INVESTIGATIONS IN THE XANTHINE SERIES AND AMONG ITS CONDENSED DERIVATIVES

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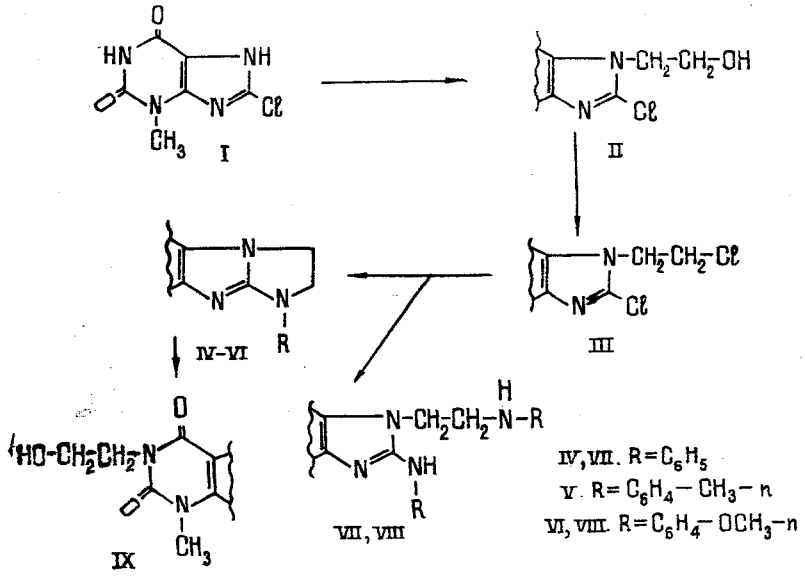
UDC 547.857.4:547.887.2

A method has been developed for obtaining derivatives of 8-methyl-2,3-dihydro-6H-imidazo[1,2-f]xanthine. It has been established that 2,3-dihydroimidazo[1,2-f]-xanthines alkylate in position 6 of the uracil fragment. A method has been developed for obtaining derivatives of 2,3-dihydroimidazo[1,2-f]purin-7-one. The structure of the compounds synthesized have been confirmed by IR and PMR spectroscopy.

One of the promising directions in the synthesis of drugs with a hypotensive and psychotropic action is a search among purine and xanthine derivatives. With this aim we have obtained a number of previously undescribed derivatives of 2,3-dihydroimidazo[1,2-f]xanthine starting from 8-chloro-3-methylxanthine [1] by the method described below.

The reaction of (I) with ethylene chlorohydrin in DMFA forms 8-chloro-7-(β-hydroxyethyl)-3-methylxanthine (II). The IR spectra of (II) show absorption bands at 1695 and 1715 cm^{-1} (C=O) and 3160 cm^{-1} (NH). The band of the stretching vibrations of an alcoholic hydroxyl appear at 3350 cm^{-1}. Treatment of (II) with thionyl chloride in DMFA yielded 8-chloro-7-(β-chloroethyl)-3-methylxanthine (III). The replacement of the hydroxy group by a chlorine atom was confirmed by the absence of the band of stretching vibrations at 3350 cm^{-1} in the IR spectrum of (III). The PMR spectrum of (III) contained the signals of the protons of a methyl group at N_3 (s, 3H, 3.72 ppm). The signals of the protons of methylene groups were recorded in the form of triplets at δ 4.0 ppm (CH_2—Cl) and 4.81 ppm (N_7—CH_2).

According to Ecksteine [2], heating 8-bromo-7-(β-bromoethyl)theophylline with high-boiling amines forms derivatives of 6,8-dimethyl-2,3-dihydroimidazo[1,2-f]xanthine. We performed the analogous cyclization by treating (III) with aromatic amines in DMFA. In this way we obtained the 1-aryl-8-methyl-2,3-dihydro-6H-imidazo[1,2-f]xanthines (IV-VI).



Zaporozh'e Medical Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 623-626, September-October, 1980. Original article submitted May 14, 1980.

 0009-3130/80/1605-0442$07.50

The IR spectra of compounds (IV)-(VI) contained the bands of stretching vibrations at (cm^{-1}) 1695 and 1712 (C=O), 1680 (C=N), 2830 (CH_2), 3043 (arom. CH), and 3150 (NH).

