2. Z. V. Pushkareva, N. P. Bel'skaya, V. I. Nifontov, et al., In: Fifth All-Union Symposium on the Targeted Search for Biologically Active Substances [in Russian], Riga (1983), p. 138.
3. C. H. Berg, Biochim. Biophys. Acta, 183, 65 (1969)
4. J. A. Montgomery, Cancer Treat. Rep., 60, 125-134 (1976).
5. P. P. Saunders G. A. Schultz, Biochem. Pharmacol., 19, 911-913 (1970).
6. Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, J. Org. Chem., 27, 125-134 (1962).

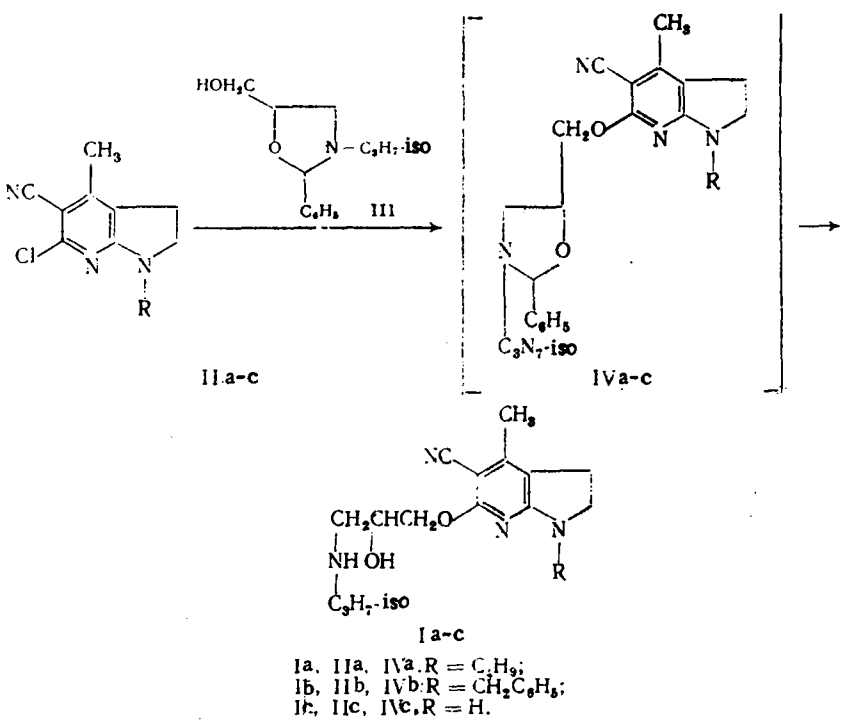
AZAINDOLES. LXVIII.* 7-AZAINDOLES AS β-ADRENOBLOCKING AGENTS

T. V. Sycheva, L. V. Ershov,
V. A. Azimov, S. D. Yuzhakov,
and L. N. Yakhontov

UDC 615.217.24:547.82

Recent reports of enhanced β-blocking activity in conjunction with vasodilatory and hypotensive properties following the introduction of cyano-substituents into benzene, pyridine, and indole in addition to the 3-isopropylamino-2-hydroxypropoxy group [7, 8, 11] are of considerable interest in selecting the best routes in the search for cardiovascular drugs. We have previously [3] shown that the introduction of these groups into the 6- and 7-positions of 5-azaindoles has a similar effect, but such compounds are readily converted into 6-oxo-7-cyano-5-azaindoles as a result of the energy advantage of the 6-oxo-5-azaindole system [6]. In contrast to 5-azaindoles, 7-azaindoles (or 7-azaindolines) are less prone to form lactams [10], and should be more stable.

We have obtained 1-benzyl- and 1-butyl-4-methyl-5-cyano-6-(3'-isopropylamino-2'hydroxypropoxy)-7-azaindoles (Ia, b) as follows:



Ia, IIa, IVa. R = C_2H_5;
Ib, IIb, IVb. R = $CH_2C_6H_5$;
Ic, IIc, IVc. R = H.

4-Methyl-5-cyano-6-chloro-7-azaindoles [5] were reacted as described in [9] using the modifications reported in [3] with 2-phenyl-3-isopropyl-5-hydroxymethyloxazolidine (III)

*For communication LXVII, see [5].

