REACTIONS OF THEOPHYLLINES. SYNTHESIS OF 8-TRIMETHYLAMMONIOTHEOPHYLLINATE

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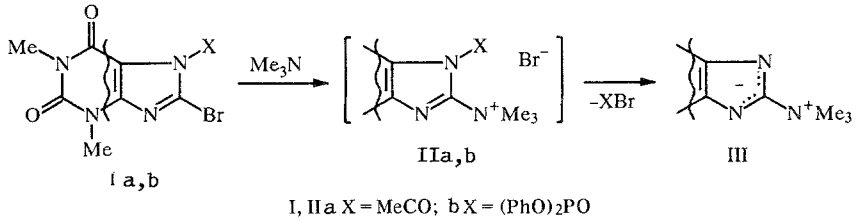
The reaction of 8-bromo- and 8-dimethylaminotheophyllines with organic acid chlorides in the presence of tertiary aliphatic amines was investigated. The direction of the reactions depends on the nature of each of the three components. Depending on the combination, it is possible to obtain 7-acyl-8-bromo-, 7-benzoyl-8-dimethylamino-, and 7-alkenyl-8-dimethylaminotheophylline and 8-trimethylammoniotheophyllinate. A convenient method is proposed for the synthesis of the latter.

Earlier we showed that 8-bromotheophylline in the presence of electrophilic agents readily exchanges the bromine atom for a pyridine residue with the formation of 8-pyridiniotheophyllinate [1,2].

We studied the analogous reactions with aliphatic tertiary amines. The production of structurally similar purinides containing a trimethylammonio group at positions 2, 6, or 8 by the reaction of the respective chloropurines with trimethylamine in a sealed tube was described in [3]. According to our data, 8-bromotheophylline does not react with trimethylamine either under these conditions or under the conditions for the production of 8-pyridiniotheophyllinates in the presence of Lewis acids ($AlCl_3$, BF_3·MeOH). A chain of transformations begins if acid chlorides are used, and the degree of reaction and the final result depend on the nature of the acid chloride and of the tertiary amine. We showed [2] that 8-bromotheophylline reacts readily with acetyl chloride or diphenylphosphoryl chloride in the presence of triethylamine and forms the corresponding 7-acetyl- or 7-diphenylphosphoryl-8-bromotheophyllines (Ia) or (Ib).

In the present work we studied the same reactions but in the presence of trimethylamine. It was found that one and the same product 8-trimethylammoniotheophyllinate (III) was unexpectedly obtained with good yields instead of 7-acyl-8-bromotheophyllines (Ia, b). It is clear that the corresponding theophyllines (Ia, b) must be formed at the first stage and then react with the excess of trimethylamine. In fact, the theophyllines (Ia, b) synthesized according to [2] enter readily into reaction with trimethylamine in chloroform, and as a result the theophyllinate (III) is formed. The mechanism of these reactions probably includes initial nucleophilic substitution of the bromine atom by the trimethylamine residue and then the formation of the unstable quaternary salt (IIa, b). Triethylamine does not react, probably, for steric reasons. The salt (IIa, b) then dissociates, eliminating the acyl bromide and forming the betaine (III), as occurs in the reactions with pyridine [1,2].



I a,b IIa,b III

I, II a X = MeCO; b X = $(PhO)_2PO$

For practical purposes, instead of the ready-made theophyllines (Ia, b), it is more convenient to use the reaction of 8-bromotheophylline with acetyl chloride or diphenylphosphoryl chloride in an excess of trimethylamine.

Unlike the compounds described above the chlorides of aromatic acids react differently with 8-bromotheophylline (IV) in the presence of trimethylamine. The reaction gives not the betaine (III) but the corresponding 7-benzoyl-8-dimethylaminotheophyllines (VIa-c). This is probably due to the fact that the intermediately formed quaternary salt (Va-c) dissociates in a

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TABLE 1. Characteristics of Compounds (III, VIa-c, VIII, XIa-c, XII)

