Reductive Ring Cleavage of Fused Pyrimidin-4(3*H*)-ones

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Summary Fused pyrimidin-4(3*H*)-ones, particularly those with a 3-aryl substituent, readily undergo a ring-cleavage at the 2,3-position on treatment with lithium aluminium hydride.

PYRIMIDINES, quinazolines, pyridopyrimidines, pteridines, and purines are all susceptible to nucleophilic attack at the 2- and 4-positions of the pyrimidine ring. Consequently many of these compounds yield di- and tetra-hydro derivatives when treated with metal hydrides.[1] Fused pyrimidin-4(3*H*)-ones are also known to yield similar compounds,[2] although under certain forcing conditions ring-cleavage of quinazolines[3] and a quinazolinone[4] have been observed. We now report some results of our own studies into the reduction of fused pyrimidin-4(3*H*)-ones which indicate that ring-cleavage is a general reaction of these compounds,

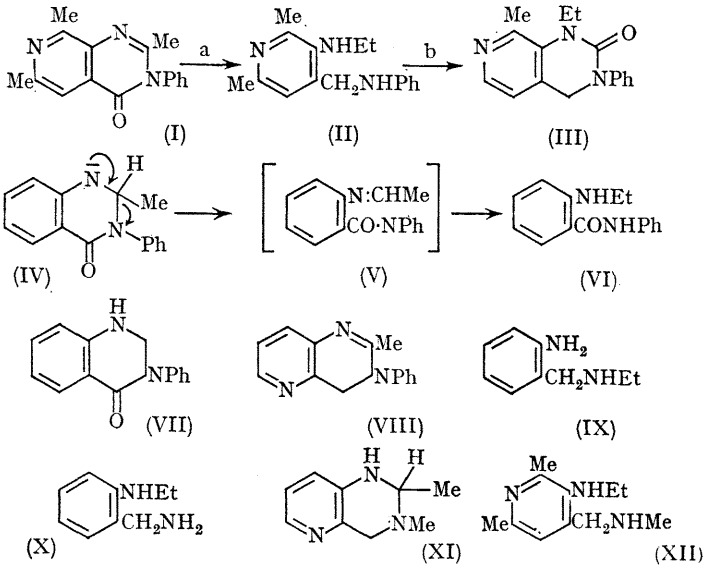
but that the ease and direction of the fission is dependent upon the substituents present in the pyrimidine ring, particularly at N(3).

Treatment of 2,6,8-trimethyl-3-phenylpyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (I) with excess lithium aluminium hydride for 1 hr. at room temperature yielded solely 4-anilinomethyl-2,6-dimethyl-3-ethylaminopyridine (II). The position of fission was proved by infrared (secondary amine absorptions), n.m.r. (presence of NHEt group), and mass spectra of the product. Chemical evidence was also obtained by the preparation of a dibenzoyl derivative, and finally by treatment with phosgene to yield again a pyridopyrimidine (III). 2-Methyl-3-phenylpyrido[3,2-*d*]-pyrimidin-4(3*H*)-one, 2-methyl-3-phenyl-quinazolin-4-(3*H*)-one, and 3-phenylquinazolin-4(3*H*)-one all underwent analogous ring-cleavage at the 2,3-position of the pyrimidine ring to yield the corresponding diamines.

The fused pyrimidin-4(3*H*)-ones have two sites which are susceptible to hydride attack; the endocyclic C=N and the exocyclic C=O. The complete specificity of the above ring-opening reactions indicates that in these examples the initial attack takes place at the C=N, probably producing an intermediate of type (IV) which then undergoes bond cleavage. Support for this view is obtained by the isolation of 2-ethylaminobenzanilide (VI) from a controlled reduction of 2-methyl-3-phenylquinazolin-4(3*H*)-one.

The main factor which controls the ring-cleavage appears to be the phenyl substituent at N(3), presumably by the stabilisation of anions such as (V). Thus, 1,2-dihydro-compounds (VII) and 3,4-dihydro-compounds (VIII) also ring-open in an analogous manner to yield the same diamines as obtained from the corresponding fused pyrimidin-4(3*H*)-ones.

Compounds with no substituent at N(3) also underwent specific ring-opening reactions. However, this occurred less readily than with the 3-phenyl compounds and the 1,2-bond was now the preferred position of cleavage. Thus, 2-methyl-quinazolin-4(3*H*)-one yielded 2-ethylamino-methylaniline (IX) (84%), and 2-aminomethyl-*N*-ethyl-aniline (X) (5%). 2-Methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one, 2-phenylquinazolin-4(3*H*)-one and quinazolin-4(3*H*)-one gave similar products. No doubt several factors are involved in determining the direction of ring-opening in these compounds and it seems likely that reduction of the carbonyl is important as this would be aided by the presence of an N(3) anion. The presence of 2-methyl-3,4-dihydroquinazoline from the mild reduction of 2-methyl-quinazolin-4(3*H*)-one lends weight to this view.



Reagents: (a) $LiAlH_4$; (b) $COCl_2$.

When methyl substituents are present at N(3) there is a marked reluctance for the compounds to undergo ring-cleavage and tetrahydro-derivatives (XI) can be isolated. Under forcing conditions the ring can be induced to open but whereas 2,3,6,8-tetramethylpyrido[3,4-*d*]pyrimidin-4-(3*H*)-one yields 3-ethylamino-2,6-dimethyl-4-methylamino-methylpyridine (XII) 2,3-dimethylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one gives a mixture of 1,2- and 2,3- ring-opened products.

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