INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXXVII.* ACTION OF α-HALO ALDEHYDES AND THEIR ACETALS ON 8-THIO DERIVATIVES OF PURINE AND THEOPHYLLINE

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Purinyl(theophyllinyl)-8-mercapto aldehydes and their acetals were synthesized by the reaction of 8-thio derivatives of purine and theophylline with α-halo aldehydes and their acetals. The IR spectra demonstrated that the indicated aldehydes exist in the solid state as tautomeric forms – 3-hydroxy derivatives of thiazolino[2,3-*f*]purines (xanthines). Dehydration of the latter gave thiazolo[2,3-*f*]purine, 6,8-dimethylthiazolo[2,3-*f*]xanthine, and their 2-alkyl-substituted derivatives. The structures of the three-ring compounds were established by reductive desulfuration to 7-alkyl-substituted purines and theophyllines.

Gordon [2] studied the reaction of 2,6-diamino-8-thiopurine with chloroacetaldehyde diethylacetal, but he was unable to isolate an individual compound. The action of α-halo aldehydes or their acetals on 8-thioxanthines has not been described in the literature.

As we have already reported in [3-7], we have investigated the reactions of 8-thiopurine (I) and 8-thiotheophylline (II) with chloroacetaldehyde, bromoacetaldehyde, and α-bromopropionaldehyde diethylacetals. It was established that, depending on the reaction conditions and structures of the starting materials, the indicated reactions give various compounds. The reaction of II with bromoacetal in absolute ethanol in the presence of sodium ethoxide gives theophyllinyl-8-mercaptoacetaldehyde diethylacetal (III), which is readily hydrolyzed in water to the corresponding aldehyde (VI) and is converted to 6,8-dimethylthiazolo[2,3-*f*]xanthine (XIII) by the action of concentrated H_2SO_4.

The reaction of I and II with chloroacetaldehyde or bromoacetaldehyde and α-bromopropionaldehyde acetals in water or aqueous methanol at 45-100°C gives purinyl(theophyllinyl)-8-mercapto aldehydes (IV-VII), in which, as in the analogous derivatives of imidazole [8,9], imidazoline [9], benzimidazole [10], and naphth[1,2-d]imidazole [11], ring–chain tautomerism occurs. Judging from the IR spectra (the absence of absorption bands of an aldehyde group and the presence of the absorption band of a hydroxyl group), these compounds exist in the solid state as 3-hydroxy derivatives of thiazolino[2,3-*f*]purine (xanthine). In solutions they are capable of undergoing conversion to the aldehyde form, as attested to by chemical reactions for the carbonyl group, particularly the formation of 2,4-dinitrophenylhydrazones (VIII-X).

Compounds IV-VII readily split out a molecule of water on reaction with dehydrating agents ($POCl_3$, H_2SO_4) or on refluxing in hydrochloric acid to give the corresponding thiazolo[2,3-*f*]purines (xanthines) (XI-XIV).

Closing of the thiazoline ring during the cyclization of the purinyl(theophyllinyl)-8-mercapto aldehydes might occur in the 7 or 9 position of the purine ring, which ultimately, after dehydration of the intermediate hydroxythiazolinopurines (xanthines), would give XI-XIV, the corresponding thiazolo[2,3-e]purine-(xanthine) derivatives, or mixtures of the isomers. In all cases we isolated only thiazolo[2,3-*f*]purine derivatives (XI, XII) and thiazolo[2,3-*f*]xanthine derivatives (XIII, XIV), the individuality of which was

*See [1] for communication LXXVI.

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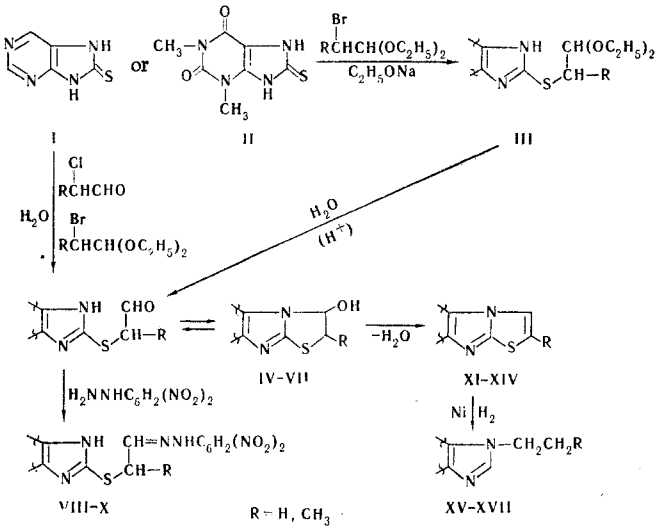
established by chromatography, and the structures of which were established by reductive desulfuration under the influence of Raney nickel [11, 12] to 7-alkyl-substituted purines (XV) and theophyllines (XVI, XVII).



