# CYCLIC N-CARBOXAMIDINES

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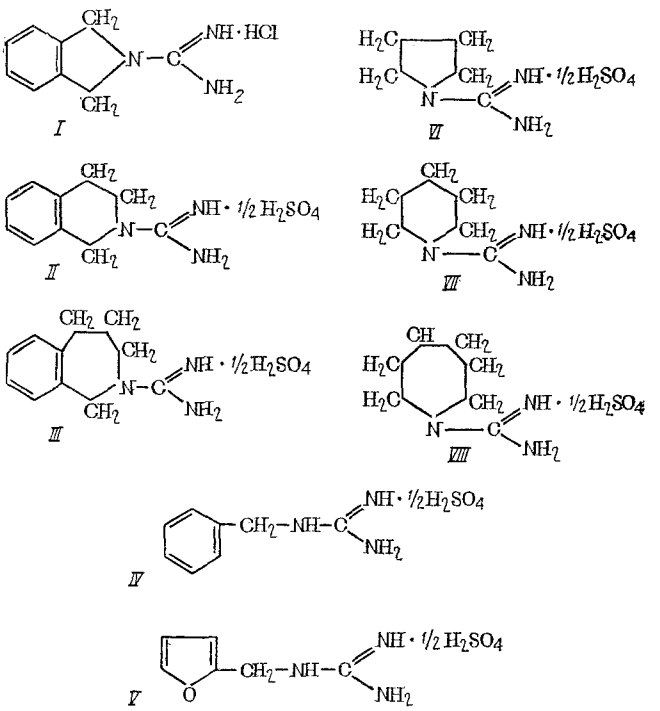
UDC 615.225.2:547.495.9

Oktadin, or 2-(1'-azacyclooctyl)-ethylguanidine sulfate, also known as ismelin, guanethidine, or octatensine [1], blocks selectively the transfer of nervous impulses in postganglionar sympathetic fibers. This property of the guanidine derivatives of the oktadin type was used to cure hypertonia. At the same time as oktadin, the hypotensive preparation ornid (darenthin, bretylan) with a simpler chemical structure, i.e., N-o-bromobenzyl-N-ethyl-N,N-dimethylammonium tosylate [2, 6], was introduced into medical practice. Shortly after the appearance of ornid, attempts were made to unite the structural elements which had the pharmacological effects of ornid and oktadin [3]. This was a basis for the preparation of several benzylguanidines, including benzanidin (N-benzyl-N',N"-dimethylguanidine sulfate) which was very thoroughly studied [4].

Despite the good results obtained during the application of the preparations of the guanidine series, these substances have side-effects (tendency to cumulation, hypertensive phase, orthostatic hypotonia, diarrhea, etc. [5]). Therefore, a search for new structures with selective activity was very desirable.



Our attention was drawn to partially hydrogenated heterocyclic systems with a benzylamine-type grouping. In the series of benzylguanidines, the best pharmacological effect was achieved by introducing a substituent into the ortho position [3]. Bases of the iso-indoline or 1,2,3,4-tetrahydroisoquinoline type satisfy these requirements. We synthesized and studied the pharmacological behavior of several such

Kaunas Medicinal Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 10, pp. 21-25, October, 1969. Original article submitted May 7, 1969.

guanidine compounds [7-9]. During the course of our work the hypotensive action of 1,2,3,4-tetrahydroisoquinoline-N-carboxamidine was reported [10], but no details were given. Later, a patent was published describing the synthesis of several carboxamidines based on tetrahydroisoquinoline and its benzo-substituted derivatives. The isoindoline and tetrahydrobenzodiazepine derivatives were also mentioned. However, no data on the pharmacological behavior of these compounds were given [11]. During the investigation of cyclic ethylguanidines, it was noted that the eight-membered ring leads to the maximum hypotensive action, but this effect decreases when the heterocyclic ring is increased further [12]. To clarify this question we synthesized and studied benzo-substituted derivatives with 5, 6, and 7 atoms in the ring, i.e., isoindoline-N-carboxamidine hydrochloride (I), 1,2,3,4-tetrahydroisoquinoline-N-carboxamidine sulfate (II), and 1,2,3,4-tetrahydrohomoisoquinoline-N-carboxamidine sulfate (III). For comparison, benzylguanidine sulfate (IV), furfurylguanidine sulfate (V), pyrrolidine-N-carboxamidine sulfate (VI), piperidine-N-carboxamidine sulfate (VII), and hexamethyleneimine-N-carboxamidine sulfate (VIII) were synthesized.

All the guanidine derivatives were obtained by the action of the appropriate base on S-methylisothiourea in an aqueous or alcoholic medium. With increase in the numbers of members in the ring, the rate of the reaction between the base and S-methylisothiourea decreased (the separation of methylmercaptan was retarded), and at the same time the yield of the guanidine derivative decreased. The solubility in water increases with increase in the ring. Thus compounds with a five-membered ring crystallize from water, while those containing a seven-membered ring crystallize only from alcohols and are hygroscopic. The purity of the compounds prepared was tested by ascending paper chromatography with the solvent n-butanol—acetic acid—water (120:30:20), using 25 mg of the substance to be analyzed. The spots were developed by moistening the dried chromatogram with an aqueous-acetone solution of sodium hydroxide, potassium ferricyanide, and sodium nitroprusside.

