SEARCH FOR NEW DRUGS

SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF 7-BENZYL(ETHYL)-1-HYDROXY-4-CARBAMOYL-3-OXO-5,6-DIHYDRO-8H-2,7-NAPHTHYRIDINES

E. G. Paronikyan,[1] S. N. Sirakanyan,[1] A. S. Noravyan,[1] T. O. Asatryan,[1] K. Zh. Markaryan,[1] and R. A. Aleksanyan[1]

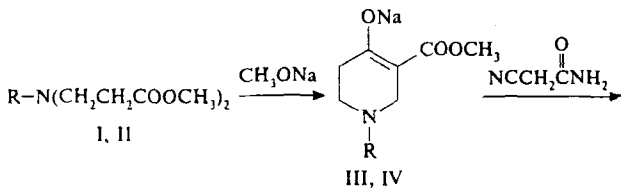
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 6, pp. 13 – 15, June, 1996.

Original article submitted January 12, 1995.

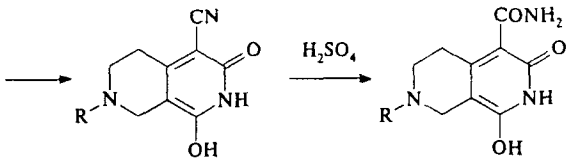
Derivatives of 2,7-naphthyridines are still insufficiently studied [1]. There are some data on their analgesic activity and tremorlike action [2, 3].

In continuation of the previous work on the synthesis of 2,7-naphthyridine derivatives [4], we have developed a method for obtaining 4-carbamoyl-2,7-naphthyridine derivatives (VII, VIII). Taking into account the presence of an amide group (like that of novocainamide) and piperidine ring (like that in quinidine) in the structure of synthesized compounds and proceeding from our earlier results [5], it was of interest to study the antiarrhythmic properties of the synthesized compound.

The synthesis was based on the cyclization of N-benzyl(ethyl)-di(β-carbomethoxyethyl)amines (I, II) [6] under the action of sodium methylate according to the Dickman reaction. Condensation of the resulting sodium salts of 1-benzyl(ethyl)-4-hydroxy-3-methoxycarbonyl-1,2,5,6-tetrahydr opyridines (III, IV) with cyanacetamide leads to 4-cyan-2,7-naphthyridines (V, VI). Hydrolysis of the latter compounds in sulfuric acid yields the target 4-carbamoyl-2,7-naphthyridines (VII, VIII).



I, II III, IV



V, VI VII, VIII

I, III, V, VII: R = $CH_2C_6H_5$;
II, IV, VI, VIII: R = CH_2CH_3.

The IR spectra of compounds V – VIII contain the absorption bands characteristic of OH, NH, and NH_2 groups (3500 – 3100 cm^{-1}) and those of the nitrile group at 2210 cm^{-1}. A wide band in the region of 1660 – 1540 cm^{-1} is due to the vibrations of the lactam group (CONH) and the C=C bond.

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on an UR-20 spectrophotometer (Germany) as vaseline oil suspensions. The ^1H NMR spectra were obtained on a Varian T-60 spectrometer using TMS as the internal standard in DMSO-d_6 (V, VI) and D_2O (IV). The mass spectrum was measured on an MX-1320 spectrometer with a system of direct sample injection into the ion source. TLC chromatograms were obtained on Silufol UV-254 plates eluted using the pyridine – ethanol 1 : 1 (III, IV) and butanol - water – acetic acid 4 : 2 : 5 (V – VIII) systems and developed by iodine vapors. The results of elemental analyses agreed with the values obtained by analytical calculations.

Sodium salts of 1-benzyl(ethyl)-4-hydroxy-3-methoxycarbonyl-1,2,5,6-tetrahydropyridines (III, IV). To a sodium methylate suspension prepared from 2.3 g (0.1 mole) sodium. 30 ml absolute methanol, and 30 ml of dry benzene was added dropwise with stirring 0.1 mole of diesters I or II. The

[1] A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences, Yerevan, Armenia.