EXPERIMENTAL

Theophyllinyl-8-mercaptoacetaldehyde Diethylacetal (III, R = H). A solution of 20 mmole of sodium ethoxide, 4.24 g (20 mmole) of II [13], and 4 g (0.02 mole) of bromoacetaldehyde diethylacetal in 80 ml of absolute ethanol was refluxed for 13 h and cooled. The solvent was removed by vacuum distillation, the residue was dissolved in chloroform, and the solution was washed with water and dried over $MgSO_4$. The solvent was removed by distillation to give 1.86 g (30%) of a product with mp 170-171° (dec., from absolute ethanol). IR spectrum, cm^{-1}: 1645, 1725 (CO), 3170 (NH). Found: C 47.2; H 6.1; N 16.9; S 10.1%. $C_{13}H_{20}N_4O_4S$. Calculated: C 47.5; H 6.1; N 17.1; S 9.8%.

3-Hydroxythiazolino[2,3-*f*]purine (IV). A. A mixture of 2.22 g (15 mmole) of I [14] and 1.37 g (15.8 mmole) of the hydrate of dimeric chloroacetaldehyde in 20 ml of water was heated at 45° for 45 min. The solution was treated with charcoal and filtered, and the filtrate was neutralized with $NaHCO_3$ and cooled to 2-3°. The precipitate was removed by filtration and washed with water to give 1.45 g (50%) of a product with mp 191-192° (dec., from water) and R*f* 0.65 (system 1) and 0.66 (system 2). IR spectrum, cm^{-1}: 3170 (OH). Found: C 43.0; H 3.1; N 28.6; S 16.4%. $C_7H_6N_4OS$. Calculated: C 43.3; H 3.1; N 28.8; S 16.5%. The picrate had mp 197° (dec., from water). Found: N 22.9%. $C_7H_6N_4OS \cdot C_6H_3N_3O_7$. Calculated: N 23.2%.

B. A solution of 1.52 g (10 mmole) of I and 2.0 g (10 mmole) of bromoacetaldehyde diethylacetal in 30 ml of 90% methanol was heated at 50-55° for 6 h and filtered. The methanol was removed by vacuum distillation, and the residue was neutralized with aqueous $NaHCO_3$. The precipitate was removed by filtration and crystallized from water to give 0.15 g (8%) of product.

2-Methyl-3-hydroxythiazolino[2,3-*f*]purine (V). A solution of 1.52 g (10 mmole) of I and 2.32 g (11 mmole) of α-bromopropionaldehyde diethylacetal in 15 ml of water was heated at 96-97° for 30 min and cooled. The mixture was neutralized with $NaHCO_3$ and extracted with chloroform. The extract was washed with water and dried with Na_2SO_4. The solvent was removed by distillation, and the residue was washed with cold acetone and recrystallized from water to give 0.3 g (16%) of a product with mp 205-206° (dec.) and R*f* 0.82 (system 1). IR spectrum, cm^{-1}: 3050 (OH). Found: C 46.1; H 4.1; N 26.8; S 15.5%. $C_8H_8N_4OS$. Calculated: C 46.1; H 3.9; N 26.9; S 15.4%. The picrate had mp 202-204° (from water).

3-Hydroxy-6,8-dimethylthiazolino[2,3-*f*]xanthine (VI). A. A mixture of 2.12 g (10 mmole) of II and 1.46 g (15 mmole) of the hydrate of dimeric chloroacetaldehyde or 2.2 g (11 mmole) of bromoacetaldehyde diethylacetal in 50 ml of water was refluxed for 4 h. The hot solution was filtered off from the unchanged II, and the filtrate was cooled. The precipitate was removed by filtration and washed with water to give 1.5-2.3 g (60-90%) of a product with mp 180-181° (from aqueous ethanol). IR spectrum, cm^{-1}: 1650, 1710 (CO); 3330 (OH). Found: C 42.6; H 3.8; N 21.8; S 12.6%. $C_9H_{10}N_3O_3S$. Calculated: C 42.5; H 4.0; N 22.0; S 12.6%.