The $R_f$ value always increased with increase in the size of the ring. Certain pharmacological effects, such as the action on the blood pressure, increase in the case of compounds with low $R_f$ values. This is possibly due to the greater sorbability of this kind of compound.

With N-monosubstituted guanidines, for example (IV), the spots developed were light cerise in color. Other cyclic bases with a benzyl group gave light cerise spots, and cyclic compounds with no benzyl group gave violet spots.

Pharmacological studies showed that all the compounds with a benzyl group are slightly toxic. The highest toxicity in this series was shown by (IV) (73 mg/kg when administered to white male mice) [13], and the lowest by compound (V) and cyclic derivatives with a benzyl residue. In the latter case the toxicity decreases with increase in the size of the ring. The same relationship was obtained for cyclic derivatives with no benzyl group. Experiments on cats and rabbits showed that compounds with a benzyl group bound to the guanidine group are strong hypotensive agents [14]. The effect of cyclic derivatives is stronger and lasts longer than that of (IV), but it weakens with increase in the size of the ring. Cyclic bases with no benzyl group have almost no hypotensive activity. The blocking of the nictitating membrane is strongly marked in all the derivatives with a benzyl group bound to the guanidine group. It is maximum for (II), and is somewhat lower for (IV). Cyclic derivatives without a benzyl radical scarcely block the nictitating membrane in cats. If adrenalin is introduced over the background of the substances prepared, the change in the activity is noted only in the case of (IV) where the adrenalin effect is increased and lasts longer. When acetylcholine was introduced over the background of these preparations, a more prolonged effect was noted for (IV) only, while the anticholine-esterase activity is absent in all the substances studied. The antihistaminic activity is characteristic and is equally marked in almost all the derivatives with a benzylguanidine residue [8].

The action on an isolated heart is not very effective in low concentrations. Depressing action is more characteristic of noncyclic derivatives, but certain cyclic derivatives increase the amplitude and slow down the rhythm. Intestinal influence is observed only if the concentration is increased ($2 \cdot 10^{-4}$–$10^{-3}$) and appears as a depressant of the contracting function of the bowels. This feature is rather more characteristic of the cyclic derivatives. Peripheric blood vessels contracted under the influence of all these compounds. The cyclic compounds were more effective than the noncyclic guanidine derivatives. With cyclic derivatives with no benzylguanidine residue, the action increased with the increase in the size of the ring, while with cyclic derivatives with a benzylguanidine residue, the effect differed very little from that of noncyclic derivatives. Sleep induced by barbamyl was prolonged by derivatives with benzylguanidine residues, but sleep induced by chloral hydrate did not change under the influence of the same group of substances. On

the other hand, cyclic derivatives without a benzylguanidine residue produced almost twice the effect of chloral hydrate (on rats), but did not change the action of barbamyl. It is known that certain guanidine derivatives sharply decrease the amount of sugar in the blood. Experiments with our preparations have shown that all the compounds with noncyclic benzylguanidine increase the amount of sugar in the blood of rabbits. This reached a maximum after 15-30 min, and did not change further during 2-4 h. When compounds with a cyclic structure were introduced, the amount of sugar in the blood of rabbits decreased for 15 min after the administration with almost all the compounds studied, and the level was then maintained for 4-6 h.

## EXPERIMENTAL

Furfurylguanidine Sulfate (V). A 9.7-g (0.1 mole) portion of furfurylamine, 13.92 g (0.05 mole) of S-methylisothiourea sulfate, and 10 ml of water were placed in a round-bottomed flask (0.1 liter) fitted with a reflux condenser and an outlet. The mixture was heated on a water bath until the evolution of gas ($CH_3SH$) ceased completely ($1\frac{1}{2}$ h). A small amount of activated charcoal was added to the hot solution, and the mixture was heated for a few minutes and filtered. A 50-ml portion of ethanol was added to the filtrate. When cool, the crystalline precipitate was filtered and washed with a small amount of ethanol. Yield: 10 g (53% of theoretical). After recrystallization from dilute alcohol, 9.5 g of a colorless crystalline substance was obtained. Decomp. 212-213°, $R_f$ 0.66. Found %: N, 22.6; S, 8.73. $C_6H_9N_3O \cdot \frac{1}{2}H_2SO_4$. Calculated %: N, 22.34; S, 8.51.

Benzylguanidine sulfate (IV). As for the preceding compound, 5.5 g of a crystalline substance, decomp. 204°, was prepared from 5.35 g (0.05 mole) of benzylguanidine, 7 g (0.025 mole) of S-methylisothiourea sulfate, and 15 ml of water. Yield: 55% of theoretical. After recrystallization from 70% ethanol, the decomposition point was 205°. According to the literature [15], the decomposition point is 206°, $R_f$ 0.76.