0091-150X/96/3006-0365$15.00

mixture was boiled with reflux for 3 h. After cooling of the mixture, the precipitated crystals were separated by filtration, washed with ethyl ether, dried, and recrystallized from ethanol. Compound III: yield, 19.3 g (71.7%); m.p., 171 – 172°C; R_f, 0.65; $C_{14}H_{16}NO_3Na$. IR spectrum (ν_{max}, cm^{-1}): 1650 (CO), 1590 (C=C). Compound IV: yield 17.0 g (82.1%); m.p., 292 – 293°C; R_f, 0.71; $C_9H_{14}NO_3Na$. IR spectrum (ν_{max}, cm^{-1}): 1660 (CO), 1600 (C=C). ^1H NMR spectrum (δ, ppm): 3.58 (s, 2H, 2-CH_2), 3.33 (s, 2H, 6-CH_2), 3.11 (s, 2H, 5-CH_2), 2.53 (s, 3H, OCH_3), 2.33 (q, 2H, J 6 Hz, $\underline{CH_2}CH_3$), 1.05 (t, 3H, J 6 Hz, $CH_2\underline{CH_3}$).

7-Benzyl(ethyl)-1-hydroxy-3-oxo-4-cyan-5,6,7,8-tetra hydro-2,7-naphthyridin-3(2H)-ones (V, VI). To a solution of 0.1 mole of compound III or IV and 0.4 g (0.01 mole) of sodium hydroxide in 150 ml absolute methanol was gradually added with stirring over 30 min 8.4 g (0.001 mole) cyanacetamide. The mixture is stirred for another 1.5 h at 20°C and then boiled with reflux for 8 h. After cooling, the precipitated crystals were filtered, dissolved in 200 ml of water and acidified with concentrated sulfuric acid to pH 7. The precipitated crystals were separated by filtration, washed with water, dried, and recrystallized from nitromethane. Compound V: yield 26.2 g (93.2%); m.p. 258 – 259°C; R_f, 0.61; $C_{16}H_{15}N_3O_2$. IR spectrum (ν_{max}, cm^{-1}): 3340 – 3120 (NH, OH), 2210 (CN), 1660 – 1540 (CO, C=C). ^1H NMR spectrum (δ, ppm): 7.46 (s, 5H, C_6H_5), 3.71 (s, 2H, $\underline{CH_2}C_6H_5$), 3.31 (s, 2H, 8-CH_2), 2.63 (bs, 4H, 5-CH_2, 6-CH_2). Compound VI: yield 16.5 g (75.2%); m.p. 294 – 295°C; R_f 0.53; $C_{11}H_{13}N_3O_2$. IR spectrum (ν_{max}, cm^{-1}): 3350 – 3120 (NH, OH), 2210 (CN), 1650 – 1550 (CO, C=C). ^1H NMR spectrum (δ, ppm): 3.11 (s, 2H, 8-CH_2), 2.56 (bs, 4H, 5-CH_2, 6-CH_2), 2.45 (q, 2H, J 7 Hz, $\underline{CH_2}CH_3$), 1.03 (t, 3H, J 7 Hz, $CH_2\underline{CH_3}$).

7-Benzyl(ethyl)-1-hydroxy-4-carbamoyl-3-oxo-5,6,7,8-tetrahydro-2,7-naphthyridin-3(2H)-ones (VII, VIII). A mixture of 0.1 mole of compound V or VI and 20 ml of concentrated sulfuric acid was boiled for 2 h on a water bath. After cooling, the mixture is poured on ice and neutralized with an aqueous solution of potassium carbonate. The precipitated crystals were separated by filtration, washed with water, dried, and recrystallized from DMSO. Compound VII yield: 2.55 g (84.9%); m.p. 206 – 207°C; R_f, 0.74; $C_{16}H_{17}N_3O_3$. IR spectrum (ν_{max}, cm^{-1}): 3500 – 3100 (NH, OH, NH_2), 1660 – 1540 (CO, C=C). Compound VI: yield 1.85 g (78.4%); m.p. 256 – 257°C; R_f 0.68; $C_{11}H_{15}N_3O_3$. IR spectrum (ν_{max}, cm^{-1}): 3450 – 3140 (NH, OH, NH_2), 1660 – 1560 (CO, C=C). Mass spectrum (m/z, %): 237 (18) (M^+), 219 (100), 210 (26), 208 (20), 195 (27), 194 (28), 193 (20), 179 (25).