S. Ordzhonikidze All-Union Chemicopharmaceutical Scientific-Research Institute, Moscow.
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 3, pp. 281-285, March, 1986. Original article submitted May 30, 1985.

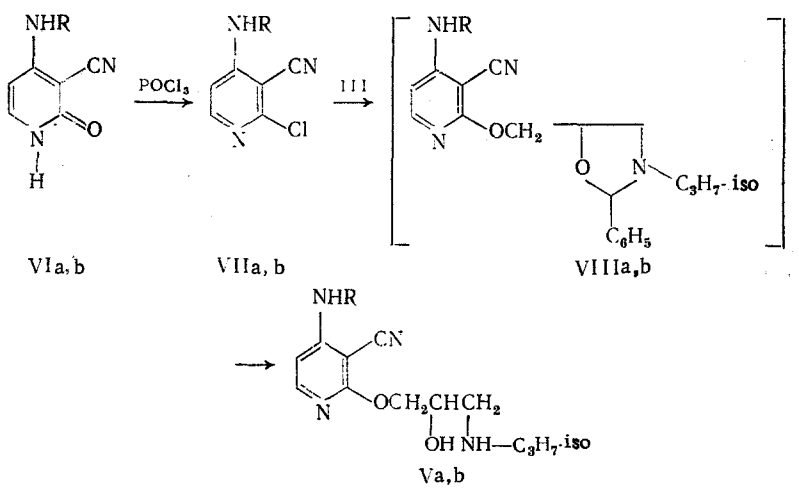
 0091-150X/86/2003-0166$12.50

TABLE 1. Pharmacological Activity and Acute Toxicities of 7-Azaindolines Ia, b and Pyridines Va, b

Compound	β-Adrenoblocking activity		Acute toxicity (LD_{50}, mg/kg intravenous)
	ED_{50} (mg/kg intravenous), suppression of isadrine tachycardia	ED_{50} (mg/kg intravenous), inhibition of the depressor effect of isadrine	
Ia	>2,0	>2,0	33,0
Ib	0,8	1,5	25,5
Ic	0,8	0,13	20,1
Va	>2,0	>2,0	100
Vb	>2,0	>2,0	43,0
Propranolol	0,42	0,092	28,0

in toluene in the presence of potassium hydroxide and the phase transfer catalyst dibenzo-18-crown-6. The products IVa, b were then hydrolyzed without isolation at pH 3.0, 50°C, the desired products Ia, b being isolated as their hydrochlorides.

The general method previously described by us [5] proved to be unsuitable for the preparation of the compound (IIc) unsubstituted on the pyrroline nitrogen, since heating the ammonium salt of 2,6-dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine with phenyl amidophosphate as described in [2] resulted in complete resinification. For this reason, it was preferable to obtain IIc from its N-benzyl derivative by debenzylation. It was found impossible to carry out this reaction by the method described for the debenzylation of 1-benzyl-2-ethoxycarbonyl-7-chloroindole, using aluminum chloride in benzene at room temperature [12], and even when the amount of aluminum chloride and the duration of the reaction were doubles, only the starting material IIb was obtained. However, raising the temperature to 80°C resulted in N-debenzylation in 67% yield. The resulting compound IIc converted into 4-methyl-5-cyano-6-(3'-isopropylamino-2'-hydroxypropoxy)-7-azaindoline hydrochloride by reacting with III in diglyme in the presence of potassium hydroxide and dibenzo-18-crown-6 followed by acid hydrolysis. As reported previously [1], the change from 6-(3'-isopropylamino-2'-hydroxypropoxy)-7-cyano-5-azaindoles to their des-aza analogs in the five membered ring resulted in a decrease or loss of p-adrenoblocking activity, but opening of the pyrroline ring enabled this activity to be retained. It was desirable to prepare also for pharmacological examination some novel 3-(3'-isopropylamino-2'hydroxypropoxy)-3-cyano-4-aralkylaminopyridines (Va, b) with different aralkyl substituents on the amino-group in the γ-position of the pyridine ring. The aralkyl substituents chosen were phenylisopropyl and 3,4-dimethoxyphenylethyl, which are present in number of drugs possessing high tropicity towards adre-



