4. A. N. Kravchenko, V. A. Chernov, L. N. Shcherbakova, et al., Farmakol. Toksikol., No. 6, 659-665 (1979).
5. N. P. Solov'eva, N. B. Marchenko, V. G. Tranik, et al., Khim. Geterotsikl. Soedin., No. 7, 914-919 (1982).
6. V. A. Chernov, Methods in Experimental Chemotherapy [in Russian], Moscow (1971), p. 537.

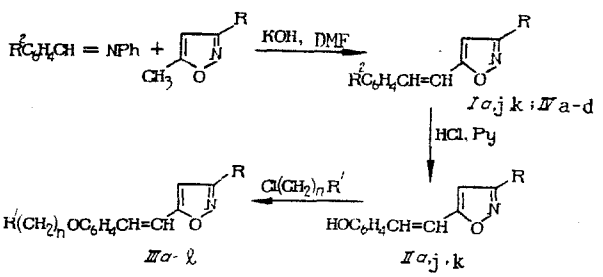
# SEARCH FOR α-ADRENOBLOCKERS AMONG β(γ)-DIALKYLAMINOALKYL DERIVATIVES OF HYDROXYSTYRYLISOXAZOLES

S. D. Sokolov, B. A. Medvedev, S. M. Vinogradova, O. G. Azarevich, M. V. Berg, and M. D. Mashkovskii

UDC 615.317.24:517.78.012.1

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.

Central Chemical Laboratory Buildings, S. Ordzhonikidze All-Union Scientific-Research Institute of the Chemical and Pharmaceutical Industry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 12, pp. 24-27, December, 1991. Original article submitted November 27, 1990.

 0091-150X/91/2512-0864$12.50 © 1992 Plenum Publishing Corporation

TABLE 1. Hydrochlorides of 5-[2(4)-(2(3)-Dialkylaminoalkoxy)phenyl]-3-methylisoxazoles IIIa-ℓ

| Compound III | Yield, % | mp., °C | Empirical formula | UV spectrum $\lambda_{max}$, nm (lg ε) |
|---|---|---|---|---|
| a | 40 | 136–137 | $C_{18}H_{25}ClN_2O_2$ | 293 (4,27)<br>325 (4,25) |
| j | 56 | 129–130 | $C_{23}H_{27}ClN_2O_2$ | — |
| b | 54 | 150–152 | $C_{19}H_{27}ClN_2O_2$ | 293 (4,28)<br>325 (4,25)<br>294 (4,23) |
| c | 45 | 168–169 | $C_{19}H_{25}ClN_2O_2$ | 324 (4,25) |
| d | 52 | 156–157 | $C_{18}H_{23}ClN_2O_3$ | —<br>227 (4,02) |
| e | 62 | 130–131 | $C_{20}H_{27}ClN_2O_2$ | 294 (4,21)<br>323 (4,18) |
| f | 68 | 162–163 | $C_{18}H_{23}ClN_2O_2$ | 294 (4,27)<br>323 (4,25)<br>231 (3,95) |
| g | 42 | 188–190 | $C_{16}H_{22}Cl_2N_3O_2$ | 295 (4,22)<br>325 (4,19) |
| h | 15 | 180–181 | $C_{24}H_{26}ClN_4O_4$ | — |
| i | 53 | 169–170 | $C_{17}H_{23}ClN_2O_2$ | 294 (4,00)<br>334 (3,95) |
| ℓ | 50 | 185–186 | $C_{15}H_{25}ClN_2O_2$ | 229 (3,96)<br>321 (4,52) |
| k | 48 | 235–236 | $C_{16}H_{21}ClN_2O_2$ | 230 (3,98)<br>321 (4,52) |

