ALLOPURINOL, ITS SYNTHESIS AND PHARMACOLOGICAL ACTIVITY

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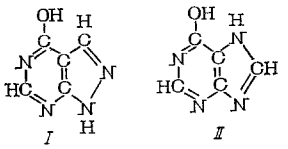
In 1963 the new preparation allopurinol was proposed for the treatment of states of disease accompanied by an increased concentration of uric acid in the organism [1-3]. At the present time, the substance is marketed abroad under the names Zyloric, Zyloprim, Milurit, Uridocid, Uriprim, Foligan, and others.

Chemically, the substance is pyrazolo[3,4-d]pyrimidin-4-ol (I); i.e., it is a pyrazole isomer of hypoxanthine (II).



I II

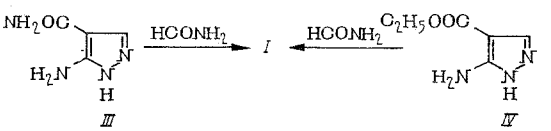
Allopurinol (I) is a white crystalline powder with mp > 330°C very sparingly soluble in water.

The mechanism of the action of (I) is connected with its capacity for competitively inhibiting the activity of xanthine oxidase [4] – an enzyme causing the conversion of (II) into xanthine and of xanthine into uric acid. Under the influence of (I) the oxidation of the purine bases stops at the stage of xanthine at (II), and no formation of uric acid takes place. Thanks to this, (I) has found use in various forms of podagra, and also in the chemotherapy of malignant neoplasias when as the result of the intensive decompositon of the tumor tissues an excess of nucleoproteins accumulates. In addition, there is information that (I) inhibits the enzymatic cleavage of mercaptopurine in the organism [5] and thereby enhances its effect.

Compound (I) was first synthesized from 3-aminopyrazole-4-carboxamide (III) [6], and somewhat later [7], it was synthesized from 3-amino-4-ethoxycarbonylpyrazole (IV). The latter method was used in our work. It includes the condensation of (IV) with formation of a bicyclic condensed system.

TABLE 1. Influence of Allopurinol (I) and of Milurit on the Concentration of Uric Acid in the Urine (mean results of experiments on 10 rats)

Preparation	Dose (mg/kg)	Decrease in the amount of uric acid (% of the initial level)		
		after the first dose	after the 14th dose	14 days after the final dose
I	100	28,6	69,96	37,3
Milurit	100	28,7	55,80	—
I	50	19,9	Not administered	Not administered
I	25	17,7	18,5	2,2
Milurit	25	14,8	28,0	10



III IV

According to the literature, the condensation requires the reactants used to be heated to a temperature of 190-200°C. The accurate reproduction of these conditions showed that the reaction product obtained is highly resinified and has a strong brownish-gray color from which it cannot be freed completely by precipitation with acid from alkaline solution. Lowering the reaction temperature to 150°C in order to reduce resini-

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TABLE 2. Influence of the Repeated (every day for 14 days) Administration of Allopurinol (I) at a Dose of 250 mg/kg on the Concentration of Uric Acid in the Urine (average results from experiments on 20 rats)

Preparation	Conc. of uric acid (mg-%)				
	before administration	after the 1st administration	after the 7th administration	after the 14th administration	7 days after the final administration
I	29,7±0,81	15,7±0,83	13,7±0,12	15,05±0,13	20,75±1,2
Control	27,8±0,11	27,0±0,12	28,2±0,10	26,85±0,80	28,6±0,11

fication led to a decrease in the yield of (I) to 58%. Accompanying it was 30% of a substance with the empirical formula $C_7H_9N_3O_3$, which is apparently 3-formamido-4-ethoxycarbonylpyrazole and is also capable of giving (I) on being heated with formamide.

We have solved the problem of eliminating the coloration of (I) by performing the condensation in the presence of concentrated hydrochloric acid. After equimolecular amounts of (IV) and concentrated hydrochloric acid had been heated with an excess of formamide at 160-180°C (preferably 170°C), on cooling about 90% of faintly colored (I) precipitates, and, after reprecipitation from an alkaline solution that has been treated with carbon, it becomes colorless or almost colorless and its quality satisfies the requirements of foreign pharmacopoeias [9].

The pharmacological activity and toxicity of the sample of (I) obtained were tested experimentally on mice, rats, and rabbits. The preparation was administered by gavage in the form of a suspension in starch paste.

The index of the activity of the preparation was taken to be its capacity for decreasing the concentration of uric acid in the urine of white rats. It was found that even with a single dose, beginning at 25 mg/kg, compound (I) decreases the amount of uric acid. With an increase in the dose and in the time of its administration, this effect is enhanced (Table 1) (for comparison the results of experiments with the administration of Milurit have been included in Table 1). At a dose of 250 mg/kg the preparation causes a decrease in the amount of uric acid by almost 60% even after a single administration (Table 2).

The toxicity of (I) is low. In rats with a single administration at a dose of up to 500 mg/kg it causes no visible toxic phenomena. Rabbits tolerate doses of the preparation of up to 100 mg/kg without significant changes in behavior and general state. In experiments on white mice, the LD_{50} was 78 mg/kg.

Foreign samples of (I) (Zyloric) have been subjected to clinical tests in the medical institutes of the USSR; the preparation is recommended by the pharmacological committee of the Ministry of Health of the USSR for use in medical practice. The indications for its use are podagra, secondary hyperuricemia, various pathological states accompanying increased decomposition of nucleoproteins (acute and chronic leukemia, multiple myeloma, psoriasis, etc.); (I) is also used for the prophylaxis of diseases of the kidneys caused by uric acid salts formed in excess in the chemotherapy or radiotherapy of malignant neoplasias [in this case, treatment with (I) is begun 5-6 days before the chemotherapy or radiotherapy].

The time of treatment with (I) varies from 2-3 weeks to 3-6 months. The preparation is prescribed in 100-mg tablets 3-5 times a day. The highest daily dose for adults is 800 mg. The preparation is prescribed for children in an amount of 8 mg/kg per day. During treatment, a daily excretion of urine of not less than 2 liters must be maintained (the urine should preferably be neutral or alkaline).

As a rule, (I) is well tolerated by the patients; in rare cases, it may cause acute attacks of podagra, and sometimes nausea, vomiting, diarrhea, skin rash, and fever. It is not recommended to prescribe the preparation to pregnant women [3].

Abroad, the preparation is marketed in 0.1-g tablets.

EXPERIMENTAL

Pyrazolo[3,4-d]pyrimidin-4-ol (Allopurinol, I). A mixture of 28 g of (IV), 112 ml of formamide, and 15 ml of concentrated hydrochloric acid was heated with stirring at a temperature of 170° in the reaction mixture for 8 h. After cooling, 100 ml of water was added, and the mixture was filtered. The substance

obtained (21.4 g) was dissolved in dilute sodium hydroxide solution, and the solution was shaken with carbon and was then acidified with 18% hydrochloric acid to pH 3-4. A white precipitate of (I) deposited. Yield 18.67 g (75.77%) of a substance not melting below 350°C. Found, %: C 44.43; H 3.12; N 41.38. $C_5H_4N_4O$. Calculated, %: C 44.12; H 2.94; N 41.18.

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