HYDROLYSIS OF 4-AMINO-3-QUINOLINESULFONAMIDES *

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Abstract - Acid hydrolysis of 4-amino-3-quinolinesulfonamides (**3**) gives 1,4-dihydro-4-oxo-3-quinolinesulfonamides (**4**), 4-aminoquinolines (**5**) or a mixture of these compounds.

INTRODUCTION

The discovery of quinolones as antibacterial agents has prompted research directed towards the synthesis of analogs with optimized pharmacological properties.[1] In order to obtain highly water-soluble quinolone antibiotics some structure modifications have been made, for example exchanging the 3-carboxyl group to a sulfonate one.[2]

1,4-Dihydro-4-oxo-3-quinolinesulfonamides (**4**) are hypotensive agents.[3] One method providing these compounds is acid hydrolysis of 4-chloro-3-quinolinesulfonamides (**2**) performed in refluxing azeotropic solution of hydrochloric acid.[4] On the other hand aminolysis of 4-chloro-3-quinolinesulfonyl chloride (**1**) gave more 4-amino-3-quinolinesulfonamides (**3**) than 4-chloro-3-quinolinesulfonamides (**2**).[5] The aim of this work has been to test if it would be possible to obtain the aforementioned quinolinones (**4**) starting from 4-amino-3-quinolinesulfonamides (**3**) instead of 4-chloro compounds (**2**).

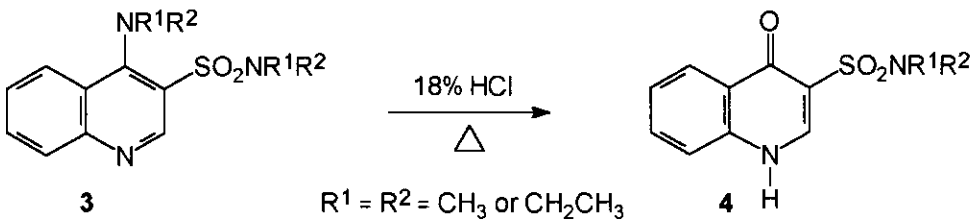
Hydrolysis of 2- and 4-aminopyridines or quinolines to give respective pyridones and quinolinones proceeds rather reluctantly. Consequently, such reactions are very seldom reported in the literature.[6] Usually pyridones or quinolinones are synthesized from chloropyridines or chloroquinolines which are readily available.[7] If reacted, however, 2- and 4-aminopyridines and quinolines demand severe conditions of reaction during both acidic and basic hydrolysis, e.g. 70% sulfuric acid at 100 °C.[8] In order to increase the susceptibility of 2- and 4-aminopyridines or quinolines to nucleophilic attack of the hydroxyl anion these compounds were transformed into pyridinium or quinolinium salts.[6,7]

RESULTS AND DISCUSSION

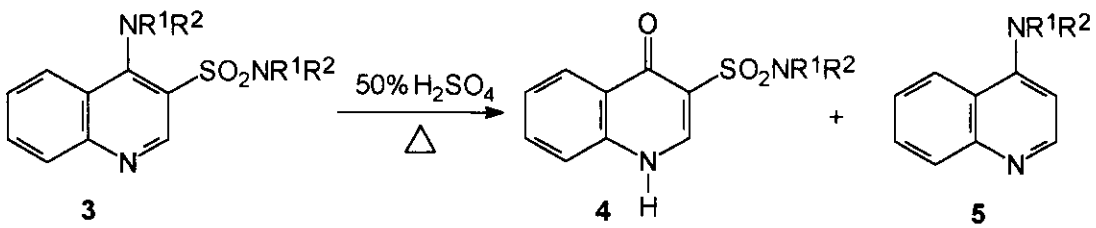
Although amino groups are not regarded as good leaving groups in aromatic nucleophilic substitution

(S_NAr) we found that amino groups are readily replaced with the hydroxyl group. Hydrolysis of 4-amino-3-quinolinesulfonamides (**3**) was performed as reported for the chloro analogs (**2**).[4] The duration of the reaction taking place in 18% hydrochloric acid was increased from 0.5 to 3 h. As expected 1,4-dihydro-4-oxo-3-quinolinesulfonamides (**4**) were formed from *N,N*-dialkylsubstituted 4-amino-3-quinolinesulfonamides (**3d**) and (**3e**). Methyl and phenyl substituted compounds (**3a**) and (**3c**) failed to react and unreacted substrates were isolated from the reaction mixtures.