VIa, b VIIa, b VIIIa, b

Va, b

Va, VIa, VIIa, VIIIa; R = $C_6H_5CH_2CH(CH_3)$;
Vb, VIb, VIIb, VIIIb; R = 3,4-$(CH_3O)_2C_6H_3CH_2CH_2$.

noreactive systems. Compounds Va, b were obtained from the appropriate 3-cyano-4-aryalkylamino-2-pyridones (VIa, b) [4], by treatment with $POCl_3$ to give the chloro-compounds VIIa, b which were then reacted with the oxazolidine III, followed by acid hydrolysis of the intermediate compounds VIIIa, b:

EXPERIMENTAL (CHEMICAL)

Mass spectra were obtained on a Varian MAT-112 instrument (Switzerland) with direct introduction of the sample into the source, ionizing electron energy 70 eV, ionization chamber temperature 180°C, PMR spectra on a JNH-4H-100, internal standard TMS, and IR spectra on a Perkin-Elmer 457 (USA) in vaseline oil.

4-Methyl-5-cyano-6-chloro-7-azaindoline (IIc). To 7.1 g (25 mmoles) of 1-benzyl-4-methyl-5-cyano-6-chloro-7-azaindoline (IIb) in 70 ml of benzene was added 13.6 g (100 mmoles) of anhydrous aluminum chloride. The mixture was stirred at the boil for 1 h, cooled, water (500 ml) added, and the mixture extracted with chloroform (4 × 100 ml). The organic layer was washed with water (2 × 100 ml), dried over magnesium sulfate, and evaporated under reduced pressure. The residue was treated with 60 ml of ether, and the insoluble residue filtered off and recrystallized from acetone to give 3.25 g (67%) of IIc as colorless crystals with a pink tinge, mp 225-226°C. The compound was soluble in chloroform and alcohols, but insoluble in benzene, ether, and water. IR spectrum, cm^{-1}: 3200 (NH), 2200 (CN); mass spectrum: 193 (100) [M]+, 192(87) [M − H]+, 178(11) [M − CH_3]+, 166(17) [M − HCN]+, 157(17) [M − HCl]+, 156(21) [M − H − HCl]+. Found, %: C 55,94; H 4.05; Cl 18.16, N 22.08. $C_9H_8ClN_3$. Calculated %: C 55.96; H 4.15; Cl 18.13, N 21. 76.

2-Chloro-3-cyano-4'-(3',4'-dimethoxyphenylethylamino)pyridine (VIIb). A mixture of 1 g (3.3 mmoles) of VIb, 10 ml of phosphoryl chloride, and 0.5 ml of dimethylaniline was boiled for 2 h. The mixture was then evaporated under reduced pressure, and the residue treated with 10 g of finely-crushed ice, and boiled for 0.5 h. The mixture was then cooled, neutralized with 10% sodium hydroxide, and the solid which separated was filtered off to give 1 g (94.2%) of VIIb, mp 149-151°C (from ethanol). Found, %: C 60.49; H 5.01; Cl 11.41; N 13.25. $C_{16}H_{16}ClN_3O_2$. Calculated, %: C 60.47; H 5.04; Cl 11, 18; N 13.23.

Similarly, from VIa there was obtained 2-chloro-3-cyano-4-phenylisopropylaminopyridine (VIIa), yield 78.8%, mp 109-111°C (from heptane). Found, %: C 66.16; H 5.02; Cl 13.08; N 15.35. $C_{15}H_{14}ClN_3$. Calculated, %: 66.30; H 5.16; Cl 13.08; N 15.47.

