SYNTHESIS OF IMIDAZOLINO[1,2-f]XANTHIN-2-ONES AND THEIR METHYLENE-GROUP-SUBSTITUTED DERIVATIVES

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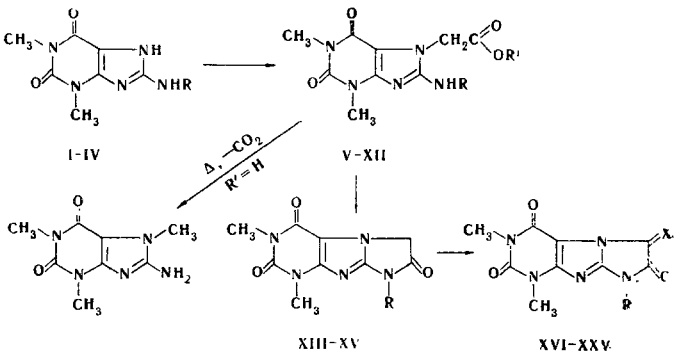
8-Amino-7-theophyllylacetic acids and their esters were obtained by reaction of 8-amino(alkylamino, arylamino)theophyllines with haloacetic acids and their esters. The structures of the products were established, and the conditions for cyclization to imidazolino[1,2-f]xanthin-2-one derivatives were studied. The corresponding methylene-group-substituted derivatives were synthesized by reaction of the imidazolino[1,2-f]xanthin-2-one derivatives with aldehydes, isatin, aromatic nitroso compounds, and arenediazonium salts. The ylidene derivatives of this three-ring system were also obtained by reaction of 8-amino-7-theophyllylacetic acids or their esters with carbonyl compounds.

In developing our earlier research [1, 2] we investigated the reaction of 8-amino(methylamino, phenyl) amino, m-tolylamino)theophyllines (I-IV) with α-haloacetic acids and their esters. It was shown that the corresponding 7-theophyllylacetic acid esters (V-IX) are formed by reaction of the potassium salts of theophyllines I-IV with haloacetic acid esters. Acids X-XII were obtained by saponification of esters V and VII-IX in acidic or alkaline media. 8-Amino-7-theophyllylacetic acid (X) was also isolated in the reaction of amine I with haloacetic acids.

The alkylation of 8-aminotheophyllines I-IV with haloacetic acids or their esters proceeds at the nitrogen atom in the 7 position of the purine ring, as proved by decarboxylation of acid X, which leads to 8-aminocaffeine, obtained by direct synthesis from 8-bromocaffeine and ammonia [3].

Acids X-XII are cyclized to give imidazolino[1,2-f]xanthin-2-one derivatives (XIII-XV) when they are heated in glacial acetic acid in the presence of anhydrous sodium acetate or in acetic anhydride. Ylidene (XVI-XXI), azomethine (XXII), and azo (XXIII-XXV) derivatives of this three-ring system are obtained by reaction of XIII-XV with aldehydes, isatin, nitroso compounds, and arenediazonium salts.



Ylidine derivatives were also synthesized by reaction of acids X-XII or esters VI-VIII with aldehydes.

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TABLE 1. 8-Amino-7-theophyllylacetic Acids and Their Esters (V-XII).