The method used enables to obtain *N,N*-disubstituted quinolonesulfonamides (**4**) in a following sequence of reactions: sulfochloride (**1**) → aminosulfonamide (**3**) → quinolone (**4**). The overall yields for such a sequence are much higher than for the one including chlorosulfonamide (**2**), e.g., the overall yield of **4d** amounts to 74% for our method, in comparison to only 22% for the reactions reported earlier.[4,5]



Hydrolysis of 4-amino-3-quinolinesulfonamides (**3**) was performed in the refluxing 50% sulfuric acid. 4-Aminoquinolones (**5**) or the mixtures of 1,4-dihydro-4-oxo-3-quinolinesulfonamides (**4**) and 4-aminoquinolines (**5**) were formed in these reactions. The mixtures can be easily separated.

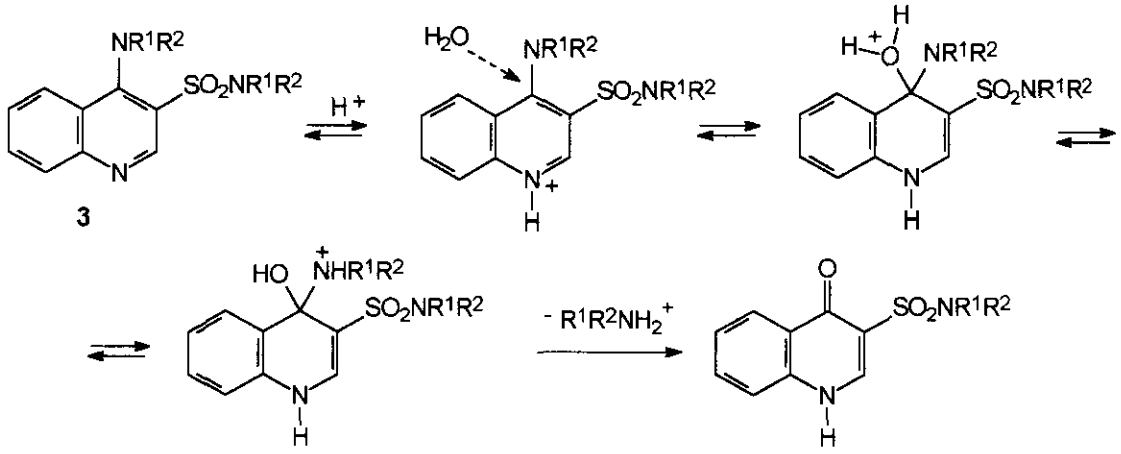


The results indicate that heating 4-amino-3-quinolinesulfonamides (**3**) in refluxing 50% sulfuric acid causes hydrolysis of the 4-amino group, which is accompanied by competing desulfonation in the 3-position of quinoline ring. Desulfonation but not the hydrolysis of the 4-amino group proceeds for the primary aliphatic amines (**3a**) and (**3b**).

Table 1

Substrates **3**			Yields of **4**		Yields of **5**	
	R^1	R^2		(%)		(%)
3a	H	CH_3	**4a**	0	**5a**	61
3b	H	CH_2CH_3	**4b**	0	**5b**	52
3c	H	Ph	No reaction			
3d	CH_3	CH_3	**4d**	23	**5d**	44
3e	CH_2CH_3	CH_2CH_3	**4e**	42	**5e**	16
3f	$CH_2CH_2OCH_2CH_2$		**4f**	75	**5f**	12
3g	$CH_2CH_2CH_2CH_2CH_2$		**4g**	49	**5g**	31

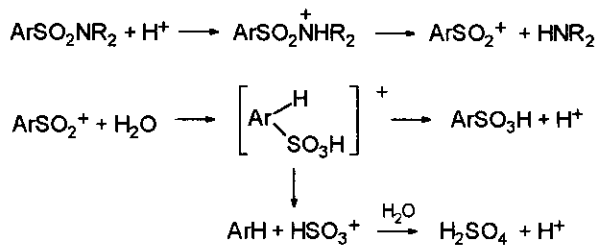
Following mechanism can be proposed for the hydrolysis of 4-amino group:



A question appeared, however, why *N*-monosubstituted 4-amino-3-quinolinesulfonamides do not hydrolyze but undergo desulfonation. The mechanism shown does not provide answer to this question directly, but it seems that the lower basicity of 4-*N*-monosubstituted amine group, in particular 4-aniline one, in comparison to *N,N*-dialkylsubstituted groups should be considered as an important factor. This fact can be explained also by the different leaving ability of the $-NHR^1R^2$, $-NH_2R$ and $-OH_2$ groups. Therefore, the sequence: $R^1R^2NH_2^+ > H_3O^+ > RNH_3^+$ explains the observed reactivity of the Meisenheimer's complex.

