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Theophylline Magnesium Salicylate, a New Xanthine Compound

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Abstract □ Interaction of 1 mole of magnesium salicylate and 2 moles of theophylline in water precipitated a crystalline compound, identified as theophylline magnesium salicylate pentahydrate from analytical and supportive physicochemical data. Similarly, barium salicylate and theophylline produced theophylline barium salicylate. No precipitates were formed with calcium salicylate or strontium salicylate under the same conditions. Theophylline magnesium salicylate is not a mixture of components and differs in composition from the known theophylline calcium salicylate dihydrate. Unlike the latter compound, it is not alkaline.

Keyphrases □ Theophylline magnesium salicylate—synthesis and properties □ Xanthines—theophylline magnesium salicylate, synthesis and properties

The methylxanthines theobromine, theophylline, and caffeine have been used to stimulate the central nervous system, to promote diuresis, and for their cardiovascular effects. While investigating theophylline as a diuretic component for a proprietary product, an insoluble product resulted from the interaction of magnesium salicylate and theophylline. This paper describes the preparation and properties of theophylline magnesium salicylate, a crystalline compound not previously reported.

BACKGROUND

Theobromine, theophylline, and caffeine are used medically as single entities, as soluble amine salts, or as the so-called double salts with alkali or alkaline earth metal salts of organic acids such as acetic, gluconic, benzoic, and salicylic acids. These double salts, believed by some to be definite compounds and by others to be simply mixtures, were prepared either to solubilize the xanthine (*e.g.*, theophylline sodium acetate and caffeine sodium benzoate) or to make insoluble products (*e.g.*, theobromine and theophylline calcium salicylates); the latter type of compound is claimed to be tolerated better in the GI tract than the parent xanthine.

Various methods have been described for the preparation of the xanthine double salts with alkali or alkaline earth metal salts of organic acids. For example, the soluble compound theophylline sodium acetate is made by heating together 1 equivalent each of theophylline and sodium hydroxide, mixing them with 1 equivalent of aqueous sodium acetate, and evaporating the mixture to dryness (1). Theobromine sodium salicylate is made in a similar fashion (2). Theobromine and theophylline calcium salicylates are prepared according to a 1925 patent (3) by dissolving the xanthine in aqueous sodium hydroxide, adding a solution of sodium salicylate followed by solutions of calcium chloride and ammonium hydroxide, and removing and drying the precipitate. The two insoluble calcium salicylate double salts are described as having the following compositions:

1. For the neutral double salt, $(C_7H_7N_4O_2)Ca(C_6H_4OHCO_2)_2Ca$. The present authors believe this empirical formula to be in error because the formula should be $(C_7H_7N_4O_2)_2Ca(C_6H_4OHCO_2)_2Ca$ or simply $(C_7H_7N_4O_2)Ca(C_6H_4OHCO_2)$ since a subsequent patent (4) indicated that the compound contains one atom of calcium and 1 mole each of theobromine and salicylic acid.
2. For the basic double salt, $(C_7H_7N_4O_2)_2Ca(C_6H_4OHO_2Ca)_2$.

The aforementioned patents also stated that the analogous strontium double salts can be made in a similar fashion.

Another patent (5), issued in 1949 for the same manufacturer as the previously cited patents, contained only one example for the preparation of neutral theobromine calcium salicylate[1] (by reacting theobromine calcium and salicylic acid), which is assigned the formula $(C_7H_7N_4O_2)$-$Ca(C_6H_4OHCO_2)\cdot H_2O$. The corresponding theophylline calcium salicylate[2] is the double salt of calcium salicylate and calcium theophylline in equimolecular proportions or $(C_7H_7N_4O_2)Ca(C_6H_4OHCO_2)\cdot 2H_2O$ (6). Both theobromine and theophylline calcium salicylates are slightly soluble in water and are alkaline (7–9).

This description of the formula and preparation of theophylline cal-

[1] Theocalcin, Knoll.
[2] Phyllicin, Knoll.