TABLE 1. Activities of Compound VIII and Novocainamide with Respect to Aconitine Arrhythmia in Rats

Compound	ED_{50}*	LD_{50}**, mg/kg	LD_{50}/ED_{50}
VIII	1.7	1780	1047.6
Novocainamide	40	105	2.4

* ED_{50} is the dose producing an antiarrhythmic effect in 50% of tests.
** LD_{50} is the dose leading to a 50% loss of animals.

EXPERIMENTAL BIOLOGICAL PART

The antiarrhythmic properties of compounds VII and VIII (in the form of sodium salts) were studied using the aconitine-, calcium chloride-, and adrenalin-induced models of arrhythmia in 48 white rats weighing 180 – 220 g narcotized by urethane (1 g/kg, i.p.), the strophanthin-induced arrhythmia model in 26 Guinea pigs weighing 250 – 350 g narcotized by sodium pentobarbiturate (40 mg/kg, i.p.) [7, 8], and the arrhythmia model induced by electric stimulation of auricles in 5 cats weighing 2.0 – 3.0 kg narcotized by hexenal (100 mg/kg, i.p.) [9]. The test compounds and reference preparations were injected into femoral veins of animals 1 – 2 min before application of the factor inducing disruption of the heart rhythm and conduction. In the case of arrhythmia models induced by aconitine (40 μg/kg), calcium chloride (200 mg/kg), adrenalin (200 μg/kg), and strophanthin K (0.5 mg/kg) injections, we compared the ability of compounds VII and VIII to prevent violations of the heart rhythm and conduction (or reduce their duration) and to increase the survival of test animals. The electrocardiograms were measured using the second standard leads. In the case of the electric arrhythmia model, the antiarrhythmic affect was judged by the ability of compounds to eliminate the flutter of right auricles of test cats, stimulated with a period of 1 – 2 min by rectangular pulses with a duration of 1 msec and a repetition frequency of 20 Hz, supplied from an ES-50-I electronic stimulator.

In addition, we have also studied the effect of compound VIII on the coronary blood flow in 4 narcotized cats [10].

The acute daily toxicity of the compounds was determined by intravenous injections to 80 male and female white mongrel mice weighing 18 – 22 g.

TABLE 2. Antiarrhythmic Activity of Compound VIII with Respect to Glycoside Intoxication Model

Compound	Dose, mg/kg	Period of arrhythmia, min	Lifetime, min
Strophanthin K (control)	0.5	10.5 ± 2.9	15.1 ± 3.1
Strophanthin K against the background of VIII	1.0	14.0 ± 7.4	45.0 ± 9.8*
	2.5	3.0 ± 0.7*	120.0 ± 6.3*
	4.0	12.0 ± 5.2	120.0 ± 12.7*
	5.0	20.0 ± 7.6	27.0 ± 9.2
	10.0	23.5 ± 11.3	26.0 ± 8.6

* $p < 0.05$ relative to the control.

RESULTS AND DISCUSSION

Compound VII was found to exhibit a weak antiarrhythmic activity at a dose of 2.5 mg/kg, decreasing the periods of arrhythmia 1.5 – 2 times. The same dose of compound VIII reduced the periods of arrhythmia almost 4.5 times and suppressed the ectopic effects. However, both decreased (to 1 mg/kg) and increased (to 4 and 5 mg/kg) doses of VIII produced a lower antiarrhythmic action, with the period of arrhythmia decreased only 1.5 times against the control. Under similar experimental conditions, novocainamide injections (40 mg/kg) produced a lower antiarrhythmic effect as compared to that of compound VIII (see Table 1).

