4-n-Butylaminopyrrolo[3,2-d]pyrimidine (XIIIa). A solution of 0.3 g (0.002 mole) of (XII) [3] and 0.29 g (0.004 mole) of n-butylamine in 10 ml of ethanol was boiled for 3 h. The alcohol was then evaporated off, and the residue treated with water. The solid which separated was filtered off and crystallized from 50% aqueous ethanol to give 0.18 g of (XIIIa).

Similarly obtained were the 4-aminopyrrolopyrimidines (XIIIb-e)

4-Butoxypyrrolo[3,2-d]pyrimidine (XIIIf). 0.6 g (0.0026 mole) of metallic sodium was dissolved in 15 ml of n-butanol, and to the resulting solution of sodium butoxide was added 0.3 g (0.002 mole) of (XII) [3]. The mixture was boiled for 5 h, and the solvent was then distilled off, and the residue treated with water. The solid which separated was filtered off and crystallized from 60% aqueous ethanol to give 0.2 g of (XIIIf).

4-n-Butylaminopyrrolo[3,2-d]pyrimidine Hydrochloride (XIVa). A suspension of 0.3 g of (XIIIa) in 5 ml of alcoholic HCl was kept for 10 min. The solid was then filtered off and washed with ethanol to give 0.3 g of the hydrochloride (XIVa).

Similarly obtained was the hydrochloride of 4-ethanolaminopyrrolo[3,2-d]pyrimidine (XIVb).

Attempts to prepare the hydrochlorides of the bases (XIIIc-e) resulted in recovery of the starting materials.

4-Phenylaminopyrrolo[3,2-d]pyrimidine (XVa) Hydrochloride. A mixture of 0.3 g (0.002 mole) of (XII) [3] and 0.5 g (0.004 mole) of aniline hydrochloride in 10 ml of water was heated at 80°C for 3 h. The reaction mixture was cooled, and the solid filtered off to give 0.3 g of (XVa).

Similarly obtained was 4-p-methoxyphenylaminopyrrolo[3,2-d]pyrimidine (XVb).

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AZAINDOLES. LXIV.

SEARCH FOR β-ADRENOBLOCKERS IN THE 5-AZAINDOLE SERIES

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β-Adrenoblockers play an important part in the current therapy of cardiovascular diseases. Nevertheless, clinical experience with drugs of this type shows that in 40-50% of patients with hypertonic disease they cause an increase in the overall peripheral resistance, and are less effective than methyldopa and guanethidine [1-4]. For this reason, the search for new β-adrenoblockers which are safer and more effective is of current interest. There have been recent reports [5, 6] of increasd β-adrenoblocking activity together with vasodilating and hypotensive properties when, in addition to the usual 3-isopropylamino-2-hydroxypropoxy group, typical of β-adrenoblockers, there is also introduced into the benzene or pyridine nucleus the cyano-group. Similar effects have been reported also in the indole series [7]. Azaindoles containing the 3-isopropylamino-2-hydroxypropoxy group have not been described, and there is

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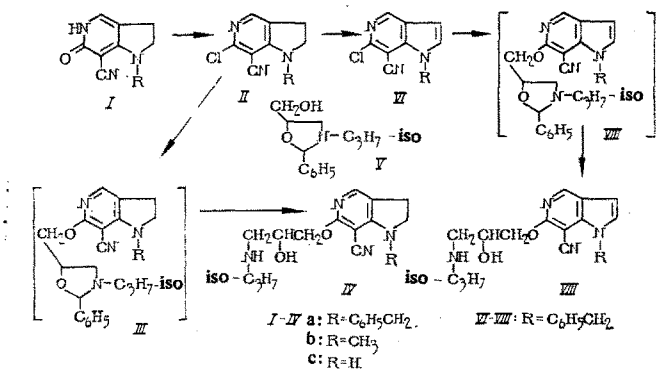
no information in the literature on the β-adrenoblocking activity of compounds of this type.

