7-(3-SUBSTITUTED AMINO-2-HYDROXYPROPYL)-8-BENZYL-, OR -8-PHENYLTHEOPHYLLINES*

Ladislav ŠTIBRÁNYI[a], Alfonz RYBÁR[a], Ján JENDRICHOVSKÝ[a], Lýdia BOŽENKOVÁ[a] and Vladimír KOVALČÍK[b]

[a] *Research Institute for Drugs, 801 00 Bratislava and*
[b] *Department of Pharmacology, Comenius University, 884 24 Bratislava*

Received July 28th, 1981

N-Substituted derivatives of 7-(3-amino-2-hydroxypropyl)-8-benzyl- (*V*), or -8-phenyltheophylline (*VI*) were prepared by addition of the appropriate amines to 7-epoxypropyl-8-benzyl- (*III*), or -8-phenyltheophyllines (*IV*). Compounds *III* and *IV* were obtained by alkylation of 8-benzyl-, or 8-phenyltheophyllines with 1-chloro-2,3-epoxypropane. Derivatives *V* and *VI* exhibited a peripheral vasodilatation effect *in vitro*.

7-(2-Substituted aminoethyl)theophyllines were those mostly studied[1,2] of basically substituted 8-benzyltheophyllines. As a result of these investigations, the analeptic, coronary vasodilator and bronchodilator Bamiphyllin (7-[2-(N-ethyl-β-hydroxyethylamino)ethyl]-8-benzyltheophylline) was introduced into the practice. Less studied were derivatives of 8-benzyltheophylline having the substituted amino group more remote from the theophylline skeleton[2]. Analogous derivatives of 8-phenyltheophylline have hitherto not been described. In continuation of our program on the 8-substituted analogues of the peripheral vasodilator xantinolnicotinate (7-[3-(N-methyl-β-hydroxyethyl)-2-hydroxypropyl]theophylline) a series of 7-(3-substituted amino-2-hydroxypropyl)-8-benzyl (*V*) and 8-phenyltheophyllines (*VI*) was synthesized and peripheral vasodilation effect tested.

Compounds *V* (Table I) were prepared from 8-benzyltheophylline (*I*) obtained according to[3,4]. An excess of 1-chloro-2,3-epoxypropane gave with *I*, under catalysis of trimethylbenzylammonium hydroxide, 8-benzyl-7-(2,3-epoxypropyl)theophylline (*III*). This procedure was exemplified in more detail in our previous paper[5] dealing with 7-(2,3-epoxypropyl)theophylline and its 8-alkyl derivatives. Transformation of 7-(2,3-epoxypropyl) derivative *III* into the final 7-(3-substituted amino-2-hydroxypropyl) derivatives *V* was effected by opening of the oxirane ring with the appropriate amines.

An analogous procedure was employed when preparing 7-(3-substituted amino--2-hydroxypropyl) derivatives *VI* starting from 8-phenyltheophylline (*II*) *via* 7-(2,3-

* Part VII in the series Purine Derivatives; Part VI: This Journal *49*, 424 (1979).

TABLE I

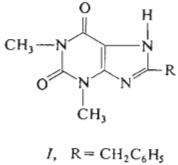
7-(3-Substituted amino-2-hydroxypropyl)-8-benzyl, or 8-phenyltheophyllines *V*, or *VI*

