SYNTHESIS OF CROWN-CONTAINING XANTHINE DERIVATIVES

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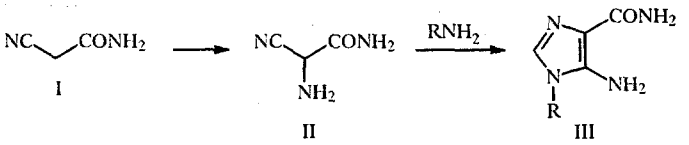
A number of new derivatives of xanthine, hypoxanthine, theophylline, and theobromine containing crown-ether substituents at the nitrogen atoms of the imidazole or pyrimidine nucleus was synthesized.

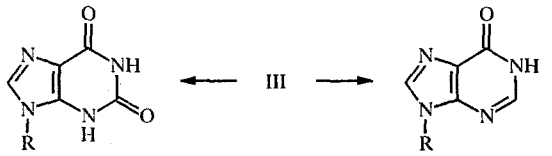
We previously reported that dibenzo-18-crown-6 derivatives containing azole, azine, azepine, and 1,4-diazepine nuclei annelated at benzene rings are physiologically active substances and exhibit anticonvulsant, antiviral, antimicrobial, and insecticidal and fungicidal activity [1-4].

We synthesized xanthine derivatives containing fragments of the crown ethers: benzo-12-crown-4, benzo-15-crown-5, benzo-18-crown-6, and dibenzo-18-crown-6, to search for new biologically active substances in the purine series.

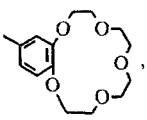
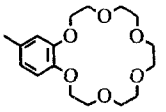
Cyanacetamide (I) was the starting compound used in synthesis, and 1-substituted 5-aminoimidazole-4-carboxamides (III) were obtained from it with the method in [5]. 4-Aminobenzo-15-crown-5, 4-aminobenzo-18-crown-6, and aniline, used as the model compound, were used as the amino components in the stage of conversion of II into III.



I II III



V III IV

III, IV. V a R=Ph, b R=  , c R= 

It was found that the 1-phenyl-substituted derivative (IIIa, R = Ph) is easily cyclized into the corresponding hypoxanthine IVa by boiling in formic acid (2h), orthoformic ester (2 h), or formamide (1 h). On the contrary, crown derivatives IIIb, c do not react with boiling formic acid even in the presence of acetic anhydride, and their cyclization time with orthoformic ester or formamide is 2-3 times greater, which is in all probability due to steric hindrances caused by macrocyclic fragments in position 1 of the imidazole ring. Use of boiling formamide (2 h) produces the best results for synthesis of hypoxanthines IV.

Crown-substituted xanthines V were obtained by melting imidazoles III with urea at 180-200°C. It is more convenient to conduct the reaction in boiling heptanol.

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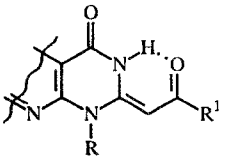
TABLE 1. Characteristics of the Compounds Synthesized

Compound	Molecular formula	M.p., °C	TLC, R_f	Yield, %
IIa	$C_{16}H_{15}N_3O$	201...202	0,75	73
IIb	$C_{17}H_{17}N_3O_2$	151...153	0,85	66
IIc	$C_{17}H_{17}N_3O$	220...222	0,65	72
IId	$C_{17}H_{17}N_3O$	170...172	0,84	60
IIe	$C_{17}H_{17}N_3O_2$	172...174	0,71	64
IVa	$C_{18}H_{17}N_3O_2$	252...254	0,72	42 (69*)
IVb	$C_{19}H_{19}N_3O_3$	221...222	0,72	67
IVc	$C_{19}H_{19}N_3O_2$	226...228	0,77	46
IVd	$C_{24}H_{21}N_3O_2$	215...217	0,81	44
V	$C_{15}H_{15}N_3O$	174...176	0,62	57

