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REACTIONS OF THEOPHYLLINES. CHEMICAL CONVERSIONS OF 8-AMINOTHEOPHYLLINATES

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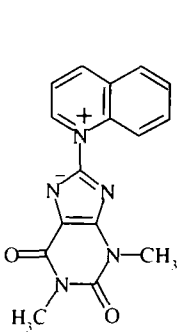
Thermally stable, colored 8-aminotheophyllinates (betaine derivatives of theophylline) form unstable, colorless salts with strong mineral acids and undergo partial decomposition to a uric acid upon prolonged refluxing with concentrated base solution. Substituted 8-pyridinium theophyllinates readily take part in typical reactions of the functional group in the substituted pyridine ring with retention of the betaine structure. The formation of the synthesized compounds was confirmed by IR and NMR spectroscopy.

Keywords: betaines, aminotheophyllinates, theophylline.

The reaction of theophylline (in the presence of an oxidant) and some 8-substituted theophyllines with quinoline, trimethylamine, pyridine, and a series of substituted pyridines gives the betaine derivatives of theophylline, 8-aminotheophyllinates **1-3a-l** [1-4]. We have established the conditions for their formation.



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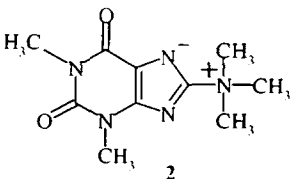

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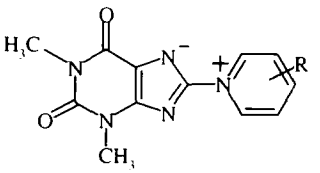

3a-l

3a R = H; **3b** R = 2-CH_3; **3c** R = 3-CH_3; **3d** R = 4-CH_3; **3e** R = 3,5-$(CH_3)_2$;
3f R = 3-COOH; **3g** R = 4-COOH; **3h** R = 4-NH_2; **3i** R = 3-CHO;
3j R = 4-CN; **3k** R = 3-C(O)NHCH$_2$-C_6H_5; **31** R = 4-C(O)NH_2-C_6H_5

A study and analysis of some physicochemical properties of the obtained 8-aminotheophyllinates has shown that betaines **1-3a-l** are comparatively stable, can be kept at room temperature for a long time, have high thermal, photo- and hydrolytic stability, and are poorly soluble in the majority of organic solvents and in water. In concentrated solutions of strong inorganic acids the colored 8-pyridinium theophyllinates **3a-e** are readily soluble

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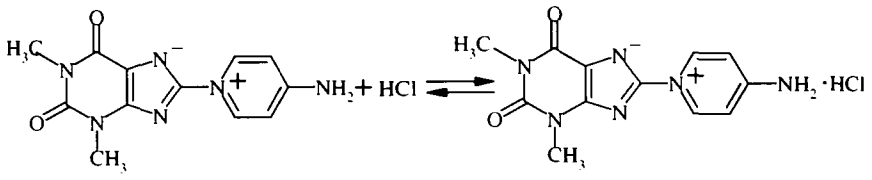
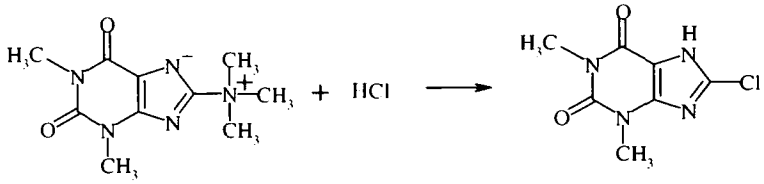
to give colorless salts which are once again converted to the starting betaines in water [3]. Only in the case of the reaction of 8-(4-aminopyridinium) theophyllinate **3h** with hydrochloric acid was a reasonably stable hydrochloride salt **4** formed and this decomposes very slowly in water to the starting betaine:



3h **4**

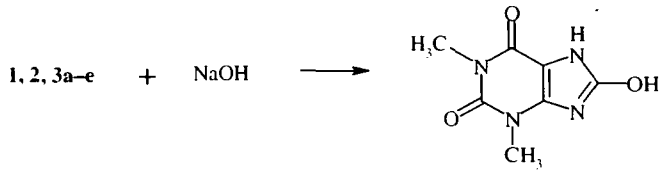
In contrast to betaines **3a-e** (which even upon prolonged refluxing with hydrochloric acid form only hydrochloride salts), 8-trimethylammonium theophyllinate **2** undergoes decomposition when refluxed with hydrochloric acid to form 8-chlorotheophylline (**5**) quantitatively:



2 **5**

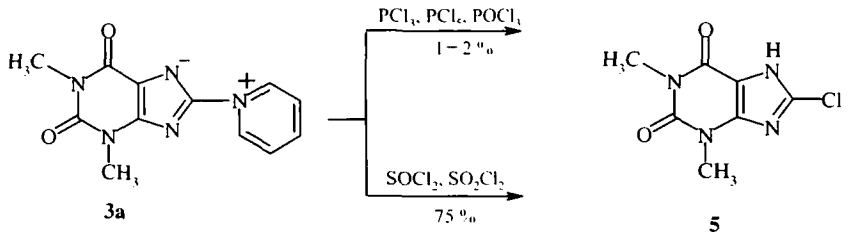
It has already been noted that betaines **1**, **3a-h** show high thermal stability and melt at temperatures above 300°C without decomposition. In contrast to these, betaine **2**, at temperatures above 300°C, isomerizes to 7-methyl-8-dimethylaminotheophylline [2].

Betaines **1-3a-e** are stable to the action of dilute base solutions but upon prolonged refluxing (8-10 h) in concentrated base solution are approximately 30% decomposed to uric acid **6**:



6

A study of the possible reaction of betaine **3a** with chlorinating agents has shown that the results of the reaction depend strongly on the chlorinating agent itself:



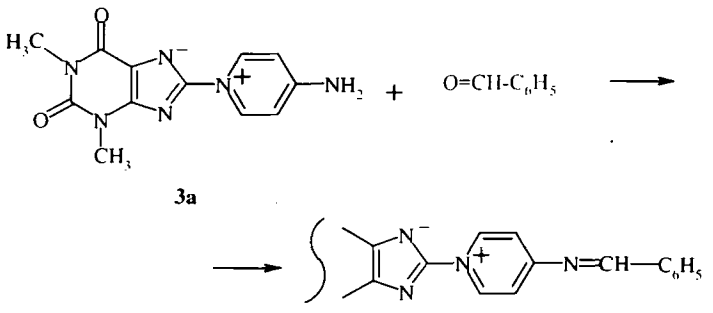
3a **5**

When treated with thionyl chloride or sulfuryl chloride, betaine **3a** decomposes to give 8-chlorotheophylline in 75% yield. Phosphorus oxychloride and phosphorus tri- and pentachloride do not decompose betaine **3a** and only 1-2% of 8-chlorotheophylline is formed in this case.

As we showed previously [3], 8-methylpyridinium theophyllinates **3a-e** react with neither methyl iodide, ethyl bromide, nor phosphoric acid chloride.

An investigation of the possibility of exchanging one of the substituted pyridine residues for another in betaine has shown that the betaine system formed is quite stable and substitution does not occur [4]. Thus, with the combined presence of pyridine and isonicotinic acid in the reaction mixture with 8-bromotheophylline, betaines **3a** and **3g** are formed at the same rate. By contrast, for 2-methylpyridine with the simultaneous presence of pyridine in the reaction mixture, a reaction with 8-bromotheophylline occurs (probably for steric reasons) only after all pyridine has reacted [4].

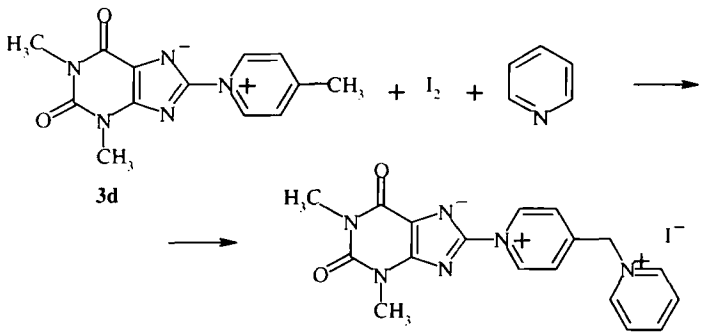
We have also studied the ability of 8-pyridinium theophyllinates to react with functional groups in the pyridine ring. As was shown, betaine **3h** forms salt **4** with hydrogen chloride. This same betaine **3h** reacts with benzaldehyde to give the Schiff base **7**, typical of primary amines.



