DIRECT SYNTHESIS OF SOME 9-AMINOALKYL ACRIDINES FROM 9-AMINO ACRIDINE USING PHASE TRANSFER CATALYSIS

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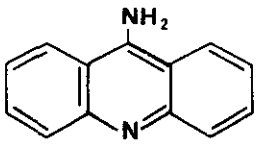
Abstract - A new method of preparation of 9-aminoalkyl acridines is described which avoid the use of 9-chloroacridine. Proton n.m.r. in trifluoroacetic acid easily differentiates 9-aminoalkyl from 9-amino 10-alkyl acridinium salts. Two dialkyl iminoacridanes have been obtained.

9-Amino substituted derivatives of acridine are well known biologically active compounds[1] and so are *the 9-aminoalkyl acridines* 2.[2-7] *However, these latter compounds*[1] *are quite difficult to prepare.* Their synthesis proposed by Dupré and Robinson,[8] is a multi-step procedure, the starting material being N-phenyl anthranilic acid. 9-Chloro acridine is then obtained as an intermediate. It must be emphasized that this compound is difficult to handle[9] due to its skin-irritating properties. 9-substituted acridines are finally prepared from the 9-chloro derivative -yields close to 45%- using a nucleophilic displacement by primary amines. It must be pointed out that a 9-phenoxy derivative can be prepared from the chloro derivative, before the nucleophilic displacement.[8] In doing so, yields are increased. On the other hand, direct alkylation does not work because a 9-amino 10-alkyl acridinium salt 5 is formed by such a process.[10]



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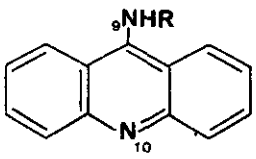

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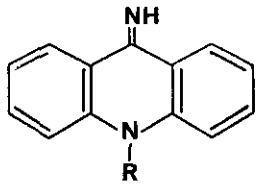

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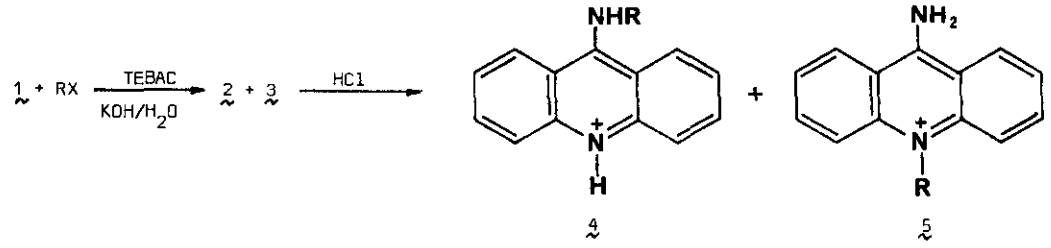
Having successfully employed phase transfer catalysis to obtain O- and N-alkyl derivatives of acridanone[11] we have tried this method for the alkylation of 9-amino acridine 1, using also triethylbenzylammonium chloride (TEBAC) as a dispersive agent. With large quantities of TEBAC the reaction *time is shortened to about two hours if a solvent with a high boiling point, such as toluene,* is used. Under these conditions, the following compounds were prepared: 2, R = n-butyl, n-pentyl, n-hexyl and n-heptyl. Experimental data on these compounds are listed in Table I.