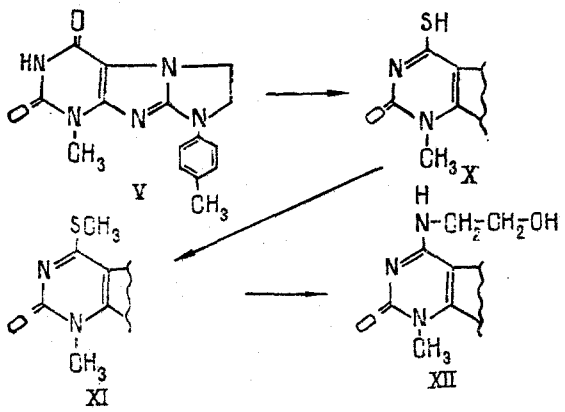
In the PMR spectrum of (IV), the signals of the protons of the methyl group at N_3 and of the methylene groups appear in a stronger field than in the case of (III). The signals of the phenyl protons are recorded in the form of a complex multiplet at 7.35-7.36 ppm (m, 5H).

The low yield of the dihydroimidazo[1,2-f]xanthines (IV)-(VI) is due to the fact that, in addition to cyclic products, 7,8-disubstituted 3-methylxanthines are also formed. Thus, in the preparation of (IV) and (VI), compounds (VII) and (VIII) were isolated and characterized.

By the reaction of (IV) with ethylene chlorohydrin in DMFA in the presence of K_2CO_3 we synthesized 6-(β-hydroxyethyl)-8-methyl-1-phenyl-2,3-dihydroimidazo[1,2-f]xanthine (IX). The alkylation reaction in the uracil fragment of the tricyclic compound takes place in a similar manner to processes described in the literature [3, 4], although under more severe conditions, which is connected with the extremely low solubility of (IV).

In the IR spectrum of (IX) stretching vibrations of a NH bond at 3150 cm^{-1} are absent, and an absorption band appears at 3400 cm^{-1} which is characteristic for the stretching vibrations of an OH group.

According to the literature [5, 6] in the reaction of xanthines with phosphorus pentasulfide a nucleophilic replacement of the oxygen atom in position 6 by a sulfur atom takes place. We applied this method of thionation to the dihydroimidazo[1,2-f]xanthines. It was established that the treatment of (V) with phosphorus pentasulfide led to the formation of 5-mercapto-8-methyl-1-(p-methylphenyl)-2,3-dihydroimidazo[1,2-f]purin-7-one (X).



The IR spectrum of compound (X) has an absorption band at 1697 cm^{-1} (C=O) in place of the two bands of the stretching vibrations of carbonyl groups in the IR spectrum of (V). The PMR spectrum of (X) recorded the signals of the protons of methyl groups at N_8 (3.63 ppm, s, 3H) and in the para position of a benzene ring (2.35 ppm, s, 3H). The methylene protons and the protons of the aromatic nucleus were recorded at δ 4.83 and 7.4 ppm in the form of singlets.

The methylation of (X) with methyl iodide in an aqueous ethanolic solution of caustic soda yielded (XI). When compound (XI) was boiled with monoethylamine in DMFA the methylthio group was replaced with the formation of 5-(β-hydroxyethylamino)-8-methyl-1-(p-methylphenyl)-2,3-dihydroimidazo[1,2-f]purin-7-one (XII).

The IR spectrum of (XII) showed the presence of the stretching vibrations of an alcohol group at 3320 cm^{-1}.

EXPERIMENTAL

IR spectra were measured on a UR-20 spectrophotometer in KBr tablets and in paraffin oil, and PMR spectra were recorded on a Tesla BS 487C spectrometer (80 mHz) with CF_3COOH as solvent. Chemical shifts are given on the δ scale from TMS. The results of elementary analyses corresponds to the calculated figures.

