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A simple HPLC-UV method for the determination of dimenhydrinate and related substances – identification of an unknown impurity

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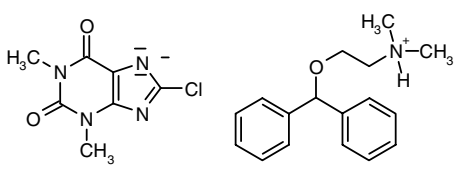
During the revision of the dimenhydrinate monograph of the European Pharmacopoeia a HPLC-UV method was developed. The procedure described allows a qualitative and quantitative determination of both dimenhydrinate compounds and of thirteen related substances. Furthermore a hitherto unknown impurity was identified and integrated into the purity check. Also 18 samples of dimenhydrinate have been tested. Thereby the relevant impurities of dimenhydrinate could be nominated and quantified.

1. Introduction

Dimenhydrinate, once known as dramamine, belongs to the small group of combined medicinal substances. The patent in terms of synthesis was presented already in 1950 in the USA (Cusic 1950). According to this the substance is made up by mixing equimolar amounts of 8-chlorotheophylline (**IV**) and diphenhydramine (**VIII**) in hot ethyl alcohol. The resulting salt is a potent drug against nausea. Various producers supply the demand of dimenhydrinate. Due to the variety of raw material, technical equipment and manufacturing technology a wide spectrum of impurities is inevitable. Though dimenhydrinate is applied for more than 50 years, literature research shows only few information about this topic. Several authors describe degradation products of dimenhydrinate or diphenhydramine found in stress tests, but none has been identified (Barbas et al. 2000; Donelly 2002; Stiles et al. 1994). The European Pharmacopoeia prescribes a specific TLC test only for theophylline (**II**) (PhEur. 2005). Henderson et al. name seven potential impurities of diphenhydramine remaining from synthesis: benzhydrol (**XII**), benzophenone (**XIII**), diphenylmethane (**XIV**), 2-(diphenylmethoxy)-*N*-methylethanamine (**VII**), 2-[(4-methylphenyl)-phenylmethoxy]-*N*,*N*-dimethylethanamine (**IX**), 2-[(4-bromophenyl)phenyl-methoxy]-*N*,*N*-dimethylethanamine (**X**) and *N*,*N*,*N*-[(2-diphenylmethoxyethyl)-(2-dimethylaminoethyl)methyl]amine (**VI**) (Henderson et al. 2001). Already in 1971 8-[(2-diphenylmethoxy)ethylmethyl-amino]theophylline (**XI**) – a dimer of **IV** and **VII** – was isolated from dimenhydrinate (Santoro and Warren 1971). The German Federal Institute for Drugs and Medical Devices discusses additionally the dibenzhydryl ether (**XV**). Because of their structural relationship also caffeine (**III**) and theobromine (**I**) must be taken into account.



Dimenhydrinate

To allow the determination of all relevant impurities within the limits of the European Pharmacopoeia the monograph ought to be revised. In the future the test of related substances should be carried out by liquid chromatography.

For determination of dimenhydrinate by HPLC some test methods have been described in the past, which mostly used reversed phases (C8 or C18) and acetonitrile and phosphate buffer as solvent. Chromatography was performed both isocratic (Kvist et al. 2000) and with gradient (Nassr et al. 2003), partly in addition of triethylamine (Barbas et al. 2000; Donelly 2002) acting as competitive base. A similar procedure includes methanol, triethylamine and acetic acid (Roos and Lau-Cam 1986).

It is noted that Donelly and Kvist et al. sign only one peak for dimenhydrinate in HPLC chromatograms. Doubtless it is 8-chlorotheophylline. Iterating the published methods diphenhydramine appears in the chromatograms late with plane and wide peaks. Therefore it has probably been overlooked. So diphenylalkylamines such as diphenhydramine are not quantifiable in this way.

Moreover the asymmetry (intense tailing) of the diphenhydramine peaks is the most important handicap of all mentioned techniques. This comes along with elution times of several minutes. As structural related substances cause the same effect no sufficient peak resolution could be achieved.

Instructions for determination of diphenhydramine – without 8-chlorotheophylline – as the European Pharmacopoeia test of related substances (PhEur. 2005) and the method from Stiles et al. (Stiles et al. 1994) have the same limits.