3a

7

Betaine **7** is a crystalline, high melting material which is insoluble in water and many organic solvents. Its characteristics are given in Table 1. Betaine **3d**, containing a 4-methylpyridinium residue, reacts at the methyl group with pyridine in the presence of iodine to form the quaternary salt **8**:



3d

8

Betaine **8** is a violet crystalline powder with a melting point above 200°C and is insoluble in water and common organic solvents, but soluble in DMF and hot acetic acid (the characteristics for compound **8** are given in Table 1).

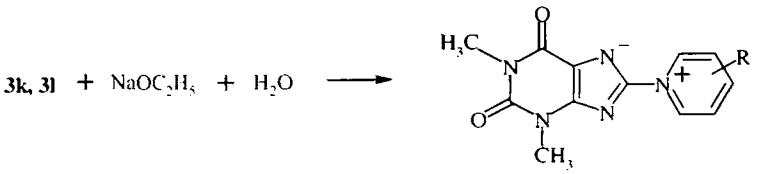
Betaines **3k,l** contain fragments of the quaternary benzylamides of nicotinic and isonicotinic acid and they react readily with sodium ethylate to form the corresponding imidole type sodium salts **9,10**.

TABLE 1. Characteristics for 7- and 8-Substituted Theophyllines

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, cm^{-1}	^1H NMR spectrum (CF_3COOH), δ, ppm (J, Hz)	Yield, %
		C	H	N				
1	2	3	4	5	6	7	8	9
3f	$C_{13}H_{11}N_5O_4$	50.90 / 51.82	3.70 / 3.65	23.58 / 23.25	321-323	3450, 1725, 1680, 1645, 1625, 1525, 1485, 1400, 1300, 1230	3.12 (3H, s, N_3-CH_3); 3.40 (3H, s, N_1-CH_3); 8.12 (1H, t, *m*-H); 9.10 (1H, d, *p*-H); 9.60 (1H, d, *o*-H); 9.90 (1H, d, *o*-H)	54
3g	$C_{13}H_{11}N_5O_4$	50.95 / 51.82	3.71 / 3.65	23.52 / 23.25	336-338	3445, 1715, 1685, 1645, 1620, 1525, 1480, 1450, 1350	3.15 (3H, s, N_3-CH_3); 3.35 (3H, s, N_1-CH_3); 8.40 (2H, d, J = 6; *m*-H); 9.40 (2H, d, *o*-H)	53
3h	$C_{12}H_{12}N_6O_2$	50.80 / 52.94	4.00 / 4.41	30.01 / 30.88	358-360	3300, 3120, 3020, 1725, 1675, 1630, 1590, 1500, 1450, 1420, 1360, 1320, 1220, 1180	3.21 (3H, s, N_3-CH_3); 3.42 (3H, s, N_1-CH_3); 8.34 (2H, s, NH_2); 8.93 (2H, d, *m*-H); 9.44 (2H, d, *o*-H)	82
3i	$C_{13}H_{11}N_5O_3$	54.01 / 54.74	3.00 / 3.86	23.85 / 24.56	270-273	3450, 3090, 2660, 2390, 2280, 1980, 1700, 1670, 1630, 1550, 1530, 1490, 1450, 1410, 1320	3.15 (3H, s, N_3-CH_3); 3.35 (3H, s, N_1-CH_3); 8.25 (1H, t, *m*-H); 9.00 (1H, d, *p*-H); 9.50 (1H, d, *o*-H); 9.80 (1H, s, *o*-H); 9.95 (1H, s, CH)	52
3j	$C_{13}H_{10}N_6O_2$	54.65 / 55.32	2.95 / 3.55	29.54 / 29.79	370-371	2235, 1685, 1650, 1600, 1560, 1525, 1480, 1420	3.42 (3H, s, N_3-CH_3); 3.60 (3H, s, N_1-CH_3); 8.25 (2H, d, J = 6; *m*-H); 9.40 (2H, d, J = 6; *o*-H)	30
3k	$C_{20}H_{18}N_6O_3$	61.00 / 61.54	4.00 / 4.62	21.00 / 21.54	342-345	3450, 2380, 1680, 1640, 1560, 1480, 1450, 1400, 1380, 1280	3.18 (3H, s, N_3-CH_3); 3.38 (3H, s, N_1-CH_3); 4.6 (2H, d, CH_2); 6.9(5H, s, C_6H_5); 8.1 (1H, t, *m*-H); 8.9 (1H, d, *p*-H); 9.3 (1H, d, *o*-H); 9.8 (1H, d, *o*-H)	74
3l	$C_{20}H_{18}N_6O_3$	61.00 / 61.54	4.00 / 4.62	21.00 / 21.54	322-325	3450, 2380, 1680, 1640, 1560, 1525, 1485, 1445, 1400, 1380, 1325, 1280	3.16 (3H, s, N_3-CH_3); 3.38 (3H, s, N_1-CH_3); 4.6 (2H, d, CH_2); 7.1 (5H, s, C_6H_5); 8.6 (2H, d, *m*-H); 9.40 (2H, d, *o*-H)	72