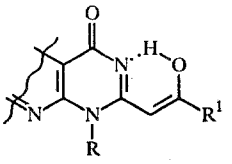
*From acylation of compound IIa.

aryl-2-acetonyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines IV a and b are formed. The melting point of compound IVa is identical with that of the substance described previously [4]. Apparently compounds II are initially formed when the amides IIIa and b react with Ac_2O, but the methyl group at C(2) in II is a sufficiently strong CH acid that it participates in the acylation reaction. To confirm this suggestion and as an indication of the structures of compounds IVa and b, the acylation of compounds IIa-c with acetic anhydride and benzoyl chloride was attempted. Compounds IVa-d were obtained.

The ^1H NMR spectra of the acetonyl and phenacyl derivatives IVa-d in $CDCl_3$ contained methyl group singlets at 1.83-2.67 ppm, aromatic proton multiplets in the 6.83-7.50 ppm range, signal for the protons of the pyridine ring at 6.60-6.73 ppm. There are also signals in the 4.23-5.00 and 13.77-14.20 ppm (1 H) ranges corresponding respectively to the ethylene protons and the proton of the chelate ring of the enaminocarbonyl (A) and enol (B) tautomers.



A



B

5,7-Dimethyl-4-oxo-1-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (V) was formed on heating compound IIIa with formamide at 190-200°C.

5,7-Dimethyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-d]pyrimidine is probably an intermediate product which is reduced by excess formamide to compound V.

EXPERIMENTAL

IR spectra were recorded in Nujol with a Zeiss UR-20 spectrophotometer, ^1H NMR spectra were recorded as 5% solutions in $CDCl_3$ with HMDS as internal standard with an RS-60 machine, and Silufol UV-254 sheets were used for TLC (1:1 butanol-benzene for compounds IIa-e, ethyl acetate for IVa-d and V).

The experimental analysis results obtained for the compounds synthesized agreed with the calculated values.

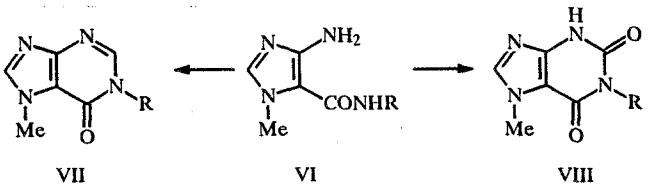
1-Aryl-2,5,7-trimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (IIa-e). A solution of 0.01 mol of compounds Ia-e was added to a mixture of 50% $HClO_4$ (2.5 ml) and acetic anhydride (25 ml) and kept for 48 h at 20°. The mixture was poured into water, the precipitate was filtered off, treated with 10% sodium hydroxide solution, and crystallized from ethanol. IR spectra: 1630-1650 cm^{-1} (CO). ^1H NMR spectra: 2.06-2.80 (3 H, s, CH_3); 6.73-7.30 ppm (s, pyridine H).

1-Aryl-2-acetonyl-5,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (IVa-c). A solution of 0.01 mol of a 2-arylamino-4,6-dimethylnicotinamide (IIIa or b) or 0.01 mol of compounds IIa-c and anhydrous sodium acetate (0.7 g, 8 mmol) in acetic anhydride (10 ml) was boiled for 8h, then poured into water and the residue recrystallized from ethanol to give compounds IVa-c. IR spectra: 1600-1630 (CO of the acetonyl group), 1660-1680 cm^{-1} (C=O of the heterocycle).