Utilisation of ion pair formation can improve the peak shape considerably. Employed are octanesulfonic acid (Paciolla et al. 2001), heptanesulfonic acid (Qi et al. 2003) and laurylsulfonic acid (Henderson et al. 2001). Two disadvantages restrain their applicability. First the reagents must be of high purity to avoid ghost peaks, especially in gradient HPLC. Secondly dilution series of diphenhydramine ion pairs have only limited linearity.

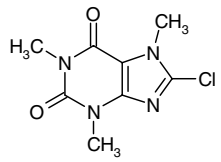
The intention of this study was to name relevant impurities of dimenhydrinate and to develop and validate a

HPLC method for qualitative and quantitative determination of the drug and related substances. For these purposes 18 samples of dimenhydrinate from several producers were available.

2. Investigations, results and discussions

2.1. Identification of an impurity in dimenhydrinate

Within the scope of the development of the HPLC method in chromatograms of two dimenhydrinate samples a peak was detected, which could not be associated with any known impurity. All substances related to diphenhydramine and 8-chlorotheophylline should be involved into the purity test. That is why identification was necessary. A content of more than one percent in two samples allowed the isolation by column chromatography. The structure elucidation qualified the substance as 8-chlorocaffeine (**V**). This special xanthine was not commercially available. By methylation of 8-chlorotheophylline a reference substance of high purity could be synthesized.



8-Chlorocaffeine

2.2. HPLC of dimenhydrinate and related substances

The Scheme shows all substances analysed. As also **VI**, **IX**, **X**, **XI** and **XV** have not been commercially available, reference substances were synthesized. Extensive tests considering the described analytical problems resulted in the following HPLC parameters:

As matrix material a high-purity, metal free, pH-stable (pH 1.5–10) silica gel with complete endcapping was chosen. Perfect spherical particles with smooth surface guaranteed symmetric peaks, short elution times and as a result good resolution of structural related substances. The eluent consisted of a 1% triethylamine solution (eluent A; pH 2.5 with phosphoric acid) and acetonitrile (eluent B). A gradient in eluent composition and flow rate (Table 1) caused the best possible resolution of fifteen compounds. The high percentage of triethylamine and an acetonitrile minimum of 40% was essential to obtain a sufficient peak shape for diphenylalkylamines, like diphenhydramine. The working temperature was 30 °C. Always 10 µl were injected. The UV detector was set at 225 nm. Separation of 15 substances occured within 30 min. Equilibration took 15 min. Fig. 1 shows a spectrum of all regarded substances. Table 2 summarizes chromatogram data of dimenhydrinate and its impurities. Beside retention times/relative retention times and peak resolution the UV-factor was determined, because of the varying UV-activity at 225 nm. The standard for comparison was diphenhydramine.

Table 1: Gradient for dimenhydrinate determination

Time (min)	Mobile phase A (% V/V)	Mobile phase B (% V/V)	Flow rate ($ml \cdot min^{-1}$)
0–15	82 → 50	18 → 50	1.2
15–20	50 → 20	50 → 80	1.2 → 2.0
20–30	20	80	2.0
30–32	20 → 82	80 → 18	2.0 → 1.2
32–45	82	18	1.2