Compound	R	R^1	mp, °C (dec.)	Empirical formula	Found, %			Calculated, %			IR spectrum, cm^{-1}		Yield, %
					C	H	N	C	H	N	CO	NH, OH	
V	H	CH_3	276—278	$C_{10}H_{13}N_5O_4$	45,4	4,8	26,5	44,9	4,9	26,2	1665, 1700, 1720	3150, 3410	84—99
VI	CH_3	CH_3	245—246	$C_{11}H_{15}N_5O_4$	46,7	5,2	24,6	47,0	5,4	24,9	1665, 1700, 1760	3350	69
VII	C_6H_5	CH_3	206—208	$C_{16}H_{17}N_5O_4$	55,8	4,8	20,6	56,0	5,0	20,4	1665, 1700, 1725	3350, 3390	51
VIII	*m*-$CH_3C_6H_4$	CH_3	193—195	$C_{17}H_{19}N_5O_4$	57,2	5,1	19,7	57,1	5,4	19,6	1670, 1700, 1725	3380	60
IX	H	C_2H_5	251—253	$C_{11}H_{15}N_5O_4$	46,8	5,2	24,8	47,0	5,4	24,9	—	—	93
X	H	H	288—289	$C_9H_{11}N_5O_4$	42,4	4,5	27,4	42,7	4,4	27,7	1650, 1695, 1740	3220, 3380	78—98
XI	C_6H_5	H	219—220	$C_{15}H_{15}N_5O_4$	54,8	4,9	21,6	54,7	4,6	21,3	1640, 1665, 1700	3350	94
XII	*m*-$CH_3C_6H_4$	H	207—209	$C_{16}H_{17}N_5O_4$	55,8	5,2	20,4	56,0	5,0	20,4	1640, 1700, 1725	3370	96

TABLE 2. 6,8-Dimethylimidazolino[1,2-f]xanthin-2-ones and Their Derivatives

Compound	R	R^2	mp, °C (dec.)	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
XIII	H	—	239—241	$C_9H_9N_5O_2$	45,7	4,0	29,5	45,9	3,9	29,8	75—78
XIV	C_6H_5	—	257—258	$C_{15}H_{13}N_5O_3$	58,2	4,6	22,7	57,9	4,2	22,5	70—80
XV	*m*-$CH_3C_6H_4$	—	238—239	$C_{16}H_{15}N_5O_3$	59,3	4,5	21,6	59,1	4,7	21,5	71—76
XVI	H	C_6H_5	>310	$C_{16}H_{13}N_5O_2$	59,9	4,1	21,5	59,5	4,1	21,7	50—54
XVII	CH_3	*p*-$(CH_3)_2NC_6H_4$	>310	$C_{19}H_{20}N_6O_3$	59,7	5,1	21,8	60,0	5,9	22,1	16
XVIII	C_6H_5	$C_6H_4CH=CH$	280—282	$C_{24}H_{19}N_5O_3$	67,4	4,7	16,6	67,7	4,5	16,5	72—94
XIX	*m*-$CH_3C_6H_4$	$(CH_3)_2CH$	165—167	$C_{20}H_{21}N_5O_3 \cdot {}^1/_2H_2O$	61,9	5,8	17,8	61,8	5,7	18,0	56
XX	*m*-$CH_3C_6H_4$	Isatin residue	278—280	$C_{21}H_{17}N_5O_4$	62,7	4,5	17,7	62,5	4,2	17,4	70—92
XXI	H	2-Furyl	>310	$C_{17}H_{12}N_6O_4$	56,3	3,5	—	56,0	3,3	—	23
XXII	C_6H_5	*p*-$(CH_3)_2NC_6H_4N$	237—239	$C_{23}H_{21}N_7O_3$	62,1	5,0	—	62,3	4,8	—	41
XXIII	H	$C_6H_5N=N$	>310	$C_{15}H_{13}N_7O_3$	53,3	4,2	29,0	53,1	3,9	28,9	60
XXIV	H	*p*-$H_2NSO_2C_6H_4N=N$	>310	$C_{15}H_{14}N_8O_5S$*	43,2	3,7	27,0	43,1	3,4	26,8	90
XXV	C_6H_5	*p*-$CH_3OC_6H_4N=N$	295—297	$C_{22}H_{19}N_7O_4$	59,5	4,3	22,2	59,3	4,4	22,0	76

* Found: S 7.6%. Calculated: S 7.7%.

The IR spectra of XVI-XXV contain distinct absorption bands of CO groups at 1620-1650, 1700-1710, and 1750-1755 cm^{-1}; compounds with a free imino group in the 1 position of the three-ring system are also characterized by the presence of a band at 3380-3400 cm^{-1}.