1-Butyl-4-methyl-5-cyano-6-(3'-isopropylamino-2'-hydroxypropoxy)-7-azaindoline Hydrochloride (Ia). To a solution of 3 g (12 mmole) of 1-butyl-4- methyl-5-cyano-6-chloro-7-azaindoline (IIa) in 50 ml of toluene was added 3.7 g (17 mmoles) of 2-phenyl-3-isopropyl-5-hydroxymethyloxazolidine (III) in 50 ml of toluene, 1.36 g (24 mmoles) of potassium hydroxide, and 0.2 g (0.6 mmole) of dibenzo-18-crown-6, and the mixture boiled with vigorous stirring for 5 h. The mixture was then cooled, poured into 100 ml of water, the toluene layer separated, and the aqueous layer extracted with 100 ml of toluene. The combined toluene extracts were washed with water until neutral, then extracted with 1 N hydrochloric acid (2 × 100 ml), and the hydrochloric acid extracts adjusted to pH 3.0 with potassium acetate. The resulting solution was kept for 2 h at 50°C, then cooled to 20°C, concentrated sodium hydroxide added to pH 13, and extracted with chloroform (3 × 100 ml). The combined chloroform extracts were dried over magnesium sulfate, and evaporated to give 1.7 g (42%) of Ia as yellowish crystals, mp 169-170°C (decomp., from ethyl acetate). The compound was readily soluble in chloroform, acetone, alcohols, and water, but insoluble in benzene and ether. IR spectrum, cm^{-1} 3320 (NH), 2200 (CN), mass spectrum: 346(2) [M]+, 303 (3) [M−C_3H_7]+, 274 (5) [M−$CH_2NHC_3H_7$]+, 232 (46) [274−$COCH_2$]+, 231 (49) [274−$COCH_3$]+, 188 (100) [231−C_3H_7]+, 100 (27) [$C_3H_7NHCH_2CO$]+, 72 (81) [CH_2=NHC_3H_7]. Found, %: C 60.01; H 8.27; Cl 9.20; N 14.86. $C_{19}H_{30}N_4$·HCl. Calculated, %: C 59.61; H 8.10; Cl 9.28; N 14.64.

1-Benzyl-4-methyl-5-cyano-6-(3(-isopropylamino-2'-hydroxypropoxy)-7-azaindoline hydrochloride (Ib) was obtained similarly to the above, from 2.83 g (10 mmole) of the chloroazaindoline IIb and 3.2 g (16 mmole) of III, yield 1.6 g (39%), greenish crystals, mp 122-123°C (decomp., from ethyl acetate). The compound was readily soluble in chloroform, acetone, alcohols, and water, but insoluble in benzene and ether. IR spectrum, cm^{-1}. 3280 (NH), 2200 (CN). PMR spectrum, δ, ppm (in $CDCl_3$): 1.46 and 1.47 [6H, $CH(CH_3)_2$]; 2.18 s (3H, CH_3); 2.85 t (2H, $3CH_2$); 3.22 m (2H, CH_2N); 3.42 m [1H, $CH(CH_3)_2$]; 3.53 t (2H, $2CH_2$); 4.46 m (1H, CH_2O), 4.56 s (2H,$CH_2C_6H_5$); 4.46m (1H,CHOH); 7.3m (5H,$CH_2C_6H_3$). Mass spectrum: 380 (<1) [M]+; 365 (1) [M−

CH_3]+, 362 (1) [M–H_2O]+, 337 (5) [M–C_3H_7]+, 308 (7) [M–$CH_2NHC_3H_7$]+, 266 (8) [M–$CH_2COCH_2NHC_3H_7$]+, 265 (100) [M–CH_2=C(OH)–$CH_2NHC_3H_7$], 174 (6) [265–$CH_2C_6H_5$]+, 188 (8) [265–C_6H_5+. Found, %: C 63.38; H 6.59; Cl 8.69; N 13.28. $C_{22}H_{22}N_4O_2 \cdot HCl$. Calculated, % C 63.46, H 6.97, Cl 8.41, N 13.46.