TABLE 2. 5-(2-Phenylethylene)isoxazoles I, II, and IV

| Compound | Yield, % | mp., °C | Empirical formula | UV spectrum, $\lambda_{max}$, nm (lg ε) |
|---|---|---|---|---|
| IIa* | 91** | — | — | — |
| IIj | 80** | 177–178 | $C_{17}H_{13}NO_2$ | — |
| IIk | 85** | 183–184 | $C_{12}H_{11}NO_2$ | 232 (3,98)<br>326 (4,53) |
| Ia | 75 | 66–67 | $C_{13}H_{13}NO_2$ | 294 (4,15)<br>323 (4,11) |
| Ij | 70 | 96–97 | $C_{18}H_{15}NO_2$ | 297 (4,35)<br>330 (4,34) |
| Ik | 76 | 110–112 | $C_{13}H_{13}NO_2$ | 232 (3,98)<br>323 (4,44) |
| IVa*** | 67 | 91–92 | — | — |
| IVb*** | 65 | 135–136 | — | — |
| IVc | 28 | 155–156 | $C_{14}H_{16}N_2O$ | 250 (3,99)<br>368 (4,45) |
| IVd | 30 | 198–199 | $C_{19}H_{18}N_2O$ | 242 (4,36)<br>372 (4,46) |

*Described in [9].
**Reported are the yields for the demethylation of compounds Ia, j, k.
***Described in [5].

The original interest in that synthesis is participation of a nonactivated methyl group of isoxazole (in contrast to, for example, [4]) in the condensation of the aldol-croton type, in which anils of aromatic aldehydes come forward as a synthetic equivalent of a carbonyl component. It is known that 3,5-dimethylisoxazole (and also 3,4,5-trimethyl- and 5-methyl-3-phenylisoxazoles) gives condensation with aldehydes only under influence of strong bases such as NaH [11] or BuLi [3], while in the anil synthesis the reaction is carried out in the presence of an excess of NaOH.

It should be noted that in all cases [4, 3, 11] the condensation proceeds selectively at the methyl group at the 5-position of the isoxazole. It was shown that also under the conditions of the anil synthesis only 5-styrylisoxazoles are synthesized selectively. For example, when analyzing the PMR spectrum of the crude product of the reaction of 3,5-dimethylisoxazole with the anil of 2-methoxybenzaldehyde we found only Ia, of which the structure was unambiguously confirmed by demethylation with pyridine hydrochloride to the known 5-(2-hydroxystyryl)isoxazole IIa [10]. We did not observe formation of an isomeric product of condensation at the methyl group at the 3-position of the isoxazole nor the corresponding 3,5-distyrylisoxazole.

Thus, the anil synthesis is promising for the preparation of hydroxystyrylisoxazoles, which are intermediates in the synthesis of biologically active compounds, in particular α-adrenoblocking compounds. Its feasibility as a general method for the preparation of styrylisoxazoles has not only been demonstrated by participation of the anil of benzaldehyde, but also by the not very reactive anil of p-dimethylaminobenzaldehyde (Table 2, IVa-d).

In connection with the fact that in the case of substituting the methyl group at the 3-position of the isoxazole for a phenyl group (compound IIIj) the α-adrenoblocking activity dropped sharply (see pharmacological part), we have varied the R' substituent in the derivatives of 3-methylisoxazole (compounds IIIa-h). Compounds IIIk, ℓ, which in contrast to corresponding compounds IIIa, b have a p-aminoethyl group, were especially prepared for comparing their pharmacological activities.

## EXPERIMENTAL (CHEMICAL)

IR spectra were taken in paraffin oil on a Perkin–Elmer 457 spectrometer. UV spectra were recorded on a Specord M-40 (FRG) spectrometer in alcohol. PMR spectra were recorded on a Varian XL-200 spectrometer in $CDCl_3$ with TMS as internal standard. Data on the prepared compounds are listed in Tables 1 and 2. Data of elemental analyses for C, H, and N corresponded with calculated values. Methods for the preparation of benzylideneanilines and β(γ)-dialkylaminoalkyl chlorides are described in [6] and [2], respectively.

TABLE 3. Pharmacological Properties and Toxicity of Hydrochlorides of Dialkylaminoalkoxyphenylethenylisoxazoles III