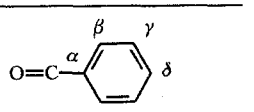
Compound	mp, °C	R_f	IR spectrum, ν, cm^{-1}	Absorption λ_{max}, nm (log ε)	Yield, %
III	305...306	0,24*	2930, 1670, 1635, 1615, 1560, 1525, 1445, 1385, 1320, 1295	—	74(A), 77(B), 80(C), 68(D)
VIa	172...174	0,85	3060, 2960, 1715, 1695, 1650, 1610, 1590, 1570, 1510	360 (3,08)	69(A), 50(B), 72(C), 35(D)
VIb	203...205	0,80	3060, 2930, 1780, 1690, 1640, 1620, 1580, 1515, 1440, 1405	415 (2,57)	65(A), 49(B)
VIc	227...229	0,75	2880, 1680, 1655, 1610, 1575, 1510, 1430, 1405, 1370, 1355	360 (4,64)	4(A), 38(B)
VIII	210...213	0,87	2920, 1730, 1690, 1650, 1605, 1590, 1520, 1440, 1420	—	80
XIa	155...157	0,70	2930, 1770, 1690, 1645, 1615, 1565, 1520, 1405, 1355, 1305	—	45
XIb	74...76	0,91	2880, 1765, 1680, 1650, 1610, 1560, 1515, 1410, 1360, 1290	—	64
XIc	134...136	0,91	2940, 1755, 1695, 1640, 1620, 1575, 1505, 1420, 1375, 1280	—	62
XII	217...218	0,31	2930, 1690, 1650, 1600, 1550, 1525, 1440, 1410, 1375, 1325, 1275	—	80(A), 38(B)

*The eluant was methanol.

TABLE 2. ^1H and ^{13}C NMR Spectra of Compounds (III, VIa-c, VIII, XIa-c, XII)

Compound	PMR spectrum, δ, ppm			
	$N_{(1)}$-CH_3 (3H, s)	$N_{(3)}$-CH_3 (3H, s)	$N(CH_3)_2$ (6H, s)	Ar or Alk
III*	3,16	3,35	3,51 (9H, s, N^+Me_3)	—
VIa	3,14	3,47	3,00	7,30...7,80 (3H, m, m- and p-H); 7,92 (2H, d, J = 7 Hz, o-H)
VIb	3,08	3,45	3,00	8,05 (2H, d, J = 8 Hz); 8,27 (2H, d J ≈ 8 Hz, m-H)
VIc	3,15	3,45	3,00 ($C_{(8)}$-NMe_2); 2,95 (Ar-NMe_2)	6,57 (2H, d, J = 8 Hz, m-H); 7,75 (2H, d, J = 8 Hz, O-H)
VIII	3,14	3,47	—	7,25...7,57 (3H, m, m- and p-H); 7,70 (2H, d J = 7 Hz, O-H)
XIa	3,25	3,45	3,05	5,37 (1H, d, J = 3 Hz, =C-H_A); 5,10 (1H, d, J = 3 Hz, =C-H_B); 2,12 (3H, s, C-CH_3)
XIb	3,22	3,35	3,00	5,55 (1H, t, J = 8 Hz =C-); 0,53...2,45 (16H, m, -CH_2- and C-CH_3)
XIc	3,25	3,40	3,05	5,46 (1H, d, J = 10 Hz, =CH-); 0,6...2,3 (16H, d, -CH_2- and C-CH_3)
XII	3,25	3,40	2,88	3,68 (3H, s, $N_{(7)}$-CH_3)

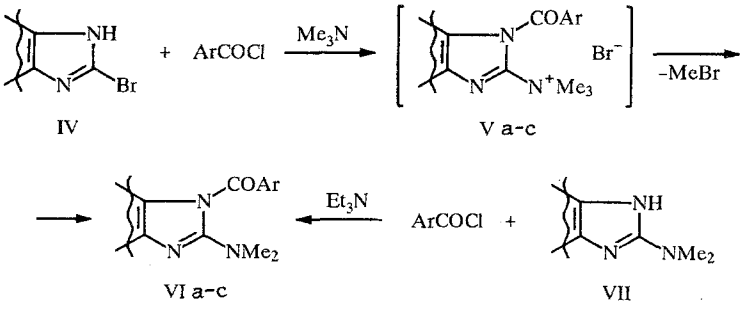
The ^{13}C NMR spectrum of compound (VIa), δ, ppm



$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(8)}$	$N_{(1)}$-CH_3	$N_{(3)}$-CH_3	$N(CH_3)_2$	C=O	$C\alpha$	$C\beta$	$C\gamma$	$C\delta$
147,2	144,8	101,9	151,1	146,3	31,1	32,9	42,8	161,9	130,7	125,0	126,5	129,2

*The solvent was trifluoroacetic acid.

different direction with the elimination not of benzoyl bromide but of methyl bromide. In order to confirm the structure we synthesized the theophyllines (VIa-c) by an alternative method, i.e., by benzoylation of 8-dimethyl-aminotheophylline (VII).

