# Reinvestigation by Carbon-13 NMR Spectroscopy of the Aluminium Chloride catalysed Cyclisation of Methyl-substituted β-Chloropropionanilides to 3,4-Dihydroquinolin-2(1*H*)-ones

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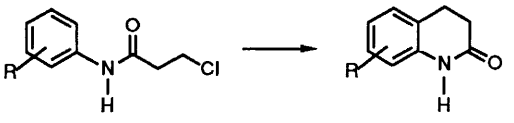
Aluminium chloride-catalysed cyclisation of methyl-substituted β-chloropropionanilides occurs *via* kinetically controlled intramolecular Friedel–Crafts cyclisation to give 3,4-dihydroquinolin-2(1*H*)-ones. In the case of the *ortho*-methylanilide, *ipso* attack is not much slower than attack at the free *ortho*-position, resulting in a mixture of both the expected 8-methyl isomer and the 5-isomer, the latter resulting from a 1,2-methyl shift *during cyclisation*. The anomalous results reported by earlier workers for the *meta*- and *para*-methylanilides are due to partial equilibration of the primary cyclisation products, brought about by excessively harsh reaction conditions and inadvertent selective crystallisation of one pure product or of mixed products from mixtures containing all four possible products.

The aluminium chloride-catalysed cyclisation of ring-substituted β-chloropropionanilides and β-chloro-3-methylpropionanilides, first reported by Mayer and co-workers[1] some sixty years ago, constitutes a useful synthesis[2] of 3,4-dihydroquinolin-2(1*H*)-ones carrying alkyl, chloro or hydroxy substituents on the aromatic ring or an alkyl substituent on the nitrogen. The precursor anilides are easily prepared in high yield from readily available starting materials and the cyclisation itself has been reported to proceed in yields ranging from 55% to quantitative.



The usefulness of the Mayer procedure has since been thrown into some doubt as a result of the work of Kametani and co-workers[3] who reported that (*a*) 3-chloro-*N*-(4-methylphenyl)propionamide gave only 7-methyl-3,4-dihydroquinolin-2(1*H*)-one rather than the expected 6-isomer; (*b*) 3-chloro-*N*-(3-methylphenyl)propionamide also gave only 7-methyl-3,4-dihydroquinolin-2(1*H*)-one rather than the mixture of the 5-and 7-isomers reported by Mayer;[1] (*c*) 3-chloro-*N*-(2-methylphenyl)-propionamide gave a mixture of 5-methyl- and 8-methyl-3,4-dihydroquinolin-2(1*H*)-one rather than only the expected 8-isomer.

Moreover, some doubt as to the reality or otherwise of the methyl shifts derives from the work of Johnston and co-workers,[4] who reported that methyl shifts did *not* occur during or after the cyclisation of methyl-substituted cinnamanilides under apparently similar reaction conditions to give the corresponding quinolin-2(1*H*)-ones. The uncertainty is compounded by the lack of satisfactory agreement between the various reported melting points for the isomeric products (Table 1) and the almost identical melting points reported by Kametani for both the 5- and 7-isomers *and* the 6- and 8-isomers.

## Results and Discussion

We had no doubts concerning the identity of 7-methyl-3,4-dihydroquinolin-2(1*H*)-one; it had previously been prepared unambiguously by Sidhu and co-workers[5] by reductive cyclisation of 4-methyl-2-nitrocinnamic acid and by Kametani[3b] by catalytic hydrogenation of 7-methylquinolin-2(1*H*)-one. The latter was prepared by rearrangement of 7-methylquinoline *N*-oxide, derived from 7-methylquinoline. The reported melting points of the compound prepared by the two routes were identical. The 5- and 8-isomers had also been prepared by Kametani[3a] by the same method.

In view of the poor overall yields and the discrepancies in reported melting points (Table 1) it was necessary to confirm the melting points of these isomers independently. We therefore prepared authentic samples of the 6- and 8-isomers by catalytic hydrogenation of the corresponding 2-quinolones, the identity of which had been established unambiguously by Buchardt and co-workers,[6] who prepared them by photolysis of the corresponding quinoline *N*-oxides. Our melting points are somewhat higher than those reported by Kametani but not so much as to suggest any errors of identification on his part.

We also isolated a pure sample of the 5-isomer by fractional crystallisation of the products of cyclisation of 3-chloro-*N*-(2-methylphenyl)propionamide. Its $^1$H NMR spectrum, like that of the 8-isomer, showed the presence of three adjacent aromatic hydrogens.

$^{13}$C NMR shifts‡ (Table 2) for the primary, secondary, tertiary, quaternary and carbonyl carbon atoms of 5-, 6- and 8-methyl-3,4-dihydroquinolin-2(1*H*)-one were measured in [$^2H_6$]DMSO. Chemical shifts for the 7-isomer were extracted from the spectrum of the mixture obtained on cyclising 3-chloro-*N*-(3-methylphenyl)propionamide (*vide infra*).