4-Methyl-5-cyano-6-(3'-isopropylamino-2'-hydroxypropoxy)-7-azaindoline hydrochloride (Ic). To a solution of 2.12 g (11 mmoles) of the chloroazaindoline (IIc) in 150 ml of diglyme was added 3.4 g (15.5 mmoles) of 2-phenyl-3-isopropyl-5-hydroxymethyloxazolidine (III) in 50 ml of diglyme, 1.8 g (32 mmoles) of potassium hydroxide, and 0.32 g (0.9 mmole) of dibenzo-18-crown-6, and the mixture stirred vigorously at 130-135° C for 4 h. The mixture was evaporated to dryness under reduced pressure, the residue cooled to 20°C, and treated with 150 ml of toluene and 100 ml of water. The toluene layer was separated, the aqueous layer extracted with 100 ml of toluene, and the combined toluene layers washed with water until neutral, extracts adjusted to pH 3.0 with potassium acetate. The resulting solution was kept for 12 h at 4-6°C, then concentrated potassium hydroxide was added to bring the pH to 13, and the mixture extracted with chloroform. The chloroform extracts were dried over magnesium sulfate, and evaporated to give 0.7 g (19.5%) of Ic as greenish crystals, mp 226-228°C (decomp., from propan-2-ol). The compound was readily soluble in water, less so in alcohols, and insoluble in acetone, ether, and benzene. Ir spectrum, cm^{-1}: 3260 (NH), 2200 (CN). Mass spectrum: 291 (3) [M+H]+, 275 (3) [M–CH_3]+, 247 (19) [M–CH $(CH_3)_2$]+, 218 (6) [M–CH_2=NH–$CH(CH_3)_2$], 175 (100) [M–CH_2=C(OH)–$CH_2NHC_3H_7$]+. Found, %: C 55.12; H 7.25; Cl 10.74, N 17.50. $C_{15}H_{22}N_4O_2 \cdot HCl$. Calculated, %: C 55.04; H 7.04; Cl 10.87, N 17.15%.

2-(3'-Isopropylamino-2'-hydroxyisopropoxy)-3-cyano-4-(α-methyl-β-phenylethylamino)pyridine Dihydrochloride Hydrate (Va). Obtained as for Ia and Ib, from 10 mmoles of VIIa and 16 mmoles of III, yield 61.3%, mp 69-70°C (triturated with ether), colorless solid, sparingly soluble in ether but more so in acetone, readily soluble in alcohols and water. Found, %: C 53.78; H 7.16; Cl 15.17; N 11.57. $C_{21}H_{28}N_4O_2 \cdot 2HCl \cdot 1.5\ H_2O$. Calculated, %: C 53,84; H 7.10; Cl 15.14; N 11.96 %;

2-(3'-Isopropylamino-2'hydroxypropoxy)-3-cyano-4-[β-(3',4'-dimethoxyphenyl)ethylamino] pyridine Dihydrochloride (Vb). Obtained as for Ia, b, from 10 mmoles of VIIb and 16 mmoles of III, yield 41.2%, mp 98-99°C, colorless hygroscopic solid, sparingly soluble in ether, benzene, and acetone, but more readily in alcohols, and readily in water found, %: C 54.07; H 7.26; Cl 14.54; N 11.29. $C_{22}H_{30}N_4O_4 \cdot 2HCl$. Calculated, %: C 54.21; H6.62; Cl 14.55; N 11.50 Molecular mass (mass spectrum) 414. Calculated, 414.49 (base).

EXPERIMENTAL (PHARMACOLOGICAL)

Compounds (Ia-c) and (Va, b) were subjected to pharmacological testing. β-Adrenoblocking activity was measured in narcotized male rats weighing 200-250 g by determination of the ED_{50} values by the intravenous route with respect to inhibition of the positive chronotropic and depressor effects of isadrine (1 μg/kg, intravenous). Acute toxicities were determined in white mice weighing 16-17 g, by the intravenous soute. The activities and toxicities of the test compounds were compared with those of the β-adreno-blocking agent propranolol.

It was found that Ib and (Ic) display β-adrenoblocking activity slightly less than that of propranolol (Table 1), and their acute toxicities were similar to that of propranolol.

We have previously shown that some 5-azaindoles containing the chain characteristic of β-adrenoblocking agents in the 6-position of the azaindoline bicycle together with a cyano-group in the 7-position, and a methyl or benzyl group in the 1-position display marked β-adrenoblocking activity *in vivo*, and especially *in vitro*. Contrary to expectation, the 7-azaindoline compounds Ib, c were less active, or even inactive (Ia) as β-adrenoblocking agents.