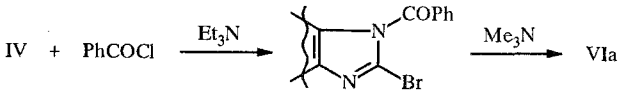


IV V a-c VI a-c VII

V, VI a Ar = Ph; b Ar = 4-NO_2-Ph; c Ar = 4-NMe_2-Ph

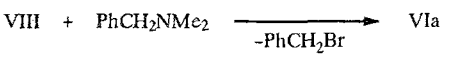
4-Dimethylaminobenzoyl chloride reacts with the theophylline (IV) substantially more slowly than other benzoyl chlorides under analogous conditions, and this gives rise to a low yield of compound (VIc). It can be obtained more conveniently by the alternative synthesis from the theophylline (VII).

If triethylamine is used instead of trimethylamine, as shown in the case of benzoyl chloride, the reaction results in the formation of only 7-benzoyl-8-bromotheophylline (VIII), which is converted readily into the theophylline (VIa) by the action of trimethylamine.



VIII

Other tertiary amines (dimethylaniline, DMFA, methylmorpholine) do not react with the theophylline (VIII) in boiling chloroform, whereas the reaction with dimethylbenzylamine under the same conditions leads to the theophylline (VIa). It is clear that dissociation of the intermediate quaternary salt in this case takes place as a result of cleavage of the more labile bond between the nitrogen atom and the benzyl group.

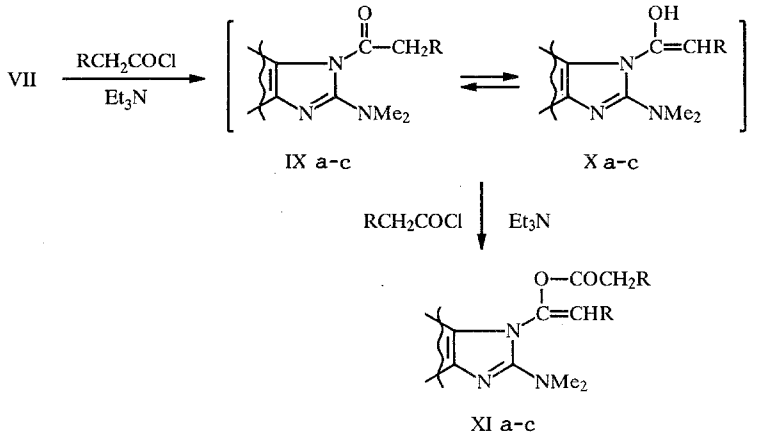


In contrast to the chlorides of aromatic acids, the chlorides of aliphatic acids acylate 8-dimethylaminotheophylline (VII) in a more complicated manner with the formation of the corresponding 7-alkenyl-8-dimethylaminotheophyllines (XIa-c). Initially, the product of normal acylation (IXa-c) is probably formed, and its enolic form (Xa-c) is more reactive than the initial theophylline (VII). Further acylation therefore takes place at the hydroxyl group of the theophylline (Xa-c) and not the amide group of compound (VII). With insufficient amount of the acyl chloride it is not possible to isolate the 7-acyl-8-dimethylaminotheophylline (IXa-c). (See scheme at the top of the next page.)

The structure of the obtained compounds was confirmed by IR and ^1H and ^{13}C NMR spectroscopy in conjunction with elemental analysis (Tables 1 and 2).

In the PMR spectrum of the theophyllinate (III) the signal of the trimethylammonio group lies in the characteristic region of 3.51 ppm [3]. In the IR spectrum the absorption bands of the carbonyl groups are shifted 15-30 cm^{-1} toward the long-wave region compared with the initial theophyllines (Ia, b), as is typical of 8-pyridiniotheophyllinates [2]. As a rule the theophyllines containing a quaternized nitrogen atom at position 8 have an intense yellow color. For example, 8-pyridiniotheophyllinates have λ_{max} (log ε) 363-378 nm (3.36-4.0) [2], and 8-nitrotheophylline [4] and 8-diazatheophylline [5] have λ_{max} 370 nm (pH 1). The obtained theophyllinate (III) was colorless. This is probably explained by the fact that in the examples given above the quaternized nitrogen atom contains a multiple bond conjugated with the theophylline molecule, while all the bonds at the charged nitrogen atom in the betaine (III) are single.

In contrast to the colorless betaine (III), the 7-benzoyl-8-dimethylaminotheophyllines (VIa-c) have a deep yellow or red color. The nature of the substituent at the para position of the benzoyl group has a significant effect on the spectral

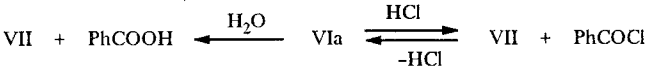


IX—XI a R = H; b R = Pr; c R = *i*-Pr

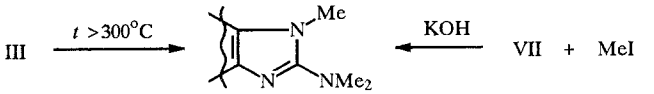
characteristics of the theophyllines (VIa-c). In the transition from compound (VIc), containing a dimethylamino group, to compound (VIb), containing a nitro group, the bathochromic shift amounts to 55 nm with an appreciable reduction in the molar absorption coefficient. This fact indicates that there is significant conjugation between the π-electron systems of the aromatic ring and the theophylline fragment through the carbonyl group.