The development of methods for the construction of the 6-hydroxy-7-cyano-5-azaindoline system from the available 2-pyrrolidone [8-10], and for the conversion of the 6-hydroxy- to the 6-chloro-compounds [9-12], together with the observation that the chlorine atom in 6-chloro-7-cyano-5-azaindolines is readily replaced by alkoxy-groups [13, 14], have enabled us to undertake the synthesis of 5-azaindolines and 5-azaindoles containing the 3-isopropylamino-2-hydroxypropoxy group (typical of the β-adrenoblocking drugs) in the 6-position, and having a cyano-group in the 7-position.

The starting materials employed for these syntheses were 6-hydroxy-7-cyano-5-azaindolines carrying in the 1-position a benzyl group (Ia) [9], a methyl substituent (Ib) [8], or a hydrogen atom (Ib) [10]. Treatment of (Ib) with phosphoryl chloride in the presence of triethylamine hydrochloride gave 85-90% yields of the chloro-compounds (IIb, c). The conversion of the hydroxy-compound (Ia) into the chloro-compound (IIa) has been reported previously [9].

The conversion of the 6-chloro-7-cyano-5-azaindoles (IIa-c) into the compounds (Ia-c), containing in the 6-position the 3-isopropylamino-2-hydroxypropoxy group typical of β-adrenoblockers, was first attempted using a method described in the patent literature [15, 16] for the introduction of this group into the pyridine ring, using 2-phenyl-3-isopropyl-5-hydroxymethyloxazolidine (V). The reaction of 2-chloro-3-cyanopyridine with the oxazolidine (V) is effected, according to the patent information, in the presence of sodium hydride in DMF at 30°C. However, under these conditions (IIa) failed to react with the oxazolidine (V), and an increase in the temperature resulted in considerable resinification. Our attention was therefore drawn to another, recently described method [17] for the introduction of the 3-isopropylamino-2-hydroxypropoxy group, by carrying out the reaction with the oxazolidine (V) in toluene at room temperature, using a phase-transfer catalyst (18-crown-6) in the presence of potassium hydroxide.



When the chloroazaindoline (IIa) was reacted with the oxazolidine (V) in the presence of potassium hydroxide and 18-crown-6 in toluene at room temperature, the process was very slow, requiring 4 days for completion. In order to accelerate the alkylation of (IIa), we examined the effect of increasing the temperature of the reaction, and we found that on boiling the reaction mixture, the nucleophilic substitution was complete in 6 h.

The function of the crown ether in this reaction is apparently not restricted to the attainment of a given concentration of potassium hydroxide in the organic phase, but is also due to an increase in the nucleophilic reactivity of the anion of oxazolidine (V). There is a literature report [18] of the influence of crown ethers on the conversion of contact ion pairs into solvate-separated pairs, resulting in weakening of the electrostatic interaction of the cation and anion, with the consequent formation of highly reactive solvated anions.

The correctness of this hypothesis of the dual function of crown ethers in this reaction was supported by our isolation of unreacted chloroazaindoline (IIa) when the 18-crown-6 was replaced by dibenzo-18-crown-6.

The compound (IIIa) formed by the nucleophilic substitution of the chlorine atom in the azaindoline (IIa) by the hydroxymethyloxazolidine residue of (V) in a weakly acidic medium (pH 3.0) at 50°C underwent hydrolysis to form the required compound (IVa), isolated as the dihydrochloride in 60% yield.

Similarly, from the chloroazaindolines (IIb, c) and 1-benzyl-6-chloro-7-cyanoazaindole (VI) [13], obtained by the previously described dehydrogenation of the azaindoline (IIa), there were obtained via the intermediates (IIIb), (IIIc), and (VII) the other 6-(3'-isopropylamino-2'-hydroxypropoxy)-7-cyano-5-azaindolines (IVb, c) and the 5-azaindole (VIII).

In the case of 6-chloro-7-cyano-5-azaindoline (IIc), which has no substituent on the pyrroline nitrogen, the reaction was complicated by the low solubility of the compound, and the reaction was carried out in diglyme at 130°C. The azaindolines (Va-c) were characterized as the free bases and the mono- and dihydrochlorides. The azaindole (VIII) is a weaker base, and forms the monohydrochloride only.

