UV, IR, and PMR spectral data. Conjugation between the benzene and isoxazole fragments in the molecule is reflected in the UV spectra by several absorption maxima at 230, 290, and 325 nm and also in the IR spectra, which have some bands of valence vibrations of conjugated system of double bonds in the region 1580-1640 cm^{-1}. To the trans configuration of the substituent at the double bond reveal the presence in the IR spectra of deformation vibrations of trans olefinic protons at 965-980 cm^{-1} and two doublets of these protons with J = 16 Hz in the PMR spectra, which, for example, for IIIa are found at 7.74 and 7.10 ppm. Moreover, the PMR spectrum of IIIa contains, in addition to the signals of the aliphatic protons, in the region of aromatic protons a singlet of the proton at position 4 of the isoxazole at 6.37 ppm and multiplets of protons of an ortho substituted benzene ring at 7.75, 760, and 7.15 ppm. Properties of compounds IIIa-ℓ are summarized in Table 1.

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