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Table I—Analysis of Theophylline Magnesium Salicylate

	Found, %	Calculated, % $(I)_2Mg(II)_2 \cdot 5H_2O$	(I)Mg(II)	$(I)Mg(II) \cdot 3H_2O$
Theophylline (I)	47.60	47.98	52.59	45.43
Salicylate (II) as salicylic acid	36.20	36.70	40.31	34.83
Magnesium	3.28	3.26	7.10	6.13
Water (Karl Fischer method)	12.80	12.06	—	13.61
Total	99.88	100.00	100.00	100.00

Table II—Analysis of Theophylline Barium Salicylate

	Found, %	Calculated, % $(I)_2Ba(II)_2$	(I)Ba(II)
Theophylline (I)	46.6	46.6	39.49
Salicylate (II) as salicylic acid	35.7	35.7	30.23
Barium	17.8	17.7	30.28
Total	100.1	100.0	100.00

cium salicylate is cited in detail because it will be shown that theophylline magnesium salicylate differs from its calcium analog, both in its composition and in the manner of its preparation.

EXPERIMENTAL

Theophylline Magnesium Salicylate Pentahydrate—Magnesium salicylate tetrahydrate[3] $[(C_6H_4OHCOO)_2Mg \cdot 4H_2O]$ (37.1 g, 0.1 mole) was dissolved in 480 ml of distilled water and warmed to 40°. Anhydrous theophylline[4] ($C_7H_8N_4O_2$) (36.0 g, 0.2 mole) was added and stirred until it dissolved. The resulting solution was filtered rapidly and allowed to stand, upon which precipitation of a white crystalline solid occurred. After standing for several hours, the precipitate was filtered off and washed quickly with three 15-ml portions of cold (5°) distilled water. The precipitate was dried at 70° for 6 hr. The product yield was 61.8 g. The analytical results are shown in Table I.

Theophylline Barium Salicylate—To compare the behavior of barium salicylate under reaction conditions similar to those used for the preparation of theophylline magnesium salicylate, 43 g (0.1 mole) of barium salicylate monohydrate[5] was dissolved in 250 ml of water, and 36 g (0.2 mole) of theophylline was dissolved in the solution. After standing for 1 day, the precipitated solid was filtered off and dried *in vacuo* for 6 hr at 70°. The yield was ~50 g. The analysis of the dried product is shown in Table II.

Attempts to Prepare Strontium and Calcium Analogs of Theophylline Magnesium Salicylate—Strontium salicylate[5] (19.9 g, 0.05 mole) was dissolved in 400 ml of water, and 18.0 g (0.1 mole) of theophylline was dissolved in this solution. No precipitation occurred on standing for several hours. Only a small amount of solid formed overnight in the refrigerator, and it was identified as theophylline by its melting point and mixed melting point with an authentic sample.

Calcium salicylate[5] (17.5 g, 0.05 mole) was dissolved in 588 ml of water, and 18.0 g (0.1 mole) of theophylline was dissolved in this solution. No precipitate formed on standing at room temperature; on standing in the refrigerator overnight, a small amount of solid deposited and was identified as theophylline.

No attempts were made to evaporate the aqueous solutions of theophylline, strontium, and calcium salicylates and to identify the residues since the principal aim was to determine if the reactants would readily yield precipitates under the same conditions employed for the reaction between magnesium and barium salicylates and theophylline.

Preparation of Magnesium Analog of Theophylline Calcium Salicylate Dihydrate—Since the cited patent literature discloses processes for making double salts of theobromine and theophylline by reacting these xanthines and their calcium or strontium salts with an equivalent molecular quantity of basic or neutral calcium or strontium salicylate, a similar procedure was used to make the analogous magnesium double salt. A solution of 37 g (0.1 mole) of magnesium salicylate tetrahydrate in 458 ml of water was placed in a blender. To this solution were added 19.45 g (0.1 mole) of magnesium hydroxide (as the 30% paste[6]) and 36 g (0.2 mole) of anhydrous theophylline, and the mixture was dispersed thoroughly. The resultant slurry was evaporated to dryness over a steam bath and then ground to a powder to yield 75 g. The analysis of the powder is given in Table III.