B. A mixture of 1.2 g of III, 20 ml of water, and two drops of acetic acid was refluxed for 5 h and cooled to 1-2°. The precipitate was removed by filtration and washed with water to give 0.9 g (92%) of VI.

2,6,8-Trimethyl-3-hydroxythiazolino[2,3-*f*]xanthine (VII). A mixture of 6.36 g (30 mmole) of II and 6.96 g (33 mmole) of α-bromopropionaldehyde diethylacetal in 100 ml of aqueous dimethylformamide (1 : 1) was heated at 50-60° for 9 h. The mixture was then neutralized with sodium acetate and poured into water. The aqueous mixture was extracted with chloroform, and the extract was dried over Na_2SO_4. The solvent was removed by distillation to a small volume, the solution was cooled, and the precipitate was removed by filtration to give 5.3 g (63%) of a product with mp 169-171° [dec., from methanol–chloroform (10 : 1)]. IR spectrum, cm^{-1}: 1665, 1715 (CO); 3180 (OH). Found: C 45.0; H 4.3; N 20.6; S 12.3%. $C_{10}H_{12}N_4O_3S$. Calculated: C 44.8; H 4.5; N 20.9; S 12.0%.

Purinyl-8-mercaptoacetaldehyde 2,4-Dinitrophenylhydrazone (VIII). A solution of 0.1 g (5 mmole) of IV and 0.1 g (5 mmole) of 2,4-dinitrophenylhydrazine in 3 ml of acetic acid was heated at 100° for 15 min. The mixture was cooled, and the yellow precipitate was removed by filtration to give 0.12 g (63%) of a product with mp 205-206° (dec., from dioxane). Found: C 41.9; H 2.8; N 29.6; S 8.4%. $C_{13}H_{10}N_8O_4S$. Calculated: C 41.7; H 2.7; N 29.9; S 8.6%.

Theophyllinyl-8-mercaptoacetaldehyde 2,4-Dinitrophenylhydrazone (IX). This was obtained in 64% yield by the method used to prepare VIII and had mp 245-247° (dec., from acetic acid–dioxane). Found: C 41.2; H 3.5; N 26.1; S 7.6%. $C_{15}H_{14}N_8O_6S$. Calculated: C 41.5; H 3.2; N 25.8; S 7.4%.

Theophyllinyl-8-mercaptopropionaldehyde 2,4-Dinitrophenylhydrazone (X). This compound was obtained in 92% yield by the method used to prepare VIII and had mp 220-222° (dec., from acetic acid). Found: N 25.0%. $C_{16}H_{16}N_8O_6S$. Calculated: N 25.0%.

Thiazolo[2,3-*f*]purine (XI). A solution of 0.6 g of IV in 30 ml of $POCl_3$ was refluxed for 45 min. The $POCl_3$ was removed by vacuum distillation, and the residue was dissolved in water. The solution was neutralized with $NaHCO_3$ and extracted with chloroform. The extract was washed with water and dried over $MgSO_4$. The solvent was removed by vacuum distillation to give 0.4 g (74%) of a product with mp 263-264° (dec., from 70% ethanol) and R_f 0.59 (systems 1 and 2). Found: C 47.7; H 2.4; N 31.7; S 18.5%. $C_7H_4N_4S$. Calculated: C 47.7; H 2.3; N 31.8; S 18.2%. The picrate had mp 234-235° (dec., from 70% ethanol). Found: N 24.2%. $C_7H_4N_4S \cdot C_6H_3N_3O_7$. Calculated: N 24.2%.

2-Methylthiazolo[2,3-*f*]purine (XII). A solution of 1.6 g of V in 10 ml of $POCl_3$ was refluxed for 5 h and worked up as described for the preparation of XI to give 0.6 g (39%) of a product with mp 284-285° (dec., from 50% methanol) and R_f 0.68 (system 1) and 0.57 (system 2). Found: C 50.5; H 3.5; N 29.6; S 16.6%. $C_8H_6N_4S$. Calculated: C 50.5; H 3.2; N 29.4; S 16.8%. The picrate had mp 209-210°. Found: S 7.5%. $C_8H_6N_4S \cdot C_6H_3N_3O_7$. Calculated: S 7.6%.