The structures of (IVa-c) and (VIII) were confirmed by their mass, IR, and PMR spectra.* The mass spectra showed low intensity peaks for the molecular ions and for the fragments ($M^+-C_3H_7$), ($M^+-CH_2NHC_3H_7$), ($M^+-C_6H_{12}NO$), indicating the presence of the 3-isopropylamino-2-hydroxypropoxy residue. In the IR spectra of the hydrochlorides of (IVa-c) and (VIII), bands were observed for stretching vibrations of the nitrile group (2200-2210 cm^{-1}), ammonium ions (2400-2700 cm^{-1}), and amino- and hydroxy-groups (3160-3360 cm^{-1}). The PMR spectra showed signals for the protons of the isopropyl groups at 2.1 ppm (6H, m, $2CH_3$) and 2.8 ppm (1H, m, $CHN(CH_3)_2$), the methyleneoxy group at 4.4 ppm (2H, d, CH_2O), the CHOH group at 4 ppm (1H, m), the methyleneamino group at 3.9 ppm (2H, d, $CH_2NCH_3H_7$), the proton in the 4 position of the diazabicycle at 7.4-7.5 ppm, and signals from the substituents at nitrogen and the protons in the 2- and 3-positions of the five-membered ring.

Compounds (IVa-c) were unstable in strongly acidic aqueous solution. For example, the azaindoline (IVa) was scarcely affected by storage in aqueous solution at pH 3.5 for 10 h, but at pH 1.0 under the same conditions, it was nearly completely converted into (Ia). Hydrolysis of (IVa) was also observed during its isolation from the reaction mixture (in addition to its isolation in 60% yield, 33% of the hydroxy-compound (Ia) was also obtained). A similar reduction in yield as a result of partial hydrolysis was also observed with (IVb) and (IVc).

Formation of the 6-hydroxy-derivatives (I) was also detected by TLC in the reaction of the chloroazaindolines (II) with the oxazolidine (V) in the presence of potassium hydroxide and 18-crown-6. It is possible that this ease of hydrolysis of (IV) is related to some features of the pharmacological effects.

EXPERIMENTAL CHEMICAL SECTION

PMR spectra were obtained on a Varian-X-100A-12 (100 MHz) spectrometer (USA), internal standard TMS, IR spectra on Perkin-Elmer-457 (Sweden) in KBr disks, UV spectra on a Perkin-Elmer-402 (Sweden) in ethanol, and mass spectra on a Varian MAT-112 (USA) instrument at 70 eV, ionizing chamber temperature 180°C.

1-Methyl-6-chloro-7-cyano-5-azaindoline (IIb). A mixture of 9.7 g (55.4 mmole) of (Ib) and 5 g of triethylamine hydrochloride was boiled with 50 ml of phosphoryl chloride until all the solid had dissolved, and boiling continued for a further 1 h. The excess of phosphoryl chloride was removed *in vacuo*, and the residue dissolved in water, basified with 1 N sodium hydroxide to pH 9.0, and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was triturated with ether and filtered to give 9.6 g (90%) of (IIb) as colorless crystals, mp 158-159°C (from isopropanol). The compound was sparingly soluble in ether and isopropanol, and readily soluble in chloroform, alcohol, and acetone. Found, %: C 55.92; H 4.40; Cl 18.25; N 21.80. $C_9H_8ClN_3$. Calculated, %: C 55.81; H 4.13; Cl 18.35; N 21.70.

6-Chloro-7-cyano-5-azaindoline (IIc) was obtained similarly to (IIb). A mixture of 8.1 g of triethylamine hydrochloride, and 45 ml of phosphoryl chloride was boiled for 5 h. The excess of phosphoryl chloride was distilled off *in vacuo*, and the residue treated with 20% aqueous sodium hydroxide until the pH reached 9.0. The solid which separated was filtered off, and washed with water to give 7.6 g (86%) of (IIc). Colorless crystals, mp 275-276°C (from DMF). The compound was sparingly soluble in water and the usual organic solvents. Found, %: C 53.36; H 3.06; Cl 19.61; N 32.46; M^+ 179. $C_8H_6ClN_3$. Calculated, %: C 53.48; H 3.34; Cl 19.78; N 23.40; M 179.