The reactivity of primary and secondary amines in nucleophilic substitution agrees with that reported by Sekiguchi *et al.* for transamination of aminodinitronaphthalenes,[9,10] but not for the one observed in reactions based on the reversed Bucherer mechanism.[11] Such reactions, however, do not proceed *via* Meisenheimer's complex and their mechanism can be seen as a sum of substitution and addition.[11]

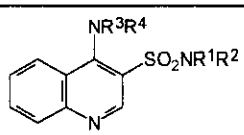
Hydro-desulfonamidation is probably a two-step reaction starting from the hydrolysis of sulfonamide to sulfonic acid followed by desulfonation of the sulfonic group. It was observed earlier[12] that desulfonation of 4-amino-3-quinolinesulfonic acids proceeds easily yielding 4-aminoquinolines. Desulfonation can also follow hydrolysis of sulfonamide during the reaction of sulfonylonium ion with water:[13]



On the other hand, desulfonation does not take place in 18% hydrochloric acid which seems to prove that hydrolysis of sulfonamide group does not occur under these conditions.

The reaction discussed does not proceed for compound (**3c**), which has aniline groups both in the position 4 and in the sulfonamide moiety. This suggests that the aniline group disables desulfonation in the position 3. In order to determine which aniline group has the influence on the reactivity towards hydrolysis and desulfonation we studied the reactions of nonsymmetrical 4-amino-3-quinolinosulfonamides (**3**) (obtained according to [ref.5]). The results are given in Table 2.

Table 2.

	 **3**				Yield of **4**		Yield of **5**	
	R^1	R^2	R^3	R^4		(%)		(%)
3h	H	Ph	H	CH_3	**4c**	0	**5a**	77*
3i	H	CH_3	H	Ph	No reaction			
3j	CH_3	CH_3	H	Ph	No reaction			

* Aniline (80%) was isolated

Aniline isolated after reaction of compound (**3h**) proved indirectly that desulfonation must follow hydrolysis which takes place first. Compound (**3h**) with the methylamino group in the position 4 and sulfonanilide group in the position 3 affords such a possibility. On the contrary, 4-anilino-3-quinoline-sulfamides (**3i**) and (**3j**) did not react. It seems that the steric factor of 4-aniline group has influence on the hydrolysis and desulfonation of the sulfonamide group.

It is possible that 1,4-dihydro-4-oxo-3-quinolinesulfonamides (**4**) formed in these reactions can also be

hydrolyzed to 1,4-dihydro-4-oxo-3-quinolinesulfonic acid or further to 4(1*H*)-quinolinone after desulfonation. A reaction of 4-methylamino-*N*-methyl-3-quinolinesulfonamide (**3a**) in diluted sulfuric acid was performed and the resulted mixture was extracted continuously with chloroform for 6 h to prove that fact. After evaporation of the solvent we found 1,4-dihydro-*N*-methyl-4-oxo-3-quinolinesulfonamide (**4a**) in only *ca.* 5% yield. This fact proves that hydrolysis of the 4-monoalkylamino groups is possible, but proceeds much more reluctantly than in the case of the 4-dialkylamino groups. It can also suggest that, under conditions studied, quinolones (**4**) do not hydrolyze and desulfonate. This supposition was proved by heating 1,4-dihydro-*N,N*-dimethyl-4-oxo-3-quinolinesulfonamide (**4d**) in 50% aqueous solution of sulfuric acid for 9 h. Unreacted substrate (92%) was isolated from the reaction mixture.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius mp apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker MSL 300 (300 MHz) spectrometer with tetramethylsilane as the internal standard. Chemical shifts are reported in ppm (δ) and *J* values in Hz. EIMS were run on a LKB GC 2091 spectrometer at 70 eV and 15 eV.

Hydrolysis of *N,N*-disubstituted 4-amino-3-quinolinesulfonamides (**3d**) and (**3e**) in 18% hydrochloric acid:

The solution of 4-amino-3-quinolinesulfonamide (**3d**) or (**3e**) (2 mmol) in 10 mL of 18% hydrochloric acid was refluxed for 3 h. After cooling the precipitate formed was filtered off, washed with 3 mL of 5% aqueous solution of sodium hydrogen carbonate and 10 mL of water. Crude quinolones (**4d**) and (**4e**) were dried on air and recrystallized from 70% aqueous ethanol. This procedure gave: 1,4-dihydro-*N,N*-dimethyl-4-oxo-3-quinolinesulfonamide (**4d**) (80%), mp 287-288 °C lit.,[4] mp 287-289 °C and 1,4-dihydro-*N,N*-diethyl-4-oxo-3-quinolinesulfonamide (**4e**) (76%), mp 272-273 °C, lit.,[4] mp 271-273 °C.

Hydrolysis of *N,N*-disubstituted 4-amino-3-quinolinesulfonamides (**3d** - **3g**) in 50% sulfuric acid.

