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Synthesis of new 7-alkylated theophyllines by chemical modification of dyphylline

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Chemical modification of the propyl side chain of 7-(2,3-dihydroxyprop-1-yl)theophylline led to a variety of heterocyclic compounds linked to the theophylline by a methylene group.

Keywords: 7-alkylated theophyllines, dyphylline

This paper is dedicated to Professor Gérard Descotes in celebration of his 68th birthday.

Xanthine derivatives have attracted considerable attention due to their numerous biological activities. Although theophylline (**I**) and euphyllin **II** have diuretic effects, dyphylline (**1**) has no effect in spite of being a water soluble analogue of **I**. On the other hand, dyphylline (**1**) is much more effective than euphyllin (**II**) in the treatment of bronchial asthma.[10] Moreover, continuing our efforts to explore new types of acyclo nucleoside have been encourged by the finding that acyclo nucleoside analogues possess potent selective antiherpes activity[11-20] and the *S*-enantiomer of 9-(2,3-dihydroxypropyl)adenine has inhibitory activity towards a number of DNA and RNA viruses.[21,22]

In the present work, two different approaches have been utilized by the derivatization of the glycerolyl residue of dyphylline as esters and acetals which may act as prodrugs as well as by the utilization of its periodate oxidation product to build different types of heterocyclic compounds of possible therapeutic value. Acetylation of dyphylline **(1)** with acetic anhydride in pyridine afforded the di-*O*-acetyl derivative **2** whose spectra agree with the assigned structure. The terminal methylene group appeared in the ^{1}H NMR spectrum as two doublets of doublets with a sufficient difference in their chemical shifts indicating the restricted rotation around C-2′– C-3′ bond. Selective *p*-toluenesulfonylation of **1** afforded the mono tosylated derivative **3**, based on the reactivity of the C-3 hydroxyl group.

Isopropylidenation of **1** with acetone in presence of sulfuric acid afforded the 1,3-dioxalane derivative **4**. The difference in the chemical shifts of the two methyl groups ($\Delta\delta = 0.07$) agreed with El Ashry's shift rule for a terminal isopropylidene ring. The rest of the spectrum agreed with the assignment. Benzylidenation of **1** with benzaldehyde in presence of zinc chloride as a catalyst gave a mixture of the *cis* and *trans* isomers of **5** with ratio (1:1) as deduced from the ^{1}H NMR spectrum.

The other approach to the chemical modification of dyphylline **(1)** utilized the synthesis of theophylline-7-acetaldehyde **(6);** reduction with sodium borohydride afforded 7-(2-hydroxyethyl)theophylline **(7),** acetylation of which gave **8**. Treatment of **6** with hydroxylamine hydrochloride, thiosemicarbazide and benzoylhydrazine afforded the oxime, thiosemicarbazone and benzoylhydrazone derivatives **9, 10** and **11**, respectively. Treatment of compounds **10** and **11** with boiling acetic anhydride caused their cyclization and subsequent acetylation to form the acylated 1,3,4-thiadiazoline and oxadiazoline derivatives **12** and **13**, respectively. Treatment of **6** with two molar equivalents of dimedone followed by boiling with 1N hydrochloric acid gave the xanthene derivative **15**.

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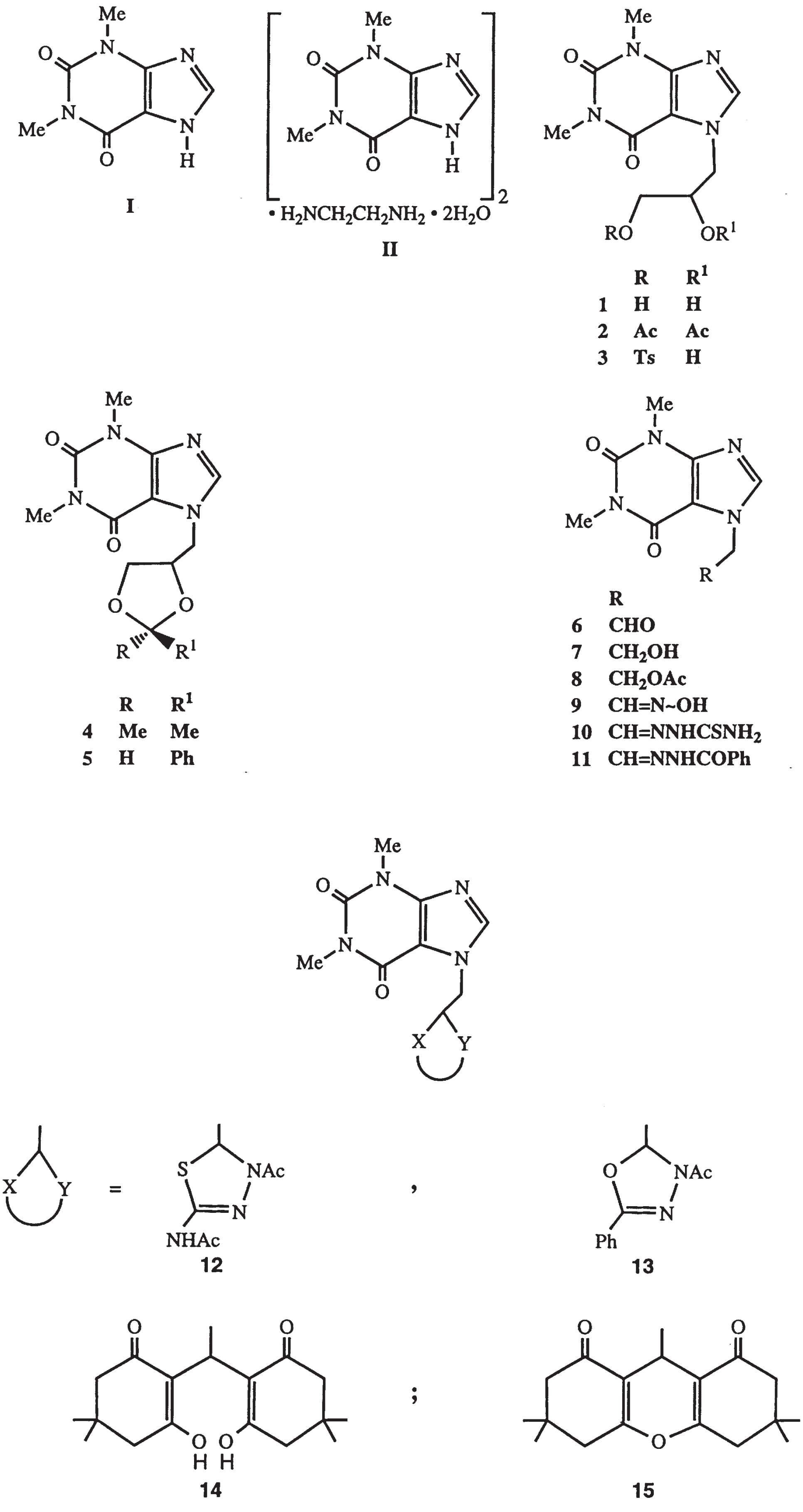
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• $H_2NCH_2CH_2NH_2$ • $2H_2O$
II
R R¹
1 H H
2 Ac Ac
3 Ts H
R R¹
4 Me Me
5 H Ph
R
6 CHO
7 CH₂OH
8 CH₂OAc
9 CH=N~OH
10 CH=NNHCSNH₂
11 CH=NNHCOPh
12
13
14
15

Scheme 1