# 7-(3-SUBSTITUTED AMINO-2-HYDROXYPROPYL)-8-HYDROXYMETHYLTHEOPHYLLINES*

Ladislav ŠTIBRÁNYI, Alfonz RYBÁR, Lýdia BOŽEKOVÁ and Sven RIPPA

*Drug Research Institute, 801 00 Bratislava*

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N-Substituted derivatives of 7-(3-amino-2-hydroxypropyl)-8-hydroxymethyltheophylline *II* were prepared by addition of the respective amines to 7-epoxypropyl-8-hydroxymethyltheophylline (*I*) and alternatively, by alkylation of the potassium salt of 8-hydroxymethyltheophylline (*IIIb*) with substituted 1-amino-3-chloro-2-propanols. Compounds *II* were tested on peripheral vasodilating activity *in vitro*.

The preparation and pharmacodynamic properties of N-substituted 3-amino-2-hydroxypropyl derivatives of theophylline were already studied[1-3]. As a result, new peripheral vasodilator „xantinol nicotinate", 7-(3-[2-hydroxyethyl]methylamino-2-hydroxypropyltheophylline, was discovered. Due to an availability of 8-hydroxymethyltheophylline (*IIIa*), a series of 7-(3-substituted amino-2-hydroxypropyl)-8-hydroxymethyltheophyllines *II* was prepared and the peripheral vasodilating activity thereof determined. Synthesis of compounds *II* was carried out by two procedures; the first one was based on the opening of the oxirane ring of 7-(2,3-epoxypropyl)-8-hydroxymethyltheophylline (*I*) with the appropriate primary or secondary amines. The second method started from 8-hydroxymethyltheophylline, which afforded its potassium salt *IIIb* with lower alkoxides. Alkylation of *IIIb* with 1-substituted amino-3-chloro-2-propanols led to the desired products *II*. The first procedure seems to be more favourable and versatile, even though the preparation of the intermediate *I* is more laborious. The second method can be used for preparation of compounds *II* having the tertiary amino group in the side chain.

Infrared spectra of substances under investigation were taken in the 3700 to 650 $cm^{-1}$, ultraviolet spectra in the 200–360 nm ranges, the latter being characterized by two typical absorption bands in the 210–212 and 275–279 nm regions. The first band corresponds to the y-band of simple purines and its molecular extinction coefficient $\varepsilon$ is by about 2·4 times higher with compounds *II*, having the secondary amino group in the side chain, and approximately three times higher with compounds *II* with the tertiary amino group, than that associated with the x-band of simple purines. Moreover, compounds *II*, having, the secondary amino group in the

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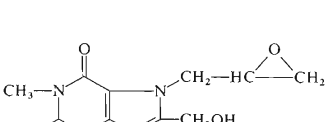
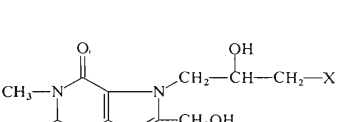
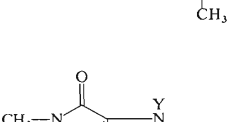
side chain, reveal a third, substantially less intense band at 234–235 nm than the first ones. Infrared spectrum of compounds *II* display very intense bands in the 1710–1705 $cm^{-1}$ (C=O in position 2) and 1680–1650 $cm^{-1}$ regions (C=O in position 6), medium intense bands at 2960–2950 and 2860–2880 $cm^{-1}$ (CH), a broad band of medium intensity at 3480–3430 $cm^{-1}$ (OH···O).



*I*



*II*



*IIIa*, Y = H
*IIIb*, Y = K

The effect of substances *II* on the peripheral circulation was investigated *in vitro*. All compounds *II* show a greater peripheral vasodilating activity than xantinol nicotinate, but a smaller one than 1-(5-oxohexyl)theobromine (pentoxiphylline) (Table II).

## EXPERIMENTAL

Melting points were measured on a Koffler hot stage. Samples for analysis were dried under a pressure not exceeding 65 Pa over phosphorus pentoxide at 70°C for 5 h. UV spectra were recorded with a Specord UV VIS (Zeiss, Jena), IR spectra of compounds *II* (in KBr discs) with a UR-20 (Zeiss, Jena) spectrophotometers.

### 7-(3-Substituted Amino-2-hydroxypropyl)-8-hydroxymethyltheophyllines (*II*)

*Method A*: To a solution of 7-(2,3-epoxypropyl)-8-hydroxymethyltheophylline[4] (*I*, 5·33 g, 20 mmol) in ethanol (60 ml) the respective amine (0·1 mol) was added and refluxed for 6 h. The excess of ethanol and the amine was removed under reduced (c. 65 Pa) pressure, the oily residue was dissolved in methanol (c. 30 ml), acidified to pH 4–5 with a methanolic solution of hydrogen chloride and the solvent distilled off under diminished pressure (c. 2 kPa). The amine hydrochloride thus obtained was crystallized from a suitable solvent.