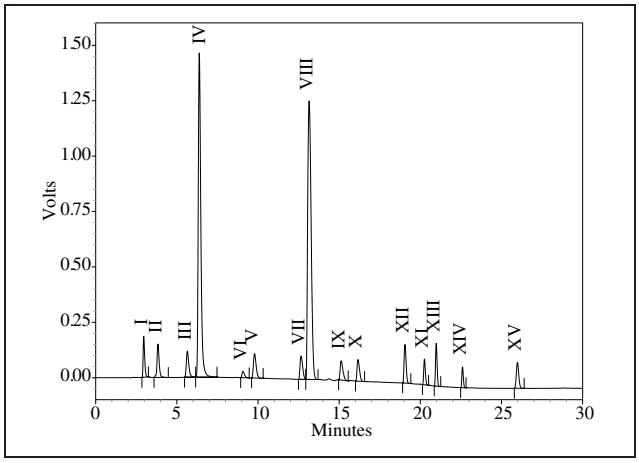
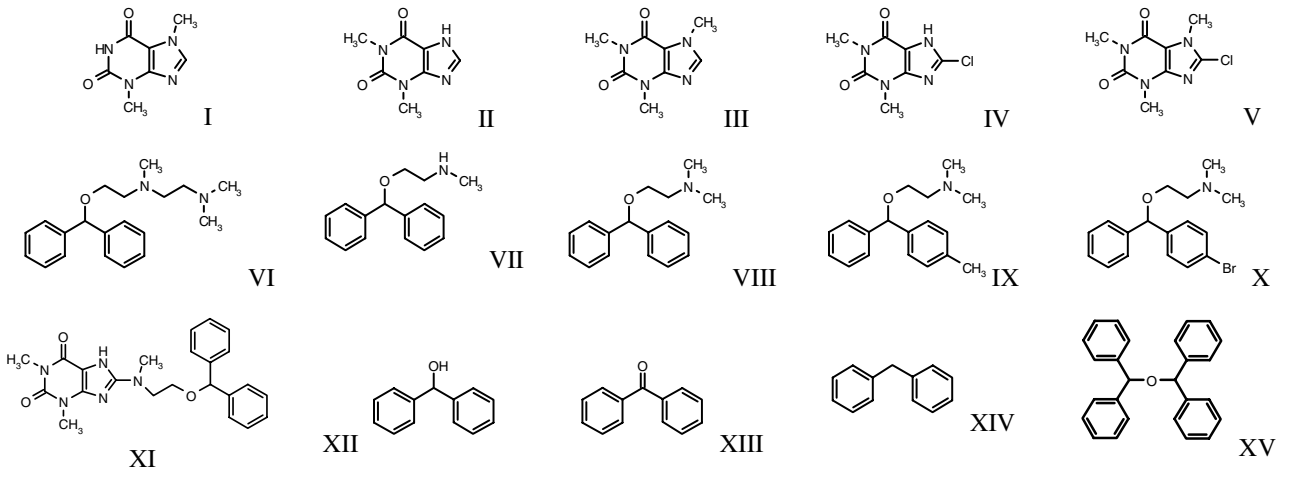


Fig. 1: Dimenhydrinate and related substances



I: theobromine; II: theophylline; III: caffeine; IV: 8-chlorotheophylline; V: 8-chlorocaffeine; VI: *N*,*N*,*N*-[(2-diphenylmethoxyethyl)-(2-dimethylaminoethyl)methyl]amine; VII: 2-(diphenylmethoxy)-*N*-methylethanamine; VIII: diphenhydramine; IX: 2-[(4-methylphenyl)-phenylmethoxy]-*N*,*N*-dimethylethanamine; X: 2-[(4-bromophenyl)phenyl-methoxy]-*N*,*N*-dimethylethanamine; XI: 8-[(2-Diphenylmethoxy)ethylmethylamino]theophylline; XII: benzhydrol; XIII: benzophenone; XIV: diphenylmethane; XV: dibenzhydryl ether

Table 2: Chromatogram data of dimenhydrinate and related substances

Substance	I	II	III	IV	VI	V	VII	VIII	IX	X	XII	XI	XIII	XIV	XV
$t_{ret.}$ (min)	2.96	3.83	5.65	6.38	9.08	9.79	12.65	13.15	15.13	16.16	19.06	20.25	20.98	22.60	26.00
Rel. $t_{ret.}$	0.23	0.29	0.43	0.49	0.69	0.74	0.96	1.00	1.15	1.23	1.45	1.54	1.60	1.72	1.98
Resolution	4.72	7.84	2.70	8.92	3.61	9.69	1.90	6.75	4.03	13.63	6.58	5.19	10.83	16.46	n.a.
UV-factor	1.06	1.20	1.08	1.09	1.24	0.93	1.08	1.00	0.72	0.84	1.15	0.94	2.10	1.87	1.19

2.3. Validation

To test the suitability of the method a validation was carried out. Table 3 shows the parameters, the requirements and the results. A high value was set on the robustness. It could be verified that variations in temperature, triethylamine percentage and pH value had no influence on retention times of the analysed substances, with exception of **VI**. In this case a raising pH value resulted in increasing retention time (Fig. 2). The effect was caused by the two-step protonation of the diamine structure. At pH 2 there was a hydrophilic cation with low retention on the lipophilic matrix. Above pH 2.8 (increasing deprotonation) the lipophilic character became more important and the retention time enhanced. This was essential to consider because above pH 3 resolution between **VI** und **V** was not possible any more.
Also the application of columns from various producers demonstrated good robustness. There was no deviation in retention times above 10%. Furthermore excellent repeatability, accuracy, linearity in a wide range and good recovery could be verified.

