

NEW REACTIONS OF 2-BROMOMETHYL-3-PHENYL-4(3H)-QUINAZOLINONE

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Summary: With increase in the reactivity, the amidine carbon becomes more susceptible to nucleophiles. However, for $\bar{C}H_2SOCH_3$ and $AgNO_3$ the $\alpha-CH_2$ group is more activated.

It is wellknown that 2-chloromethyl derivatives of quinazolines and 4(3H)-quinazolinones rearrange to benzodiazepines when treated with $NaOH$ ^{1,2}. However no such report is available on their bromo derivatives. This paper deals with our studies on I and describes some novel reactions observed with this compound while attempting to accomplish such rearrangement.

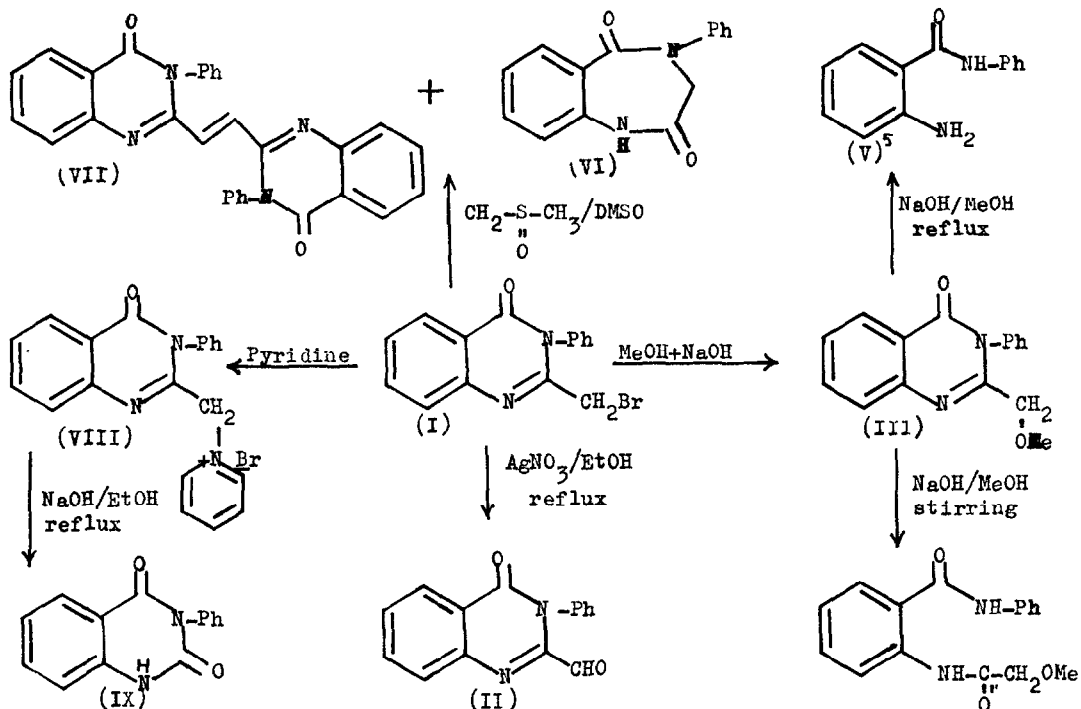
Thus I was found to undergo oxidation with refluxing ethanolic $AgNO_3$ to give II (MS: m/e 250, mp 208³, 75.3%). The IR spectrum of the product obtained by interrupting the reaction showed the involvement of the 2-hydroxymethyl derivative as the intermediate in this transformation.

In another reaction I gave III (mp 109-10, 87.7%)⁴ with methanolic $NaOH$. This compound suffered C_2-N_3 bond cleavage to give IV (mp 181-82, 80.98%) when the above reaction mixture was refluxed for some time. Failure to get VI in this case may reasonably be attributed to the markedly delicate difference in the nature of chloro and bromo substituents. Thus the better leaving ability of the bromo group facilitates its substitution by OMe group rather than attack of the OH ions on the amidine carbon which would have been the case with the chloro derivative.²

When I was treated with $\bar{C}H_2SOCH_3/DMSO$, a mixture of VI (mp. 203-4, 52.4%, IR: $\nu_{C=O}$ 1690 cm^{-1} ; NMR: 3.27, CH_2 ; 5.2, NH) a dimeric product (VII, mp 300³, 10.09%, MS: m/e 468) was obtained. Formation of these products may be visualised as a demonstration of the ambident nature of the DMSO anion which may be considered as existing as (a) and (b) ($CH_3-S-\bar{C}H_2 \leftrightarrow CH_3-S=CH_2$). Thus the attack of (b) causes oxidation of the amidine carbon and that of (a) facilitates the formation of the dimeric product via proton abstraction from the CH_2Br group.

Formation of VI is envisaged as proceeding via oxidation and ring cleavage of the pyrimidine ring followed by ring closure. That the oxidation step involves the oxygen atom of DMSO, by analogy with the mechanism of oxidation of alcohols with $DMSO-DCC$ ⁶, is supported by two observations.

(1) The residue obtained after removal of the excess DMSO under anhyd. conditions gave
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VI only on the addition of some hydroxy solvent (abst. MeOH). (2) To the above residue when, instead of MeOH, a solution of 2-hydroxymethyl-3-phenyl-4(3H)-quinazolinone was added, the oxidised product(II) was obtained in good yield (39.5%).

In yet another observation, VIII gave IX (mp.274-75⁷, 80.10%) on being refluxed with ethanolic NaOH. This transformation appears to proceed by simple nucleophilic displacement of the C₂-substituent by OH ions and tautomerization of the enol thus formed. Whether the C₂-substituent is removed in the form of pyridinium-N-methyl ylid or in some other form is not clear. However, the remarkable feature of this reaction is the increased stability of the C₂-N₃ bond of the pyrimidine ring and preferential cleavage of the C₂-C bond. This is in contrast to our observation in the case of 2-methyl-3-phenyl-4(3H)-quinazolinones bearing electron withdrawing substituents like alkoxy, bromo and dibromo at the methyl group, which frequently suffered C₂-N₃ bond cleavage to give open amides with mild bases.

Summary: With increase in the reactivity, the amidine carbon becomes more susceptible to nucleophiles. However, for CH_2SOCH_3 and AgNO_3 the $\alpha\text{-CH}_2$ group is more activated.

References & Notes

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