NEW METHOD FOR OBTAINING 8-PYRIDINIOTHEOPHYLLINATES

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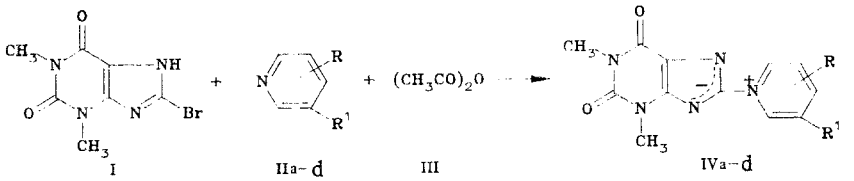
A new method for the synthesis of 8-pyridiniotheophyllinates by the action of pyridine or alkylpyridines on theophylline or 8-bromotheophylline in the presence of oxidizing agents was developed. The oxidation of 8-bromotheophylline gives the best results. This method was used to obtain 8-(2-methylpyridinio)theophyllinate, which could not be synthesized previously.

Interest in the chemistry of 8-pyridiniotheophyllinates is due to their physiological activity. We have previously [1, 2] investigated the reaction of 8-bromotheophylline (I) with pyridines IIa-d in the presence of various electrophilic reagents such as acetic anhydride (III), which leads to the corresponding ylids IVa-d.



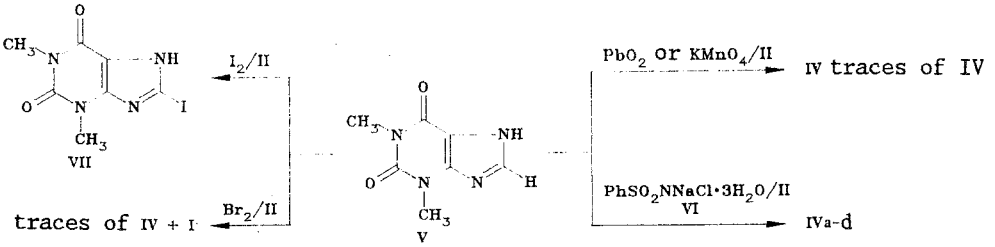
I IIa–d III IVa–d

II, IV a R=R¹=H; b R=*m*-CH_3, R¹=H; c R=R¹=*m*-CH_3; d R=*p*-CH_3; R¹=H

In the present research we attempted to carry out a similar reaction with theophylline (V). It is apparent that the formal replacement of a hydride ion by pyridine is possible only in the presence of an oxidizing agent. Iodine, bromine, monochloramine B (VI), lead dioxide, potassium permanganate, and 30% hydrogen peroxide, which were used in equimolar amounts, were tested as oxidizing agents.

In contrast to 8-bromotheophylline, prolonged refluxing of theophylline in pyridine in the presence of air oxygen does not lead to the formation of ylid IVa even in trace amounts. The corresponding 8-halotheophyllines are formed instead of the expected IVa when free halogens (iodine, bromine) are added. The reaction proceeds slowly with iodine, and the yield of 8-iodotheophylline (VII) is 10%, but IVa is not formed even upon prolonged refluxing of the reaction mixture. The reaction proceeds rapidly at room temperature with bromine, and 8-bromotheophylline (I) is obtained in high yield, along with an appreciable amount (7%) of ylid IVa.

Oxygen-containing oxidizing agents — lead dioxide and potassium permanganate — form ylids IV only in trace amounts under the reaction conditions. The addition of water to a pyridine solution of theophylline (2:1) in the case of potassium permanganate increases the yield of IVa to 14%. In contrast to these oxidizing agents, 30% hydrogen peroxide does not give even traces of the desired product, evidently due to oxidation of primarily pyridine itself to its N-oxide [3].



