INVESTIGATION OF THE REACTION OF 2-AMINOTHEOPHYLLINES WITH GLYCEROL EPICHLOROHYDRIN

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Depending on the nature and amount of the base used, as well as the reaction time, the following compounds are formed in the reaction of 8-aminothiophyllines with glycerol epichlorohydrin in anhydrous propanol; 7-(2-hydroxy-3-chloro-1-propyl)-8-arylaminotheophylline, 1,3-bis(8-arylamino-7-theophyllinyl)-2-hydroxypropane, 7-(2,3-epoxy-1-propyl)-8-alkyl(aryl)aminothiophyllines or 9-alkyl(aryl)-7-hydroxy-1,3-dimethyl-6,7,8,9-tetrahydropyrimido[2,1-f]purine-2,4-(1H,3H)diones. The structures of the compounds were confirmed by alternative synthesis and by data from the IR spectra. The mass spectrum of one of the compounds is presented.

It is known [1, 2] that the alkylation of thiophylline derivatives with olefin oxides proceeds via an S_N2 mechanism to give 7-substituted theophyllines and is catalyzed by bases. However, this reaction has not been studied in the 8-aminotheophylline series. In the present research we investigated the reaction of 8-aminotheophyllines Ia-c with glycerol epichlorohydrin (II). We found that the principal factors that determine the structures of the products of this reaction are the nature and amount of the base used and the reaction time.

Thus 7-(2-hydroxy-3-chloro-1-propyl)-8-phenylaminotheophylline (IIIc) was obtained in 78% yield in the reaction of equivalent amounts of 8-phenylaminotheophylline (Ic) with chlorohydrin II in propanol in the presence of catalytic amounts of pyridine or alkali. An increase in the amount of pyridine to one equivalent leads to 1,3-bis(8-phenylamino-7-theophyllinyl)-2-hydroxypropane (IVc) in 82% yield and, as a side product, 7-(2,3-epoxy-1-propyl)-8-phenylaminotheophylline (Vc) in 6% yield, which we were able to separate owing to their different solubilities in hot ethanol. When we carried out the reaction of theophyllines Ia-c with II in the presence of an equivalent amount or an excess amount of sodium propoxide for 1.5 h, we obtained 7-(2,3-epoxy-1-propyl)-8-aminotheophyllines Va-c in 60-70% yields, whereas when we carried out the reaction for 14 h, we isolated 9-phenyl-7-hydroxy-1,3-dimethyl-6,7,8,9-tetrahydropyrimido[2,1-f]purine-2,4-(1H,3H)dione (VIc) in 41% yield. The formation of purinediol VIc from theophylline Ic can be represented by the intermediate steps Ic→IIIc→Vc→VIc. To confirm this assumption we accomplished the synthesis of VIc by refluxing theophylline IIIc for 2 h in an alcohol solution of alkali with subsequent cyclization of product Vc by refluxing in propanol for 12 h in the presence of catalytic amounts of sodium propoxide, as well as directly from IIIc by refluxing for 12 h in propanol in the presence of excess sodium propoxide. The fact that the cyclization of epoxy derivative Vc requires a long time is explained by the low nucleophilicity of the nitrogen atom of the amino group in the 8 position of the xanthine two-ring system. It should be noted that the reactions indicated above were carried out in an anhydrous medium, since the presence of moisture leads to the formation of 7-(2,3-dihydroxy-1-propyl)-8-phenylaminotheophylline (VIIc).

Absorption bands of hydroxy and amino groups at 3340-3520 and 3180-3240 cm^{-1} are observed in the IR spectra of IIIc, IVc, and VIIc. The presence in the IR spectra of absorption bands of an epoxide ring at 1260-1270 cm^{-1} and of an amino group at 3185-3220 cm^{-1} is characteristic for Va-c.