The solution of 4-amino-3-quinolinesulfonamide (**3d** - **3g**) (2 mmol) in 10 mL of 50% aqueous sulfuric acid was refluxed for 5 h. After cooling the precipitate was filtered off, washed with 5 mL of 5% aqueous solution of sodium hydroxide and 5 mL of water. Crude 1,4-dihydro-4-oxo-3-quinolinesulfonamide (**4d** - **4g**) formed were recrystalized from ethanol or mixtures of water and ethanol. This procedure gave: 1,4-dihydro-*N,N*-dimethyl-4-oxo-3-quinolinesulfonamide. (**4d**) (23%), mp 287-288 °C, lit.,[4] mp 287-289 °C, 1,4-dihydro-*N,N*-diethyl-4-oxo-3-quinolinesulfonamide (**4e**) (42%), mp 270-271 °C, lit.,[4] mp 271-273 °C, 1,4-dihydro-4-oxo-3-quinolinesulfonemorpholide (**4f**) (75%), mp 298-300 °C (decomp), lit.,[4] mp 297-298 °C, 1,4-dihydro-4-oxo-3-quinolinesulfonepiperidide (**4g**) (49%), mp 295-297 °C (decomp), lit.,[4] mp 295-297 °C.

The solution of sulfuric acid was alkalized with 10% aqueous sodium hydroxide and extracted with

chloroform (2 x 5 mL). Crude 4-aminoquinolines (**5d** - **5g**), after the evaporation of solvent under vaccum, were purified by extraction with boiling hexane. This procedure gave: 4-dimethylaminoquinoline (**5d**) (44%), oil, lit.,[12] oil, 4-diethylaminoquinoline (**5e**) (16%), oil, lit.,[12] oil, 4-morpholinoquinoline (**5f**) (12%), mp 77-79 °C, lit.,[12] 78-80 °C and 4-piperidinoquinoline (**5g**) (31%), mp 84-86 °C, lit.,[14] 84 °C.

Hydrolysis of *N*-monosubstituted 4-amino-3-quinolinesulfonamides (**3a**, **3b** and **3h**) in 50% sulfuric acid.

The solution of 4-amino-3-quinolinesulfonamide (**3a**, **3b** or **3h**) (2 mmol) in 10 mL of 50% aqueous sulfuric acid was refluxed for 5 h. After cooling water was added (30 mL). The solution (no solid was observed) was alkalized with 10% aqueous solution of sodium hydroxide. The precipitating 4-aminoquinolines (**5a**) and (**5b**) were filtered off and recrystallized from ethanol to give: 4-methylaminoquinoline (**5a**) (61% and 77% from (**3a**) and (**3h**), respectively), mp 226-228 °C lit.,[12] mp 226-228 °C, and 4-ethylaminoquinoline (**5b**) (52%), mp 187-189 °C, lit.,[12] mp 189-190 °C.

The alkaline solution resulting from the reaction of compound (**3h**) was extracted with chloroform (2 x 10 mL) to give aniline (80%).

REFERENCES

* Part LIII in the series of Azinyl Sulfides.

1. U. Petersen, S. Bartel, K-D. Bremm, T. Himmler, A. Krebs, and T. Schenke, *Bull. Soc. Chim. Belg.*, 1996, **105**, 683 and literature cited therein.
2. Ch. U. Kim and B-Y. Luh, *Heterocycles*, 1988, **27**, 1119.
3. R. V. Davies, J. Fraser, and K. J. Nicol, European Pat. 0 206 616 A2, (09.06.1986) (*Chem.Abstr.*, 1987, **107**, P 58881g).
4. L. Skrzypek and A. Maślankiewicz, *Heterocycles*, 1997, **45**, 2015.
5. A. Maślankiewicz and L. Skrzypek, *Heterocycles*, 1994, **38**, 1317.
6. R. C. Elderfield, Heterocyclic Compounds, Wiley, New York, Chapman and Hall, London, Vol. I, 1950, Vol. IV, 1952,
7. E. W Rodd, Chemistry of Carbon Compounds IV ^{F}- Heterocyclic Coumpounds, II-Edition, ed. by S. Coftey, New York, 1976.
8. A. I. Titow, *Ber.*, 1936, **69**, 1884.
9. S. Sekiguchi, T. Horie, and T. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1988, 698.
10. S. Sekiguchi, T. Suzuki, and M. Hosokawa, *J. Chem. Soc., Perkin Trans. II*, 1989, 1783.
11. A. Rieche and H. Seeboth, *Ann.*, 1960, **638**, 66.
12. L. Skrzypek, *Heterocycles*, 1998, **46**, 71.
13. S. Searles and S. Nukina, *Chem. Rev.*, 1959, **59**, 1077.
14. J. Renault and J. C. Cartron, *Chim. Ther.* 1966, **66**, 339.

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