The best result is obtained when chloramine VI is used. Ylid IVa is formed in almost quantitative yield after 15 min at room temperature. In addition to pyridine IIa itself, theophylline (V) reacts readily under these conditions with 3-methyl- and 3,5-dimethylpyridine (IIb and IIc) to give the corresponding ylids IVb, c in high yields. In

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TABLE 1. Reaction of Theophyllines I and V with Pyridines IIa-e in the Presence of Oxidizing Agents

Reaction product	Starting compound	Pyridine	Yield, %, in the oxidizing agents					
			I_2	Br_2	$PhSO_2NNaCl\cdot 3H_2O$	PbO_2	$KMnO_4$	H_2O_2 (30%)
IVa	I	IIa	Tr./38*	95	95	95	75	Tr.
IVb	I	IIb	Tr.**	84	91	93	70	Tr.
IVc	I	IIc	Tr.	79	88	79	61	Tr.
IVd	I	IId	Tr.	Tr.	Tr.	Tr.	Tr.	Tr.
IVe	I	IIe	—	—	50***	—	—	—
IVa	V	IIa	—/—*	7	95	Tr.	5	—
IVb	V	IIb	—	Tr.	81	Tr.	Tr.	—
IVc	V	IIc	—	Tr.	70	Tr.	Tr.	—
IVd	V	IId	—	Tr.	Tr.	Tr.	Tr.	—
IVe	V	IIe	—	—	22***	—	—	—

*The reaction mixture was refluxed for 3 h.
**Traces (Tr.) of the corresponding ylid IV were detected by TLC.
***Ylids IVe were obtained under different conditions (see the experimental section).

contrast to them, the reaction with 4-methylpyridine (IId) leads to pronounced resinification of the reaction mixture, and the corresponding IVd is formed only in trace amounts. This is probably associated with the increased reactivity of the 4-methyl group [3], which leads to side reactions.

Using this method — oxidation of theophylline with chloramine VI in the presence of 2-methylpyridine (IIe) — we were able to synthesize ylid IVe in low yield (22%); this ylid could not be obtained by an earlier method [2]. The most suitable conditions for obtaining this compound are carrying out the reaction in the minimum amount of water and using a 1.5-fold excess of 2-methylpyridine. In comparing the conditions of the reaction of theophylline with pyridine or with 2-methylpyridine in the presence of chloramine VI we found that the reaction proceeds much faster in the first case. This is confirmed by the fact that, when the reaction is carried out in a mixture of 2-methylpyridine and pyridine (95:5), exclusively pyridine reacts initially, and 2-methylpyridine begins to react only after it is tied up.

2,6-Dimethylpyridine is even more inert, and the formation of even minimal amounts of the corresponding ylid could not be detected under the reaction conditions (see Table 1).

To arrive at a more profound understanding of these reactions it seems of interest to compare the results of the oxidation of theophylline and 8-bromotheophylline. The oxidation of 8-bromotheophylline was carried out similarly with the same oxidizing agents. The results were somewhat unexpected. The formation of the corresponding ylids IV proceeds much more readily with 8-bromotheophylline than with theophylline (see Table 1). Under comparable conditions in the presence of iodine the formation of IVa is insignificant, but the yield increases to 38% upon refluxing for 3 h. With bromine, lead dioxide, or chloramine VI the reaction with pyridine proceeds almost quantitatively, while the yield of ylid IVa reaches 75% when potassium permanganate. Virtually no reaction takes place in the presence of 30% hydrogen peroxide, probably also because of the formation of pyridine N-oxide.

$$I + [O] + IIa \xrightarrow{-B} IVa\text{—}B,$$

$$[O] = I_2,\ Br_2,\ PhSO_2NNaCl\cdot 3H_2O,\ PbO_2,\ KMnO_4$$

Ylids IV are similarly formed in high yields in the reaction with 3-methyl- and 3,5-dimethylpyridine (IIb and IIc). As in the case of theophylline, pronounced resinification of the reaction mixture is observed with 4-methylpyridine (IId), and only traces of ylid IVd are formed. The reaction of 8-bromotheophylline with 2-methylpyridine proceeds best only under certain conditions: in the case of excess (1.5:1) 2-methylpyridine in the minimum amount of DMF the desired ylid IVe is formed in 50% yield. It must be noted that this reaction pathway is realized only in the presence of chloramine VI, while resinification occurs under the influence of all of the other oxidizing agents under the same conditions, and not even traces of IVe can be detected. The more sterically hindered 2,6-dimethylpyridine does not react with 8-bromotheophylline under these conditions. Thus, if one compares the ease of obtaining ylids IV by the various methods — from 8-bromotheophylline and pyridine in the presence of electrophilic agents [1, 2] (A), from 8-bromotheophylline and pyridine in the presence of suitable oxidizing agents (B), and from theophylline and pyridine in the presence of chloramine VI (C) — ylid IV is formed most rapidly and