*All the spectra were obtained in the laboratory for physicochemical methods of investigation (head, Prof. Yu. N. Sheinker) of the VNIKhFI (S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry), by O. S. Anisimova, K. F. Turchin, and E. M. Peresleni, to whom the authors wish to express their sincere thanks.

1-Benzyl-6-(3'-isopropylamino-2'(hydroxypropoxy)-7-cyano-5-azaindoline (IVa). To a solution of 3 g (11 mmole) of 1-benzyl-6-chloro-7-cyano-5-azaindoline (IIa) in 50 ml of toluene was added 3.2 g (16 mmole) of 2-phenyl-3-isopropyl-5-hydroxymethyloxazolindine (V) [19] in 50 ml of toluene, 1.36 g (24 mmole) of potassium hydroxide, and 0.2 g (0.8 mmole) of 18-crown-6, and the mixture was boiled with vigorous stirring for 5 h. The reaction 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, extracted with 1 N hydrochloric acid (2 × 100 ml), and the hydrochloric acid extracts neutralized with sodium acetate to pH 3.0. The resulting solution was kept for 2 h at 50°C, cooled to 20°C, concentrated aqueous sodium hydroxide added to pH 13.0, and extracted with ethyl acetate (3 × 100 ml). The combined ethyl acetate extracts were dried over magnesium sulfate, and evaporated. Treatment of the residue with an excess of alcoholic hydrogen chloride gave 2.88 g (60%) of (IVa) dihydrochloride. Colorless crystals, mp 140-142°C (decomp.). The compound was readily soluble in water and alcohols, and insoluble in acetone and ether. UV spectrum, λ_{max}, nm (log ε): 218 (4.40), 242 (3.87), 260 (3.59), 322 (3.55). IR spectrum, ν, cm^{-1}: 2200D(C≡N), 2420, 2510 ($R_3\overset{+}{N}H$), 3360 (NH, OH). PMR spectrum, δ, ppm (in $CDCl_3$): 2.1 (6H, d, $2CH_3$), 2.75 (2H, t, $3CH_2$), 2.8 (1H, m, $CHMe_2$), 3.6 (2H, t, 2-H), 3.9 (2H, d, CH_2NHPr-i), 4 (1H, m, CHOH), 4.4 (2H, d, CH_2O), 4.89 (2H, s, $CH_2C_6H_5$), 7.3 (5H, m, $CH_2C_6H_5$), 7.45 (1H, s, 4-CH). Mass spectrum: 366 [(M^+)], 347 [$(M-H_2O)^+$], 323 [$(M-C_3H_7)^+$], 294 [$(M-CH_2NHC_3H_7)^+$], 252 [$(M-C_6H_{12}NO^+)$]. Found, %: C 57.00; H 6.67; N 12.38. $C_{21}H_{26}N_4O_2 \cdot 2HCl$. Calculated, %: C 57.40; H 6.42; N 12.75.

(IVa) Hydrochloride. Colorless crystals, mp 138-140°C (decomp.). Found, %: C 62.40; H 6.78; N 13.69. $C_{21}H_{26}N_4O_2 \cdot HCl$. Calculated, %: C 62.60; H 6.76; N 13.9.

Free Base (IVa). Colorless crystals, mp 75-76°C. The compound was readily soluble in alcohols, chloroform, acetone, and ether, and sparingly soluble in water. Found, %: C 68.80; H 6.90; N 15.30; M^+ 366. $C_{21}H_{26}N_4O_2$. Calculated, %: C 68.83; H 7.15; N 15.90; M 366.