TABLE I

Characteristic Data of 7-(3-Substituted Amino-2-hydroxypropyl)-8-hydroxymethyltheophyllines *II*

| Compound | X | Mol. formula (mol. weight) | Calculated/Found % C | % H | % N | M.p., °C solvent | Method yield, % | $\lambda_{max}$, nm ($\varepsilon \cdot 10^{-3}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *IIa* | NH—$CH(CH_3)_2$.HCl | $C_{14}H_{24}ClN_5O_4$ (361·8) | 46·47 46·76 | 6·68 6·73 | 19·35 19·71 | 236—238 [a,b] | *B* 77 | 211 26·6 | 234 5·4 | 279 11·3 |
| *IIb* | NH—$C(CH_3)_3$.HCl | $C_{15}H_{26}ClN_5O_4$ (375·9) | 47·93 47·35 | 6·97 6·96 | 18·63 18·08 | 262—264 [a,b] | *A* 53 | 211 27·6 | 234 5·4 | 279 11·3 |
| *IIc* | NH—⬡.HCl | $C_{17}H_{28}ClN_5O_4$ (401·9) | 50·80 50·34 | 10·23 10·11 | 17·42 17·23 | 248—252 [a] | *A* 62 | 211 27·6 | 235 7·7 | 279 11·3 |
| *IId* | $N(C_2H_5)_2$. nicotinate | $C_{21}H_{30}N_6O_6$ (463·5) | 53·53 53·28 | 6·54 6·49 | 18·17 17·92 | 131·5—132·5 [c] | *B* 62 | 211 37·3 | — — | 277 13·0 |
| *IIe* | $N(CH_3)CH_2CH_2OH$. nicotinate | $C_{20}H_{28}N_6O_7$ (464·8) | 51·71 51·58 | 6·07 6·11 | 18·09 18·23 | 136—138 [c] | *C* 42 | 211 37·3 | — — | 275 13·0 |
| *IIf* | N⬡. nicotinate | $C_{22}H_{30}N_6O_6$ (475·5) | 55·56 55·68 | 6·57 6·55 | 17·67 17·73 | 160—161·5 [c] | *C* 52 | 211 38·6 | — — | 275 12·6 |
| *IIg* | N⬡O.HCl | $C_{15}H_{24}ClN_5O_5$ (389·8) | 46·20 46·11 | 6·20 6·03 | 17·96 17·59 | 237—239 [a] | *A* 82 | 210 45·3 | — — | 275 17·6 |
| *IIh* | N⬡N—⬡ dinicotinate | $C_{33}H_{43}N_8O_8$ (674·7) | 58·74 58·75 | 5·68 5·52 | 16·61 16·31 | 158—161·5 [c] | *A* 61 | 212 55·0 | — — | 276 15·0 |

[a] Methanol, [b] ether, [c] acetonitrile.

TABLE II

Evaluation of the Peripheral Vasodilatation of Compounds *II* (Reference substance acetylcholine)

| Compound | Ratio of the reference effect, % | |
|---|---|---|
| | method 1[a] | method 2[b] |
| *IIa* | 8·5 | 22 |
| *IIb* | 35 | 18 |
| *IIc* | 21 | 11 |
| *IId* | 68 | 30 |
| *IIe* | 7 | — |
| *IIf* | 33 | 61 |
| *IIg* | 32 | 60 |
| *IIh* | 29 | — |
| Xantinol nicotinate | 21 | 33 |
| Pentoxiphylline | 150 | 150 |

[a] Determined on the isolated rabbit ear preparation according to Krawkow–Pissemský method. The effect of acetylcholine 100%. [b] According to Grisk method. The effect of acetylcholine 100%.

*Method B*: A mixture consisting of 7-(2,3-epoxypropyl)-8-hydroxymethyltheophylline (*I*, 5·33 g, 20 mmol), the appropriate amine (30 mmol) and water (1 ml) was heated in an autoclave at 100°C for 10 h. The excess of the amine was after cooling removed *in vacuo* and the residue was worked up analogously as with method *A*.

*Method C*: 8-Hydroxymethyltheophylline[5] (*IIIa*, 4·48 g, 20 mmol) was suspended in ethanol (20 ml) and an equivalent of 0·1 molar solution of potassium methanolate in methanol was added. Compound *IIIa* dissolved at 50–60°C; removal of the solvent afforded its potassium salt (*IIIb*).

A solution of 3-substituted amino-1-chloro-2-propanol[6,7] (22 mmol) in dimethylformamide (50 ml) was dropwise added to the stirred solution of *IIIb* in dimethylformamide (30 ml) at 60°C during 45 min and then the mixture was kept at 45°C for 6 h. The precipitate was filtered off after cooling, the filtrate evaporated under diminished pressure, the oily residue dissolved in methanol (30–40 ml) and neutralized with nicotinic acid (20 mmol) in methanol to afford the nicotinate, which was purified by crystallization from a suitable solvent.

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