7-(2,3-EPOXYPROPYL)-8-SUBSTITUTED THEOPHYLLINES AND THEIR MASS SPECTRA*

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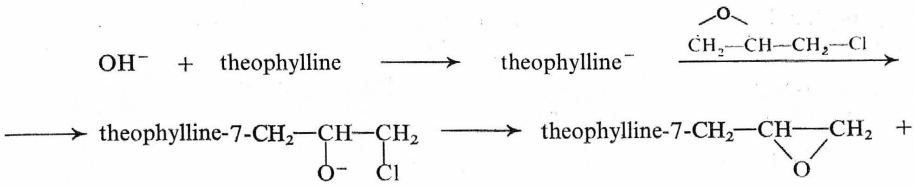
The preparation of 7-(2,3-epoxypropyl)theophylline and its 8-substituted derivatives was investigated. The most advantageous was found the method according to which theophylline and its analogues were reacted with an excess of 1-chloro-2,3-epoxypropane under catalysis of Triton B. The reaction of 8-hydroxymethyltheophylline with 1-chloro-2,3-epoxypropane in aqueous medium afforded *VII* with a perhydro-1,4-oxazepine ring.

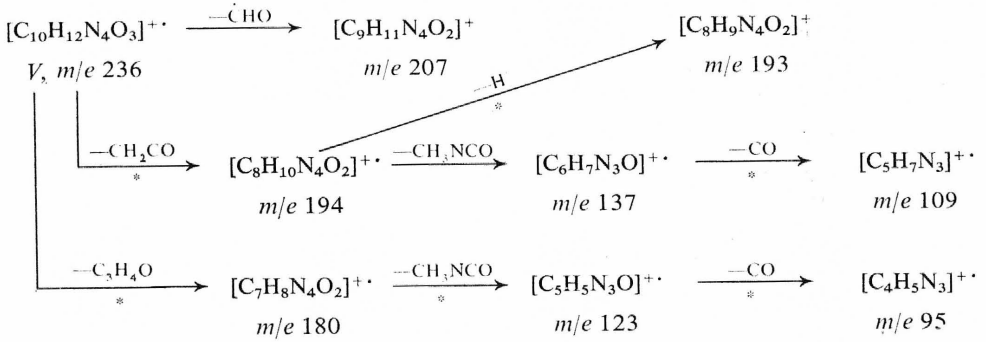
Epoxypropyl derivatives of purines were little investigated as yet, the exception being 7-(2,3-epoxypropyl)theophylline (*V*), which is an intermediate in the synthesis of a peripheral vasodilator xantinolnicotinate. It was prepared from the silver salt of theophylline and 1-chloro-2,3-epoxypropane in xylene under reflux[1], or alternatively using the sodium salt in approximately 50% yield[2]. The aim of this paper was to prepare analogous epoxypropyl derivatives of 8-hydroxymethyltheophylline (*IV*) and 8-methoxymethyltheophylline (*VI*). We were unable to increase yields of the reaction of potassium salt of 8-substituted theophylline with 1-chloro-2,3-epoxypropane at various temperatures either in the excess of 1-chloro-2,3-epoxypropane, or in dimethylformamide. Yields about 50% were also obtained when using 1-bromo-2,3-epoxypropane in dimethylformamide, or in the excess of reagent. The 8-substituted 7-(2,3-epoxypropyl)theophyllines *IV*, *VI* and 8-unsubstituted one *V* were well prepared from theophylline, or its analogues *I* and *III* with an excess of 1-chloro-2,3-epoxypropane under catalysis of benzyltrimethylammonium hydroxide (Triton B). We presume that the reaction is triggered by the hydroxyl anion of Triton B, which forms a theophylline anion from theophylline. Such an N-anion affords with two molecules of 1-chloro-2,3-epoxypropane epoxypropyltheophylline and 1,3-dichloro-2-propanol, as shown in Scheme 1.

If the reaction of 1-chloro-2,3-epoxypropane with sodium salt of 8-hydroxymethyltheophylline was carried out in the presence of water, the epoxide *V* was obtained in a small yield, the main product being compound *VII* without an epoxy group.