TABLE 1 (continued)

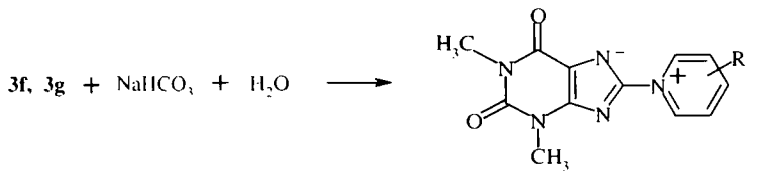
1	2	3	4	5	6	7	8	9
4	$C_{12}H_{13}ClN_6O_2$	47.21 / 46.68	4.00 / 4.21	27.00 / 27.23	370-372	3380, 2950, 1730, 1700, 1650, 1560, 1525, 1480, 1450, 1350, 1320, 1200	3.21 (3H, s, N_3-CH_3); 3.42 (3H, s, N_1-CH_3); 8.34 (2H, s, NH_2); 8.93 (2H, d, *m*-H); 9.44 (2H, d, *o*-H)	81
5	$C_{11}H_{11}ClN_4O_2$	39.85 / 39.16	4.02 / 3.26	26.28 / 26.11	297-299 (DMF)		3.45 (3H, s, N_3-CH_3); 3.57 (3H, s, N_1-CH_3)	
6	$C_{11}H_6N_4O_3$	43.05 / 42.86	4.28 / 4.08	28.12 / 28.57	410 (water)	3440, 1690, 1655, 1555, 1420, 1405	3.17 (3H, s, N_3-CH_3); 3.32 (3H, s, N_1-CH_3)	
7	$C_{19}H_{16}N_6O_2$	63.95 / 63.33	4.90 / 4.44	23.90 / 23.33	302-303	3460, 1680, 1640, 1560, 1540, 1480, 1400, 1380, 1280	3.25 (3H, s, N_3-CH_3); 3.40 (3H, s, N_1-CH_3); 6.82(5H, s, C_6H_5); 8.61 (1H, s, *m*-H); 8.9 (1H, d, N=CH); 8.9 (2H, s, *m*-H); 9.30 (2H, s, *o*-H)	81
8	$C_{18}H_{13}IN_6O_2$	44.92 / 45.38	4.00 / 3.57	17.05 / 17.65	226-228	3020, 2990, 1680, 1640, 1560, 1525, 1480, 1450, 1410, 1330, 1270, 1220	3.26 (3H, s,N_3-CH_3); 3.40 (3H, s, N_1-CH_3); 6.40 (2H, s, CH_2); 8.2 (4H, d, q, *m*-H); 8.6 (1H, q, *p*-H); 9.0 (2H, d, *o*-H); 9.4 (2H, d, *o*-H)	22
9	$C_{20}H_{17}NaN_6O_3$	61.10 / 60.61	4.85 / 4.29	21.04 / 21.21	335-338	1660, 1620, 1570, 1550, 1520, 1360, 1210	identical to **3k**	85
10	$C_{20}H_{17}NaN_6O_3$	61.10 / 60.61	4.85 / 4.29	21.04 / 21.21	338-340	1660, 1620, 1580, 1545, 1520, 1355, 1220	identical to **3l**	83
11	$C_{13}H_{10}NaN_5O_4$	48.25 / 48.30	3.52 / 3.10	22.05 / 21.67	360	1690, 1620, 1570, 1520, 1450, 1370	identical to **3f**	85
12	$C_{13}H_{10}NaN_5O_4$	48.25 / 48.30	3.52 / 3.10	22.05 / 21.67	360	1680, 1620, 1570, 1530, 1450, 1370	identical to **3j**	87