TABLE 1. Physicochemical Properties of Compounds III-V, VI-VIII, XI, and XII

Compound	R	Mp, °C	M^+	PMR spectrum, δ, ppm	Yield, %
IIIb	B-15-K-5	184	392	7,34 (1H, s, =CH); 7,15...6,99 (3H, m, Ph); 6,95 & 6,80 (1H, s, $CONH_2$); 5,76 (2H, s, NH_2); 4,16...3,67 (16H, m, CH_2O)	65
IIIc	B-18-K-6	150	422	7,34 (1H, s, =CH); 7,12...7,0 (3H, m, Ph); 6,95 & 6,79 (1H, s, $CONH_2$); 5,65 (2H, s, NH_2); 4,20...3,58 (20H, m, CH_2O)	70
IVb	B-15-K-5	283	402	8,45 (1H, s, NH); 8,13 (1H, s, 2-H); 7,39...7,14 (3H, m, Ph); 7,37 (1H, s, 8-H); 4,16...3,67 (16H, m, CH_2O)	84
IVc	B-18-K-6	242	432	8,46 (1H, s, NH); 8,12 (1H, s, 2-H); 7,40 (1H, s, 8-H); 7,33...7,16 (3H, m, Ph); 4,26...3,61 (20H, m, CH_2O)	80
Vb	B-15-K-5	306	418	11,23 & 10,95 (1H, s, NH); 7,90 (1H, s, =CH); 7,65...7,08 (3H, m, Ph); 4,15...3,66 (16H, m, CH_2O)	76
Vc	B-18-K-6	269	448	11,25 & 10,98 (1H, s, NH); 7,93 (1H, s, =CH); 7,70...7,10 (3H, m, Ph); 4,28...3,65 (20H, m, CH_2O)	73
VIa	B-12-K-4	—	362	9,18 (1H, s, NH); 7,14 (1H, s, =CH); 6,94...6,62 (3H, m, Ph); 4,23 (2H, s, NH_2); 3,67...3,49 (16H, m, CH_2O); 3,55 (3H, s, CH_3N)	70
VIb	B-15-K-5	72	406	8,82 (1H, s, NH); 6,97 (1H, s, =CH); 6,65...6,50 (3H, m, Ph); 4,44 (2H, s, NH_2); 3,87...3,54 (12H, m, CH_2O); 3,61 (3H, s, CH_3N)	74
VIIa	B-12-K-4	158	372	7,93 (1H, s, 2-H); 7,79 (1H, s, 8-H); 6,99...6,82 (3H, m, Ph); 4,09...3,73 (12H, m, CH_2O); 3,93 (3H, s, CH_3N)	83
VIIb	B-15-K-5	146	416	8,01 (1H, s, 2-H); 7,82 (1H, s, 8-H); 6,90...6,63 (3H, m, Ph); 4,16...3,79 (16H, m, CH_2O); 4,03 (3H, s, CH_3N)	80
VIIIa	B-12-K-4	186	394	9,34 (1H, s, NH); 7,73 (1H, s, =CH); 6,96...6,72 (3H, m, Ph); 3,98 (3H, s, CH_3N); 4,15...3,70 (12H, m, CH_2O)	75
VIIIb	B-15-K-5	175	432	9,31 (1H, s, NH); 7,71 (1H, s, =CH); 6,97...6,75 (3H, m, Ph); 4,0 (3H, s, CH_3N); 4,17...3,75 (16H, m, CH_2O)	70
XI	DB-18-K-6	183	552	8,3 (1H, s, =CH); 7,1...6,9 (7H, m, Ph); 5,4 (2H, s, CH_2); 4,1...3,5 (16H, m, CH_2O); 3,4 & 3,2 (3H, s, CH_3)	85
XII	BB-18-K-6	240	552	8,1 (1H, s, =CH); 7,0 (7H, m, Ph); 5,0 (2H, s, CH_2); 4,1...3,6 (16H, m, CH_2O); 3,9 & 3,4 (3H, s, CH_3)	84

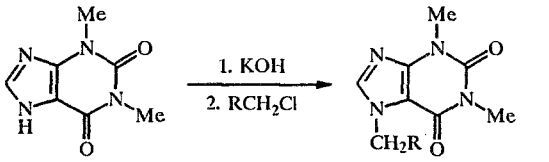
Compounds VII and VIII were obtained similarly from amide VI [6] in boiling in formic acid or as a result of melting with urea, respectively.