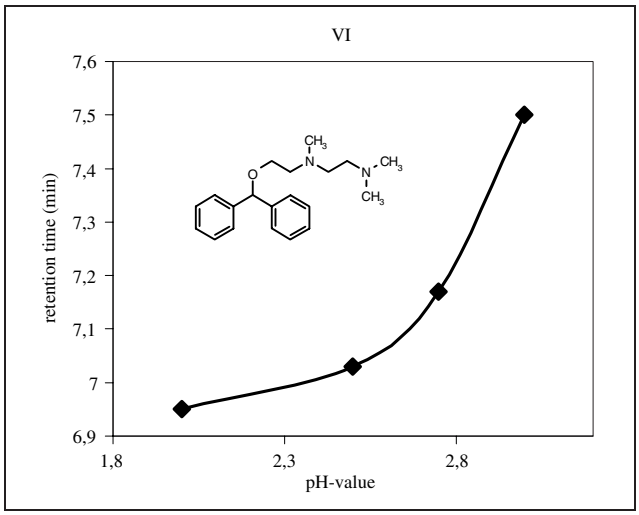


Fig. 2: pH-sensitivity of VI

2.4. Sample tests

To evaluate the relevance of the suspected impurities, all available samples of dimenhydrinate have been analysed. Table 4 shows the results. **II**, **V**, **VI** and **VII** are of high importance. Amounts up to 1.3% were determined. **IX**, **X**, **XII** und **XV** could be detected only in traces. **I**, **III**, **XI**, **XIII** and **XIV** have not been found. Nevertheless **III**, **XI** and **XIII** should be taken into account because of a higher probability of appearance in dimenhydrinate samples. **I** and **XIV** need not be included into succeeding purity tests.

Table 3: Validation data

Test item	Test range	Requirement	Results
Peak symmetry*	0–1.2 mg · ml^{-1}	symmetry factor 0.8–1.5	<1.45
pH robustness*	pH 2.0–pH 2.8	rel. retention time 0.95–1.05	0.98–1.02
TEA robustness*	0.5%–1.5%	rel. retention time 0.95–1.05	0.98–1.02
Temperature robustness*	25 °C–35 °C	rel. retention time 0.95–1.05	0.98–1.01
Stability of solution**	134 h	content 99.0–101.0%	100.1–100.8
Column material*	3 columns	rel. standard deviation of retention time max. 10%	<10%
Selectivity*	15 substances	resolution at least 1.5	>1.9
Repeatability**	6 injections	rel. standard deviation of peak areas max. 0.85%	<0.25%
Accuracy**	6 weighted samples	rel. standard deviation of peak areas max. 2.0%	<1.5%
Linearity**	0–1.3 mg/ml	coefficient of correlation at least 0.990	0.9997
Linearity*	0–0.1 mg/ml	coefficient of correlation at least 0.990	0.9987–1.0
Recovery**	6 samples	content 98–102%	100.2–101.8%
Limit of determination*	15 substances	<0.001 mg · ml^{-1} (10 ng)	<0.001 mg · ml^{-1}

* dimenhydrinate and impurities, ** dimenhydrinate only

Table 4: Contents of impurities in 18 dimenhydrinate samples (%)

Impurity	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
II	0.44	1.50	0.17	0.12	0.06	0.05	0.02	0.04	0.06	0.07	0.05	0.02		0.02	0.05	0.20	0.24	0.13
V	1.37	0.01														0.86	1.00	
VI			0.02	0.04	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.02	0.01	0.01			0.06
VII	0.02	0.02	0.09	0.13	0.26	0.14	0.17	0.18	0.15	0.16	0.23	0.13	0.18	0.13	0.13	0.18	0.04	0.04
IX			0.01	0.03							0.01					0.01		
X			0.01				0.01											
XII	0.06	0.07		0.02												0.02	0.02	0.02
XV	0.05	0.05														0.02	0.01	
other	0.44	0.47	0.16	0.13					0.01		0.04			0.01		0.17	0.29	0.04
total	2.38	2.12	0.46	0.47	0.33	0.20	0.22	0.23	0.23	0.26	0.34	0.17	0.21	0.18	0.19	1.36	1.61	0.30

For purity checks it is recommended to accept at most 0.2% of **II** and **VII**. It seems to be difficult to avoid the formation of these by-products in syntheses. Also there is no information about toxic effects. According to the European Pharmacopoeia every other impurity should be restricted to 0.1%.