6,8-Dimethylthiazolo[2,3-*f*]xanthine (XIII). A. A mixture of 4.24 g (20 mmole) of II and 2.1 g (22 mmole) of the hydrate of dimeric chloroacetaldehyde or 4.4 g (22 mmole) of bromoacetaldehyde diethylacetal in 30 ml of 25% HCl was refluxed for 2 h, cooled, and neutralized with ammonium hydroxide. The precipitate was removed by filtration and washed with water to give 4-4.1 g (86-87%) of a product with mp 250-252° (dec., from aqueous ethanol) and R_f 0.87 (system 3) and 0.78 (system 4). IR spectrum, cm^{-1}: 1665, 1710 (CO). Found: C 45.3; H 3.2; N 23.8; S 13.2%. $C_9H_8N_4O_2S$. Calculated: C 45.7; H 3.4; N 23.7; S 13.6%.

B. A 0.66-g sample of III or 0.51 g of VI in 10 ml of 25% HCl was refluxed and worked up as in experiment A to give 0.4-0.42 g (86-89%) of product.

C. A solution of 0.35 g of III or 0.25 g of VI in 3 ml of 96% H_2SO_4 was allowed to stand for 15 h and poured into water. The aqueous mixture was neutralized with ammonium hydroxide, and the precipitate was removed by filtration to give 0.19-0.2 g (80-85%) of product.

D. A 5-g sample of VI was refluxed in 50 ml of $POCl_3$ for 2 h, after which the $POCl_3$ was removed by vacuum distillation. Water was added to the residue, and the mixture was neutralized with $NaHCO_3$. The precipitate was removed by filtration to give 4.5 g (98%) of product. The samples obtained by the various methods did not depress one another's melting points.

2,6,8-Trimethylthiazolo[2,3-*f*]xanthine (XIV). This compound was obtained by the methods (a and d) used to obtain XIII and also by refluxing II with α-bromopropionaldehyde diethylacetal in water for 4 h to

give 84-89% of a product with mp 217-219° (dec., from aqueous ethanol) and R_f 0.84, 0.91, and 0.82 (in systems 1, 3, and 4, respectively). IR spectrum,* cm^{-1}: 1675, 1715 (CO). Found: C 47.7; H 3.7; N 22.2; S 13.0%. $C_{10}H_{10}N_4O_2S$. Calculated: C 48.0; H 4.0; N 22.4; S 12.8%.

7-Ethylpurine (XV). A mixture of 1.15 g of XI and 20 g of an alcohol paste of Raney nickel in 50 ml of ethanol was refluxed for 1 h and filtered. The ethanol was removed by vacuum distillation, and the residue was crystallized from cyclohexane to give 0.3 g (27%) of a product with mp 106-107°, in agreement with the value given in [12].

7-Ethyltheophylline (XVI). This compound was obtained from XIII by a method similar to that used to prepare XV (by refluxing for 2 h) and had mp 154° (sublimed). The product did not depress the melting point of an authentic sample of XVI [15].

7-Propyltheophylline (XVII). This compound was obtained from XIV by a method similar to that used to prepare XVI and had mp 100-101° (sublimed). The product did not depress the melting point of a genuine sample of XVII [15].

Methods Used to Chromatograph Thiazolo[2,3-*f*]purine(xanthine) Derivatives. The chromatographic characteristics of XI-XIV were obtained by the ascending method [16] on Leningrad M paper in the following systems: n-butyl alcohol saturated with 20% pyridine solution (system 1), methanol–water (1 : 4) (system 2), chloroform–methanol–water (13 : 6 : 1) (system 3), and n-butyl alcohol–acetic acid–water (4 : 1 : 2) (system 4). The brick-red spots were developed as a result of successive spraying of the dry chromatograms with 0.1 N $AgNO_3$ solution, 0.5% $K_2Cr_2O_7$ solution, and 0.5 N HNO_3, or with iodine vapors. The latter developer proved to be more reliable for thiazolo[2,3-*f*]xanthine derivatives.

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