Such a favorable energy state probably gives rise to the high thermal stability of the theophyllines (VIa-c). For example, the theophylline (VIa) distills under vacuum (bp 255-260°C/10 mm Hg) with partial decomposition. At normal pressure this compound decomposes at temperatures above 350°C with the formation of a mixture of products, in which benzaldehyde and theophylline (VII) were identified by TLC.

The theophyllines (XIa-c) are characterized by the presence of an absorption band for the C=O bond of one acyl group at 1755-1770 cm^{-1} in the IR spectrum. In the PMR spectra the signals for the protons at the double bond are in the normal region of 5.10-5.46 ppm. For compound (XIa) the geometrically nonequivalent protons of the vinylidene group give two different signals (5.10 and 5.37 ppm), and this is also typical of disubstituted ethylenes [6]. Among the chemical characteristics of the synthesized substances it should be noted that the theophylline (VIa) is hydrolyzed in boiling water after 3-4 h with the formation of benzoic acid and the theophylline (VII). Under the influence of concentrated hydrochloric acid hydrolysis takes place even at room temperature. Dry hydrogen chloride leads to the cleavage of compound (VIa) into benzoyl chloride and the theophylline (VII).



Like other betaines [2], the theophyllinate (III) exhibits high thermal stability. It melts at a temperature above 300°C with simultaneous isomerization to 7-methyl-8-dimethylaminotheophylline (XII), the structure of which was confirmed by an alternative synthesis by methylation of theophylline (VII) with methyl iodide in the presence of alkali.



XII

It is seen from the presented data that the direction of the reaction of 8-bromo- and 8-dimethylaminotheophyllines with organic acid chlorides in the presence of tertiary nitrogen bases depends substantially on the nature of each of the three components of the reaction.

EXPERIMENTAL

The electronic spectra were recorded in isopropanol on an MPS-5000 spectrophotometer. The IR spectra were recorded in tablets with potassium bromide on a Perkin-Elmer 325 spectrometer. The PMR spectra were obtained in deuterochloroform on a Tesla BS-486 instrument at 80 MHz. The ^{13}C NMR spectrum was obtained on a Bruker WH-90 instrument at 22.62 MHz in deuterochloroform. The mass spectrum was recorded on a Varian MA-112 spectrometer at 20 eV with direct injection into the ion source. Thin-layer chromatography was conducted on Silufol 254 plates with development in UV light and with acetonitrile as eluant.

The elemental analyses for C, H, N, and Br agreed with the calculated data.

8-Bromotheophylline was obtained according to [4], and 8-dimethylaminotheophylline according to [7].

8-Dimethylammoniotheophyllinate (III) ($C_{10}H_{15}N_5O_2$). A. A mixture of 3.01 g (10 mmole) of the theophylline (Ia) and 50 ml of chloroform was saturated with dry trimethylamine (~2 g) at room temperature. The mixture was kept at this temperature for 3 h. The precipitate was separated, washed with water (2 × 30 ml), and recrystallized from water.

B. The compound was obtained similarly from 4.91 g (10 mmole) of the theophylline (Ib).

C. A mixture of 2.6 g (10 mmole) of 8-bromotheophylline (IV) and 50 ml of chloroform was saturated with an excess of dry trimethylamine (~2.3 g) at room temperature. To the obtained solution we added 3.22 g (12 mmole) of diphenylphosphoryl chloride. The mixture was kept at this temperature for 3 h. The product was then isolated according to method A.

D. The compound was obtained similarly to method C from 0.94 g (12 mmole) of acetyl chloride.

7-Benzoyl-8-bromotheophylline (VIII) ($C_{14}H_{11}BrN_4O_3$). A mixture of 2.6 g (10 mmole) of 8-bromotheophylline (IV), 2.1 g (15 mmole) of benzoyl chloride, 3 ml of triethylamine, and 40 ml of chloroform was boiled for 3 h. The obtained solution was evaporated under vacuum, and the solid residue was washed with 10 ml of cold water and 10 ml of ether, dried under vacuum, and recrystallized from benzene.