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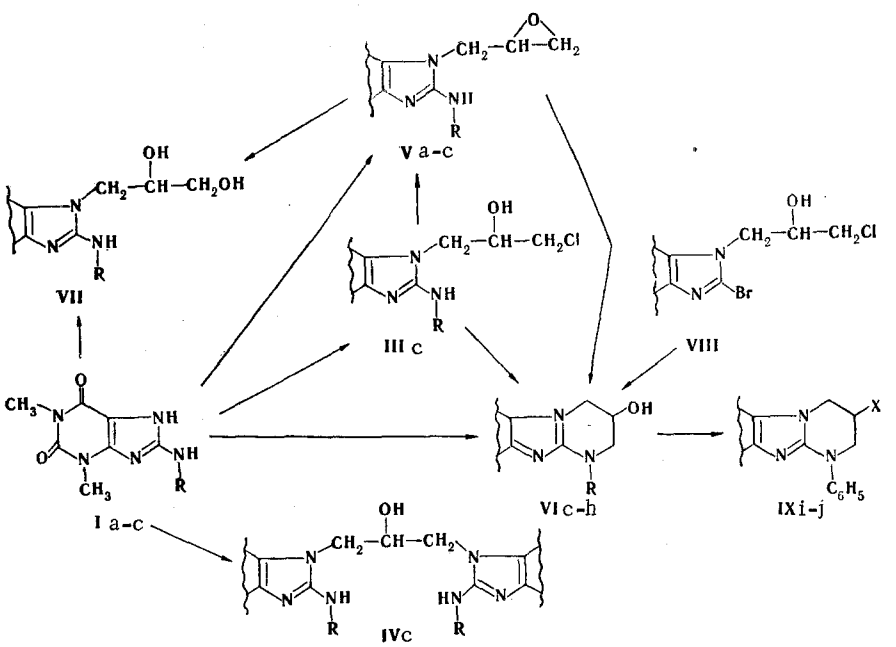
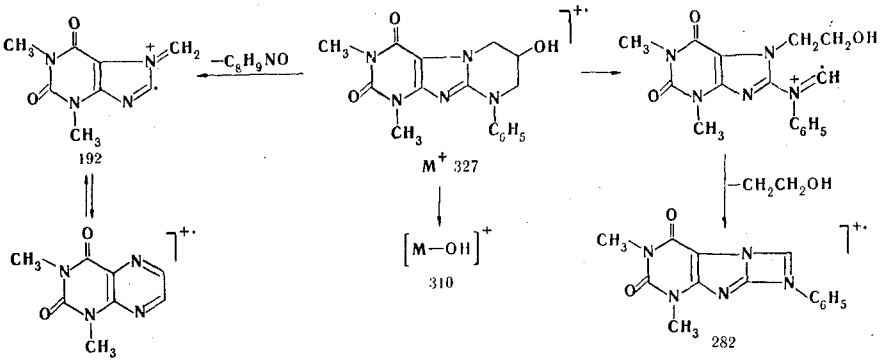


Ia, Va R=CH_3; Ib, Vb R=C_2H_5; Ic, III—VIIc R=C_6H_5; VId R=C_6H_4—CH_3-*p*; VIe R=C_6H_4—OCH_3-*p*; VIf R=C_6H_4—CH_3-*m*; VIg R=C_6H_4—OC_2H_5-*p*; VIh R=C_6H_{11}; IXi X=Cl; IXj X=$OCOCH_3$

It is known [3] that xanthine derivatives that contain a condensed tetrahydropyrimidine ring have multifaceted biological activity. In order to search for pharmacological preparations in this series of compounds and to obtain rigorous proof for the structure of VI we accomplished the synthesis of a number of new tetrahydropyrimido[2,1-f]xanthine derivatives (VIc-h) by the reaction of 7-(2-hydroxy-3-chloro-1-propyl)-8-bromotheophylline (VIII) with primary amines. The IR spectra of VIa-f do not contain absorption bands of an amino group that are characteristic for I, III, and V, but absorption bands of a hydroxy group are observed at 3350-3450 cm^{-1}. The presence of a hydroxy group in VIc-h was also confirmed by the formation of chloro (IXi) and acetyl (IXj) derivatives.