9, 10

9 R = 3-C(ONa)=N-$CH_2C_6H_5$, **10** R = 4-C(ONa)=N-$CH_2C_6H_5$

Sodium salts **11** and **12** of betaines **3f,g** contain carboxyl groups at positions 3 or 4 of the pyridine ring and are readily obtained in the same way:



11, 12

11 R = 3-COONa, **12** R = 4-COONa

Salts **9-12** are high melting, crystalline materials, readily soluble in water (Table 1).

Study of the properties of betaine derivatives of theophylline has shown that the majority of them show high thermal stability but, at the same time, quite readily undergo reaction at functional groups in the pyridine ring without destruction of the betaine structure, thus pointing to a marked energetic advantage and stability. This observation opens up broad possibilities for the synthesis of novel betaine derivatives of theophylline.

EXPERIMENTAL

The electronic spectra were taken on an MRS-5000 spectrometer (water solvent), and IR spectra on a Perkin-Elmer 325 spectrometer (for KBr tablets). ^{1}H NMR spectra were recorded on Tesla BS-486 (80 MHz) machine using CF_3COOH solvent. TLC was performed on Silufol UV 254 plates. Characteristics for compounds **3f-l** and **4-12** are given in Table 1.

The method for synthesis of compound **1** was reported in [1], compound **2** in [2], compounds **3a-e** in [3, 4], and the starting theophyllines were obtained by known methods [5-7].

8-(3-Carboxypyridinium) Theophyllinate (3f). A. A mixture of 8-nitrotheophylline (0.87 g, 3.9 mmol), nicotinic acid (0.98 g, 8 mmol), acetic anhydride (1 ml), and DMF (10 ml) was stirred at 120°C for 3 h. The mixture was cooled, dioxane (10 ml) was added, and the precipitated theophyllinate **3f** formed was filtered off. It was recrystallized from water, 1:10.

B. A mixture of 8-nitrotheophylline (0.87 g, 3.9 mmol), nicotinic acid (0.98 g, 8 mmol), and DMF (15 ml) was stirred at 60-70°C until complete solution of the precipitate, cooled to 30-40°C, and there was added monochloramine B (1.1 g, 3.9 mmol) in small portions. The mixture was stirred for a further 1 h. The precipitated betaine **3f** produced was filtered off and recrystallized from water.

8-(4-Carboxypyridinium) Theophyllinate (3g) was obtained from isonicotinic acid similarly to the synthesis of **3f**. It was recrystallized from water, 1:4.

8-(4-Aminopyridinium) Theophyllinate (3h) was obtained as for betaine **3f** from 4-aminopyridine. It was recrystallized from DMF, 1:10.

8-(3-Formylpyridinium) Theophyllinate (3i). A mixture of 8-bromotheophylline (52 g, 20 mmol), 3-pyridine aldehyde (4 g, 40 mmol), and acetic anhydride (4 ml) was refluxed with stirring for 3 h. It was then cooled and the precipitate formed was filtered off and recrystallized from DMF, 1:5.

8-(4-Cyanopyridinium) Theophyllinate (3j) was prepared as for betaine **3f** using method B from a mixture of 8-bromotheophylline (1.3 g, 5 mmol) and 4-cyanopyridine (1.0 g, 10 mmol). It was recrystallized from DMF, 1:10.

8-(3-Benzylcarbamoylpyridinium) Theophyllinate (3k) was synthesized similarly to compound **3i** from 8-bromotheophylline (5.2 g, 20 mmol) and N-benzylamide of nicotinic acid (8.4 g, 40 mmol) in Ac_2O (4 ml). It was recrystallized from DMF, 1:5.

8-(4-Benzylcarbamoylpyridinium) Theophyllinate (3l) was prepared similarly to compound **3k** from N-benzylamide of isonicotinic acid (8.4 g, 40 mmol). It was recrystallized from DMF, 1:5.