Pyrrolidine-N-carboxamidine sulfate (VI). A mixture of 7.1 g (0.1 mole) of pyrrolidine, 13.92 g (0.05 mole) of S-methylisothiourea sulfate, and 10 ml of water was carefully heated on a water bath. To avoid too vigorous reaction, the flask was withdrawn from the bath at short intervals of time. When the reaction was carried out with large amounts of the starting substances, the mixture was cooled or S-methylisothiourea sulfate was added in small portions. After the evolution of gas had ceased (2 h), the mixture was cooled and filtered. Yield of colorless, crystalline substance was 6 g (40%), decomp. 290-292°. An additional amount of the substance could be obtained by evaporating the mother liquor. After recrystallization from a small amount of water or alcohol (50%), a compound was obtained, decomp. 294° (carbonization). $R_f$ 0.64. Found %: N, 25.92; S, 10.09. $C_5H_{11}N_3 \cdot \frac{1}{2}H_2SO_4$. Calculated %: N, 25.92; S, 9.89.

Piperidine-N-carboxamidine sulfate (VII). By the above method, 21 g (60%) of the substance was obtained, decomp. 280-281°, from 17.2 g (0.2 mole) of piperidine, 27.84 g (0.1 mole) of S-methylisothiourea sulfate, and 20 ml of water. After recrystallization from 70% ethanol, decomp. was 282-283°. $R_f$ 0.68. Found %: N, 23.89; S, 8.90. $C_6H_{13} \cdot \frac{1}{2}H_2SO_4$. Calculated %: N, 23.86; S, 9.09.

Hexamethyleneimine-N-carboxamidine sulfate (VIII). The reaction was carried out as described above. A mixture of 19.82 g (0.2 mole) of hexamethyleneimine, and 27.84 g (0.1 mole) of S-methylisothiourea sulfate in 25 ml of ethanol was heated on a water bath until the evolution of gas ceased. After cooling the mixture and diluting it with a mixture of methylcellosolve-ethyl acetate (1:1), the yield was 7 g (18.4%) of a crystalline substance, decomp. 227-228°. The recrystallization could be effected only with difficulty, since the substance is very hygroscopic, and is readily soluble in most organic solvents and water. $R_f$ 0.72. Found %: N, 21.90; S, 8.52. $C_7H_{15}N_3 \cdot \frac{1}{2}H_2SO_4$. Calculated %: N, 22.11; S, 8.33.

Isoindoline-N-carboxamidine hydrochloride (I). A mixture of 18.72 g of isoindoline hydrochloride, 10.2 g of sodium bicarbonate, and 50 ml of water was heated on a water bath until the evolution of carbon dioxide was complete. The mixture was then treated with 16.8 g of S-methylisothiourea sulfate and heated under reflux on a boiling water bath until the evolution of the gas completely ceased (2 h). The hot solution was filtered through a heated column and cooled, and the crystalline substance that precipitated was filtered. This was dried, and 23-24 g (98%) of a colorless substance, decomp. 247°, was obtained. After two recrystallizations from a small amount of water, the decomposition point was 248-249°. $R_f$ 0.67. Found %: N, 21.5; S, 18.1. $C_9H_{11}N_3 \cdot HCl$. Calculated %: N, 21.22; Cl, 17.91.

1,2,3,4-Tetrahydroisoquinoline-N-carboxamidine sulfate (II). As for furfurylguanidine sulfate, 16 g of a crystalline substance, decomp. 262°, was obtained from 14 g (0.1 mole) of 1,2,3,4-tetrahydroisoquinoline (containing a 4% admixture of isoquinoline), 14 g (0.05 mole) of S-methylisothiourea sulfate, and 13 ml of water, which were heated for 3 h on a boiling water bath and cooled. Yield: 71.4% of theoretical. After crystallization from a dilute alcohol, the decomp. was 269° (according to the literature [10], 273.5°), $R_f$ 0.72.

2,3,4,5-Tetrahydro-(1-H)-2-benzazepine-2-carboxamidine sulfate (III). The crystalline substance, decomp. 270°, was isolated in a yield of 7.25 g (60%) from a mixture of 7.35 g (0.05 mole) of homo-1,2,3,4-tetrahydroisoquinoline, 7 g (0.025 mole) of S-methylisothiourea sulfate, and 10 ml of water by the method used for 1,2,3,4-tetrahydroisoquinoline-N-carboxamidine sulfate after cooling the mixture and adding an n-propanol—acetone mixture (40 ml). After recrystallization from dilute propanol, the decomp. was 272°. $R_f$ 0.82. Found %: N, 17.52; S, 6.81. $C_{11}H_{15}N_3 \cdot \frac{1}{2}H_2SO_4$. Calculated %: N, 17.65; S, 6.72.

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