A molecular ion peak with m/e 327,* which corresponds to the molecular mass of a substance with the proposed structure, was recorded in the mass spectrum of VIc. The presence of a 3-hydroxy-N-phenylpyrimidine ring in VIc is confirmed by its fragmentation via the following scheme:



Opening of the partially hydrogenated pyrimidine ring at the C_2—C_3 bond with migration of an α-hydrogen atom as in [4, 5] precedes the elimination of a C_2H_5O particle and a molecular ion. The uracil fragment of VIc is characterized by a parallel process involving splitting out of a CH_3NCO molecule from the $[M - OH]^+$, $[M - C_2H_5O]^+$, and $[M - C_8H_9NO]^+$ ions with the formation of 253, 225, and 135 ions, respectively [6, 7].

*The numbers that characterize the ions in the text and in the scheme are the m/e values.

TABLE 1. Products of the Reaction of 8-Aminotheophyllines with Glycerol Epichlorohydrin

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIIc	171—172*	—	—	18,9	$C_{16}H_{18}ClN_5O_3$	—	—	19,3	78
IVc	>320†	—	—	23,4	$C_{29}H_{30}N_{10}O_5$	—	—	23,8	82
Va	276—277*	—	—	27,3	$C_{11}H_{15}N_5O_3$	—	—	26,8	62
Vb	>300*	51,2	6,0	24,9	$C_{12}H_{17}N_5O_3$	51,6	6,1	25,1	69
Vc	225—226*	—	—	21,4	$C_{16}H_{17}N_5O_3$	—	—	21,1	70
VIc	279—280‡	58,5	5,2	21,5	$C_{16}H_{17}N_5O_3$	58,7	5,2	21,4	87
VId	288—290‡	—	—	20,8	$C_{17}H_{19}N_5O_3$	—	—	20,5	60
VIe	276—277‡	57,2	5,3	19,3	$C_{17}H_{19}N_5O_4$	57,3	5,4	19,6	66
VIf	255—257‡	—	—	20,7	$C_{17}H_{19}N_5O_3$	—	—	20,5	67
VIg	280—281‡	57,7	6,0	—	$C_{18}H_{21}N_5O_4$	58,2	5,7	—	68
VIh	146—148‡	—	—	21,0	$C_{16}H_{23}N_5O_3$	—	—	21,0	76
VIIc	251—252*	55,8	5,7	20,5	$C_{16}H_{19}N_5O_4$	55,6	5,6	20,3	68 80
IX i[d]	275—277‡	—	—	19,9	$C_{16}H_{16}ClN_5O_2$	—	—	20,3	57
IXj	218—219*	—	—	19,2	$C_{18}H_{19}N_5O_4$	—	—	19,0	91

*From propanol. †From dimethylformamide. ‡From dioxane.
**Found: Cl 9.3%. Calculated: Cl 9.7%.

EXPERIMENTAL

The IR spectra of KBr pellets and mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The mass spectrum was recorded with a Varian MAT-311 spectrometer with direct introduction of the sample into the ion source at an accelerating voltage of 3 kV, a cathode emission current of 300 μA, an ionization energy of 70 eV, and an ion-source temperature of 180°C.

8-Aminotheophyllines Ia-c were synthesized by the reaction of 8-bromotheophylline with primary amines by the method in [8].

7-(2-Hydroxy-3-chloro-1-propyl)-8-bromotheophylline VIII was obtained from 8-bromotheophylline by the method in [9].

7-(2-Hydroxy-3-chloro-1-propyl)-8-phenylaminotheophylline (IIIc). A mixture of 2.71 g (0.01 mole) of 8-phenylaminotheophylline (Ic), 0.93 g (0.01 mole) of chlorohydrin II, and four to five drops of dry pyridine in 50 ml of propanol was refluxed for 1.5 h, after which it was filtered and cooled, and the white crystalline precipitate was removed by filtration.

