An unusual reduction path of chloropurine derivatives

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Summary. Reduction of 7- and 9-alkylchloropurines by sodium borohydride in methanol leads to 7,8-dihydropurines without affecting the chlorine atoms.

The classical route to 7-methylpurine involves reduction of 2,6-dichloro-7-methylpurine (**1**) by either Pd/C and H_2, or other reducing agents as HI and phosphorous derivatives[1]. However, yields are low, the working-up of the reaction mixture is tedious and the results are not reproducible. To circumvent these difficulties we sought for some better reducing agents. Usually, halopurines behave very similarly to alkyl halides by being susceptible towards nucleophilic displacements[2]. Since alkyl halides are efficiently reduced by sodium borohydride[3], it was anticipated that the latter reagent would reduce **1** similarly. Surprisingly, the reduction of **1** in boiling methanol took a completely different course to yield (40%) a new purine derivative to which the structure 2,6-dichloro-7-methyl-7,8-dihydropurine (**2**) is assigned on the following grounds:

a) The product (decomposing at about 187 °C after crystallization from benzene) gave a positive Beilstein test and analysed as $C_6H_6N_4Cl_2$[4]. Mass spectrum gave a molecular peak at m/e 205(M^+), i.e. addition of 2 mass units to **1**.

b) Product **2** ($pK_a \simeq 8$) had one ionisable proton and could be reprecipitated by acids from alkaline solutions.

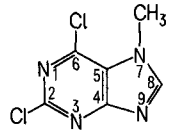
c) UV-spectrum of **2** (λ_{max} 317 nm, log ε 3.8 in MeOH) was similar to the open-chain analogue 4,5-diamino-2,6-dichloropyrimidine[5].

d) PMR in TFA (TMS as internal standard) showed 2 signals at δ 3.25 (s,3,CH_3) and δ 5.25 (s,2,CH_2). The starting purine **1** had (TFA) signals at δ 4.48 (s,3,CH_3) and δ 9.46 (s,1,CH). Thus, upon converting **1** to **2** the N-7 methyl group is shifted upfield indicating that the imidazole ring in **1** has lost its 'aromatic' character[6].

No reduced product was obtained from 2,6-dichloropurine and $NaBH_4$ in MeOH. In this case the purine sodium salt, which was rapidly formed, resisted any further nucleophilic attack of BH_4^-.

In order to explain the nucleophilic attack at C-8 in preference to any other position we have calculated the superdelocalisabilities for nucleophilic attack[7]. By using literature parameters[8] we find C-2 and C-6 to have an average value of 0.615 while C-8 showed the value of 0.716, i.e. more susceptible towards nucleophilic reagents.

Some other 7- and 9-alkyl-chloropurines behaved similarly to **1** upon reduction with BH_4^-. These reactions may open a new entry to the synthesis of compounds otherwise difficult to obtain.



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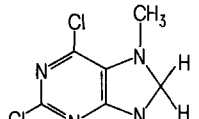

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2 J.H. Lister, in: The Purines, p. 152. Wiley-Interscience, New York 1971.
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4 All compounds gave satisfactory micro-analysis.
5 The dichloropyrimidine had λ_{max} 305 nm (MeOH). A similar difference in the UV-spectrum of a pyrimidine derivative and its 7,8-dihydropurine analogue has been reported previously and rationalized[6].
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Addition of sulphydryl groups to biliverdin

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Summary. Sulphydryl groups add to the central methine bridge of biliverdin in organic solvents as well as in aqueous solution (pH 7.4). The addition reaction is favoured by albumin but reversed in acid media.

Biliverdin (**1**) has long been recognised as the intermediate in the physiological conversion of haem into bilirubin (**2**, X=H)[1-3]. Biliverdin does not occur in normal sera[4] but it can be detected in the serum of patients with biliary obstruction (re-oxidation of bilirubin)[5,6], hepatic disease[5-7] and malnutrition[8]. Reduction of biliverdin to bilirubin has been performed in vitro by a partially purified enzyme from guinea-pig liver[9-11], rat liver and kidney[12], and bovine spleen[13]. Nevertheless, considering the unusually pronounced electron acceptor properties of biliverdin[14,15], the possibility that part of it is reduced in vivo nonenzymatically cannot be excluded a priori. Particularly, one could presume that sulphydryl group-bearing compounds present in body tissues act directly as reductants of biliverdin[16], it being generally accepted (but not proven) that cysteine and glutathione rapidly reduce the green bile pigment[9]. We report here that sulphydryl groups do indeed interact with biliverdin in organic solvents as well as in aqueous solution: in each case examined, however, no bilirubin was formed but an adduct of the type **2** (X=SR).