8-(4-Aminopyridinium) Theophyllinate Hydrochloride Salt (4). A mixture of compound **3h** (2.72 g, 10 mmol) and concentrated hydrochloric acid (8 ml) was refluxed to full solution of the precipitate. The solution was cooled and the precipitate was filtered off, washed with acetonitrile and ether, and then dried.

8-(4-Benzylideneaminopyridinium) Theophyllinate (7). A mixture of compound **3h** (1.4 g, 5 mmol), benzaldehyde (5 ml), and BF_3·MeOH (0.5 ml) was stirred at 160°C for 8 h. After cooling, the precipitate formed was filtered off and recrystallized from DMF, 1:8

8-(4-Pyridiniummethylpyridinium) Theophyllinate Iodide (8). A mixture of compound **3d** (0.4 g, 15 mmol), iodine (0.38 g, 15 mmol), and pyridine (5 ml) was refluxed for 2 h and then left for 10 h. Acetonitrile (10 ml) was added to the reaction mixture and it was stirred and the precipitate filtered off, washed with acetonitrile, and recrystallized from acetic acid, 1:3.

Sodium Salt of 8-(3-Benzylcarbamoylpyridinium) Theophylline (9). Sodium (0.16 g, 7 mmol) was dissolved in ethyl alcohol (200 ml) and compound **3k** (2.7 g, 7 mmol) was added to the clear solution. The mixture was stirred at room temperature for 1 h. The precipitate obtained was filtered off and recrystallized from ethyl alcohol, 1:10.

Sodium Salt of 8-(4-Benzylcarbamoylpyridinium) Theophylline (10) was prepared similarly to salt **9** from compound **3l**.

Sodium Salt of 8-(3-Carboxypyridinium) Theophyllinate (11). A solution of sodium bicarbonate (0.85 g, 10 mmol) was added portionwise with stirring to a solution of theophylline **3f** (3.0 g, 10 mmol) in ethyl alcohol (20 ml) at 0°C. The mixture was stirred for 30 min and the solvent was evaporated in vacuo. The obtained precipitate was recrystallized from 30% ethyl alcohol, 1:3.

Sodium Salt of 8-(4-Carboxypyridinium) Theophyllinate (12) was prepared similarly to **11** from theophylline **3g**.

Reaction of 8-Trimethylammonium Theophyllinate 2 with Hydrochloric Acid. Conc. HCl (6 ml) was added to compound **2** (0.47 g, 2 mmol) and refluxed for 1 h. The reaction mixture was treated with water (20 ml) and then allowed to stand overnight. The white precipitate formed was filtered, dried, and recrystallized from DMF to give 8-chlorotheophylline **5** (0.42 g, 99%) [5].

Reaction of 8-Trimethylammonium Theophyllinate 2 with Base. A mixture of compound **2** (1.2 g, 5 mmol) and NaOH (0.8 g, 20 mmol) in water (5 ml) was refluxed for 8 h. The cooled mixture was neutralized with hydrochloric acid to pH 5-6. The precipitate formed was filtered, washed with water, and dried to give uric acid **6** (0.31 g, 29%) [6]. The reaction with betaines **1** and **3a-e** occurred similarly.

Reaction of 8-Pyridinium Theophyllinate with Chlorinating Agents. A mixture of compound **1** (1.3 g, 5 mmol) and sulfuryl chloride or thionyl chloride (15 ml) was refluxed for 8 h. The solution was then evaporated and isopropanol (10 ml) was added to the residue. The product was stirred and the precipitate formed was filtered off to give 8-chlorotheophylline **5** (1.6 g, 75%) [5].

Reaction of 8-Pyridinium Theophyllinate 1 with Diphenylphosphoric Acid Chloride. Diphenylphosphoric acid chloride (1.4 g, 5 mmol) was added dropwise with stirring at 60-70°C to a mixture of compound **1** (1.3 g, 5 mmol) and triethylamine (1.5 ml) in dry acetonitrile (10 ml). The mixture was refluxed for 3 h. No spots differing from starting material were seen on chromatographic analysis.

Reaction of 8-Pyridinium Theophyllinate 1 with Isonicotinic Acid. A mixture of compound **1** (0.3 g), isonicotinic acid (0.3 g), and acetic anhydride (2 ml) in DMF (10 ml) was refluxed for 3 h. No spots differing from starting material were seen on chromatographic analysis.

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