Compound VIII at a dose of 1 – 4 mg/kg also increased the survival of test animals in the case of strophanthin-induced arrhythmia, while doses ≥ 2.5 mg/kg reduced the period of the arrhythmia (see Table 2).

Preliminary introduction of VIII at a dose of 1 mg/kg reduced the period of adrenalin-induced arrhythmia: the sinus rhythm was restored in 1.1 min (against 5.9 min in the control). The other manifestations of the violations of heart rhythm and conduction (bradycardia, extrasystole, AV block, P-wave inversion, R-amplitude reduction) were also more frequent and pronounced in the control experiments. However, the protective effect tended to decrease with increasing dose of VIII (≥ 2.5 mg/kg).

Neither of compounds VII and VIII at a dose of 5 mg/kg produced any noticeable effect on the auricular-type arrhythmia (polytopic auricular systole, auricle flutter) induced by calcium chloride.

2,7-Naphthyridine VIII at a dose of 1 – 10 mg/kg was unable to prevent from the electric-pulse-stimulated auricle flutter in cats, while a dose of 3 mg/kg increased the coronary blood flow on the average by 85.5 ± 3.1% during 45 – 60 min.

The LD_{50} of compounds VII and VIII for the intravenous introduction to white mice was 1125 mg/kg (ranging within 1071 – 1273 mg/kg) and 1780 (1614 – 1946) mg/kg, respectively.

Thus, the above data suggest that disodium salt of 4-aminocarbonyl-7-benzyl-5,6,7,8-tetrahydro-1,3-dioxy-2,7-naphthyridine (VIII) possesses antiarrhythmic activity with respect to aconitine, strophanthin, and adrenalin induced arrhythmia models, while showing almost no effect on the calcium chloride induced and electric-pulse-stimulated models.

It is therefore expedient to continue the study of 2,7-naphthyridine derivatives in the search for the new antiarrhythmic drugs.

REFERENCES

1. A. S. Noravyan, E. G. Paronikyan, and S. A. Vartanyan, *Khim.-Farm. Zh.*, **19**(7), 790 – 800 (1985).
2. E. Mueller, R. Maier, and W. Diederen, FRG Patent No. 1939.809, (1971); *Chem. Abstr.*, **74**, 88047g (1971).
3. B. Holmstedt and G. Lundgren, Ann. New York Acad. Sci., 142, 126 – 142 (1967); *Chem. Abstr.*, **67**, 20278h (1967).
4. E. G. Paronikyan, A. S. Noravyan, and S. A. Vartanyan, *Arm. Khim. Zh.*, **40**(9), 587 – 593 (1987).
5. K. Zh. Markaryan, Author's Abstract of the Candidate (Med. Sci.) Thesis, Erevan (1987).
6. B. Devausand and H. R. Pacheco, FRG Patent No. 2510.831 (1975); *Chem. Abstr.*, **84**, 17157b (1976).
7. N. V. Kaverina and Z. P. Senova, in: *Methodological Recommendations on the Experimental (Pharmacological) Characterization of Preparations Proposed for Clinical Testing as Medicinals for Prophylaxis and Treating of Heart Rhythm Disruptions* [in Russian], Moscow (1981), pp. 5 – 10.
8. M. D. Savina, *Farmakol. Toksikol.*, **49**(3), 47 – 50 (1986).
9. O. M. Avakyan, in: *Gangleron and Experience of Its Clinical Testing* [in Russian], Izd. Akad. Nauk Arm. SSR, Erevan (1959), pp. 100 – 105.
10. N. V. Kaverina, *Pharmacology of Coronary Blood Circulation* [in Russian], Medgiz, Leningrad (1963).