Reaction of 7-(2-mesyloxy-2-phenylethyl)theophylline with amines: Synthesis of 1,2,3,6-tetrahydro-6-imino-2-oxo-7H-purine derivatives

Shigetada Kozai, Kyoko Ogimoto, Hideko Okamoto and Tokumi Maruyama
Institute of Pharmacognosy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

ABSTRACT
Theophylline was converted to 7-(2-phenyl-2-methanesulfonyloxy)ethyl congener and the product was treated with ammonia or primary amines in a mixture solution of water and organic solvents. Two products were proven to be the styrene analogue and 7-(2-amino-2-phenylethyl)theophylline. The structure of the third product was elucidated as the 1,2,3,6-tetrahydro-6-imino-2-oxo-7H-purine derivatives by spectroscopic analysis including HMBC correlation and X-ray crystallography.

INTRODUCTION
Recently, the iminooxopurines, amidine analogues of xanthine, have emerged as strong inhibitors of PDEs. However, synthesis of these compounds was achieved by ring construction, and conversion of commercially available caffeine or theophylline to iminooxopurine, an amidine analogue of xanthine, has not been examined. Those backgrounds prompted us to develop a new method for the synthesis of the 7-substituted-1,2,3,6-tetrahydro-6-imino-2-oxo-7H-purine from theophylline.

RESULTS AND DISCUSSION
The 2-hydroxy-2-phenylethyl derivative (2a) was prepared from theophylline (1a) in 2 steps and converted to the mesylate (2b) by the conventional manner. Then 2b was treated with 28% ammonia in the mixture of dioxane and MeOH. After work-up of the reaction mixture, the products were separated by silica gel chromatography. From the first fraction, the styrene analogue (3), which shows absorption maximum at 308 nm on UV spectrum, was obtained in 31% yield. The most polar substance from the third fraction was proven as the 2-amino-2-phenylethyl compound (4a, 3.3%). The second fraction was evaporated to produce the new compound (5a, 40%) as white crystals. The UV spectrum of 5a was different from the caffeine analogue such as 1b and 2a,b and showed an absorption maximum at 297.5 nm in an acidic condition. The bathochromic effect in the acidic condition suggests a modification of the chromophore. Reaction of 2b with primary amines also gave 5b,c. The iminooxopurine structure was confirmed by HMBC spectrum of the N-ethyl derivative (5c) which shows a C-H correlation between methylene protons of ethyl group and C6. The presence of the ethyl group
near C6 strongly suggests that a nucleophilic attack of amines at C6 occurred during the reaction. Podona et al. reported that neighboring group participation of the side-chain was observed in the reaction of N-(2-bromoethyl)-glutarimide with primary amine to afford N-(2-hydroxyethyl)iminoglutarimide. Consequently the new products were estimated as iminooxopurines (5a-c). The structure of 5a was finally determined by the X-ray diffraction method. The mechanism to form 5a-c could be explained as the following: At first the carboxcation (S-1) was formed from starting material, then intramolecular electrophilic attack of the cation to the O6 formed the ammonium of the ring structure (S-2).

Nucleophilic substitution of amines at C6 and the subsequent elimination of proton formed 5a-c. The ratio of the amidine derivatives (5) to the substitution product (4) is changeable by the amines. The reason is under investigation (Chart).

REFERENCES