3. Experimental

3.1. Materials

Acetonitrile (gradient grade for liquid chromatography) was obtained from Merck (Germany), triethylamine, phosphoric acid and methylamine solution (33% in ethyl alcohol) from Fluka (Germany). Theobromine (**I**), theophylline (**II**), caffeine (**III**) and 15 samples of dimenhydrinate were provided by the German Federal Institute for Drugs and Medical Devices. Two dimenhydrinate samples were purchased from Synopharm. Also dimenhydrinate-CRS was available. 8-Chlorotheophylline (**IV**) was bought from Aldrich, diphenhydramine hydrochloride (**VIII**) likewise from Synopharm, benzhydrol (**XII**) from Lancaster, benzophenone (**XIII**) from Jenapharm and diphenylmethane (**XIV**) also from Fluka. 2-Chloroethyldiphenylmethyl ether was offered by Frinton Laboratories. Water was obtained from a purification system (Millipore). Eluent A was filtered through a 0.45 μm cellulose nitrate membrane.

3.2. Apparatus

Liquid chromatography was performed with a Dionex system. The equipment consisted of a pump P 680, an autosampler Gina 50, an UV detector UVD 170 U and a column oven STH 585 (software: Chromeleon 6.50). The column was a Luna C18(2) 250 × 4.6 from Phenomenex. For validation a second Luna column and additional a EC 250 × 4.6 Nucleodur 100-5 C18 ec (Machery-Nagel) had been used. NMR-spectra were recorded with a Gemini 300 spectrometer (Varian).

3.3. Isolation of 8-chlorocaffeine (V)

The isolation of 8-chlorocaffeine (**V**) from dimenhydrinate was carried out by column chromatography. A glass column (length 60 cm, diameter 3 cm, downward reducing) was packed with silica gel. The solvent consisted of dichloromethane/methanol/ammonia solution (90/9/1). From 1.3 g dimenhydrinate 10 mg of 8-chlorocaffeine were obtained in about 80% purity; m.p. 178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.44 (3 H, s), 3.58 (3 H, s), 3.99 (3 H, s); MS m/z: 228 (M^+), 207, 193, 171, 143, 82, 67.

3.4. Syntheses

The syntheses based on known procedures which have partly been adapted to similar reactants. Also there were some modifications in techniques to improve the purity and the yield of the required products. New or differing analytical data have been added.

3.4.1. 8-Chlorocaffeine (V)

1.93 mmol (414 mg) of 8-chlorotheophylline were suspended in 20 ml of DMF. After addition of 3.86 mmol (533 mg) of K_2CO_3 and 2.51 mmol (156 μl) of methyl iodide the mixture was stored for 6 h at room temperature. Afterwards 40 ml of water were added. Thereby a clear solution was obtained. From this solution 8-chlorocaffeine precipitated in colourless needles after 2 h at 4 °C (Vollmann and Müller 2002): yield 100%; m.p. 188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.43 (3 H, s), 3.58 (3 H, s), 3.99 (3 H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 28.2 (CH_3), 30.0 (CH_3), 32.9 (CH_3), 108.5 (C), 139.2 (C), 147.3 (C), 151.5 (C), 154.8 (C); IR cm^{-1}: 3446, 3130, 1713, 1641, 1550, 1449, 1375, 1216, 984; MS m/z: 228 (M^+), 207, 193, 171, 143, 128, 82, 67 (Sono et al. 1996).