We also investigated the bacteriostatic action of XVI-XXV. It was found that they all display weak activity, suppressing the growth of Staphylococcus aureus, Escherichia coli, Salmonella typhosa, and dysetery bacilli in a 1:4000 culture.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer.

8-(m-Tolylamino)theophylline (IV). This compound was obtained in the same way as 8-aminotheophyllines I-III by the method in [4].

8-Amino(alkylamino, arylamino)-7-theophyllylacetic Acid Esters (V-IX, Table 1). A) A 0.012-mole sample of methyl or ethyl chloro-, bromo- or iodoacetate was added to a suspension of 0.01 mole of the potassium salts of aminotheophyllines I-IV in 75-150 ml of anhydrous methanol, and the mixture was refluxed with stirring for 5-6 h. The solvent was then removed by distillation to half its original volume, and the residual solution was cooled. The precipitated ester was removed by filtration.

B) A mixture of 2.53 g (0.01 mole) of X and two to three drops of concentrated sulfuric acid in 50 ml of anhydrous methanol was refluxed for 2 h, after which it was worked up as in experiment A. The yield of ester V was almost quantitative.

Compounds V-VIII were purified by crystallization from anhydrous methanol, and IX was purified by crystallization from ethanol.

8-Amino(arylamino)-7-theophyllylacetic Acids (X-XII, Table 1). A) A solution of 0.01 mole of V or VII-IX in 25 ml of 36% hydrochloric acid was refluxed for 1 h, after which it was cooled, and precipitated acids, XI and XII were removed by filtration and washed with a small amount of water. In the preparation of acid X the reaction mixture was evaporated to dryness, and the residue was washed with water.

B) A solution of 0.01 mole of V or IX in 20 ml of 20% sodium hydroxide solution was refluxed for 1 h, after which it was cooled and acidified to pH 4-5 with hydrochloric acid. Precipitated acid X was removed by filtration and washed with water.

C) A 9.8-g (0.05 mole) sample of 8-aminotheophylline (I) and 0.055 mole of chloro-, bromo-, or iodacetic acid were added to a solution of 0.1 mole of sodium hydroxide or potassium hydroxide in 150 ml of water, and the mixture was refluxed for 5 h. It was then cooled and filtered, and the filtrate was acidified to pH 4-5 with hydrochloric acid. The precipitated X was removed by filtration and washed with water. Compounds X-XII were purified for analysis by crystallization from 50% acetic acid.

6,8-Dimethylimidazolino[1,2-f]xanthin-2-ones (XIII-XV, Table 2). A) A mixture of 0.01 mole of X-XII and 2.0 g of anhydrous sodium acetate in 50 ml of glacial acetic acid was refluxed for 1-2 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with water. Compounds XIII-XV were obtained in 78, 70, and 73% yields respectively.

B) A 0.01-mole sample of X-XII was refluxed in 35 ml of acetic anhydride for 3 h (for 1 h in the case of XI), after which the mixture was cooled, and the precipitate was removed by filtration. Compounds XIII-XV were obtained in 75, 80, and 76% yields, respectively. Compounds XIII and XV were purified for analysis by crystallization from 50% acetic acid, and XIV was purified by reprecipitation from dioxane solution by the addition of water. Bands of stretching vibrations of CO groups at 1665-1670, 1715-1725, and 1745-1770 cm^{-1} were observed in the IR spectra of XIII-XV; the spectrum of XIII has a narrow absorption band at 3320-3380 cm^{-1} (NH).

Ylidene Derivatives of 6,8-Dimethylimidazolino[1,2-f]xanthin-2-one (XVI-XXI Table 2). A) A 0.01-0.011 mole sample of aldehyde was added to a solution of 0.01 mole of XIII-XV and anhydrous sodium acetate (in an amount equal to the weight of XIII-XV) in a mixture of 35-40 ml of glacial acetic acid and acetic anhydride (1:1), and the mixture was refluxed for 1-3 h. It was then cooled and diluted with water, and the precipitated XVI-XX were removed by filtration. These compounds were also obtained from theophyllines VI-VIII and X-XII by a similar method.