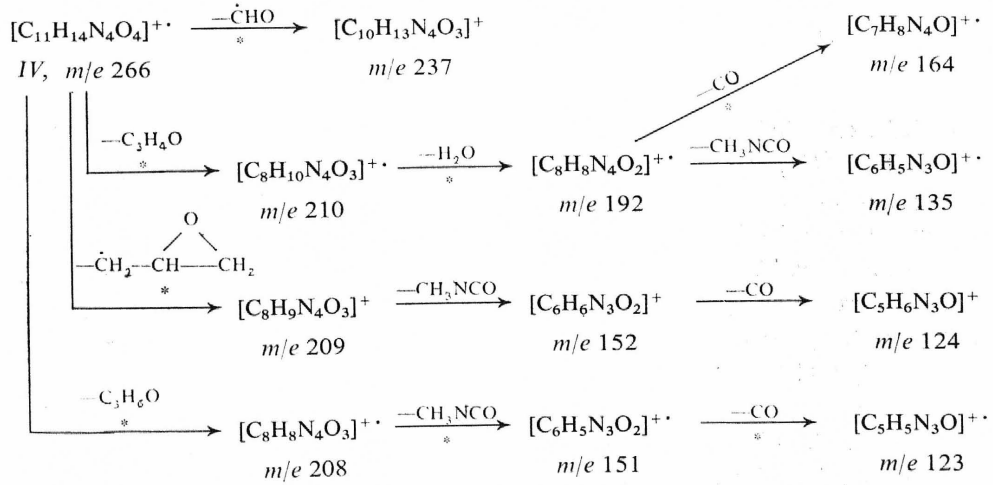
* Part V in the series Purine Derivatives; Part IV: This Journal *38*, 1571 (1973).



SCHEME 1

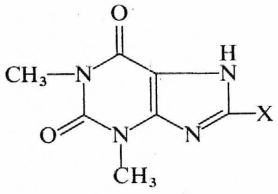


SCHEME 2

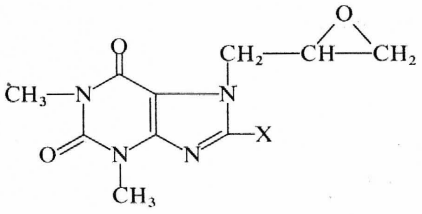


SCHEME 3

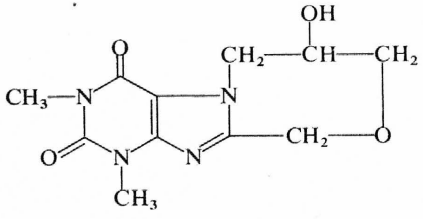
Although both substances are of the same elemental composition, they have considerably different melting points, solubilities in organic solvents and affinity to amines. The latter, in contrast to epoxypropyl derivative does not undergo a reaction with amines and can even be crystallized from them. Compound *VII* originated also from cyclization of *IV* in an aqueous alkaline medium.



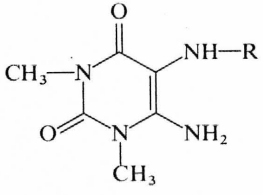
I, X = CH_2OH
II, X = H
III, X = CH_2OCH_3