3.4.2. Dibenzhydryl ether (XV)

Benzhydrol (1.84 g) was pulverized in a mortar with 3.08 g of $Fe(NO_3)_3 \cdot 9\,H_2O$. Then the mixture was heated gently for 30 min at 55 °C in a round-bottom flask (Namboodiri and Varma 2002). Afterwards the resulted auburn mass was suspended in 20 ml of water and extracted with 80 ml of diethyl ether. After drying with anhydrous sodium sulphate the organic layer was evaporated on a rotary evaporator. The residue contained dibenzhydryl ether, benzhydrol and benzophenone (TLC reaction control: hexane/ethyl acetate 9/1). Purification was carried out by column chromatography (silica gel, hexane/ethyl acetate 9/1): yield 50 %; m.p. 106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.62 (2 H, s), 7.44-7.58 (20 H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 80.4, 127.69, 127.88, 128.84, 124.64; MS m/z: 168, 167, 105, 77.

3.4.3. 2-[(4-Methylphenyl)phenylmethoxy]-N,N-dimethylethanamine – hydrochloride (IX)

Sodium hydride (2 g) was suspended in 200 ml of ice cooled absolute toluene. To the suspension, 4 g of methylbenzhydrol in 20 ml of toluene were added dropwise. Then the mixture was heated up to 95 °C. After 30 min 4 g of 1-chloro-2-dimethylaminoethane hydrochloride were added in portions. Then the temperature in the reaction vessel was kept for four additional hours at 95 °C. Next the suspension was cooled down, and 50 ml of cold water were dropped in carefully to inactivate remained sodium hydride. Subsequently the organic layer was washed with water (50 ml) three times and then extracted with hydrochloric acid (1 M, 150 ml). The acid extract was alkalified with sodium hydroxide solution (1 M, about 200 ml) to pH 12–13. The white product precipitated and was extracted with diethyl ether (Wolf and Schunack 1996). The diethyl ether was concentrated to a small volume. By gassing with hydrogen chloride gas from heated hydrochloric acid the salt sedimented (Müller et al. 2001). After recrystallization from ethyl acetate white crystals were obtained: yield 10%; m.p. 148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.81 (1 H, s), 2.36 (3 H, s), 2.89–2.92 (6 H, m), 3.30–3.33 (2 H, m), 3.95–3.98 (2 H, m), 5.44 (1 H, s), 7.16–7.39 (9 H, m).

3.4.4. 2-[(4-Bromophenyl)-phenylmethoxy]-N,N-dimethylethanamine maleate (X)

Bromobenzene (8 ml) was heated with 10.5 g of benzoyl chloride and 11.3 g of aluminium chloride at 80–90 °C. After 10 h the light brown substance hardened during cooling. The residue was dissolved in 100 ml acetone and filtered through a frit with 10 g of aluminium oxide. Recrystallization in 40 ml petroleum ether yielded 6.9 g of bromobenzophenone.
Bromobenzophenone (4 g) was mixed with 5.6 g of $NaBH_4$ in a mortar and stored for five days, stirred once a day (TLC reaction control: $CHCl_3$). The powder was extracted with diethyl ether. Then the organic layer was evaporated and the oily product solidified during 12 h in the fridge; 3 g of bromobenzhydrol were obtained (Toda et al. 1989).
The alcohol was etherified according to 3.4.3., precipitated in diethyl ether with maleic acid and recrystallized in acetone. The separated powder was flocculent and white. The ratio of base and acid was 1/1: yield 10 %; m.p. 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.93 (6 H, s), 3.33 (2 H, s), 3.96 (2 H, s), 5.45 (1 H, s), 6.50 (maleic acid), 7.09–7.52 (Ph, m).