B) A 1.47-g (0.01 mole) sample of isatin and two to three drops of piperidine were added to a suspension of 2.35 g (0.01 mole) of XIII in 100 ml of ethanol, and the mixture was refluxed for 40 h. It was then cooled,

and the precipitated XXI was removed by filtration and washed with water. Compounds XVI, XVII, and XX (light-brown), XVIII (orange), XIX (light-yellow), and XXI (red) were obtained as crystalline substances and were purified for analysys by crystallization from glacial acetic acid (XVI-XIX) 50% acetic acid (XX), or dimethylformamide (DMF) (XXI).

1-Phenyl-3-(p-dimethylaminophenylimino)-6,8-dimethylimidazolino[1,2-f]xanthin-2-one (XXII, Table 2). A 1.5-g (0.01 mole) sample of p-nitrosodimethylaniline and two to three drops of piperidine were added to a suspension of 3.11 g (0.01 mole) of XV in 80 ml of ethanol, and the mixture was refluxed for 24 h. The solvent was removed by distillation to dryness, and the residue was washed with ether and purified by reprecipitation from ethanol solution by the addition of ether.

3-Arylazo-6,8-dimethylimidazoline[1,2-f]xanthin-2-ones (XXIII-XXV, Table 2). A mixture of 0.01 mole of XIII or XV, 2.5-3.5 g of anhydrous sodium acetate, and 0.011 more of arendediazonium tetrafluoroborate in 25-40 ml of glacial acetic acid was heated on a boiling-water bath for 20-30 min, after which it was cooled and diluted with 60-80 ml of water. The precipitated azo compounds (XXIII-XXV) were removed by filtration and washed with water and methanol.

Crystalline XXIII and XXV (yellow) and XXIV (orange) were purified for analysis by crystallization from glacial acetic acid (XXIV) and DMF (XXIII) or by reprecipitation from DMF by the addition of water (XXV).

LITERATURE CITED

1. V. I. Nosachenko and A. A. Tkachenko, Chemical Research in Pharmacy [in Russian], Zdorov'e, Kiev (1970), p. 44.
2. A. A. Tkachenko, B. A. Priimenko, V. S. Ponomar', M. V. Povstyanoi, V. I. Nosachenko, V. A. Grin', N. G. Rybalko, N. G. Liverskaya, V. A. Zdorenko, and P. M. Kochergin, Modern Problems of Pharmaceutical Science and Practice (Summaries of Papers Presented at the Second Conference of Pharmacists of the Ukrainian SSR) [in Russian], Kiev (1972), p. 378.
3. E. Fischer, Ann., 215, 253 (1982).
4. C. F. Boehringer und Söhre, German Patent No. 156,900; Frdl., 7, 677 (1904).

RESEARCH ON RIBOFLAVIN ANALOGS

VIII.* 7-TRIFLUOROMETHYL-8-CHLOROISOALLOXAZINES

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A number of 7-trifluoromethyl-8-chloro-10-R-isoalloxazines (where R = H, CH_3, CH_2CH_2OH, ribityl, galactyl, sorbityl, and rhamnityl) and 7-trifluoromethyl-8-(β-hydroxyethyl)aminoisoalloxazines with substituents such as ribityl and β-hydroxyethyl in the 10 position were synthesized.

Replacement of the hydrogen atoms in a metabolite molecule by fluorine atoms or replacement of a methyl group by a chlorine atom, which have quite close van der Waals radii, is one of the proven methods for modification of metabolite molecules.

We have previously reported the synthesis of 7- or 8-mono- and 7,8-bis(trifluoromethyl) analogs of riboflavin [1]. The aim of the present research was the synthesis of 7-trifluoromethyl-8-chloro derivatives of

*See [1] for communication VII.

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