Compound	X	Formula (mol.weight)	Calculated/Found				M.p., °C solvent	Method Yield	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)		
			% C	% H	% N	% Cl					
Va	NH—$CH(CH_3)_2$.HCl	$C_{20}H_{28}ClN_5O_3$ (421·9)	56·93 56·60	6·69 6·69	16·60 16·13	8·40 8·52	225—227 ethanol	*B* 58	210 (39·3)	233 (8·3)	277 (14·6)
Vb	NH—$C(CH_3)_3$.HCl	$C_{21}H_{30}ClN_5O_3$ (435·9)	57·85 57·45	6·94 6·48	16·07 16·30	8·13 8·17	231—234 methanol–ether	*B* 80	211 (33·6)	233 (7·0)	277 (12·3)
Vc	NH—  .HCl	$C_{23}H_{32}ClN_5O_3$ (462·0)	59·79 59·77	6·98 7·05	15·16 15·03	7·67 7·68	215—219 methanol–ether	*B* 57	208 (35·3)	233 (6·0)	276 (12·0)
Vd	 .HCl	$C_{22}H_{30}ClN_5O_3$ (448·0)	58·98 58·95	6·75 6·55	15·64 15·75	7·91 7·94	241—243 acetonitrile–ether	*B* 64	207 (35·3)	233 (5·0)	276 (11·6)
Ve	 .HCl	$C_{21}H_{28}ClN_5O_3$ (433·9)	58·12 57·50	6·50 6·39	16·14 16·82	8·17 8·08	198—199·5 acetonitrile–ether	*B* 65	210 (38·3)	232 (8·3)	277 (13·3)
Vf	 —CH_3.2 HCl	$C_{22}H_{32}Cl_2N_6O_3$ (499·4)	52·90 52·45	6·46 6·31	16·83 16·73	14·20 14·13	245—248 methanol–water	*A* 56	211 (33·6)	233 (7·0)	277 (12·3)
Vg	 .HCl	$C_{21}H_{27}ClN_5O_4$ (488·9)	56·18 55·89	6·06 6·24	15·60 15·35	7·89 7·75	201—204 methanol	*B* 55	210 (35·6)	232 (7·6)	277 (12·6)

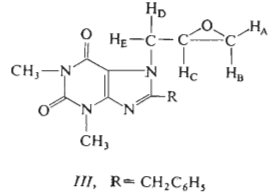
VIa	NH—$CH(CH_3)_2$.HCl	$C_{19}H_{26}ClN_5O_3$	55·94	6·43	17·17	8·69	240—243	*B*	207	231	293
		(407·9)	55·77	6·39	17·20	8·54	methanol–ether	84	(28·6)	(24·3)	(18·0)
VIb	NH—$C(CH_3)_3$.HCl	$C_{20}H_{28}ClN_5O_3$	56·93	6·69	16·60	8·40	245—247	*A*	207	231	293
		(421·9)	56·85	6·64	16·64	8·37	methanol–ether	69	(30·3)	(25·3)	(18·6)
VIc		$C_{22}H_{30}ClN_5O_3$	58·98	6·75	15·64	7·91	270—273	*A*	207	232	294
		(447·9)	59·20	6·21	15·64	7·81	methanol	68	(27·6)	(23·0)	(16·6)
VId		$C_{21}H_{28}ClN_5O_3$	58·12	6·50	16·14	8·17	265—267	*A*	205	233	292
		(433·9)	58·02	6·57	15·98	8·31	acetonitrile	67	(37·0)	(29·3)	(21·0)
VIe		$C_{20}H_{26}ClN_5O_3$	57·20	6·24	16·68	8·44	251—253	*A*	205	233	292
		(419·9)	56·77	6·42	16·72	8·53	acetonitrile	68	(31·0)	(23·6)	(16·6)
VIf		$C_{21}H_{30}Cl_2N_6O_3$	51·96	6·23	17·32	14·61	223—225	*A*	204	233	292
		(485·4)	51·25	6·29	17·06	14·48	ethanol–water	91	(34·6)	(25·6)	(18·6)
VIg		$C_{20}H_{27}ClN_5O_4$	55·10	6·02	16·04	8·13	239—242	*A*	207	233	294
		(435·9)	55·34	6·10	16·25	8·12	methanol–water	60	(25·2)	(22·0)	(14·8)

-epoxypropyl)-8-phenyltheophylline (*IV*). The starting product was synthesized according to[6].

