INVESTIGATIONS ON LACTAMS

# XI. A New Heterocyclic System — Thiazano[4,3-e]purine*

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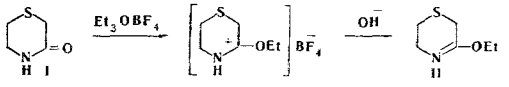
3-Ethoxy-3,4-dehydrothiazane has been synthesized by the reaction of 3-thiazanone with triethyloxonium fluoroborate. The condensation of 3-ethoxy-3,4-dehydrothiazane with α-amino-α-cyanoacetamide has given 3-amino-2-carbamoylimidazo [2,1-c]thiazane, which is the key compound for the synthesis of a new series of heterocyclic compounds, 4-substituted thiazano[4,3-e]purines.

Already for quite a number of years condensed derivatives of the purines have attracted the attention of investigators as possible antagonists of the natural purines, which are constituents of the nucleic acids. In this case, the concept of an antimetabolite is expressed in the fact that this type of tricyclic purine retaining the purine skeleton excludes the possibility of the formation of a nucleoside through positions 7 and 9 of the purine molecule [1].

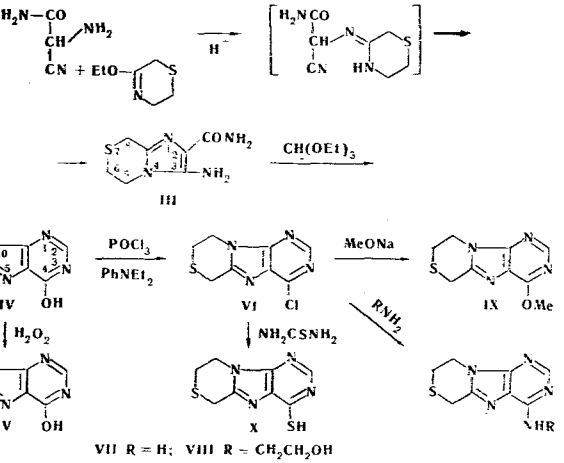
In view of this, a whole series of condensed purines has been synthesized, including tricyclic purines containing sulfur-containing thiazole [2–4] and thiazine [5] rings. However, in all these compounds, the sulfur-containing ring was condensed with the *f* side of the purine molecule, which determined the position of the double bond in the imidazole ring of the latter as $C_{(8)}=C_{(8)}$, while the $N_{(7)}=C_{(8)}$ position of the double bond is characteristic for the natural β-purines. In view of this, we set ourselves the task of synthesizing for biological investigations sulfur-containing tricyclic analogs of such compounds as adenine, 6-mercaptopurine, and others, with the retention of the $N_{(7)}=C_{(8)}$ position of the double bond as in the natural compounds.

To carry out the task mentioned, as starting material we took 3-thiazanone (I), which is readily formed by the condensation of ethyl thioglycolate with ethyleneimine [6].

The alkylation of I with triethyloxonium fluoroborate [7], like the alkylation of 3-morpholone [8], gave 3-methoxy-3,4-dehydrothiazane (II) containing, judging from the analysis and the qualitative tests for fluorine, the borofluorate as impurity. The structure of II was confirmed by the IR spectrum (presence of an absorption band of the C=N bond at 1690 $cm^{-1}$) and also by its subsequent transformation.



Using the reaction [9] of lactim ethers with α-amino-α-cyanoacetamide, we succeeded in achieving the conversion of II into 3-amino-2-carbamoylimidazolo-[2,1-c]thiazane (III). The structure of the latter was confirmed by the qualitative reaction characteristic for 5(4)-aminoimidazoles (the coupling of the diazonium salt III with α-naphthol, taking place with the formation of a purple dye), and also by its cyclization with orthoformic ester to 4-hydroxythiazano-[4,3-c]purine (IV), the UV spectrum of which, as in the case of the polymethylenehypoxanthines [10], had a single maximum at 258 nm. The oxidation of IV with hydrogen peroxide in glacial $CH_3COOH$ gave the sulfoxide IV (V), the structure of which was confirmed by its IR spectrum (the presence of absorption bands at 1050 $cm^{-1}$, characteristic for sulfoxides, and at 1690 $cm^{-1}$, characteristic for an amide carbonyl group). When IV was heated with phosphorus oxychloride in the presence of diethylaniline, 4-chlorothiazano[4,3-e]purine (VI) was obtained and by reaction with ethanolic solutions of ammonia and ethanolamine it was converted into 4-amino- (VII) and 4-(β-hydroxyethyl)amino- (VIII) -thiazano-[4,3-e]purines, respectively. Similarly, when VI was heated with sodium methoxide and with thiourea in ethanol, we obtained 4-methoxy-(IX) and 4-mercapto- (X) -thiazano[4,3-e]purines, respectively.