7-Benzoyl-8-dimethylaminotheophylline (VIa) ($C_{16}H_{17}N_5O_3$). A. A mixture of 2.6 g (10 mmole) of 8-bromotheophylline (IV) and 50 ml of chloroform was saturated with an excess of dry trimethylamine (~2.3 g) at room temperature. To the obtained solution we added 1.7 g (12 mmole) of benzoyl chloride. The mixture was stirred at this temperature for 3 h and left overnight. The solution was filtered and evaporated under vacuum. The oily residue was rubbed in isopropanol. The crystals were filtered off, washed with 10 ml of water, dried, and recrystallized from a 1:1 mixture of benzene and hexane.

B. A mixture of 2.23 g (10 mmole) of the theophylline (VII), 1.7 g (12 mmole) of benzoyl chloride, 3 ml of trimethylamine, and 50 ml of chloroform was boiled for 3 h and left overnight. The product was isolated according to method A. Mass spectrum, m/z: M^+ 327, 275, 273, 224, 223, 181, 150, 123, 107, 106, 78.

C. To a solution of ~2.3 g of dry trimethylamine in 50 ml of chloroform we added 3.63 g (10 mmole) of the theophylline (VIII). The mixture was stirred at room temperature for 3 h and left overnight. The product was then isolated according to method A.

D. A mixture of 3.63 g (10 mmole) of the theophylline (VIII), 2.70 g (20 mmole) of dimethylbenzylamine, and 50 ml of chloroform was boiled for 12 h. The product was then isolated according to method A.

7-p-Nitrobenzoyl-8-dimethylaminotheophylline (VIb) ($C_{16}H_{16}N_6O_5$). The compound was obtained from p-nitrobenzoyl chloride by methods A and B analogous with those used for the synthesis of the theophylline (VIa). The product was crystallized from benzene.

7-p-Dimethylaminobenzoyl-8-dimethylaminotheophylline (VIc) ($C_{18}H_{22}N_6O_3$). A. The compound was obtained from p-dimethylaminobenzoyl chloride by method A for analogy with the synthesis of the theophylline (VIa).

B. A mixture of 2.23 g (10 mmole) of the theophylline (VII), 2.01 g (11 mmole) of p-dimethylaminobenzoyl chloride, 3 ml of trimethylamine, 50 ml of benzene, and 20 ml of acetonitrile was boiled for 8 h. The mixture was cooled, and the solution was filtered and evaporated under vacuum. The solid residue was recrystallized from toluene.

7-(1-Acetoxyvinyl)-8-dimethylaminotheophylline (XIa) ($C_{13}H_{17}N_5O_4$). A mixture of 2.23 g (10 mmole) of the theophylline (VII), 2.36 g (30 mmole) of acetyl chloride, and 50 ml of chloroform was cooled to +5°C, and 6 ml of trimethylamine was added drop by drop. The reaction mass was kept at 5°C for 1 h and at room temperature for 12 h and was boiled for 0.5 h. The solvent was evaporated, and the residue was extracted with hot benzene (50 ml). After cooling the solution was filtered, and the solvent was distilled. The solid residue was recrystallized from carbon tetrachloride.

7-(1-Valeryloxy-1-pentenyl)-8-dimethylaminotheophylline (XIb) ($C_{19}H_{29}N_5O_4$). A mixture of 3.35 g (15 mmole) of the theophylline (VII), 7.2 g (60 mmole) of valeryl chloride, 6 ml of trimethylamine, and 50 ml of chloroform was boiled for 4 h. The solution was evaporated under vacuum, and the residue was extracted with 80 ml of hot benzene. After cooling the solution was filtered, and the solvent was distilled. The residue (a colorless oil) was crystallized after 2 h at 0°C. The product was recrystallized from hexane.

7-(1-Isovaleryloxy-3-methyl-1-butenyl)-8-dimethylaminotheophylline (XIc) ($C_{19}H_{29}N_5O_4$). The compound was obtained similarly to the theophylline (XIb) from isovaleryl chloride.

7-Methyl-8-dimethylaminotheophylline (XII) ($C_{10}H_{15}N_5O_2$). A. A 1.0-g sample (4.21 mmole) of the theophyllinate (III) was heated to melting (300°C) and kept at this temperature for 5 min. After cooling to room temperature the substance was recrystallized from DMFA.

B. To a hot solution of 2.23 g (10 mmole) of the theophylline (VII) and 0.66 g (12 mmole) of potassium hydroxide in 80 ml of methanol we added 2.13 g (15 mmole) of methyl iodide. The mixture was left at room temperature for 12 h. The methanol was evaporated, and the solid residue was washed with water (3 × 10 ml) and recrystallized from DMFA.

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