Thus, we obtained for the first time the dienic N,S-acetals of the pyrimidine series by direct reaction of thiols of the pyrimidine series with alkenynylamines.

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# REACTION OF 8-BROMOTHEOPHYLLINE WITH PYRIDINE AND ALKYLPYRIDINES. 8-PYRIDINIOTHEOPHYLLINATES

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*The reaction of 8-bromotheophylline with pyridine or alkylpyridines in the presence of electrophilic reagents proceeds with the formation of 8-pyridiniotheophyllinates. The possible mechanism of the reaction is discussed.*

We have previously [1] shown that in the reaction of 8-bromotheophylline (I) with o-phenylenephosphoryl isocyanate in the presence of pyridine, substitution of the bromine atom by pyridine takes place with the formation of 8-pyridiniotheophyllinate (IIa) instead of the expected carbamoylation of theophylline.

The aim of the present work was to study the mechanism of this reaction. It is known that on prolonged boiling in pyridine, 8-chlorotheophylline forms a pyridinium ylide IIa in a yield of 53% [2].

We found that under similar conditions bromotheophylline I converts in the course of 4 h into ylide IIa to the extent of 11%. In the presence of acidic additives, taken in equimolar amounts [HCl, HBr, $BF_3 \cdot CH_3OH$, $(CH_3)_3SiCl$, $P_2O_5$), the yield of the desired end product during the same reaction time increases to 20-40%. Contrary to this, alkaline agents of sodium methylate type completely inhibit this reaction. Better results are obtained on using acid chlorides of phosphorus acids – $PCl_3$ and $POCl_3$. In this case, the yield of compound IIa is 60-70%, but the reaction is accompanied by strong resinification. Diphenylphosphoryl chloride and acetic anhydride were found to be the most effective. In the presence of these reagents the yield of ylide IIa after 30 min is 80-90%.

Considering the properties of these reagents, it can be assumed that phosphorylation or acetylation of 8-bromotheophylline at the $N_{(7)}$ first takes place, and the corresponding theophyllines III and IV react directly with pyridine (see scheme on page 1287.

To confirm this supposition, we synthesized and isolated substituted theophyllines III and IV in the pure state. Compounds III, IV were obtained from 8-bromotheophylline I and the corresponding acid chlorides of diphenylphosphoric or acetic acid in dry dioxane in the presence of triethylamine. The thus synthesized compounds III and IV are colorless crystalline substances, which are readily soluble in many aprotic solvents. In water and alcohols they are gradually hydrolyzed to the starting 8-bromotheophylline, and the 7-phosphorylated 8-bromotheophylline III is in particular readily hydrolyzed. Theophyllines III and IV react with pyridine even in the cold, while on boiling, according to the TLC data, the reaction is completed in 30 min with the formation of ylide IIa. Thus, the formation of 7-substituted intermediates of 8-bromotheophylline promotes their more rapid conversion with pyridine into ylides IIa. It is assumed that isocyanates [1] also react in the same way.

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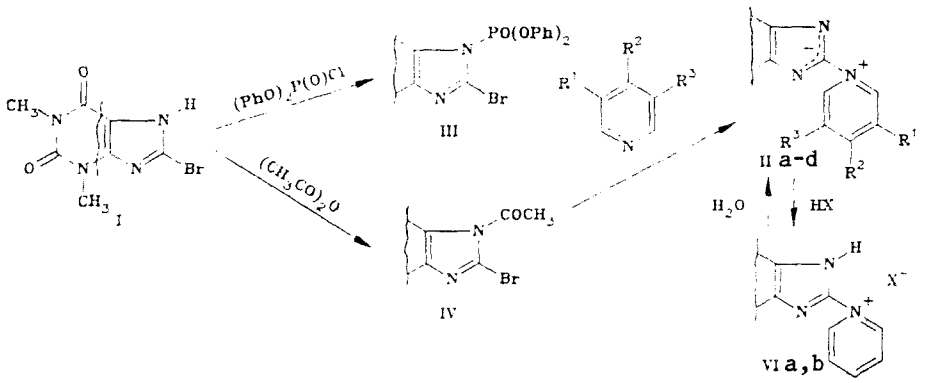
TABLE 1. Characteristics of 7- and 8-Substituted Theophyllines