under the mildest conditions via method B. In our opinion, there is no fundamental difference between methods A and B. The action of the oxidizing agent evidently reduces to cleavage of the $N_{(7)}$—H bond and the formation of a labile $N_{(7)}$—[O] bond. The strongly expressed electron-acceptor properties of the oxidizing agents increase the electrophilicity of the $C_{(8)}$ atom to a greater degree than ordinary electrophilic reagents. Two facts provide evidence in favor of this assumption. First, lead dioxide, used in an equimolar amount, in contrast to the other oxidizing agents, remains unchanged, i.e., it is not reduced, after the reaction. Even a catalytic amount of lead dioxide markedly accelerates the reaction of 8-bromotheophylline with pyridine, although more time is required for its completion because of the heterogeneity of the system. Thus lead dioxide as a strong oxidizing agent acts as an efficient catalyst in this case. Second, 7-acetyl-8-bromotheophylline [2], which reacts readily with pyridine and its 3- and 4-methyl-substituted derivatives, does not react at all with 2-methylpyridine. It follows from this that not every electrophilic substituent attached to the $N_{(7)}$ atom can activate the 8-bromotheophylline molecule to a sufficient extent in these reactions.

The mechanism of the reaction of theophylline with pyridine via method C is rather complex and requires special study.

EXPERIMENTAL

The electronic spectra of solutions in water were recorded with an MPS-5000 spectrophotometer. The IR spectra of KBr pellets were obtained with a Perkin—Elmer 325 spectrometer. The PMR spectra were recorded with a Tesla BS-486 spectrometer (80 MHz). Thin-layer chromatography was carried out on Silufol-254 plates with development by UV light.

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

General Method for Obtaining Ylids IVa-d from Theophylline or 8-Bromotheophylline [4] and Pyridines IIa-e in the Presence of Oxidizing Agents (Iodine, Monochloramine B, Lead Dioxide, Potassium Permanganate, and 30% Hydrogen Peroxide. A mixture of 0.9 g (5 mmole) of theophylline or 1.3 g (5 mmole) of 8-bromotheophylline and 20 ml of the corresponding pyridine IIa-e was heated until the solid material had dissolved completely, after which the solution was cooled to 30-40°C so that the solution remained clear. A 5-mmole sample of the corresponding oxidizing agent was added in small portions at the same temperature with vigorous stirring in the course of 5 min, after which the mixture was stirred for 10 min at room temperature and then diluted with dioxane (1:1). The diluted mixture was stored for 1 h in a refrigerator, and the resulting precipitate was removed by filtration and crystallized from water (for IVa) or from DMF (for IVb, c). The melting points and IR spectra of ylids IVa-c were in agreement with the data previously obtained [1, 2]. The yields of IVa-d are presented in Table 1.

8-Iodotheophylline (VII, $C_7H_7IN_4O_2$). A mixture of 1.8 g (10 mmole) of theophylline, 2.54 g (10 mmole) of iodine, and 20 ml of pyridine was refluxed for 3 h, after which the solvent was evaporated in vacuo, and the residue was washed with hot water (3 × 5 ml) and methanol to remove traces of iodine, and crystallized from DMF to give VII with mp 308-310°C and R_f 0.80 (CH_3CN). IR spectrum: 2850 (NH); 1690, 1650 (C=O); 1590, 1440 cm^{-1}. PMR spectrum (CF_3COOH): 3.57 [3H, s, $N_{(1)}$—CH_3], 3.45 ppm [3H, s, $N_{(3)}$—CH_3. The yield was 0.3 g (10%).

8-(2-Methylpyridinio)theophyllinate (IVe, $C_{13}H_{13}N_5O_2$). **A.** A 1.33-g (5 mmole) sample of VI was added in portions at room temperature with stirring to a mixture of 0.9 g (5 mmole) of theophylline, 5 ml of water, and 0.69 g (7.5 mmole) of 2-methylpyridine, after which the mixture was stirred for 1 h and allowed to stand overnight. The next day, the aqueous layer was separated from the liberated oil, and the oil was treated with 10 ml of hot water. The aqueous extracts were combined, cooled, filtered, and evaporated in vacuo. The residue was treated with 10 ml of isopropyl alcohol, the sodium chloride was removed by filtration, and the solution was allowed to stand overnight in a refrigerator. The precipitated dark-yellow ylid IVe was removed by filtration and crystallized from DMF to give a product with mp 273-275°C and R_f 0.39 [CH_3OH—H_2O (1:1)]. IR spectrum: 1680, 1645 (C=O); 1610, 1560, 1520, 1490, 1445, 1410 cm^{-1}. UV spectrum, λ_{max} (log ε): 363 nm (3.36). PMR spectrum (CF_3COOH): 2.45 (3H, s, C—CH_3), 3.10 [3H, s, C—CH_3], 3.10 [3H, s, $N_{(1)}$—CH_3], 3.25 [3H, s, $N_{(3)}$—CH_3], 7.75 (2H, d and q, J = 7 Hz, o-H), 8.32 (1H, q, J = 7 Hz, p-H), 8.55 ppm (1H, d, J = 6 Hz, o-H).