The mother liquors following extraction with ethyl acetate of (IVa) were further extracted with 3 × 100 ml of chloroform. The chloroform extract was dried over magnesium sulfate, and the solvent evaporated to give 1.1 g (33%) of 1-benzyl-6-hydroxy-7-cyano-5-azaindoline (Ia), identical by mixed melting point and its IR spectrum with an authentic sample of (Ia) [9].

1-Benzyl-6-(3'-isopropylamino-2'-hydroxypropoxy)-7-cyano-5-azaindole (VIII). To a solution of 3.29 g (12 mmole) of 1-benzyl-6-chloro-7-cyano-5-azaindole (VI) in 50 ml of toluene was added a solution of 3.54 g (16 mmole) of (V) in 50 ml of toluene, 1.46 g of potassium hydroxide, and 0.53 g (2 mmole) of 18-crown-6. The mixture was boiled with vigorous stirring for 11 h, 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, extracted with 1 N hydrochloric acid (3 × 100 ml), and the hydrochloric acid extracts neutralized with sodium acetate to pH 3.0. The resulting solution was kept for 2 h at 50°C, cooled to 20°C, concentrated aqueous sodium hydroxide added to pH 13.0, extracted with chloroform (3 × 100 ml), and the chloroform extract dried over magnesium sulfate and evaporated. Yield 1.1 g (24%) of (VIII). Colorless crystals, mp 138-139°C. The compound was readily soluble in alcohols, sparingly soluble in ethyl acetate, chloroform, acetone, and water, and insoluble in hexane and ether. Mass spectrum: 364 [$(M)^+$], 346 [$(M-H_2O)^+$], 321 [$(M-(CH_3)_2CH^+$], 292 [$(M-CH_3)_2$ $CHNHCH_2)^+$], 262 [$(M-(CH_3)_2$ $CHNHCH_2$ $CHOH)^+$], 250 [$(M-C_6H_{12}$-$NO)^+$]. Found, %: C 69.60; H 6.43; N 15.03; M^+ 364. $C_{21}H_{27}N_4O_2$. Calculated, %: C 69.21; H 6.64; N 15.38; M 364.

(VIII) Hydrochloride. Colorless crystals, mp 157-159°C. The compound was readily soluble in water, alcohols, and chloroform, and sparingly soluble in tetrahydrofuran, acetone, and ether. UV spectrum. λ_{max}, nm (log ε): 210 (4.23), 237 (4.47), 295 (3.72), 322 (3.75). IR spectrum, ν, cm^{-1}: 2210 (C≡N), 2660-2780 ($R_3\overset{+}{N}H$); 3160-3360 (OH, NH). Found, %: C 62.90; H 6.27; Cl 9.0; N 13.95. $C_{21}H_{24}N_4O_2 \cdot HCl$. Calculated, %: C 62.91; H 6.28; Cl 8.96; N 13.98.

1-Methyl-6-(3'-isopropylamino-2'-hydroxypropoxy)-7-cyano-5-azaindoline (IVb). To a solution of 4 g (21 mmole) of 1-methyl-6-chloro-7-cyano-5-azaindoline (IIb) in 50 ml of toluene was added 6.63 g (30 mmole) of the oxazolidine (V) in 50 ml of toluene, 2.58 g (46 mmole) of potassium hydroxide, and 0.47 g (4 mmole) of 18-crown-6. The mixture was boiled with vigorous stirring for 6 h, cooled, and poured into 100 ml of water. The toluene layer was separated, and the aqueous layer extracted with 100 ml of toluene. The combined toluene extracts were washed with water until neutral, extracted with 1 N hydrochloric acid (2 × 100 ml),

TABLE 1. Results of a Pharmacological Study of 6-(3'-isopropylamino)-2'-hydroxypropoxy)-7-cyano-5-azaindolines (IVa-c) and 5-Azaindole (VIII)