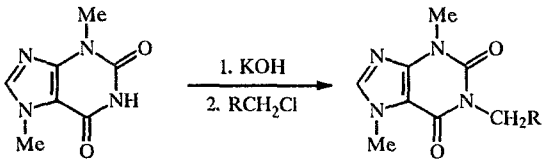
VII VI VIII

VI, VII, VIII a R= , b R=

The reaction of potassium salts of theophylline (IX) or theobromine (X) with 4-chloromethyldibenzo-18-crown-6 [7] in DMF yields the corresponding derivatives XI and XII containing a crown ether fragment.



IX XI



X XII

XI, XII R=

The individuality of the synthesized substances was monitored by TLC and mass spectrometry. The proton signals in the PMR spectra of all substances obtained corresponded to the assigned structures. Their physicochemical properties are reported in Table 1.

EXPERIMENTAL

The course of the reaction was monitored and the individuality of the substances was evaluated by TLC on Silufol UV-254 plates in chloroform—ethanol system, 5:1, and silica gel 100/250 was used for column chromatography. The mass spectra were made on a Varian MAT 112 with direct sample introduction and 70 eV ionizing radiation energy at 40-50°C above the melting point of the samples. The PMR spectra were obtained on a Bruker AM-250 with a 250 MHz working frequency in $CDCl_3$ or deuterated DMSO.

The data from elemental analysis for C, H, and N corresponded to the calculated data.

Synthesis of Hypoxanthines IVa-c. Method A. A mixture of 2.02 g (0.01 mole) of compound IIIa, 100 ml of formic acid, and 20 ml of acetic anhydride was boiled for 2 h. After cooling, the solution was poured in water, and the precipitated sediment was filtered and recrystallized from formamide.

Method B. Here 0.01 mole of compound III was boiled with 2.9 g (0.02 mole) of orthoformic ester in 50 ml of DMF for 2 h (for 6 h for the crown derivatives). The solvent was distilled off in a rotor evaporator and the sediment was washed with ethanol and recrystallized from formamide.

Method C. Here 0.01 mole of compound III in 50 ml of formamide was boiled for 1 h (2 h for crown derivatives). After cooling of the solution, the crystalline sediment was filtered off.

Synthesis of Xanthines Va-c. Method A. Here 0.01 mole of substance III was melted with 6 g (0.1 mole) of urea at 180-200°C for 2 h. The reaction mixture was cooled and boiled with methanol. The insoluble sediment was recrystallized in DMF.

Method B. Here 0.01 mole of substance III and 3 g (0.05 mole) of urea were boiled in 100 ml of heptanol for 2 h. The sediment was filtered from the hot reaction mixture.

Synthesis of Hypoxanthines VIIa, b. Here 0.01 mole of compound VI was boiled in 30 ml of formic acid for 2 h. The acid was then distilled dry in a rotor evaporator and the sediment was chromatographed in a column, chloroform—ethanol eluent, 5:1.

Synthesis of Xanthines VIIIa, b. Here 0.01 mole of substance VI and 3 g (0.05 mole) of urea were boiled in 100 ml of pentanol for 5 h. The solvent was distilled dry. The product was separated by extraction with chloroform.

Synthesis of Derivatives of Theophylline XI and Theobromine XII. Here 0.45 g (0.0025 mole) of theophylline (IX) or theobromine (X) and 0.14 g (0.0025 mole) of potassium hydroxide in 10 ml of water was stirred until a solution formed. The water was distilled off, and the sediment was dried at 120-140°C to a constant weight. Then 1 g (0.0025 mole) of 4-chloromethyldibenzo-18-crown-6 in 50 ml of DMF was added and heated in a water bath for 3 h. After cooling, the reaction mixture was poured in water and the sediment was filtered off.

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