Table III—Analysis of the Magnesium Analog of Theophylline Calcium Salicylate Dihydrate

	Found, %	Calculated, % $(I)Mg(II) \cdot 3H_2O$	$(I)_2Mg(II)_2 \cdot 5H_2O$
Theophylline (I)	45.6	45.54	47.98
Salicylate (II) as salicylic acid	35.4	34.66	36.70
Magnesium	6.1	6.15	3.26
Water (Karl Fischer method)	13.9	13.65	12.06
Total	101.0	100.00	100.00

Physical Data—To support the fact that theophylline magnesium salicylate is a definite crystalline compound and not a physical mixture of its components, UV and IR spectrograms, X-ray powder diffraction data, and thermograms were evaluated.

The UV spectrogram of theophylline magnesium salicylate pentahydrate was compared to the spectra of magnesium salicylate and theophylline, and no significant structural changes could be deduced.

The IR spectrum obtained[7] from a physical mixture in mineral oil containing 2 moles of theophylline and 1 mole of magnesium salicylate was essentially the sum of the spectra of theophylline and magnesium salicylate (Fig. 1). This finding was confirmed by grinding theophylline in mineral oil and then adding magnesium salicylate to it. The spectrum from this suspension was identical to the spectrum of the physical mixture. In contrast, the IR spectrum of theophylline magnesium salicylate pentahydrate (Fig. 2) differed from that of the physical mixture. Beside the difference in the NH stretching region (3120 cm^{-1}), the carbonyl band at 1715 cm^{-1} in the physical mixture was not present in the spectrum of theophylline magnesium salicylate.

X-ray diffraction measurements were made to compare theophylline magnesium salicylate, a physical mixture of theophylline and magnesium salicylate in a 2:1 molar ratio, and the individual components. The samples, positioned in a Bakelite holder, were placed in the sample compartment of a spectrogoniometer[8] arranged in the diffractometry mode and irradiated with CuK radiation. The diffraction patterns from 5 to 20° 2θ were obtained. The relative peak intensities were calculated, and the interplanar d spacings corresponding to the diffraction peaks were calculated using a trigonometric package program[9] adapted to determine 2θ values from d values and to determine d values from 2θ values. Only the data from the physical mixture and theophylline magnesium

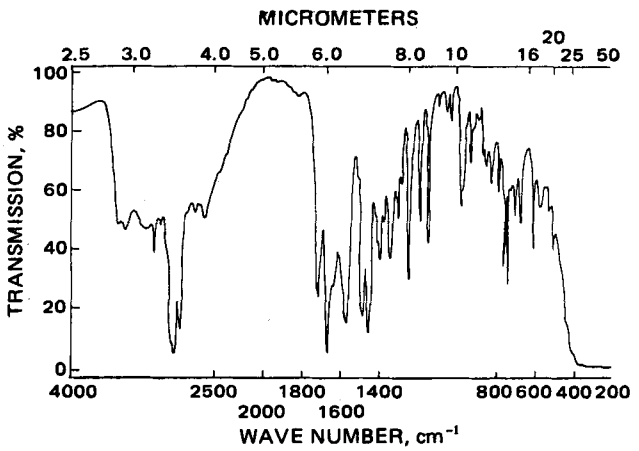

Figure 1—*IR spectrogram of a physical mixture of theophylline and magnesium salicylate in a 2:1 molar ratio.*

[3] S. B. Penick & Co.
[4] Ganes Chemical Works.
[5] Pfaltz and Bauer.
[6] Hydromagma, Merck.
[7] Perkin-Elmer model 283.
[8] General Electric GE XRD-6.
[9] Wang Laboratories.