1,3-Bis(8-phenylamino-7-theophyllinyl)-2-hydroxypropane (IVc). A mixture of 2.71 g (0.01 mole) of theophylline Ic, 0.93 g (0.01 mole) of chlorohydrin II, and 0.79 g (0.01 mole) of dry pyridine in 50 ml of propanol was refluxed for 1.5 h, after which it was cooled, and the precipitate was removed by filtration and washed with three 50-ml portions of hot ethanol. Evaporation of the filtrate gave Vc in 6% yield.

7-(2,3-Epoxy-1-propyl)-8-aminotheophyllines (Va-c). A) A 0.01-mole sample of theophyllines Ia-c and 0.01 mole of chlorohydrin II were added to a solution of sodium propoxide prepared from 0.23 g (0.01 mole) of sodium metal in 50 ml of propanol, and the mixture was refluxed for 1.5 h. It was then filtered and cooled, and the resulting precipitate was removed by filtration and washed with cold ethanol and water.

B) A 3.64-g (0.01 mole) sample of IIIc was added to a solution of 0.4 g (0.01 mole) of NaOH in 50 ml of absolute ethanol, and the mixture was refluxed for 2 h. It was then filtered and cooled, and the precipitate was treated as in method A to give epoxy compound Vc in 63% yield.

9H-Substituted 7-Hydroxy-1,3-dimethyl-6,7,8,9-tetrahydropyrimido[2,1-f]purine-2,4-(1H,3H) diones (VIa-f). A mixture of 0.02 mole of VIII and 0.06 mole of the corresponding amine in 50 ml of o-xylene was heated with constant refluxing. A precipitate began to form 0.5-1 h from the resulting solution 0.5-1 h after refluxing commenced. After 6 h, the mixture was cooled, and the precipitate was removed by filtration and washed with ethanol and water. Compound VIc was also obtained by refluxing equivalent amounts of Ic and II or theophylline IIIc in propanol in the presence of an equivalent amount of sodium propoxide for 12-14 h or from Vc by refluxing for 12 h in propanol with 0.05 of an equivalent of

sodium propoxide; the products were obtained in 41, 60, and 63% yields, respectively. Mass spectrum of VIc, m/e (peak intensity, %): 55 (8.5), 65 (7.4), 66 (6.0), 67 (30.0), 68 (8.1), 76 (5.1), 77 (63.1), 78 (6.4), 81 (9.8), 82 (10.7), 91 (39.2), 92 (5.2), 104 (21.2), 105 (7.4), 117 (9.0), 118 (11.2), 119 (5.8), 121 (7.4), 131 (15.5), 135 (5.9), 158 (17.2), 163.5 (11.2), 192 (12.4), 225 (11.2), 253 (11.6), 282 (20.9), 283 (6.9), 310 (87.3), 311 (14.3), 327 (100.0), 328 (18.3). (The peaks with intensities greater than 5% of the maximum peak are presented.)

7-(2,3-Dihydroxy-1-propyl)-8-phenylaminotheophylline (VII). This compound was obtained in 75-80% and 67-70% yields, respectively, by refluxing equvalent amounts of Ic and II or epoxy derivative Vc in 80% propanol in the presence of an equivalent amount of NaOH or triethylamine.

9-Phenyl-7-chloro-1,3-dimethyl-6,7,8,9-tetrahydropyrimido[2,1-f]purine-2,4-(1H,3H)dione (IXi). A mixture of 3.27 g (0.01 mole) of VIc and 3.12 g (0.015 mole) of PCl_5 in 20 ml of chloroform was refluxed for 4 h, after which it was evaporated to dryness, and the residue was treated with 50 g of finely crushed ice. The resulting precipitate was removed by filtration and washed repeatedly with water.

9-Phenyl-7-acetoxy-1,3-dimethyl-6,7,8,9-tetrahydropyrimido[2,1-f]purine-2,4-(1H,3H)-dione (IXj). This compound was obtained by refluxing 1.63 g (0.005 mole) of VIc in 25 ml of acetic anhydride for 1 h.

Data on the synthesized compounds are presented in Table 1.

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