IV, X = CH_2OH
V, X = H
VI, X = CH_2OCH_3



VII

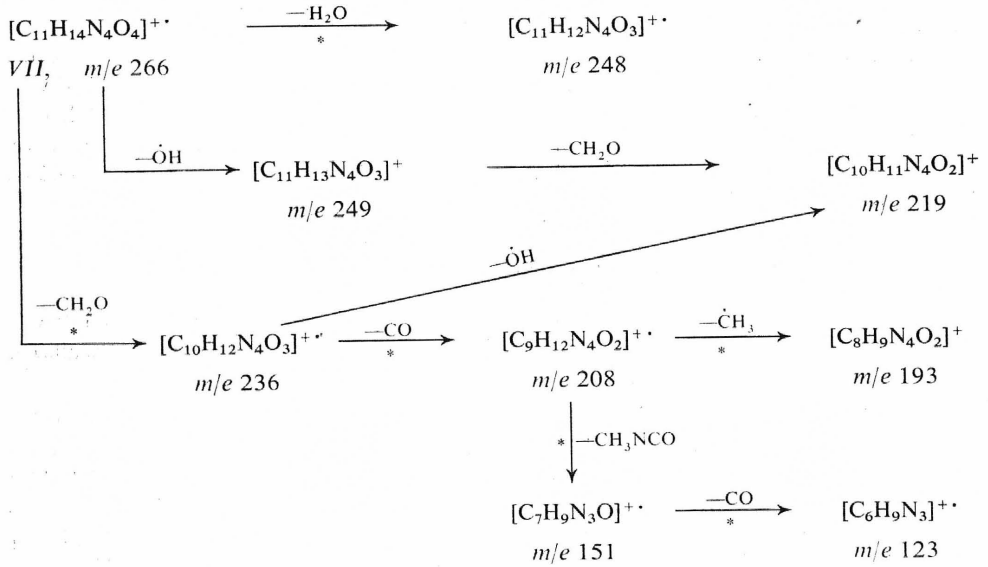


VIII, R = H
IX, R = CO—CH_2—OCH_3

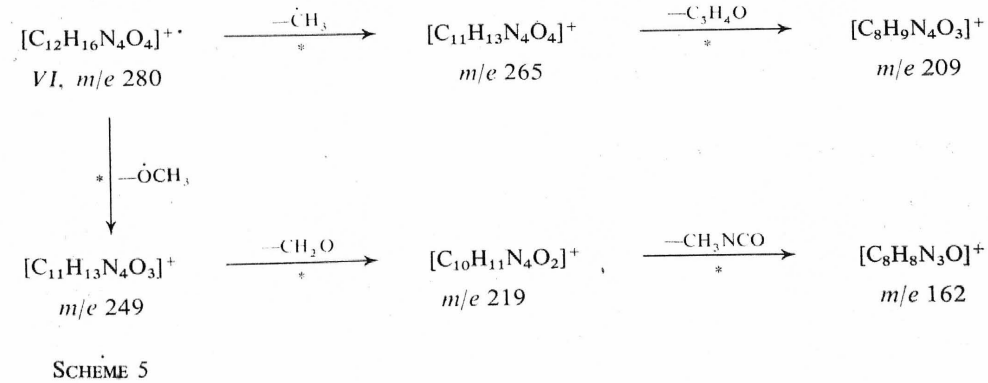
8-Hydroxymethyltheophylline (*I*) was prepared according to[3], 8-methoxymethyltheophylline (*III*) was synthesized from 1, 3-dimethyl-4,5-diaminouracil (*VIII*) and methoxyacetic acid *via* the corresponding 5-methoxyacetamido derivative *IX*.

Compounds *IV*–*VII* showed in their mass spectra peaks of molecular ions at the highest intensity. The fragmentation pattern of compound *V* is given in Scheme 2. The presence of an epoxypropyl group offers the possibility to cleave the neutral molecule C_3H_4O from the molecular ion under a hydrogen transfer. The resulting species $[C_7H_8N_4O_2]^{+\bullet}$, *m/e* 180 undergoes a further fragmentation as described with theophylline[4]. The presence of a hydroxymethyl group in compound *IV* is associated with the formation of ions at *m/e* 249 (M-17), 248 (M-18) and 235 (M-CH_2OH). The formation of further peaks, important from the viewpoint of the structure of the substance under investigation, is shown in Scheme 3. Although substances *IV* and *VII* have the same molecular formula, as determined by high re-

solution measurement, they differ in certain ions, so that their isomeric nature is seen at the first glance. Thus the absence of the peak at *m/e* 210 (M-C_3H_4O) excluded the epoxypropyl group in the molecule. Basing upon both the interpretation of mass spectra of substances *IV–VI* and the characteristic fragmentation[4–6], one is entitled to say that compound *VII* belongs to purines and therefore, we propose the structure *VII* with perhydro-1,4-oxazepine ring to it. It is our presumption that it was formed in the aqueous alkaline medium by addition of the hydroxymethyl group to the epoxide. The principal fragmentation of the molecular ion of compound *VII* is seen in Scheme 4, that of *VI* is analogous to *IV*. The presence of a methoxymethyl group gives rise to primary fragment ions at *m/e* 265 and 249 (Scheme 5).



SCHEME 4



SCHEME 5

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage. Samples for analysis were dried under reduced pressure over phosphorus pentoxide at 70°C and minimum 65 Pa for 5 h. The ultraviolet spectra were taken with a Specord UV VIS (Zeiss, Jena) spectrophotometer, mass spectra with an AEI 902 S apparatus with a direct inlet system at 70 eV electron energy, 100 μA trap current and 100—120°C ionization chamber temperature. High resolution mass spectra were measured employing the "peak matching" technique at resolution 25000 (10% valey definition) using heptacosafluorobutylamine as a background.

7-(2,3-Epoxypropyl)-8-hydroxymethyltheophylline (*IV*)

8-Hydroxymethyltheophylline (*I*, 21·0 g, 0·10 mol) was suspended in 1-chloro-2,3-epoxypropane (210 ml); benzyltrimethylammonium hydroxide (40% solution in methanol, 4 drops) was added as a catalyst and the suspension was refluxed under stirring till 8-hydroxymethyltheophylline was dissolved (*c.* 1—1·5 h). The excess of 1-chloro-2,3-epoxypropane was distilled off and the residue was mixed with acetone (30 ml). The precipitated product was filtered off, washed with acetone and dried under diminished pressure at room temperature. Yield 18·1 g. (69%), m.p. 185—187°C (chloroform–hexane). UV spectrum $\lambda_{max}^{C_2H_5OH}$, nm, (ε . 10^{-3}): 208·3 (26·3), 277·8 (9·3). For $C_{11}H_{14}N_4O_4$ (266·3) calculated: 49·62% C, 5·30% H, 21·04% N; found 49·51% C, 5·35% H, 20·96% N.