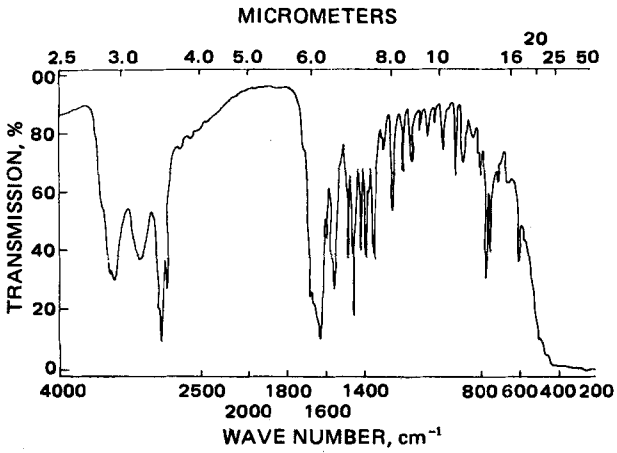

Figure 2—*IR spectrogram of theophylline magnesium salicylate.*

salicylate are shown in Table I and Figs. 3 and 4. The diffraction data show that theophylline magnesium salicylate is a true compound that exists in a crystalline form different from its components and a physical mixture of each component.

Thermograms (Fig. 5) were obtained with magnesium salicylate, theophylline, a 2:1 theophylline–magnesium salicylate mixture, and theophylline magnesium salicylate using a scanning calorimeter[10]. Thermal transitions occurred in theophylline and magnesium salicylate at 283 and 117–118°, respectively. Only one thermal transition, at 139–140°, occurred with theophylline magnesium salicylate. Upon cooling, this melt again was subjected to thermal analysis, and one transition at 139–140° was found. The 2:1 molar mixture of components showed two bands, one corresponding to magnesium salicylate at 118° and another at 139–140°. The latter band probably arises from a reaction between the two components in the molten state to form theophylline magnesium salicylate.

Pharmacological Data on Theophylline Magnesium Salicylate—The acute oral toxicity in mice (72 hr) was determined as: theophylline magnesium salicylate, 665 ± 35 mg/kg; anhydrous theophylline, 460 ± 35 mg/kg; and magnesium salicylate, 1200 ± 53 mg/kg.

The toxicity appears to be a summation of the toxicities of the theophylline and magnesium salicylate entities of the compound, which is not unexpected since the compound contains ~48% theophylline and 40% magnesium salicylate. When the compound was given intravenously to a dog at 4 mg/kg, it showed a slight but transient elevation of blood pressure. In the inflamed rat paw test (10), the compound given orally

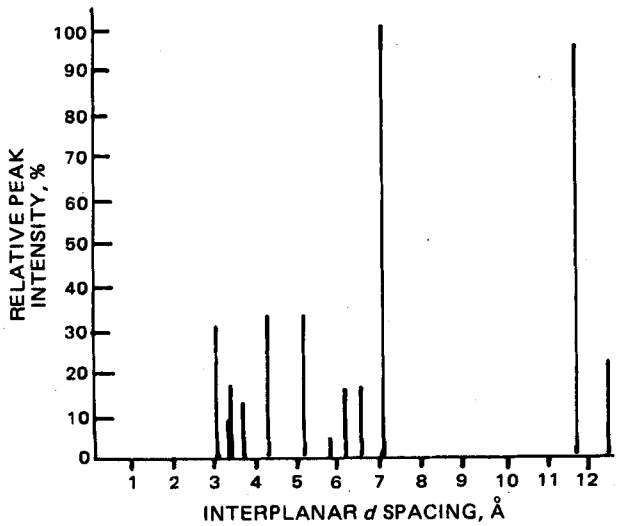

Figure 3—*X-ray diffraction data showing relative peak intensities of a 2:1 molar physical mixture of theophylline and magnesium salicylate.*

[10] Perkin-Elmer DSC-1B.