8-Chloro-7-(β-hydroxyethyl)-3-methylxanthine (II). A mixture of 4.76 g (0.02 mole) of (I) and 1.6 ml (0.024 mole) of ethylene chlorohydrin was boiled in 40 ml of DMFA for 1.5 h, and then the mixture was cooled, the precipitate (KCl) was filtered off, and the filtrate was evaporated to dryness in vacuum. The residue was treated with 30 ml of acetone, which precipitated compound (II) with the composition $C_8H_9ClN_4O_3$, mp 236-238°C (from water), yield 55.3%.

8-Chloro-7-(β-chloroethyl)-3-methylxanthine (III). A suspension of 1.9 g (8 mmole) of (II) in 10 ml of DMFA was treated dropwise with 10 ml of thionyl chloride and was then heated in a boiling water bath for 2 h. After cooling, the reaction mixture was poured into 200 ml of water and was neutralized with ammonia solution. After 12 h, the precipitate of (III) was filtered off and was washed with water and acetone: $C_8H_8Cl_2N_4O_2$, mp 278-280°C (from DMFA), yield 70%.

8-Methyl-1-phenyl-2,3-dihydroimidazo[1,2-f]xanthine (IV). A mixture of 1 g (3.8 mmole) of (III) and 1.1 ml (11.4 mmole) of aniline in 3 ml of DMFA was boiled for 3 h and was then cooled, and the resulting precipitate was filtered off and was washed with water and acetone; $C_{14}H_{13}N_5O_2$, mp 340°C (from DMFA), yield 45.8%.

Compound (V), with the composition $C_{15}H_{15}N_5O_2$, mp 350°C, was obtained similarly with a yield of 50.5%, and so was compound (VI) with the composition $C_{15}H_{15}N_3O$, mp 334-336°C (decomp., from DMFA), yield 44.7%.

3-Methyl-8-phenylamino-7-(β-phenylaminoethyl)xanthine (VII). The filtrate after the separation of the (IV) was diluted with water, and the resulting precipitate of (VII) was filtered off; $C_{20}H_{20}N_6O_2$, mp 218-220°C (from propanol), yield 34.5%. Compound (VIII) was obtained similarly; $C_{22}H_{24}N_6O_4$, 212-214°C (aqueous dioxane), yield 27.5%.

6-(β-Hydroxyethyl)-8-methyl-1-phenyl-2,3-dihydroimidazo[1,2-f]xanthine (IX). A mixture of 1.42 g (5 mmole) of (IV), 4.6 ml (6 mmole) of ethylene chlorohydrin and 0.72 g (5.2 mmole) of K_2CO_3 was boiled in 10 ml of DMFA for 40 h, and it was then cooled and diluted with water, and the resulting precipitate of (IX) was filtered off; $C_{16}H_{17}N_5O_3$, mp 250-252°C (aqueous methanol), yield 73.1%.

5-Mercapto-8-methyl-1-(p-methylphenyl)-2,3-dihydro-6H-imidazo[1,2-f]purin-7-one (X). A mixture of 5.5 g (18.5 mmole) of (V) and 4.22 g (19 mmole) of phosphorus pentasulfide in 80 ml of γ-picoline was boiled for 8 h, cooled, and poured into 200 ml of water. The precipitate of (X) was filtered off and was washed with water and acetone; $C_{15}H_{15}N_5OS$, mp 350°C (from DMFA), yield 69%.

8-Methyl-5-methylthio-1-(p-methylphenyl)-2,3-dihydroimidazo[1,2-f]purin-7-one (XI). A mixture of 1.56 g (0.005 mole) of (X) 1.86 ml (0.03 mole) of methyl iodide, 0.56 g (0.01 mole) of KOH, 20 ml of water, and 20 ml of n-propanol was boiled for 5 h and cooled, and the precipitate of (XI) was filtered off and was washed with water and acetone; $C_{16}H_{17}N_5OS$, mp 301-303°C (decomp., from DMSO), yield 99%.

5-(β-Hydroxyethylamino)-8-methyl-1-(p-methylphenyl)-2,3-dihydroimidazo[1,2-f]purin-7-one (XII). A mixture of 1 g (3 mmole) of (XI), 5 ml of monoethanolamine, and 5 ml of DMFA was boiled for 10 h and cooled, and then 20 ml of acetone was added and the resulting precipitate of (XII) was filtered off and washed with ether; $C_{17}H_{20}N_6O_2$, mp 286-288°C (decomp., from DMFA) yield 20%.