| Compound | Empirical formula | mp, °C | UV spectrum, $\lambda_{max}$, nm ($\varepsilon \cdot 10^{-4}$) | IR spectrum, $cm^{-1}$ | PMR spectrum ($CF_3COOH$),* δ, ppm (J, Hz) | Yield, % |
|---|---|---|---|---|---|---|
| IIa | $C_{12}H_{11}N_5O_2$ | 335...337 | 382 (0,9) | 1680, 1640, 1560, 1525, 1475 | 3,50 (3H, s, $N_{(3)}$—$CH_3$); 3,62 (3H, s, $N_{(1)}$—$CH_3$); 8,27 (2H, q, *m*-H, *J*=6); 8,75 (1H, q, *p*-H, *J*=7); 9,37 (2H, d, *o*-H, *J*=5) | 82 |
| IIb | $C_{13}H_{13}N_5O_2$ | 330...332 | 378 (1,0) | 1685, 1630, 1560, 1520, 1490 | 2,62 (3H, s, C—$CH_3$); 3,50 (3H, s, $N_{(3)}$—$CH_3$); 3,62 (3H, s, $N_{(1)}$—$CH_3$); 8,15 (1H, q, *m*-H, *J*=6); 8,58 (1H, d, *p*-H, *J*=7); 9,25 (2H, s and d, *o*-H, *J*=5) | 68 |
| IIc | $C_{13}H_{13}N_5O_2$ | 274...276 | 372 (1,1) | 1680, 1630, 1560, 1520, 1490 | 2,75 (3H, s, C—$CH_3$); 3,42 (3H, s, $N_{(3)}$—$CH_3$); 3,60 (3H, s, $N_{(1)}$—$CH_3$); 8,00 (2H, d, *m*-H, *J*=6); 9,17 (2H, d, *o*-H, *J*=6) | 63 |
| IId | $C_{14}H_{15}N_5O_2$ | 340...343 | 374 (1,0) | 1675, 1635, 1555, 1530, 1480 | 2,60 (6H, s, C—$CH_3$); 3,42 (3H, s, $N_{(3)}$—$CH_3$); 3,60 (3H, s, $N_{(1)}$—$CH_3$); 8,35 (1H, s, *p*-H); 9,00 (2H, s, *o*-H) | 71 |
| III | $C_{19}H_{16}BrN_4O_5P$ | 148...151 | — | 1700, 1650, 1580, 1540, 1510, 1480 1210 | 3,42 (3H, s, $N_{(3)}$—$CH_3$); 3,60 (3H, s, $N_{(1)}$—$CH_3$); 7,2...7,7 (10H, m, Ar) | 61 |
| IV | $C_9H_9BrN_4O_3$ | 195...198 | — | 1755, 1690, 1650, 1520 | 2,20 (3H, s, C—$CH_3$); 3,42 (3H, s, $N_{(3)}$—$CH_3$); 3,60 (3H, s, $N_{(1)}$—$CH_3$) | 47 |
| VIa | $C_{12}H_{12}ClN_5O_2$ | 328...330 | — | 2400, 1695, 1665, 1570, 1540, 1510 1480, 1460 | —** | 84 |
| VIb | $C_{12}H_{12}BrN_5O_2$ | 310...312 | — | 2150, 1695, 1665, 1570, 1540, 1510 1480, 1460 | —** | 85 |

*For compound III, the solvent was DMSO-$D_6$.

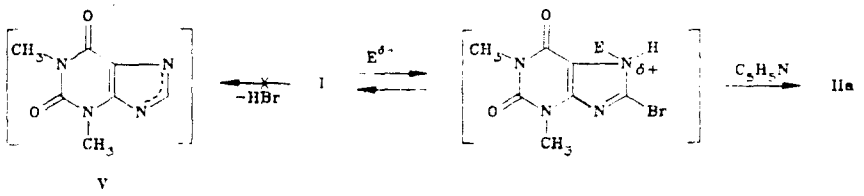
**The PMR spectra of salts VIa, b and ylide IIa are identical.



IIa,cR¹=H,b,d R¹=$CH_3$;a,b,dR²=H, c R²=$CH_3$;a,b,cR³=H, d R³=$CH_3$; VI a X=Cl, b X=Br

It should be noted that not all the 7-substituted 8-bromotheophyllines react with pyridine. Thus, on prolonged boiling in pyridine, 7-ethyl-8-bromotheophylline does not form even traces of ylide IIa and is isolated in unchanged state. Potassium salt of 8-bromotheophylline also practically does not react with boiling pyridine.

Apparently, two conditions are necessary for 7-substituted 8-bromotheophyllines to react with pyridine with he formation of ylides IIa: The substituent at the $N_{(7)}$ atom should have electron-acceptor properties, and its bond with $N_{(7)}$ atom should be fairly labile. The same factors can probably explain the catalytic action of strong acids and Lewis acids. Besides the formation mainly of a complex with pyridine, the electrophilic particle $E^{\delta+}$ can to a certain extent add to the $N_{(7)}$ or $N_{(9)}$ atoms of 8-bromotheophylline I, increasing the electrophilicity of the $C_{(8)}$ atom, thus increasing the rate of the reaction.