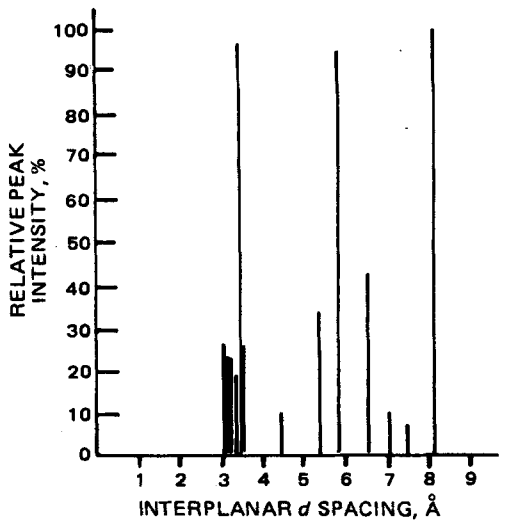

Figure 4—*X-ray diffraction data showing relative peak intensities corresponding to interplanar* d *spacings of theophylline magnesium salicylate.*

at 200 mg/kg showed the expected salicylate (anti-inflammatory and antipyretic) effects of moderate duration (2–3 hr).

RESULTS AND DISCUSSION

As indicated by the data in Table I, the precipitated product conformed most nearly to the pentahydrate. When 0.5–2.0 moles of magnesium salicylate was reacted with 1 mole of theophylline under similar conditions, the precipitated solids, after drying, showed analyses quite similar to those reported here, indicating that the insoluble product in each case was $(I)_2Mg(II)_2{\cdot}5H_2O$. The substance was a white, bitter, crystalline compound containing ~48% theophylline, 40% magnesium salicylate, and 12% water of hydration. It had no definite melting point and was sparingly soluble in water (~2% at 25°) and in ethanol (~1% at 25°). One-percent solutions were slightly acidic (pH 6). The dried product conformed to the formula $(I)_2Ba(II)_2$ (Table II).

From the data in Table III, the product made by this procedure can be approximated to be theophylline magnesium salicylate trihydrate, which is the magnesium analog of theophylline calcium salicylate dihydrate. A 1% aqueous dispersion of this product had a pH of 8.4. This product does not appear to have been reported in the literature, and it has a different composition than the crystalline theophylline magnesium salicylate pentahydrate described earlier in this report.

The known theophylline calcium salicylate was stated earlier as being composed of calcium theophylline $[Ca(C_7H_7N_4O_2)_2]$ and calcium salicylate in molecular proportions, or it could be represented by the simple

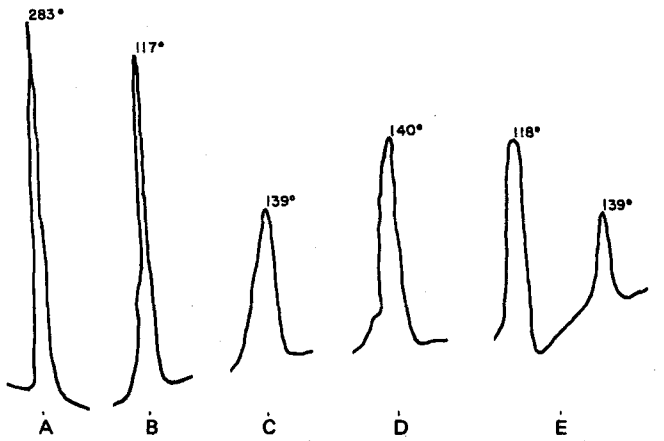

Figure 5—*Thermograms of theophylline (A), magnesium salicylate (B), theophylline magnesium salicylate (C), cooled melt of theophylline magnesium salicylate (D), and a 2:1 molar mixture of theophylline and magnesium salicylate.*

Table IV—Analysis of Commercial Theophylline Calcium Salicylate

	Found, %	Calculated, % (I)Ca(II)·$2H_2O$	Calculated, % $(I)_2Ca(II)_2$
Theophylline (I)	43.9	45.66	53.27
Salicylate (II) as salicylic acid	34.1	34.94	40.77
Calcium	10.2	10.21	5.96
Water (Karl Fischer method)	11.8	9.19	—
Total	100.0	100.00	100.00

formula $(C_7H_7N_4O_2)Ca(C_6H_4OHCO_2)$. To ascertain with certainty that this formula was correct for theophylline calcium salicylate, a commercial sample[2] of this product was analyzed. The results are given in Table IV. These results confirm that theophylline calcium salicylate can be represented by the formula $(C_7H_8N_4O_2)Ca(C_6H_4OHCO_2)\cdot 2H_2O$.