7-Hydroxyperhydro-1,4-oxazepino[3,4-*f*]theophylline (*VII*)

A) A suspension of *IV* (2·0 g, 7·5 mol) in 0·25% aqueous sodium hydroxide (40 ml) was refluxed for 1 h during which the solid dissolved; after cooling to 5°C compound *VII* crystallized. Yield 1·7 g (85%), m.p. 226—228°C (water).

B) A solution of sodium hydroxide (4·0 g, 0·1 mol) in water (6 ml) was dropwise added during 1 h to a mixture of *I* (21·0 g, 0·1 mol), water (85 ml) and 1-chloro-2,3-epoxypropane (23·1 g, 0·25 mol) at 50—55°C and allowed to stand at the same temperature for additional 7 h. The product was after cooling filtered off and crystallized from water. Yield 18·7 g (72%), m.p. 226 to 227·5°C. UV spectrum $\lambda_{max}^{C_2H_5OH}$, nm, (ε . 10^{-3}): 208·8 (27·3), 272·3 (9·2). For $C_{11}H_{14}N_4O_4$ (266·3) calculated: 49·62% C, 5·30% H, 21·04% N; found: 49·62% C, 5·33% H, 20·72% N.

7-(2,3-Epoxypropyl)theophylline (*V*)

This substance was prepared analogously as *IV* starting from theophylline (*II*, 18·0 g, 0·1 mol) and 1-chloro-2,3-epoxypropane (180 ml). Instead of acetone methanol (30 ml) was used for isolation. Yield 16·0 g (72%), m.p. 161—163°C, reported[2] m.p. 160—162°C. UV spectrum $\lambda_{max}^{C_2H_5OH}$, nm, (ε . 10^{-3}): 205·8 (23·4), 274·7 (8·0).

8-Methoxymethyltheophylline (*III*)

1,3-Dimethyl-4,5-diaminouracil (*VIII*, 10·0 g, 59 mmol) was homogenized with methoxyacetic acid (10·0 g, 0·11 mol) and the mixture was heated to 100°C under occasional stirring for 1 h. The mixture began to thicken after approximately 5—10 min and finally, it solidified. It was then dissolved in boiling water (20 ml), cooled and the separated crystals were the next day filtered off and washed with a minimum amount of ice-cold water, dried under diminished pressure at 50—60°C, and the acyl derivative *IX* (90·3 g, 64%) was crystallized from water. M.p.

228—231°C. UV spectrum $\lambda_{max}^{C_2H_5OH}$, nm, ($\varepsilon \cdot 10^{-3}$): 197·1 (14·7), 267·8 (14·4). For $C_9H_{14}N_4O_4$ (242·2) calculated: 44·62% C, 5·83% H, 23·13% N; found: 44·28% C, 5·83% H, 22·82% N.

Cyclization: A solution of sodium hydroxide (1·40 g, 35 mmol) in water (30 ml) was added to the acyl derivative *IX* (9·03 g, 35 mmol) and heated to 100°C for 0·5 h. The pH of the solution was after cooling adjusted with acetic acid to 5—6; the separated product was the next day filtered off, washed with water and dried under reduced pressure. Yield of *III* 6·15 g (79·5%), m.p. 229—232°C (water). UV spectrum $\lambda_{max}^{C_2H_5OH}$, nm, ($\varepsilon \cdot 10^{-3}$): 206·6 (28·5), 274·6 (10·2). For $C_9H_{12}N_4O_3$ (224·2) calculated: 48·21% C, 5·40% H, 24·99% N; found: 47·95% C, 5·49% H, 25·14% N.

7-(2,3-Epoxypropyl)-8-methoxymethyltheophylline (*VI*)

Starting from 8-methoxymethyltheophylline (22·4 g, 0·1 mol) and 1-chloro-2,3-epoxypropane (220 ml), this substance was prepared as described with *IV*. Yield 21·2 g (78·5%), m.p. 131·5 to 133·5°C (chloroform–hexane). UV spectrum $\lambda_{max}^{C_2H_5OH}$, nm. ($\varepsilon \cdot 10^{-3}$): 205·8 (23·4), 274·7 (8·0). For $C_{12}H_{15}N_4O_4$(279·3) calculated: 51·61% C, 5·41% H, 20·06% N; found; 51·47% C, 5·60% H, 20·03% N.

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