The cyanopyridine Va which contains a phenyl-isopropylamine residue in the 4-position, a cyano-substituent in the 3-position of the pyridine ring, and a 3-isopropylamino-2-hydroxypropoxy residue in the 2-position, is devoid of β-adrenoblocking activity. It is noteworthy that the introduction of two methoxy groups into the para- and meta-positions of benzene ring of the 4-phenylethylamino residue in the pyridine nucleus (Vb) results in loss of β-adrenoblocking activity, although in analogous compounds the introduction of a single methoxy-group into the meta- or the para-position of the benzene ring results in an increase in the affinity of the compounds for the vascular β_2-adrenoreceptors [1].

LITERATURE CITED

1. V. A. Azimov, V. G. Granik, S. I. Grizik, et al., Khim.-farm. Zh., No. 8, 947-952 (1985).
2. Z. A. Arutyunyan, V. I. Gunar, E. P. Gracheva, and S. A. Zav'yalov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 3, 655 (1969).
3. N. N. Bychikhina, V. A. Azimov, V. G. Granik, et al., Khim.-farm. Zh., No. 11, 1343 (1982).
4. L. V. Ershov and V. G. Granik, Khim. Heterotsikl. Soedin., No. 5, 646-649 (1985).
5. T. V. Sycheva and L. N. Yakhontov, Ibid., No. 1, 84.
6. M. Ya. Uritskaya, V. A. Loginova, and L. N. Yakhontov, Ibid., No. 10, 1311 (1973).
7. D. Atlas, M. L. Steer, and A. Levitzki, in: Strategy in Drug Research, Noordwükerhout (1981), p. 10.
8. J. J. Raldwin, E. L. Engelhardt, R. Hirchman, et al., J. Med. Chem., 23, 65 (1980).
9. A. T. S. Duggan, E. J. J. Grabowski, and W. K. Russ, Synthesis, No. 7, 573 (1980).
10. L. N. Jakhontov (Yakhontov), D. M. Krasnokutskaya, E. M. Peresleni, et al., Tetrahedron, 22, 3233 (1966).
11. W. E. Kreigbaum, W. L. Matier, R. D. Dennis, et al., J. Med. Chem., 23, 285 (1980).
12. Y. Murakami, T. Watanabe, A. Kobayashi, and Y. Yokoyama, Synthesis, No. 9, 738 (1984).

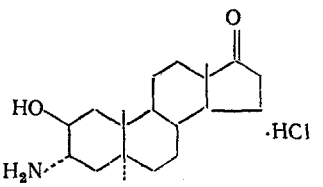
SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF 3 α-AMINO-5-α-ANDROSTAN-2 β-OL-17-ONE

S. D. Shuvalova, N. I. Men'shova,
G. S. Grinenko, K. A. Zaitseva,
and M. D. Mashkovskii

UDC 615.22.012.1.07

There have been a few reports in the literature of the occurrence of antiarrhythmic activity in compounds of steroidal structure. For example, it has been reported [3] that the steroidal sex hormones testosterone, progesterone, and estradiol are able to decrease the maximum reproducible frequency of contraction of isolated rabbit auricle, and they also terminate fibrillation in cat auricle induced by electrical stimulation. The highest activity is shown by testosterone, with progesterone and especially estradiol being less active. Antiarrhythmic properties are also possessed by the mineralocortocoid desoxycorticosterone and the synthetic steroid spironolactone, in which quinidine-like activity has been observed experimentally [1], whereas the spironolactone antagonist aldosterone and the glucocorticoid prednisolone are devoid of these properties [5].

Reports have recently appeared in the foreign literature of the experimental study of antiarrhythmic activity in 3α-amino-5α-androstan-2 β-ol-17-one hydrochloride (VI, ORG 6001) [8, 10, 12].



According to these workers, the compound ORG 6001 shows antiarrhythmic properties in several types of experimental arrhythmia. Chemically speaking, this compound may be regarded as an analog of testosterone.

We repeated the synthesis of VI from 5α-androst-2-en-17-one (I) as described in [2, 4]:

S. Ordzhonikidze All-Union Chemicopharmaceutical Scientific-Research Institute, Moscow.
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 3, pp. 286-289, March, 1986. Original article submitted January 28, 1985.

 0091-150X/86/2003-0170$12.50