| Compound | Narcotized cats | | | Narcotized rats | | Grouped mice | | Mice, $LD_{50}$, mg/kg (iv) |
|---|---|---|---|---|---|---|---|---|
| | dose of the compound, mg/kg (iv) | lowering of the pressor effect of adrenaline, % of starting value | minimal dose lowering the arterial pressure, mg/kg (iv) | dose of the compound, mg/kg (iv) | lowering of the pressor effect of mezaton, % of starting value | dose of the compound, mg/kg (ip) | lowering of the toxicity of phenamine, % of surving animals | |
| IIIa | 0,02 | 50 | 0,01 | 0,02 | 34 | 4 | 30 | 37 |
| | | | | 0,1 | 56 | 20 | 100 | |
| IIIj | 0,1 | 10 | 0,05 | 0,1 | 0 | 8 | 30 | 80 |
| | | | | 1 | 10 | 40 | 100 | |
| IIIb | 0,02 | 40 | 0,02 | 0,02 | 29 | 5 | 0 | 44 |
| | | | | 0,1 | 48 | 20 | 100 | |
| IIIc | 0,02 | 80 | 0,002 | 0,02 | 54 | 3 | 80 | 28 |
| | | | | 0,1 | 74 | 10 | 100 | |
| IIId | 0,02 | 40 | 0,02 | 0,02 | 27 | 5 | 0 | 50 |
| | | | | 0,1 | 51 | 20 | 100 | |
| IIIe | 0,02 | 80 | 0,002 | 0,02 | 45 | 2 | 20 | 20 |
| | | | | 0,1 | 62 | 10 | 100 | |
| IIIf | 0,02 | 80 | 0,002 | 0,02 | 51 | 2 | 10 | 23 |
| | | | | 0,1 | 82 | 10 | 100 | |
| IIIg | 0,02 | 50 | 0,02 | 0,02 | 16 | 3 | 0 | 34 |
| | | | | 0,1 | 37 | 15 | 100 | |
| IIIh | 0,1 | 50 | 0,05 | 0,1 | 0 | 20 | 0 | 180 |
| | | | | 1 | 12 | 50 | 100 | |
| IIIi | 1 | 20 | 0,2 | 0,1 | 0 | 5 | 0 | 48 |
| | | | | 1 | 40 | 20 | 100 | |
| IIIℓ | 1 | 0 | >5 | 0,02 | 0 | 50 | 0 | 60 |
| | | | | 1 | 0 | | | |
| IIIk | 1 | 0 | >5 | 0,02 | 0 | 50 | 0 | 104 |
| | | | | | 0 | | | |
| Phentolamine | 0,05 | 50 | 0,05 | 0,02 | 33 | 8 | 70 | 85 |
| | | | | 0,1 | 46 | 20 | 100 | |

*Average of experiments with 3-4 animals.

3-Methyl-5-[2-(2-methoxyphenyl) ethenyl]isoxazole (Ia). A mixture of 15 g of finely ground KOH in 300 ml of DMF, 6.0 g (62 mmole) of 3,5-dimethylisoxazole, and 10.5 g (50 mmole) of 2-methoxybenzylideneaniline is stirred under an inert gas atmosphere at 60-70°C for 3-4 h,* the KOH was filtered off. The filtrate is poured out in 1.5 ml [sic] of cold water, the precipitate is filtered off, washed with water, and dried. Yield 6.3 g (75%) of Ia, mp 66-67°C. $C_{13}H_{13}NO_2$. UV spectrum, $\lambda_{max}$, nm, (log ε): 294 (4.15), 323 (4.11).

Compounds Ib, c and IVa-d were prepared in much the same way (see Table 2).

3-Methyl-5-[2-(2-hydroxyphenyl)ethenyl]isoxazole (IIa). A flask equipped with a descending condenser is charged with a solution of 3.5 g (16 mmole) of compound Ia in 10 ml of pyridine, with stirring is added 13.5 ml of concentrated hydrochloric acid, the temperature is increased to 160°C, and the mixture is kept at that temperature for 1-1.5 h during which a mixture of water and pyridine is distilled off. After the distillation has stopped the temperature is slowly increased to 200-230°C and heating at that temperature is continued for 2-3 h. After cooling 75 ml of water is added, the precipitate is filtered off, washed with water, and dried. Yield 2.9 g (91%) of IIa mp 236-238°C [10].

Compounds IIb, c, of which data are listed in Table 2, were prepared in much the same way.