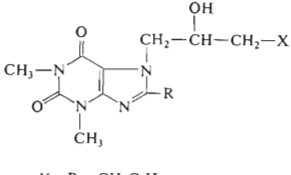
Ultraviolet and infrared spectra of the compounds under study were measured in the 200–360 nm and 3 700–650 cm^{-1} regions, respectively. The UV spectra of compounds *V* and *VI* were characterized by three absorption bands. Derivatives of 8-benzyltheophylline had these bands at 207–211, 232–233 and 272–276 nm, those of 8-phenyltheophylline *VI* were at 204–207, 231–233 and 291–294 nm, respectively. The value of the extinction coefficient ε of the first band of compounds *V* (corresponding to the *y*-band of simple purines) was found to be by 2·7 to 3·0 greater than that of the third band (corresponding to the *x*-band of the simple purines). This value in compounds *VI* was only 1·6 to 1·9 times greater with the first band than with the third. The intensity of the second band was substantially greater with compounds *VI* (approximately 80% of the value of the first band) than with com-compounds *V* (approximately 20% of the first band). The IR spectra of compounds *I* to *VI* revealed very intense bands at 1 650–1 670 (CO in position 2) and 1 690 to 1 715 cm^{-1} (CO in position 6). Derivatives *V* and *VI* displayed medium intense bands at 2 860–2 880 and 2 950–2 970 cm^{-1} (CH) and a broad band of medium intensity at 3 270–3 330 cm^{-1} (OH...H). The band at 1 230 cm^{-1} (C—O—C) was seen with compounds *III* and *IV*.



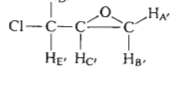
I, R = $CH_2C_6H_5$
II, R = C_6H_5



III, R = $CH_2C_6H_5$
IV, R = C_6H_5



V, R = $CH_2C_6H_5$
VI, R = C_6H_5



VII

Structures of compounds *III* and *IV* were also verified by ^{1}H NMR spectra (δ, ppm), which showed characteristic singlets of methyl protons at 3·57 (*III*) and 3·60 (*IV*, $N_{(3)}$—CH_3) and 3·36 (*III*) and 3·43 (*IV*, $N_{(1)}$—CH_3), as well as multiplets of protons of benzene ring at 7·25 and 7·68, respectively. Both compounds had multiples indicative of the epoxypropyl substitution. Signals of the individual protons of epoxypropyl groups were ascribed on the basis of comparison with an analogous spectrum of 1-chloro-2,3-epoxypropane (*VII*): H_A 2·56, H_B 2·75, H_C 3·16, H_D 3·38, H_E 3·68. Terminal protons H_A (2·50 and 2·60, resp.) and H_B (2·77 and 2·88, resp.) were closest to the compared model substance. The greater deviation found with protons H_C (3·46 and 3·51, resp.), H_D 4·10 and 4·25, resp.), H_E (4·70 and 4·78, resp.) is due to the interchange of chlorine of 1-chloro-2,3-epoxypropane for nitrogen of the $N_{(7)}$--theophylline ring. The coupling constants $J_{E,D}$ in both compounds, *III* and *IV* have the same value (−15 Hz), what is in a good accordance with the analogous value of 1-chloro-2,3-epoxypropane (−11·84 Hz, ref.[7]). Other vicinal coupling constants were +2·5 to +6·5, what is, again, in a good agreement with analogous values of the model epoxide *VII* (+2·5 to 6 Hz).

Compounds *V* and *VI* were tested for peripheral circulation *in vitro*; as found, all investigated substances showed greater activity than xantinolnicotinate, but did not reach that of pentoxiphylline. The obtained results are listed in Table II.

TABLE II

Peripheral vasodilatation effect of compounds *V* and *VI* (reference acetylcholine)

Compound	Effect[c]	
	method 1[a]	method 2[b]
Va	18	55
Vb	52	—
Vc	53	—
Vg	54	—
VIa	—	46
VIb	—	60
VIc	—	75
Xantinolnicotinate	21	33
Pentoxiphylline	150	150

[a] Determined on an isolated rabbit ear by the Krawkow–Pissemský method. [b] Determined on an isolated rat extremity by the Grisk method. [c] % of the reference.

EXPERIMENTAL

Melting points were measured on Kofler micro hot-stage. Samples for analysis were dried at 70°C and 65 Pa, or less, over phosphorus pentoxide for 5 h. The UV spectra of ethanolic solutions were measured with a Specord UV VIS (Zeiss, Jena) apparatus, the IR spectra with a UR-20 (Zeiss, Jena) spectrophotometer. Compounds *III* and *IV* were measured in chloroform or tetrachloromethane in a 0·1 mm cell, *V* and *VI* in KBr.