The *ortho*-, *meta*- and *para*-methyl-substituted 3-chloro-*N*-phenylpropionamides were then cyclised by heating with two molar equivalents of anhydrous aluminium chloride for 15 min at 100 °C. The yields of crude products were essentially quantitative.

The results of analysis of the total reaction mixtures by $^{13}$C NMR spectroscopy (Table 3) are as follows. (*a*) The *para*-substituted anilide initially gave mainly 6-methyl-3,4-dihydroquinolin-2(1*H*)-one as reported by Mayer (although his compound was in fact a mixture—*vide infra*) and contrary to Kametani. (*b*) The *meta*-substituted anilide initially gave mainly 5- and 7-methyl-3,4-dihydroquinolin-2(1*H*)-one as reported by Mayer (although one of his products was in fact a mixture—*vide*

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‡ The assignment of the $^{13}$C and $^1$H chemical shifts for all four isomers forms the subject of a subsequent paper.

**Table 1** Reported melting points of methyl-substituted 3,4-dihydroquinolin-2(1*H*)-ones

| Isomer | Source | M.p./°C | Isomer | Source | M.p./°C |
|---|---|---|---|---|---|
| 5-Me | Mayer[a] | 131 or 160 | 7-Me | Mayer[a] | 160 or 131 |
| | Kametani[b] | 162–163 | | Sidhu[f] | 162–163 |
| | This work | 167–168 | | Kametani[g] | 160–161 |
| 6-Me | Mayer[a] | 106 | 8-Me | Mayer[a] | 112 |
| | Kametani[c] | 131.5–132.5 | | Kametani[b] | 131–132 |
| | Henze[d] | 114–115 | | This work | 135.5–136.5 |
| | Bubnovskaya[e] | 124–125 | | | |
| | This work | 134.5–135.5 | | | |

[a] Ref. 1. [b] Ref. 3*a*. [c] Ref. 3*c*. [d] By decarboxylation of the corresponding 4-carboxylic acid (H. R. Henze and C. M. Blair, *J. Am. Chem. Soc.*, 1933, **55**, 4621). [e] By Mayer method [V. N. Bubnovskaya, V. S. Shvarts and F. S. Babichev, *Ukr. Khim. Zh.* (*Russ. Ed.*), 1967, **33**, 924; *Sov. Prog. Chem.* (*Eng. Transl.*), 1967, **33** (9), 41]. [f] Ref. 5. [g] Ref. 3*b*.

**Table 2** $^{13}C$ NMR shifts (ppm relative to TMS) for methyl-substituted 3,4-dihydroquinolin-2(1*H*)-ones in [$^2H_6$]DMSO

| Carbon | 5-Me | 6-Me | 7-Me | 8-Me |
|---|---|---|---|---|
| Carbonyl | 169.87 | 170.02 | 170.04 | 170.79 |
| Quaternary | 138.14 | 135.80 | 138.14 | 136.37 |
| | 135.29 | 130.64 | 136.17 | 124.37 |
| | 121.72 | 123.32 | 120.45 | 123.52 |
| Tertiary | 126.51 | 128.19 | 127.48 | 128.76 |
| | 123.60 | 127.33 | 122.48 | 125.37 |
| | 113.00 | 114.83 | 115.47 | 121.86 |
| Secondary | 29.97 | 30.47 | 30.59 | 30.72 |
| | 21.39 | 24.79 | 24.41 | 25.29 |
| Methyl | 18.90 | 20.26 | 20.73 | 17.18 |

**Table 3** Typical analysis by $^{13}C$ NMR spectroscopy of mixed methyl-substituted 3,4-dihydroquinolin-2(1*H*)-ones in [$^2H_6$]DMSO

| Nucleus | δ | Intensity | Percent[a] | Isomer |
|---|---|---|---|---|
| $CH_3$– | 17.139 | 3.659 | 16.5 | 8-Me |
| | 18.927 | 4.249 | 19.2 | 5-Me |
| | 20.270 | 6.958 | 31.4 | 6-Me |
| | 20.734 | 7.296 | 32.9 | 7-Me |
| 4-$CH_2$– | 21.444 | −5.268 | 20.1 | 5-Me |
| | 24.406 | −8.212 | 31.3 | 7-Me |
| | 24.804 | −8.867 | 33.8 | 6-Me |
| | 25.269 | −3.907 | 14.9 | 8-Me |
| 3-$CH_2$– | 30.018 | −5.509 | 20.1 | 5-Me |
| | 30.479 | −8.809 | 32.4 | 6-Me |
| | 30.594 | −9.048 | 33.0 | 7-Me |
| | 30.683 | −3.948 | 14.4 | 8-Me |

[a] Averages calculated from $^{13}C$ intensities of methyl and both methylene groups, assuming relaxation times constant within a group. Estimated uncertainty < 2%.