E = $AlCl_3$, $BF_3 \cdot CH_3OH$, HCl, HBr

Not only pyridine itself, but also certain of its alkyl derivatives may undergo reaction with 8-bromotheophylline in the presence of the above-indicated reagents (Table 1). The possibility of the occurrence of this reaction is determined by the absence of a substituent at the o-position. Thus, 3-methyl-, 4-methyl-, and 3,5-dimethylpyridines form the corresponding ylides IIb-d, while 2-methyl-, 2,4-dimethyl-, 2,6-dimethyl-, and 2,4,6-trimethylpyridines practically do not react with 8-bromotheophylline under the same conditions.

The data on the influence of acid catalysts, and also of the o-substituent in pyridine on the rate of formation of ylides II, indicate that the reaction of 7-R-8-bromotheophyllines with pyridines proceeds by the $S_N2$ mechanism.

The alternative $S_N1$ mechanism with splitting off of RBr and formation of diimide V appears to be less probable since, for example, the energetically favorable splitting off of KBr from a potassium salt of 8-bromotheophylline does not occur under the reaction conditions.

The synthesized ylides IIa-d are high-melting crystalline yellow-green colored substances, which are soluble in hot alcohol and in water. They fluoresce intensely in UV light (Table 1). Despite the separated charges in the molecule, ylides II are not alkylated by $CH_3I$ or $C_2H_5Br$.

In a strongly acid aqueous solution, ylide IIa becomes protonated with the formation of colorless VIa, b, but on heating above 200°C or on dissolution in water, it readily decomposes to the starting components.

These facts indicate that in ylides II, the negative charge is not localized on nitrogen atoms, but to a great extent is delocalized in o- and p-positions of pyridine, as in the case of pyridine N-oxides or pyridinium ylides [3].

## EXPERIMENTAL

The electronic spectra were run on a MRS-5000 spectrophotometer (in water) and the IR spectra – on a Perkin–Elmer 325 spectrophotometer (in KBr tablets). The PMR spectra were recorded on a Tesla BS-486 spectrometer (80 MHz). The TLC was carried out on Silufol-254 plates.

The characteristics of compounds IIa-d, III, IV, and VIa, b are given in Table 1. The elemental analysis data correspond to the calculated values.

During the recrystallization of ylides IIa-d, the unreacted 8-bromotheophylline is often coprecipitated together with them. To prevent this, a small amount of triethylamine should be added to the solvent, with which 8-bromotheophylline forms a readily soluble complex.

**8-Pyridiniotheophyllinates (IIa-d).** **A.** A mixture of 10 mmoles of 8-bromotheophylline, 8 ml of the corresponding pyridine, and 2 ml of acetic anhydride was heated at 125-135°C for 2 h, and was then allowed to stand overnight at room temperature. The precipitate that separated out was filtered off, washed with isopropanol and compounds IIa, b were recrystallized from water and IIc, d from ethanol.

**B.** A mixture of 10 mmoles of theophylline III or IV and 8 ml of pyridine was boiled for 30 min and was then allowed to stand overnight. The precipitate that separated out was filtered off, and recrystallized from water. The yield of ylide IIa was 86 (from III) and 92% (from IV).

**7-O,O-Diphenylphosphoryl-8-bromotheophylline (III).** A mixture of 10 mmoles of 8-bromotheophylline, 12 mmoles of diphenylphosphoryl chloride, 12 mmoles of triethylamine, and 50 ml of benzene was boiled for 3 h. The solution was cooled, the triethylamine salt was filtered off, and the filtrate was evaporated to a volume of 10 ml. After addition of 20 ml of hexane, a crystalline precipitate of the phosphorylated theophylline III separated out. It was recrystallized from a carbon tetrachloride–heptane (1:1) mixture.

**7-Acetyl-8-bromotheophylline (IV).** A mixture of 10 mmoles of 8-bromotheophylline, 12 mmoles of acetyl chloride, 12 mmoles of triethylamine, and 40 ml of dry dioxane was boiled for 3 h. The solution was cooled, filtered from the salt, and evaporated in vacuo. The residue was crystallized from benzene, $R_f$ 0.86 ($CH_3CN$).

**8-Pyridiniotheophyllinate Hydrochloride Salt (VIa).** Concentrated HCl was added in small portions to 10 mmoles of 8-pyridiniotheophyllinate IIa with boiling of the mixture until the entire precipitate was dissolved. After cooling the precipitate was filtered, washed with $CH_3CN$ and ether, and dried in vacuo.

**8-Pyridiniotheophyllinate hydrobromide salt (VIb)** was obtained in a similar way from 8-pyridiniotheophyllinate IIa and concentrated HBr.

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