Compound	β-Adrenoblocking activity					α-Adrenoblocking activity in isolated vas deferens, pA_2	LD_{50}, mg/kg
	in vitro, in operations on isolated guinea pig auricles, pA_2	in vivo					
		intravenous		peroral			
		inhibition of isadrine tachycardia	inhibition of depressor effect of isadrine	inhibition of isadrine tachycardia	duration of effect, h		
		ED_{50}, mg/kg					
IVa	9,7	0,06	0,07	2,0	4	4,2	67,5
IVb	11,2	1,6	0,1	40,2		3,9	65,0
IVc	7,56	—	2,0	—		4,3	31,5
VIII		0,4	0,1				16
Propranolol	8,7	0,42	0,09	50,0	8		28,0
Pindolol	8,7	0,02	0,02	0,05			29,0
Labetalol	6,2	0,70	3,30			4,5	

Note. All the compounds were tested as their hydrochlorides.

and the hydrochloric acid extracts neutralized with sodium acetate to pH 3.0. The resulting solution was kept for 2 h at 50°C, cooled to 20°C, concentrated aqueous sodium hydroxide added to pH 13.0, extracted with ethyl acetate (2 × 200 ml) and the ethyl acetate extract dried over magnesium sulfate and evaporated to give 2.23 g (37%) of (IVb). Colorless crystals, mp 110-112°C. The compound was readily soluble in alcohols, chloroform, ethyl acetate, and acetone, sparingly soluble in benzene and ether, and insoluble in water. IR spectrum, ν, cm^{-1}: 2210 (C≡N), 3100, 3260 (OH, NH). PMR spectrum, δ, ppm ($CDCl_3$): 2.1 (6H, d, $2CH_3$), 2.75 (2H, t, 3-CH_2), 2.8 (1H, m. $CHMe_2$), 3.25 (3H, s, 1-CH_3), 3.6 (2H, t, 2-CH_2), 3.9 (2H, d, CH_2NHPr-i), 4.0 (1H, m, CHOH), 4.4 (2H, d, CH_2O), 7.5 (1H, s, 4-CH). Found, %: C 62.09; H 7.64; N 19.30. $C_{15}H_{22}N_4O_2$. Calculated, %: C 62.04; H 7.64; N 19.30.

(IVb) Hydrochloride Hemihydrate. Colorless crystals, mp 128-130°C. Readily soluble in water and alcohols, insoluble in chloroform, acetone, and ether. Found, %: C 53.55; H 6.89; N 16.76. $C_{15}H_{22}N_4O_2 \cdot HCl \cdot {}^1/_2H_2O$. Calculated, %: C 53.64; H 7.20; N 16.68.

(IVb) Hydrochloride Hydrate. Colorless crystals, mp 194-195°C. Found, %: C 47.00; H 7.10; N 14.63. $C_{15}H_{22}N_4O_2 \cdot 2HCl \cdot H_2O$. Calculated, %: C 47.25; H 6.87; N 14.69.

6-(3'-Isopropylamino-2'-hydroxypropoxy)-7-cyano-5-azaindoline (IVc). To a solution of 4 g (22 mmole) of 6-chloro-7-cyano-5-azaindoline (IIc) in 300 ml of diglyme were added 6.8 g (31 mmole) of the 5-oxazolidine (V) in 100 ml of diglyme, 3.6 g (64 mmole) of potassium hydroxide, and 1.3 g (5 mmole) of 18-crown-6. The mixture was kept for 4 h at 130°C with vigorous stirring, then evaporated to dryness *in vacuo*. To the cooled residue was added 100 ml of 1 N hydrochloric acid, the mixture stirred thoroughly, and the pH brought to 3.0 by adding sodium acetate. The solution was kept for 2 h at 50°C, cooled to 20°C, and brought to pH 13.0 by the addition of concentrated aqueous sodium hydroxide. It was then extracted with ethyl acetate (4 × 100 ml), the ethyl acetate extract dried over magnesium sulfate, evaporated, and the residue treated with acetone (2 × 100 ml). The acetone solution was treated with saturated alcoholic hydrogen chloride, and the solid which separated was filtered off and crystallized from ethanol to give 1.08 g (21%) of (IVc) hydrochloride. Colorless crystals, mp 157-159°C. Readily soluble in water, alcohols, and DMF, sparingly soluble in chloroform and ethyl acetate, and insoluble in heptane, benzene, and ether, IR spectrum, ν, cm^{-1}: 2210 (C≡N), 2680, 2760 ($R_3\overset{+}{N}H$), 3160, 3349 (NH, OH). Mass-spectrum: 276 $[(M)^+]$, 258 $[(M-H_2O)^+]$, 233 $[(M-CH_3)_2CH)^+]$, 204 $[(M-(CH_3)_2CHNHCH_2)^+]$, 174 $[(M-(CH_3)_2CHNHCH_2\ CHOH)^+]$, 162 $[(M-C_6H_{12}NO)^+]$. Found, %: C 48.25; H 6.70; Cl 20.10; N 16.08; M^+ 276. $C_{14}H_{20}N_4O_2 \cdot 2HCl$. Calculated, %: C 41.14; H 6.35; Cl 20.30; N 16.04; M 276.