3.4.5. N,N,N-[(2-diphenylmethoxyethyl)-(2-dimethylaminoethyl)methyl]-amine maleate (VI)

To 105 g of iced 80% formic acid 16 g of 2-(2-aminoethylamino)ethanol were added carefully. After the yellow liquid was heated up to 105 °C 53 g of formalin (30%) were dropped into the mixture (vigorous evolution of carbon dioxide). Then the reaction mixture was boiled under reflux for 4 h (Nakajima 1961). The light brown fluid was cooled down to room temperature and 45 ml of hydrochloric acid (6 N) were added. Afterwards the solution was evaporated under reduced pressure. To the resulting viscous substance 100 ml of sodium hydroxide solution (30%) were added. The pH value had to be at least 12. The alkaline liquid was extracted exhaustively with diethyl ether (10 × 70 ml!). After the removal of the diethyl ether the residue (yellow oil) was distilled under vacuum. 2-[(2-Dimethylaminoethyl)methylamino]ethanol was obtained as a colourless oil, yield: 70%; refraction index 1,4545 (25 °C). 16,5 g of 2-[(2-Dimethylaminoethyl)methylamino]ethanol were etherified with 23 g of chlorodiphenylmethane according to 3.4.3. (TLC reaction control: acetonitrile/chloroform/triethylamine 1/1/0.1). The base was precipitated from diethyl ether with maleic acid. The mole ratio of base to acid was 1 : 2. After recrystallization white crystals were obtained: yield 10%; m.p. 152–156 °C (lit. 155–156 °C (Stelt and Tersteege 1964)); ^{1}H NMR (300 MHz, D_2O) δ (ppm): 2.72 (6 H, s), 2.83 (3 H, s), 3.39 (2 H, s), 3.48 (4 H, s), 3.77 (2 H, s), 5.52 (1 H, s), 6.20 (maleic acid), 7.25–7.39 (10 H, m).

3.4.6. 8-[(2-Diphenylmethoxy)ethylmethylamino]theophylline (XI)

2-Chloroethyldiphenylmethyl ether (300 μl, 340 mg) was dissolved in 10 ml of ethyl alcohol and added dropwise into 50 ml of methylamine solution (33% in ethyl alcohol). The mixture was stirred for 14 days at room temperature. Then the colourless liquid was evaporated. The residue was dissolved in ethyl ether. After the addition of maleic acid in ethyl ether white crystals of 2-(diphenylmethoxy)-*N*-methylethanamine maleate were formed: yield 75 %; m.p. 159 °C; ^{1}H NMR (300 MHz, DMSO) δ (ppm): 2.58 (3 H, s), 3.17 (2 H, t), 3.57 (2 H, t), 5.51 (1 H, s), 6.02 (maleic acid, s), 7.24–7.41 (10 H, m), 8.45 (1 H, s).
For the final reaction the maleic acid was removed from 175 mg **XI**-maleate by addition of 20 ml of 1 M NaOH and extraction with 50 ml of dichloromethane. The organic layer was evaporated. Afterwards the basic residue was diluted in ethyl alcohol together with 57 mg of 8-chlorotheophylline. The mixture was stirred under reflux for 14 days. Then it was evaporated again. For the separation of the product from the starting substances column chromatography was used (silica gel; dichloromethane/

methanol/ammonia solution, 98/2/1). After recrystallization from ethyl alcohol white crystals were obtained: yield 10%; m.p. 205 °C; ^{1}H NMR (300 MHz, DMSO) δ (ppm): 3.07 (3 H, s), 3.18 (3 H, s), 3.32 (3 H, s), 3.55 (2 H, t), 3.68 (2 H, t), 5.44 (1 H, s), 7.25–7.4 (10 H, m). MS m/z: 419, 252, 167, 152.

3.5. Determination of mole ratio in maleates

The mole ratio of base to acid in the salts was determined indirectly measuring the content of maleic acid by the HPLC-method which was already described. 10 µl of 2-[(4-bromophenyl)-phenylmethoxy]-*N*,*N*-dimethylethanamine maleate (0.605 mg · ml^{-1}; $PA_{maleic\ acid} = 42.8$), *N*,*N*,*N*-[(2-diphenylmethoxyethyl)-(2-dimethylaminoethyl)methyl]amine maleate (0.419 mg · ml^{-1}; $PA_{maleic\ acid} = 48.6$) and a dilution series of maleic acid (0.169 mg · ml^{-1} − 0.844 mg · ml^{-1}: y (PA) = 254.99 × +4.4362) were chromatographed. For 2-[(4-bromophenyl)-phenylmethoxy]-*N*,*N*-dimethylethanamine maleate a content of 24.9% was calculated which corresponded to a mole ratio of 1 : 1 (theoretical percentage: 25.7%). *N*,*N*,*N*-[(2-Diphenyl-methoxyethyl)-(2-Dimethylaminoethyl)methyl]amine maleate contained 41.3% of maleic acid which corresponded to a mole ratio of 1 : 2 (theoretical percentage 42.6%). (PA = peak area).

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