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

8-Phenyltheophylline[6] (*II*, 25·7 g, 0·1 mol) was suspended in a fresh-distilled 1-chloro-2-epoxypropane (300 ml), *c.* 5 drops of 40% methanolic Triton B being added, and refluxed with stirring untill all material was dissolved (*c.* 2 h). The excess of 1-chloro-2,3-epoxypropane was distilled off under diminished pressure, the oily residue dissolved in chloroform, filtered through a bed of alumina and precipitated with n-hexane. The product was filtered off, washed with methanol (cooled to 0°C) and dried *in vacuo*. Yield 21·9 g, 70%, m.p. 166–169°C. The sample for analysis was crystallized from chloroform–n-hexane (19·1 g, 61%, m.p. 168–169·5°C). UV spectrum λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 207 (25·6), 233 (28·0), 294 (15·2). For $C_{16}H_{16}N_4O_3$ (313·3) calculated: 61·55% C, 5·16% H, 17·94% N; found 61·18% C, 5·25% H, 17·73% N.

7-(2,3-Epoxypropyl)-8-benzyltheophylline (*III*)

This compound was synthesized from 8-benzyltheophylline[3,4] (*I*, 40·7 g, 0·15 mol) and 1-chloro-2,3-epoxypropane (800 ml), by a procedure analogous to *IV*. Yield 36·3 g, 74%, m.p. 125–130°C. The sample for analysis was crystallized from chloroform–n-hexane; yield 31·4 g, 64%, m.p. 128–130·5°C. UV spectrum λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 210 (36·6), 278 (20·3). For $C_{17}H_{18}N_4O_3$ (327·4) calculated: 62·38% C, 5·85% H, 17·12% N; found: 62·38% C, 5·50% H, 17·17% N.

7-(3-Substituted Amino-2-hydroxypropyl)-8-phenyltheophyllines *VI* and 7-(3-Substituted Amino-2-hydroxypropyl)-8-benzyltheophyllines *V*

A) A mixture of epoxypropyl derivatives *IV* (6·3 g, 20 mmol), ethanol (70 ml) and the appropriate amine (40 mmol) was refluxed for 6 h. The mixture was evaporated, the residue dissolved in ethanol (50 ml) and the pH of this solution adjusted to 2 with ethanolic HCl. The solution was concentrated under diminished pressure and the product (HCl salt) precipitated with ether. The sample for analysis was crystallized from an appropriate solvent.

B) The mixture of epoxypropyl derivative *III*, or *IV* (20 mmol), the amine (0·2 mol) and water (2 ml) was heated in an autoclave with agitating at 100°C for 15 h. The excess of amine and the water were distilled off *in vacuo* and the residue worked up as under *A*. Compounds *V* and *VI* and their properties are listed in Table I.

Our thanks are due to Dr V. Ostrovská and Mrs S. Markusová, Analytical Department of This Institute (Head Dr P. Králik), for elemental analyses and measurement of UV *and* IR *spectra.*

REFERENCES

1. de Ridder R. R.: Brit. 947 495 (1964); Chem. Abstr. *60*, 15892 (1964).
2. de Ridder R. R.: Brit. 947 496 (1964); Chem. Abstr. *60*, 15 892 (1964).
3. Kostolanský A., Mokrý J., Tamchyna J.: Chem. Zvesti *10*, 102 (1956).

4. Hager G. P., Kranz J. C. jr, Harmon J. B.: J. Amer. Pharm. Assoc. Sci. Ed. *42*, 36 (1953).
5. Rybár A., Štibrányi L., Leško J.: This Journal *43*, 3414 (1978).
6. Goldner H., Dietz G., Carstens E.: Justus Liebigs Ann. Chem. *691*, 142 (1966).
7. MacDonald J. C., Theodor S.: Can. J. Chem. *48*, 1033 (1970).

Translated by Z. Votický.