SUMMARY

A method has been developed for obtaining derivatives of 8-methyl-2,3-dihydro-6H-imidazo [1,2-f]xanthine. It has been established that 2,3-dihydroimidazo[1,2-f]xanthine alkylate at position 6 of the uracil fragment of the molecule.

A method has been developed for obtaining derivatives of 2,3-dihydroimidazo[1,2-f]purin-7-one.

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SYNTHESIS AND SOME TRANSFORMATIONS BASED ON 8-CHLORO-3-METHYLXANTHINE

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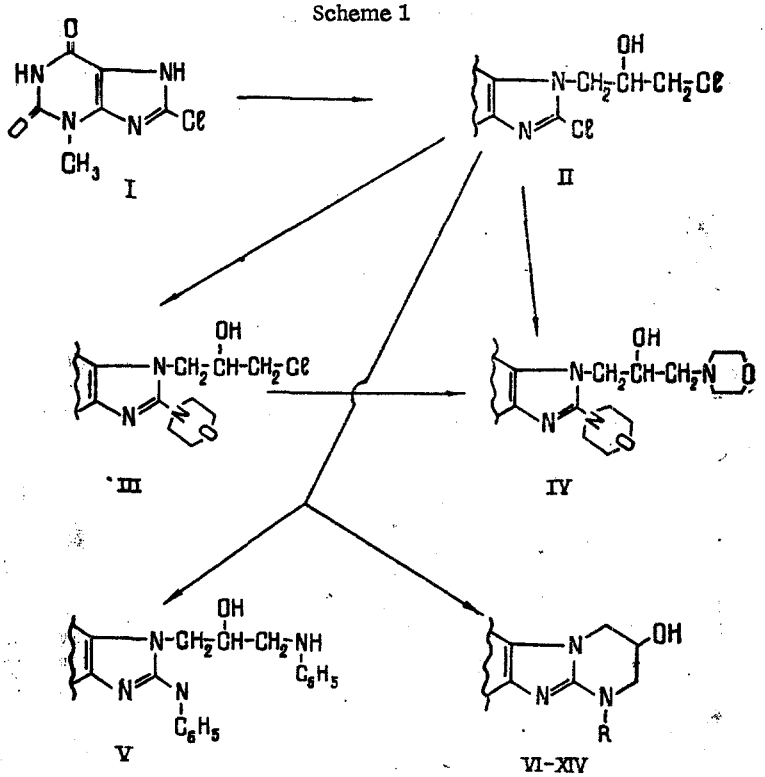
UDC 547.857.4:853.5

The reactions of 8-chloro-7-(β-chloro-γ-hydroxypropyl)-3-methylxanthine with primary and secondary amines have been studied. A method has been developed for obtaining derivatives of 7-hydroxy-1-methyl-6,7,8,9-tetrahydro-3H-pyrimido[2,1-f]-xanthine. The structures of the compounds synthesized have been confirmed by IR and PMR spectroscopy.

It is known that xanthine and purine derivatives are highly active substances of natural origin. 6-Amino derivatives of purine are used as plant growth regulators [1, 2], 7,8-disubstituted xanthines possess a coronarolytic and central-nervous-system-stimulating action [3], and condensed xanthine derivatives exhibit psychotropic and antiinflammatory activity [4].

With the aim of broadening the arsenal of biologically active compounds we have carried out the series of transformations shown in Scheme 1 starting from 8-chloro-3-methylxanthine (I), which was described by Fischer and Ach [5].

Scheme 1



VI. R=C_6H_5; VII. R=C_6H_4-CH_3-n; VIII. R=$-CH_2-C_6H_5$; IX. R=C_6H_4-OC_2H_5-n; X. R=C_6H_4-CH_3-m; XI. R=C_6H_4-OCH_3-m; XII. R=C_6H_4-Br-n; XIII. R=C_6H_4-Cl-m; XIV. R=C_6H_4-OCH_3-n

Zaporozh'e Medical Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 626-629, September-October, 1980. Original article submitted May 14, 1980.

0009-3130/80/1605-0445$07.50