*infra*) and contrary to Kametani. (*c*) The *ortho*-substituted anilide initially gave mainly 5- and 8-methyl-3,4-dihydroquinolin-2(1*H*)-one as reported by Kametani rather than just the 5-isomer as reported by Mayer.

In each case detectable amounts of the isomers expected from a single 1,2-methyl shift to or from the 5-, 6- and 7- (but not the 8-) positions are formed; there was no evidence of intermolecular methyl migration. These results are consistent with kinetically controlled cyclisation, with *ipso*-attack at the methyl-carrying carbon of the *ortho*-substituted anilide not much slower than attack at the other *ortho*-position, followed by a much slower rearrangement of the primary cyclisation products.

The use of harsher reaction conditions leads to considerable changes in the product isomer composition, consistent only with at least partial equilibration of the initially formed aluminium chloride complexes. For example, cyclisation of the *para*-toluidide with five molar equivalents of aluminium chloride for 4 h at 140 °C gave the following isomer distribution: 5-Me, 20%; 6-Me, 32%; 7-Me, 32%; 8-Me, 16%. On the other hand, the use of 1.1 molar equivalents of aluminium chloride at 140 °C for 24 h gave only the 6-isomer, with 20% recovered starting material and no detectable rearrangement products.

It is thus clear that the anomalous results obtained by Kametani are *not* consequent upon any special mechanism of cyclisation. They are entirely explicable in terms of excessively harsh reaction conditions leading to subsequent rearrangement of the initially formed aluminium chloride complexes and to inadvertent fractional crystallisation of the 7-isomer from mixtures containing all four isomers. Moreover, it is clear that all of Mayer's compounds, other than possibly the 7-isomer, were in fact mixtures.

The mechanism proposed by Kametani [3*b*] to account for the formation of 7-methyl-3,4-dihydroquinolin-2(1*H*)-one from 3-chloro-*N*-(4-methylphenyl)propionamide is therefore unnecessary and incorrect. Apart from the fact that both the starting material and product are almost certainly present as their aluminium chloride complexes, no methyl shift to the 7-position occurs during cyclisation. Moreover, even if such a shift had taken place, a mechanism involving the interconversion of two vinylic carbocations in a cyclohexadienoid system would hardly seem probable.

The implications of our results concerning the utility of the reaction for preparative purposes are quite simple. 6-Alkyl-3,4-dihydroquinolin-2(1*H*)-ones should be readily preparable from the corresponding *para*-substituted β-chloropropionanilides by using only a slight excess of aluminium chloride and correspondingly extended reaction times. Cyclisation of the *ortho*- and *meta*-alkyl-substituted compounds will, even at the best of times, lead to a mixture of two isomers which may or may not be easily separable.

## Experimental

Proton and Carbon-13 NMR spectra were run in [$^2H_6$]DMSO using a Bruker AC200 Fourier Transform spectrometer. Chemical shifts were measured relative to DMSO or internal TMS and are reported relative to TMS.

Authentic samples of 6- and 8-methyl-3,4-dihydroquinolin-2(1*H*)-one were prepared by hydrogenation of the corresponding 2-quinolones in ethanol over 10% palladium on charcoal

and recrystallised from aqueous ethanol (5-methyl, m.p. 167–168 °C (lit.,[3a] 162–163 °C); 6-methyl, m.p. 135.5–136.0 °C (lit.,[3c] 131.5–132.5 °C); 8-methyl, m.p. 135.5–136.5 °C (lit.,[3a] 131–132 °C).

3-Chloro-*N*-(2-, 3- and 4-methylphenyl)propionamides were prepared from the corresponding toluidines and β-chloropropionyl chloride in acetone containing pyridine and recrystallised from aqueous ethanol (2-methyl, m.p. 81–82 °C (lit.,[3a] 79–80 °C); 3-methyl, m.p. 89–90 °C (lit.,[1] 90 °C); 4-methyl, m.p. 121–122 °C (lit.,[1] 121 °C). They were shown by $^1$H and $^{13}$C NMR spectroscopy to be free of detectable isomers.

Aluminium chloride ('wasserfrei sublimiert zur Synthese') was obtained from Merck-Schuchardt. The cyclisation procedure used was essentially that of Mayer[1] and Kametani.[3] The mixture was heated and stirred in an oil bath to effect cyclisation. It was then treated with dilute HCl to hydrolyse the aluminium complexes, extracted with dichloromethane and the extract dried over sodium sulfate and evaporated to dryness. Yields of crude products were essentially quantitative.

Product compositions were calculated from $^{13}$C NMR line intensities. These were routinely determined from spectra obtained by the J-modulated spin-echo mode using the Bruker JMODXH.AU program. The validity of the results was checked in selected cases from spectra obtained by the more time intensive inverse-gated heteronuclear mode and program INVGATE.AU.

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