Hydrochloride of 3-Methyl-5-{2-[2-(2-piperidinoethoxy)phenyl]ethenyl}isoxazole (IIIc). To a solution of 1.8 g (9 mmole) of IIa in 25 ml of DMF is added 0.7 g of sodium hydride (60% suspension in paraffin oil) and the mixture is stirred under an inert atmosphere at room temperature for 1 h. Then a solution of 1.4 g (9 mmole) of freshly distilled β-piperidinoethyl chloride in 10 ml of DMF is added, the mixture is stirred for 48 h, DMF is evaporated under vacuum, the residue is treated with water, and extracted with ether. The ethereal solution is filtered through a silica gel layer, concentrated, and treated with ethanol saturated with hydrochloric acid to pH 2-3. The precipitate is filtered off, washed with absolute ether, and recrystallized from acetone and ether. Yield 1.5 g (45%) of IIIc, mp 168-169°C. $C_{19}H_{25}ClN_2O_3$. UV spectrum, $\lambda_{max}$, nm (log ε): 294 (4.23), 324 (4.25). Com-

*Compounds IVa-d were isolated by pouring out the reaction mixture in 250 ml of hydrochloric acid.

pounds IIIa-ℓ, of which the properties are listed in Table 1, were prepared under similar conditions.

## EXPERIMENTAL (PHARMACOLOGICAL)

The α-adrenoblocking properties were studied in cats weighing 2.2-4 kg narcotized with urethane (0.7 g/kg) intraperitoneally) and chloralose (50-60 mg/kg intravenously), and in rats weighing 250-300 g narcotized with urethane (1 g/kg intraperitoneally). α-Adrenoblocking activity was indicated by lowering of the hypertensive reaction of the arterial pressure resulting from intravenous administration of adrenaline (15 μg/kg) or mezaton (20 μg/kg). In cats the pressure was recorded in the common carotid artery by means of a mercury manometer and in rats with an electromanometer. The compounds were administered intravenously.

In narcotized cats we studied the effect of the compounds on the arterial pressure in the case of intravenous administration. We determined the minimal dose that caused lowering of the pressure.

We also studied the effect of the compounds on the arterial pressure of nonnarcotized normotensive rats weighing 220-320 g in the case of administration into the stomach in the relatively large dose of 5 mg/kg. In these experiments the systolic blood pressure was measured in the caudal artery by means of KN-209 intrument of the firm Natsume after the animals had stayed for 10 min in a room heated at 38-40°C. Measurements were taken before 1.3 and 5 h after administering the compounds.

We studied the effect of the compounds on the toxicity of phenamine in grouped mice [7], the general action of the compounds, and their toxicity in mice in the case of intravenous administration. $LD_{50}$ was calculated according to [12].

In experiments with narcotized cats the compounds lower the hypertensive reaction of the arterial pressure evoked by adrenaline or mezaton. With the most active compounds that effect begins to manifest itself at a dose of 10 μg/kg. When the dose of the pyrrolidino (IIIf), piperidino (IIIc), and hexamethyleneimino (IIIe) derivatives is increased to 20 μg/kg, the lowering of the adrenaline hypertension reaches 80% in comparison with the starting reference value (Table 3). An effect similar in strength to that of phentolamine is produced at a dose of 0.1 mg/kg. In narcotized rats the compounds also lower hypertension evoked by adrenaline or mezaton. The most active compounds (IIIc, IIIe, and IIIf) are more active than phentolamine (see Table 3). The lowering of the hypertensive reaction upon administration of α-adrenomimetic compounds was caused by the α-adrenoblocking properties of the compounds under investigation because hypertension evoked by intravenous administration of angiotensin (0.1 μg/kg) did not change under influence of the compounds under investigation. When the dose in cats and rats was increased to 0.5 mg/kg the interaction with adrenaline was eliminated, completed, or (in cats) reversed. Compounds IIIk and IIIℓ did not have α-adrenoblocking activity; of low activity are also compounds IIIj, IIIi, and IIIh.

In narcotized cats the compounds lower the arterial pressure in the case of intravenous administration. In that respect the most active compounds (IIIc, IIIe, and IIIf) show a minimal effect at a dose of 2 μg/kg (see Table 3). Compounds IIIa, IIIb, IIIj, IIIi, and IIIh lower the pressure on administration of considerably higher doses or are inactive.

On introduction into the stomach of rats the compounds do not change the arterial pressure. Probably, they are not rapidly enough absorbed from the gastrointestinal tract.