From the foregoing experimental data, it is evident that theophylline magnesium salicylate pentahydrate is a crystalline compound that differs in composition from its calcium analog, theophylline calcium salicylate dihydrate. Moreover, theophylline magnesium salicylate shows a slightly acidic reaction in water, in contrast to the alkaline character of the theophylline and theobromine calcium salicylates and to many of the so-called double salts derived from the reaction of these xanthines with metal salts of organic acids. While the alkali metal salts of salicylic acid usually combine with the xanthines to yield water-soluble complexes, the alkaline earth metal salicylates usually yield insoluble complexes. However, calcium and strontium salicylates did not yield precipitates with theophylline under the present experimental conditions, whereas magnesium and barium salicylates produced theophylline derivatives with similar compositions.

A French patent (11) disclosed the preparation of a double salt of theophylline with barium salicylate for which the formula $(C_7H_8N_4O_2)_2Ba(C_7H_5O_3)_2$ or $(I)_2Ba(II)_2$ was given. According to the patent, this compound was made by dissolving theophylline in an aqueous solution of barium salicylate, filtering, and then evaporating the filtrate to dryness *in vacuo*. The resulting compound was said to be easily soluble in water. From the present experiments using barium salicylate and theophylline, the resultant product readily precipitated from the aqueous solution of the reactants, and it was only sparingly soluble in water. Analysis of the product showed it to conform to the formula $(I)_2Ba(II)_2$ (Table V). Although the French patent assigned this formula to their product, the inventors had to resort to evaporation *in vacuo* to obtain it. Moreover, the same patent assigned the formula $(C_8H_{10}N_4O_2)$-$Ba(C_7H_5O_3)_2$ or (caffeine)Ba(salicylate)$_2$ to the double salt of caffeine and barium salicylate (prepared in similar fashion as the theophylline double salt). Since analyses were not given in this patent for either the theophylline or caffeine barium salicylates, it is not clear how the inventors arrived at their formulas.

Table V—X-Ray Diffraction Patterns for a 2:1 Molar Ratio Mixture of Theophylline and Magnesium Salicylate (A) and Theophylline Magnesium Salicylate (B)

A			B		
2θ	d, Å	I/I_1	2θ	d, Å	I/I_1
7.14°	12.3803	23	10.89°	3.1241	100
7.57°	11.6780	96	11.83°	7.4806	8
12.57°	7.0418	100	12.55°	7.0530	11
13.47°	6.5733	17	13.52°	6.5491	43
14.32°	6.1849	17	15.25°	5.8098	95
15.27°	5.8022	5	16.52°	5.3659	24
17.19°	5.1582	34	19.79°	4.4860	11
20.28°	4.3787	34	25.25°	3.5270	27
24.12°	3.6896	13	25.92°	3.4373	97
25.54°	3.4876	18	26.97°	3.3058	19
26.39°	3.3772	10	28.12°	3.1732	24
28.85°	3.0945	32	29.02°	3.0768	27

The diversity of opinion concerning the nature of the interaction of xanthines with the metal salts of organic acids, variously referred to as double salts, mixtures, or complexes, has long been recognized (12). The complexation of salicylic acid and its sodium salt with caffeine (13, 14), theobromine (13), and theophylline (15, 16) has been studied extensively, and a good review of the literature on caffeine complexation was given by Stamm (17) in 1969. The relative roles of such factors as hydrophobic binding, hydrogen bonding, and donor–acceptor forces were considered in these publications. The factors involved in the formation of theophylline magnesium salicylate await further exploration.

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