VII R = H; VIII R = $CH_2CH_2OH$

## EXPERIMENTAL

**3-Ethoxy-3,4-dehydrothiazane (II).** A solution of 59 g of 3-thiomorpholone (I) in 150 ml of chloroform was added gradually at 10° C over 1 hr to a solution of triethyloxonium fluoroborate (prepared from 104 g of boron trifluoride etherate and 52 g of epichlorohydrin) in 50 ml of dry chloroform.

In the reaction, an oil deposited which gradually solidified. The reaction mixture was left overnight and then 100 ml of water was added and it was cooled with ice and, with vigorous stirring, 8% of NaOH was slowly added to pH ~8. After the separation of the organic layer, the aqueous layer was extracted with chloroform, the combined extracts were dried with $Na_2SO_4$ and evaporated in vacuum, and the residue was distilled, giving 34.5 g of II, bp 88–91° C (20 mm).

*Investigation carried out in the chemical laboratory of Cambridge University, England.

**3-Amino-2-carbamoylimidazo[2,1-c]thiazane (III).** A mixture of 8.5 g of II, 6 g of aminocyanoacetamide, and 60 ml of absolute methanol was treated with 1 ml of a 20% solution of HCl in ethanol and was boiled for 4 hr. During heating, the consistency of the solid matter changed. On the following day the reaction mixture was filtered and the residue was washed with water and ethanol and dried. Yield 7.4 g (53.7%), mp 290–293° C. Sparingly soluble in water, in the majority of organic solvents, and in dilute alcohols, readily soluble in acids; for analysis it was crystallized from water (1:700), mp 292–294° C. Found, %: C 42.84; H 5.56; N 28.4. Calculated for $C_7H_{10}N_4OS$, %: C 42.42; H 5.05; N 28.28%.

**4-Hydroxythiazano[4,3-e]purine (IV).** A mixture of 4.7 g of III, 30 ml of orthoformic ester, and 20 ml of acetic anhydride was boiled with stirring for 3 1/2 hr, the dark solution was evaporated to dryness in vacuum, and the residue was boiled with 100 ml of water for 2 hr. After cooling in ice, the solid matter was filtered off and was washed with water and ethanol. Yield 4.6 g (93%), mp > 300° C. Sparingly soluble in the majority of organic solvents and in acids, readily soluble in dilute alkalies; for analysis it was crystallized from water (1:140). Found, %: C 46.2; H 3.9; N 27.3%. Calculated for $C_8H_5N_4OS$, %: C 46.15; H 3.90; N 26.92.

**S-Oxide of 4-hydroxythiazano[4,3-e]purine (V).** With vigorous stirring, 2 ml of 30% hydrogen peroxide was added dropwise to a suspension of 1.7 g of IV in 2 ml of acetic anhydride and 7 ml of glacial acetic acid at 0–2° C, and stirring was continued at this temperature for 3 1/2–4 hr. During this process a change in the consistency of the mass took place and a white precipitate was formed which was filtered off, washed with ethanol, and dried. Yield 1.6 g (87.4%), decomp. p. ~290° C. Sparingly soluble in the majority of organic solvents, soluble in dilute alkalies and acids. For analysis, it was crystallized first from aqueous ethanol and then from water, mp 290–292° C (decomp). Found, %: C 42.75; H 3.70; N 24.95; S 13.87, 14.53. Calculated for $C_8H_8N_4O_2S$, %: C 42.85; H 3.57; N 25.00; S 14.28.

