REARRANGEMENT OF 9-ALKYLTHEOPHYLLINES TO THE 7-ALKYL ANALOGUES

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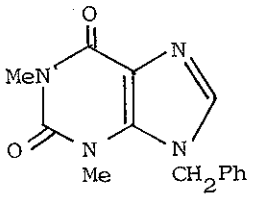
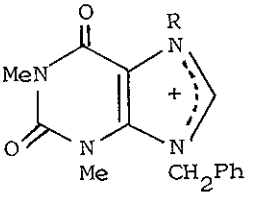
Under thermal conditions 9-benzyltheophylline (1) with either benzyl bromide or hydrobromic acid undergoes rearrangement in dimethylformamide to the 7-benzyl isomer(3).

During benzylation studies with theophylline derivatives[1] the quaternization of 9-benzyltheophylline (1) to the 7,9-dibenzylbromide salt (2) was attempted with benzyl bromide in dimethylformamide under reflux, (3 hr) i.e. using standard conditions[2] for the formation of quaternary xanthine derivatives. The product obtained (>50%) was not the required dibenzylated purine (2) but the 7-benzyl isomer[1] (3) of the starting material. As no corresponding isomerization was observed on heating 9-benzyltheophylline itself in dimethylformamide a simple thermal rearrangement was precluded. However, a mechanism which could involve a charged form intermediate, was given support by the fact that the hydrobromide salt of 9-benzyltheophylline on heating (2 hr) in the same amide solvent isomerised, in good

yield, also to the 7-benzyl derivative (3). By contrast 7-benzyltheophylline, either as base or hydrobromide, remained unchanged when subjected to similar thermal treatment.

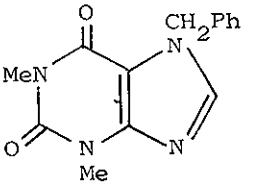


(1)

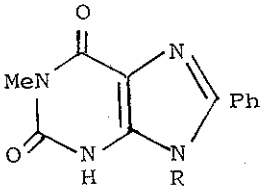


(2)

(R=H or CH_2Ph)

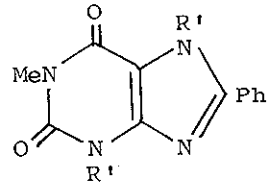


(3)



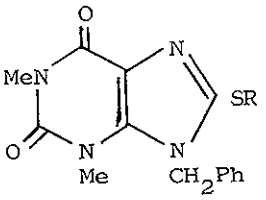
(4) R=Pr^n

(5) R=Me



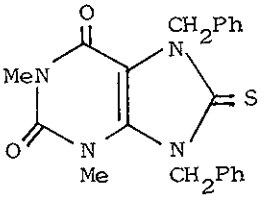
(6) R'=Me

(7) R'=Et



(8) R=CH_2Ph

(9) R=H



(10)

Two somewhat related examples of this type have been reported recently [3] in which alkylation (with methyl or ethyl iodide) of the 9-substituted 1-methyl-8-phenylxanthines (4 and 5) has given 1,3,7-trimethyl-8-phenyl- (6) and 3,7-diethyl-1-methyl-8-phenyl-xanthine (7) respectively. The authors have suggested that initial alkylation occurs at N-3 this being followed by quaternization at N-7 with subsequent loss of the 9-substituent. A noteworthy feature is that the literature shows that 7,9-dialkylxanthine quaternary derivatives are usually obtained either from acid or neutral not alkaline media whereas in these two cases potassium carbonate in excess was initially present during the formation of the 7-alkyl derivatives.

An attempt to effect the N-9 to N-7 rearrangement of the benzyl group of the 9-benzyl-8-benzylthio homologue (8), using the hydrobromide salt, gave largely starting material containing some of the S-debenzylated purine (9).

Although the latter (9) can be readily converted in alkali back to the 8-thiobenzyl derivative (8) the expected 7,9-dibenzyl-8-thioxopurine (10) has not been obtained under more drastic (dimethylformamide under reflux) conditions where N- rather than S-benzylation would be expected to take place.

REFERENCES.

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3. F. Yoneda and T. Nagamatsu, *J.C.S. Perkin I*,1976, 1547.

Received, 5th January, 1977