In the case of parenteral administration to mice at relatively high doses of $^1/_3$-$^1/_2$ of the $LD_{50}$, in the animals developed sedation lasting 2-3 h, occasionally short-lasting narcosis and ptosis that was estimated at 3-4 points [13] and lasted more than 5 h. These phenomena are characteristic of antiadrenergic compounds (aminazine and others). It was of interest to study the effect of the compounds on the toxicity of phenamine in grouped mice. The compounds were administered at doses of about $^1/_{10}$ and $^1/_3$-$^1/_2$ of the $LD_{50}$, 30 min before subcutaneous administration of phenamine at a dose of 9-10 mg/kg. The percentage of animals protected from death (in comparison with the control, in which the number of deaths approached 95-100%) is shown in Table 3. The most active compound in this test proved to be piperidino derivative (IIIc), which at a dose of $^1/_{10}$ $LD_{50}$ protects 80% of the animals against death. At large doses of $^1/_3$-$^1/_2$ of the $LD_{50}$, activity is shown by all the compounds (with the exception of IIIk and IIIℓ) and they protect grouped mice completely against lethal doses of phenamine.

Thus, the reported investigations show that derivatives of 5-styrylisoxazole have α-adrenoblocking properties as a consequence of which they lower, remove completely, or reverse the hypertensive reaction on intravenous administration of adrenaline (or mezaton) in narcotized cats and rats, and do not change hypertension evoked by angiotensin. Probably, confirmation of α-adrenoblocking activity is also the hypotension observed in the case of intravenous administration of the compounds under investigation at relatively small doses. And, finally, lowering of the toxicity of phenamine under influence of the compounds in grouped mice may also be considered as indirect evidence of antiadrenergic activity of the compounds studied.

The most active α-adrenoblocking compounds proved to be dialkylaminoethoxy derivatives of 3-methyl-5-styrylisoxazole and among their cyclic analogs the pyrrolidino, piperidino, and hexamethyleneimino derivatives. The activity is lowered when the cyclic systems mentioned are replaced by dimethyl- and diethylamino groups, or by 4-methylpiperazine of morpholino rings. The α-adrenoblocking properties are even more significantly decreased on introduction of a 4-furoylpiperazine group (IIIh) or when the ethoxy chain is lengthened to a propoxy chain (IIIi), and also when the methyl group at position 3 of the isoxazole is replaced by a phenyl group (IIIj) or in the cases when the substituents at the phenyl ring are not in the ortho but in the para position (IIIk and IIIℓ).

The compounds under investigation that have α-adrenoblocking activity proved to be more toxic than phentolamine. With regard to the total properties, α-adrenoblocking activity and toxicity, they are not superior to phentolamine.

## LITERATURE CITED


1. German Pat., 2045050 (1972); Chem. Abstr., 77, 61979 (1972).
2. Synthesis of Organic Compounds [in Russian], Vol. 4, Moscow (1953), p. 167.
3. S. D. Sokolov, L. A. Kazitsina, and L. K. Guseva, Zh. Org. Khim., 2, 731-738 (1966).
4. S. D. Sokolov and S. M. Vinogradova, Khim. Geterotsikl. Soedin., No. 9, 1192-1193 (1979).
5. V. N. Chistokletov, A. G. Troshchenko, and A. A. Petrov, Zh. Obshch. Khim., 33, 789 (1963).
6. N. I. Bogert, J. Org. Synth., 5, 13 (1925).
7. M. R. A. Chame, J. Pharmacol. Exp. Ther., 87, 214-219 (1946).
8. I. J. Fletcher and A. E. Siegrist, Adv. Heterocycl. Chem., 23, 171-261 (1978).
9. A. Franke, F. F. Frickel, R. Schlecker, and P. D. Fhierne, Synthesis, 712-714 (1979).
10. A. Franke, F. F. Frickel, J. Gries, et al., J. Med. Chem., 24, 1460-1464 (1981).
11. Ch. Kashima and Y. Tsuda, Bull. Chem. Soc. Jpn., 46, 3533-3536 (1973).
12. Ch. Miller and M. Z. Tainter, Proc. Soc. Exp. Biol. (N. Y.), 57, 216-266 (1944).
13. B. Rubin, J. Pharmacol. Exp. Ther., 120, 125-136 (1957).