EXPERIMENTAL PHARMACOLOGICAL SECTION

The β-adrenoblocking activity of the compounds was assessed in both *in vivo* and *in vitro* experiments. In experiments on isolated guinea pig auricles, perfused with Krebs solution and a mixture of oxygen (95%) and carbon dioxide (5%), β-adrenoblocking activity was assessed by the pA_2 value in respect of the positive chronotropic effect of isadrine ($1\text{-}2 \cdot 10^7$ M). β-Adrenoblocking activity was assessed in narcotized male rats weighing 250-300 g by the ED_{50} values

with respect to the positive chronotropic and depressor effects of isadrine (1 μg/kg). α-adrenoblocking activity was determined in experiments on isolated rat vas deferens perfused with Krebs solution and a mixture of oxygen (95%) and carbon dioxide (5%), by the pA_2 value in comparison with the spasmogenic effect of noradrenaline. The acute toxicities of the compounds were determined in mice weighing 16-17 g by the intravenous route. The activities and toxicities of the test compounds were compared with those of propranolol and pindolol, and with those of the α- and β-adrenoblocker, labetalol.

It was found that the test compounds (IVa-c) possess differing β- and similar α-adrenoblocking activities (Table 1). The greatest and most constant β-adrenoblocking effect was displayed by (IVa). This compound was ten times more active than propranolol and pindolol *in vitro*. The *in vitro* activity of (VII) was not determined. In the *in vivo* experiments it was more active than propranolol, but less so than pindolol. Compound (IVb) displayed very high β-adrenoblocking activity *in vitro* (it was several hundred times more active than propranolol or indolol), but its *in vivo* activity was low. Compound (IVc) possessed moderate β-adrenoblocking activity *in vitro*, but not *in vivo*. In comparison with the standard adrenoblockers, (VII) was of low activity. The duration of the β-adrenoblocking effect of the compound which was most active by the peroral route (IVa, 10 mg/kg) did not exceed 4 h, whereas propranolol (50 mg/kg) blocked the chronotropic effects of isadrine for 8 h. Compounds (IVa-c) did not differ significantly in their α-adrenoblocking activity from labetalolol, although its β-adrenoblocking activity was much greater. The acute toxicities of (IVa-b) were half those of propranolol, pindolol, and (IVc), and the acute toxicity of (VIII) was greater than that of propranolol or pindolol.

Hence, compounds containing the grouping characteristic of β-adrenoblockers in the 6-position of the 6-azaindole bicycle, a cyano-substituent in the 7-position, and a methyl or benzyl group on the 1-nitrogen atom possess high β-adrenoblocking activity *in vitro*, although *in vivo* they are less active than pindolol and the duration of their effect is less than that of propranolol, possibly owing to their hydrolysis in the acid stomach contents. The N-substituted compound (IVc) has much lower β-adrenoblocking activity *in vitro* than the N-substituted compounds, and is virtually devoid of activity *in vivo*. The α-adrenoblocking activity of these compounds is independent of the type of substituent at nitrogen.

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