**4-Chlorothiazano[4,3-e]purine (VI).** A mixture of 10.7 g of IV, 5 ml of diethylaniline, and 200 ml of phosphorus oxychloride was boiled with stirring for 6 hr. On the following day, the reaction mixture was evaporated to dryness in vacuum, and ground ice was added to the residue in small portions. After the decomposition of the phosphorus oxychloride, the reaction mixture was brought to pH 7.5–8 with 2 N NaOH and extracted with chloroform. The extract was dried with $Na_2SO_4$ and evaporated to dryness in vacuum; the residue was triturated with ether, cooled with ice, filtered, and dried. Yield 8.2 g (70.3%), mp 170° C (decomp). Soluble on heating in ether and ethyl acetate; readily soluble in chloroform, ethanol, acetone, and benzene; for analysis it was crystallized from petroleum ether, mp 177–182° C (decomp). Found, %: C 42.9; H 2.68; Cl 15.9; N 24.62. Calculated for $C_8H_7N_4ClS$, %: C 43.14; H 3.08; Cl 15.67; N 24.72.

**4-Mercaptothiazano[4,3-e]purine (X).** To a solution of 1.75 g of VI in 100 ml of absolute ethanol 0.6 g of thiourea was added and the mixture was heated in the water bath with stirring for 3 hr. The precipitate that had deposited was filtered off, washed with ethanol, and dried. The field of X was 1.4 g (80.9%), decomp. p. ~250° C, mp 289–293° C. Sparingly soluble in the majority of organic solvents, in water, and in acids, readily soluble in dilute alkalies; for analysis it was crystallized from water (1:700). Found, %: C 43.1; H4.0; N 25.7. Calculated for $C_8H_8N_4S_2$, %: C 42.85; H. 3.57; N 25.00.

**4-Methoxythiazano[4,3-e]purine (IX).** To a solution of sodium methoxide (prepared from 0.35 g of Na and 100 ml of absolute methanol) 1.2 of VI was added, and the mixture was boiled for 2 1/2 hr and filtered from the NaCl that had deposited. After neutralization with acetic acid to pH 6.5, the mother solution was evaporated to dryness in vacuum and the residue was suspended in 40 ml of water and extracted with chloroform. After being dried with $Na_2SO_4$, the extract was evaporated to dryness in vacuum and the residue was triturated with ether, filtered off, and dried. Yield 0.85 g (72.6%), mp 148–150° C. Soluble in the majority of organic solvents, sparingly soluble in water; for analysis it was crystallized from ether, mp 150–152° C. Found, %: C 48.54; H 4.80; N 25.37. Calculated for $C_9H_{10}N_4OS$, %: C 48.64; H 4.50; N 25.22.

**4-Aminothiazano[4,3-e]purine (VII).** A mixture of 1.2 g of VI and 50 ml of a 12% ammonia in methanol was heated at 160° C in an autoclave for 6 hr. After cooling, the reaction mixture was evaporated to dryness, and the residue was crystallized from 100 ml of water. Yield 0.9 g (82%), mp 280–285° C (decomp). Sparingly soluble in the majority of organic solvents and in water, insoluble in alkalies, soluble in acids on heating. Found, %: C 46.83; H 4.72; N 33.71. Calculated for $C_8H_7N_5S$, %: C 46.37; H 4.34; N 33.81.

**4-(β-Hydroxyethyl)aminothiazano[4,3-e]purine (VIII).** A solution of 0.95 g of VI and 1 ml of monoethanolamine in 20 ml of ethylcellosolve was boiled for 2 hr. After the end of the reaction, the mixture was evaporated to dryness in vacuum, the residue was dissovled in 10 ml of water, and the solution was extracted with chloroform. After being dried with $Na_2SO_4$, the extract was evaporated to dryness in vacuum and the residue was triturated with ether, filtered off, and dried. Yield 0.75 g (71%), mp 142–148° C. Sparingly soluble in petroleum ether and diethyl ether, soluble on heating in ethyl acetate, benzene, and water, readily soluble in chloroform and in dilute acids; for analysis it was crystallized from ethyl acetate, mp 148–150° C. Found, %: C 47.2; H 5.29; N 24.42. Calculated for $C_{10}H_{13}N_5OS$, %: C 47.73; H 5.17; N. 27.88.

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