B. A mixture of 2.6 g (10 mmole) of 8-bromotheophylline, 10 ml of DMF, and 1.4 g (15 mmole) of 2-methylpyridine was heated to the boiling point, after which it was cooled to room temperature, and 2.7 g (10 mmole) of VI was added in portions with stirring at this temperature in the course of 5 min. The white starting 8-bromotheophylline gradually dissolved, and an orange precipitate of ylid IVe formed. The mixture was stirred for 1.5 h at 20°C, and the resulting precipitate was removed by filtration and crystallized from DMF to give IVe with mp 273-275°C. The yield was 1.35 g (50%).

The substance was identical to that obtained by method A.

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IMINE—ENAMINE TAUTOMERISM OF DIHYDROAZOLOPYRIMIDINES. 3.* 5-ARYL-SUBSTITUTED 4,7(6,7)-DIHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES

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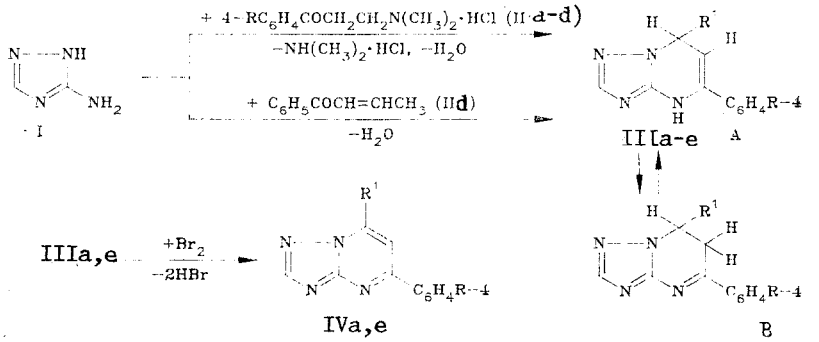
5-Aryl-substituted 4,7(6,7)-dihydro-1,2,4-triazolo[1,5-a]pyrimidines were obtained by condensation of 3-amino-1,2,4-triazole with β-dimethylaminopropiophenone hydrochlorides or crotophenone. The effect of steric and electronic factors on the position of the imine—enamine equilibrium in solutions of the synthesized substances is examined. 5-Phenyl-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine was subjected to x-ray diffraction analysis.

We have previously established [1] that the steric and electronic effects of substituents in the pyrimidine ring of dihydropyrimido[1,2-*a*]benzimidazoles may have a substantial effect on the position of the imine—enamine tautomeric equilibrium. The aim of the present research was to investigate this phenomenon in a series of aromatic substituted 4,7(6,7)-dihydro-triazolo[1,5-*a*]pyrimidines IIIa-e.

Substances IIIa-d were obtained by condensation of 3-amino-1,2,4-triazole (I) with β-dimethylaminopropiophenone hydrochlorides IIa-d, while 7-methyl-substituted IIIe was obtained by the reaction of amine I with 1-phenyl-2-buten-1-one (IIe) in DMF. In the synthesis of IIId under these conditions we observed appreciable resinification, which markedly decreases the yield of the reaction product (Table 1) and can be avoided by using isopropyl alcohol as the solvent. Ketones IIa-c also react with amine I in isopropyl alcohol, while crotophenone (IIe) is not sufficiently reactive and, like chalcones [2], does not react with amine I.

The dehydrogenation of IIIa, e to give their heteroaromatic analogs IVa, e was accomplished by the action of bromine in acetic acid.



II—IVa, e R=H, b R=CH_3, c R=Cl, r R=NO_2; a-d R^1=H, e R^1=CH_3

*See [1] for Communication 2.

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