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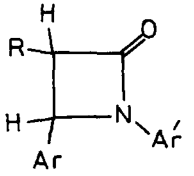
REARRANGEMENTS OF TRANS-3-CHLORO-1,4-DIARYL-2-AZETIDINONES IN CONCENTRATED SULPHURIC AND IN POLYPHOSPHORIC ACID

Derek Johnson and Hans Suschitzky*
The Ramage Laboratories, Department of Chemistry and Applied Chemistry,
University of Salford, Salford M5 4WT.

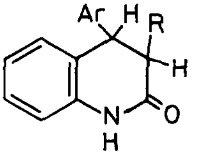
The isomerisation of 1,4-diaryl-2-azetidinones in cold concentrated sulphuric acid to give the corresponding 3,4-dihydro-4-arylquinolin-2(1H)-ones (e.g. 1a → 2a) was first reported by Knunyants and Gambaryan[1] and the results were recently confirmed and extended[2].

We have found that the chloro-compounds (1b) behave analogously in cold concentrated sulphuric acid or in polyphosphoric acid (PPA) at 78° to give the expected 4-aryldihydroquinolinones (2b), but at higher temperatures in PPA isomerisation is accompanied by loss of hydrogen chloride, and in some cases followed by aryl migration to give 3-aryl-quinolin-2(1H)-ones (4). For instance, treatment of <u>trans</u>-3-chloro-1,4-diphenyl-2-azetidinone[3] (1b, Ar=Ar'=Ph) with PPA at 140° gave with evolution of hydrogen chloride, a white solid (70%) of m.p. 230°. Its analytical and spectral data corresponded to a phenylquinolinone (e.g. 3, Ar=Ph), i.e. isomerisation appeared to have been followed by loss of hydrogen chloride. However, comparison (m.p. and spectra) with authentic 3-phenyl-[4] and 4-phenyl-quinolin-2(1H)-one[5] showed the product to be the 3-phenyl isomer (4, Ar=Ph). Since in cold concentrated sulphuric acid or PPA at 78°, <u>trans</u>-3-chloro-3,4-dihydro-4-phenylquinolin-2(1H)-one* (2b, Ar=Ph) was isolated, phenyl migration could not have occurred during fission of the azetidinone nor during the subsequent cyclisation to the 4-aryldihydroquinolone. Treatment of the 3-chloro-3,4-dihydroquinolinone (2b) with ethanolic potassium hydroxide resulted in dehydrochlorination without phenyl migration to give 4-phenylquinolin-2(1H)-one (3, Ar=Ph) identical with the authentic sample. Moreover, the 4-phenylquinolin-2(1H)-one (3, Ar=Ph) does not isomerise to the 3-phenylquinolin-2(1H)-one (4, Ar=Ph) under the reaction conditions (i.e. PPA at 78°). However, treatment of <u>trans</u>-3-chloro-3,4-dihydro-4-phenylquinolin-2(1H)-one (2b, Ar=Ph) with PPA at 140° gave the 3-phenylquinolin-2(1H)-one (4) in high yield. Phenyl migration thus takes place during the dehydrochlorination step by hot PPA but high boiling solvents (xylene, diglyme or acetic anhydride) have no effect.

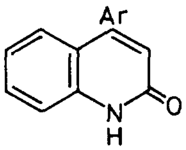
We envisage that this novel aryl migration involves participation of the aryl ring as a "phenonium ion" (cf. scheme). In keeping with this suggestion we found that the azetidinone (1b) in which the 4-phenyl group was replaced by p-MeOC$_6$H$_4$- or p-MeC$_6$H$_4$- rearranged in higher yield (88 and 79% respectively) and at lower temperature (110^0) to give the 3-arylquinolones (4, Ar=p-MeOC$_6$H$_4$ or p-MeC$_6$H$_4$). The milder reaction conditions are consistent with the migratory aptitudes of the substituents decreasing in the order MeOC$_6$H$_4$ > MeC$_6$H$_4$ > Ph, which is reminiscent of the formally related carbonium ion rearrangements[5].



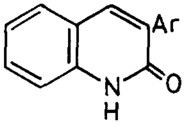
(1) a) R = H
b) R = Cl



(2)



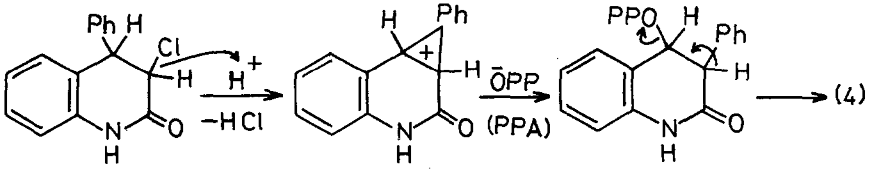
(3)



(4)

p-MeO C$_6$ H$_4$ CH:CClCONHPh

(5)



Scheme

The mode of the azetidinone fission was further elucidated when on heating (1b, Ar=4-MeO-C_6H_4-, Ar'=Ph) in PPA at 78° we obtained instead of the expected 3-chloro-quinolin-2(1H)-one (2b, Ar=p-MeOC_6H_4) the p-methoxy-α-chloro-cinnamanilide (5), which at higher temperature cyclised with loss of hydrogen chloride to 3-(4-methoxyphenyl)-quinolin-2(1H)-one (4, Ar=p-MeO-C_6H_4-). This observation confirms Knunyant's suggestion that isomerisation of azetidinones involves cinnamanilide derivatives as intermediates (e.g. 1b → 5 → 4). Similarly, we isolated p-methyl-α-chloro-cinnamanilide (5, p-MeO=Me) from the trans-3-chloro-azetidinone (1b, Ar=p-MeC_6H_4, Ar'=Ph) in PPA at 78° which gave the appropriate 3-quinolin-2(1H)-one (4, Ar=p-Me-C_6H_4) on further warming in hot PPA. Thus PPA treatment of 2-azetidinones of type (1b) produces unstable 4-aryl-3-chlorodihydroquinolinones (2b) which can be made to rearrange to 3-arylquinolinones (4) with loss of hydrogen chloride (e.g. 2b → 4).

The very low yields (2-7%) in the preparation of 2-azetidinones with electron withdrawing groups in the 4-aryl ring made isomerisation studies of this reaction impracticable. Hot acetic or trifluoroacetic acid or acetic anhydride had no effect on the 2-azetidinones (1b). The presence of a hydrogen at the 3-position of the azetidinone (1b) appears to be a prerequesite for its isomerisation since 3,3-dimethyl-1,4-diphenyl-2-azetidinone gave the anilide of isobutyric acid and not the corresponding dihydroquinoline when treated with hot PPA or concentrated sulphuric acid at 0° whereas trans-3-methyl-1,4-diphenyl-2-azetidinone (1, R=Me, Ar=Ar'=Ph) gave the expected 3-methyl-3,4-dihydro-4-phenylquinolin-2(1H)-one (2, R=Me, Ar=Ph) under similar conditions. Recently, Indian workers[7] have observed phenyl migration in the Pictet-Gams synthesis of isoquinolines leading to 4-phenyl and not the expected 3-phenylisoquinoline, which could be interpreted by a mechanism analogous to our scheme.

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* All new compounds had correct analyses and spectral data.