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THEOPHYLLINE DERIVATIVES 5[1]. SELECTIVE ALTERNATIVE REACTIVITY OF 7-CHLOROMETHYL-OXAZOLOPURINE TOWARDS POTASSIUM PHTALIMIDE

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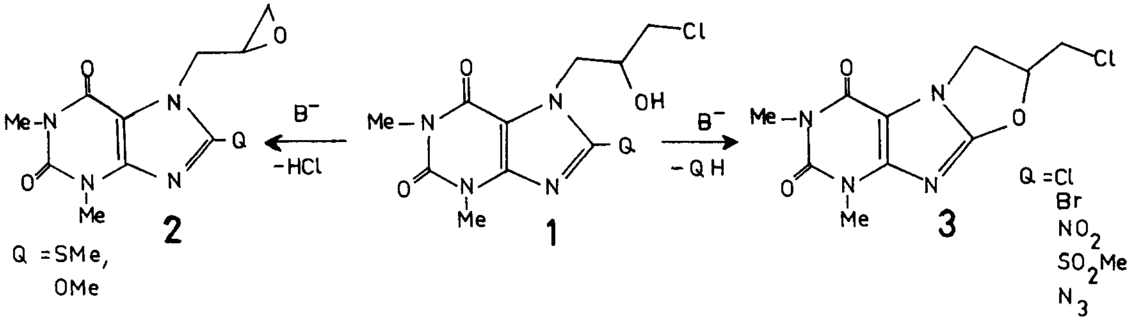
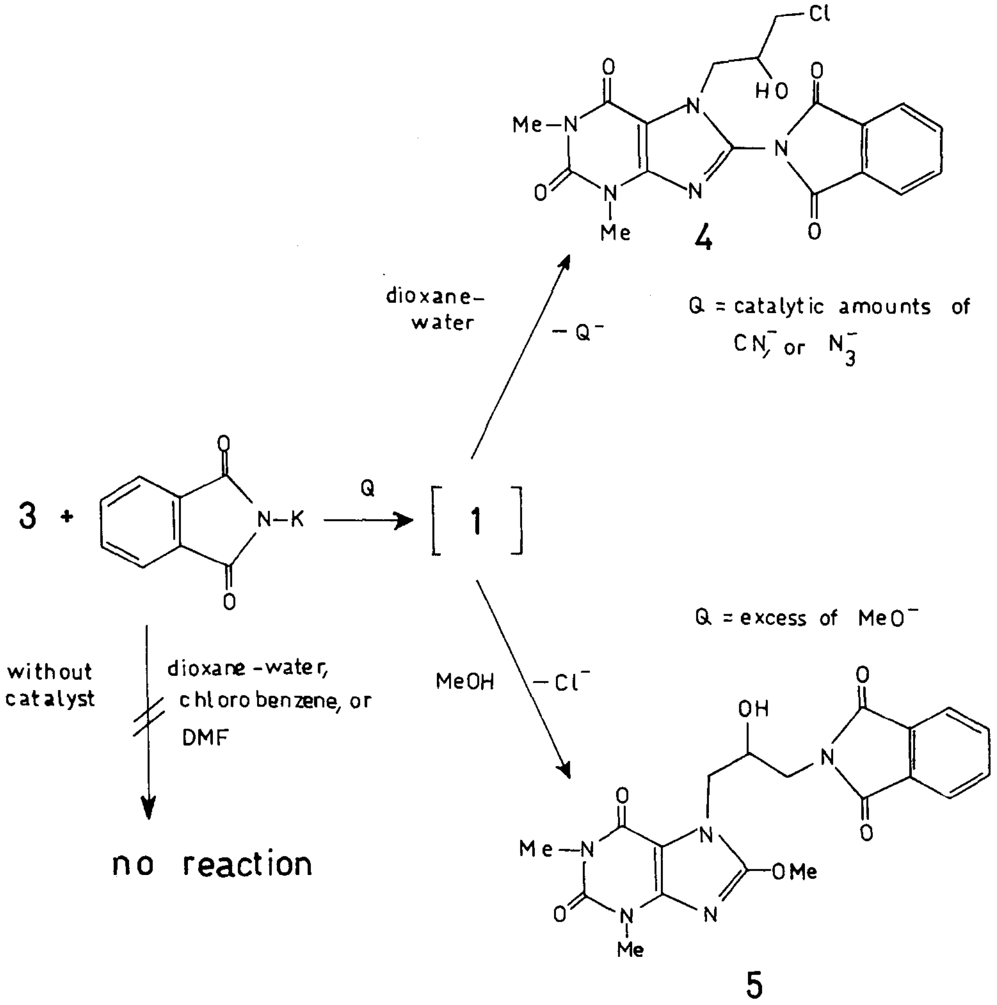
Earlier we have discussed correlation between leaving group properties of C^8 substituents in purines 1 and in the epoxypropyl derivatives 2 and the formation of the chloromethyl-oxazolopurines 3 further exhange of chlorine and the cleavage of the C^9-O^8 bond by various nucleophiles in 3[1,2]. We have established that mobility of chlorine was much restricted by the oxazolidine ring and that of the two electrophilic centers /CH$_2$ of the side chain, C^9 of the tricycle/ coupled with the opening of the oxazolidine ring, first C^9 was substituted[2]. This was in accord with findings of RYBÁR et al.[3] who reported that with 8-substituted 7-halogenoalkyl-theophyllines deactivation of halogen atoms at the C^7 side chain was due to steric hindrance by the C^8 substituents.



Now we have found that both side chain chlorine and oxazoline ring of 3 are remarkably resistent towards potassium phtalimide as nucleophile, a result which can be mainly attributed to steric hindrance. Earlier we have observed[4] that some small and highly nucleophilic anions, e.g. cyanide, which could be also eliminated, catalysed efficiently attack at the C-O bond of heterocyclic ethers. Accordingly when 3 was reacted with potassium phtalimide in the presence of 0.01 molar eq. of KCN or NaN$_3$ the phtalimido-purine 4 was obtained in good yield. An increase of molarity of either the catalyst or of potassium phtalimide did not result in further substitution indicating that in 4 chlorine was also deactivated by the bulky phtalimido group[3].

Transformation 3-4 is presumably initiated by oxazolidine ring opening by CN^- or N_3^- resulting in 1 / Q=CN or N_3 /. Steric hindrance is thus releaved and gives way to substitution of the cyanide or azide group by phtalimide to give a C^8 substituted theophylline. If a small nucleophile capable to cleave the C^9-O^8 bond but not prone to substitution was applied, the deactiviting effect of the oxazoline ring was lifted and chlorine at the side chain could be substituted by phtalimide. In fact reaction of 3 with potassium phtalimide in the presence of excess methoxide gave 5.



References:

1. Part 4. K. Harsányi, R. Szebeni and D. Korbonits, J.prakt.Chem.,317,745 /1975/.
2. R. Szebeni, Ph.D. Thesis, Technical University, Budapest 1976.
3. A. Rybár, L. Stibrányi and M. Uher, Coll.Czeh.Chem.Commun.,37,3936 /1972/
4. D. Korbonits and K. Harsányi, Chem.Ber.,99, 273 /1966/