Table I

Compound	R	m.p.	Yield	Microanalysis (a) C	H	N	^{1}H NMR Spectra ($CDCl_3$)
2a	nC_4H_9	104°C	42%	81.60 81.74	7.20 7.49	11.20 11.07	8.1 (m, 4H); 7.6 (m, 2H); 7.3 (m, 2H); 5.5 (unresolved signal, 1H); 3.7 (t, 2H); 1.8 (m, 2H); 1.4 (m, 2H); 0.9 (t, 3H)
2b	nC_5H_{11}	105°C	43%	81.82 81.63	7.57 7.43	10.60 10.36	8.1 (m, 4H); 7.6 (m, 2H); 7.3 (m, 2H); 5.3 (unresolved signal, 1H); 3.6 (t, 2H); 1.6 (m, 2H); 1.25 (m, 4H); 0.8 (t, 3H)
2c	nC_6H_{13}	116°C	47%	82.01 81.88	7.91 7.93	10.07 9.94	8.1 (m, 4H); 7.6 (m, 2H); 7.3 (m, 2H); 5.2 (unresolved signal, 1H); 3.65 (t, 2H); 1.65 (m, 2H); 1.2 (m, 6H); 0.8 (t, 3H)
2d	nC_7H_{15}	115°C	45%	82.19 81.93	8.21 7.98	9.58 9.26	8.1 (m, 4H); 7.7 (m, 2H); 7.35 (m, 2H); 5.2 (unresolved signal, 1H); 3.65 (t, 2H); 1.65 (m, 2H); 1.2 (m, 8H); 0.8 (t, 3H)

[a] For every compound there are calculated values on the first line and experimental values on the second one.

As can be seen, yields are rather low; presumably other compounds are formed in the reaction. In order to characterise them, the crude mixture was treated by hydrochloric acid. Doing so, a mixture of isomeric salts 4 and 5, corresponding to the free bases 2 and 3, was isolated.



4 5

When R = n-butyl, we have succeeded in separating the isomers 4a and 5a by fractional crystallization in alcohol-ether. When R = $CH_2CH_2NEt_2$, only the isomer 5e is obtained according to such a crystallization.

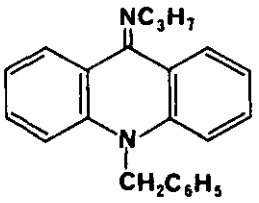
Experimental results concerning the salts 4 and 5 are collected in Table II. Such isomers were easily identified by ^{1}H NMR using trifluoroacetic acid as a solvent: the methylenic protons of compounds 4 appear at 4.3 ppm whereas those of compound 5 appear at 4.9 ppm.

Table II

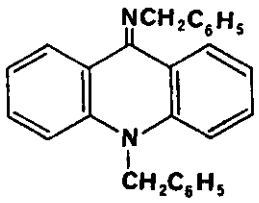
Compound	R	m.p.	Yield	Microanalysis (a) C	H	N	^{1}H NMR Spectra (CF_3CO_2D)
4a	nC_4H_9	189°C [b]	32%	71.20 71.05	6.63 6.41	9.77 9.34	8.4 (m, 2H); 7.9(m, 4H); 7.6 (m, 2H); 4.3 (t, 2H); 2.1 (m, 2H); 1.65 (m, 2H); 1.1 (t, 3H)
5a	nC_4H_9	329°C	18%	71.20 70.80	6.63 6.30	9.77 9.25	8.55 (m, 2H); 8.1 (m, 4H); 7.7 (m, 2H); 4.9 (t, 2H); 2.2 (m, 2H); 1.75 (m, 2H); 1.2 (t, 3H)
5e	CH_2CH_2 - $-NEt_2$	284°C	22%	62.12 61.82	7.08 6.94	11.44 10.72	8.6 (m, 2H); 8.3 (m, 4H); 7.8 (m, 2H); 5.3 (unresolved signal, 2H); 3.8 (unresolved signal, 6H); 1.7 (t, 6H)

[a] See footnote in Table I; [b] Lit., 189-190°C[8,13]

This remark allows the identification of a side product obtained with a 6% yield in the reaction of 1 with n-propyl bromide: this product, 6f, has the n-propyl group bounded to N_9 (δNCH_2=5.7 ppm in TFAA).



6f



6g

Such a compound is formed by reaction of the 9-aminoacridine anion with TEBAC,[12] present in a large amount in the reaction medium.

The dibenzyl derivative 6g is the only product isolated when the very reactive benzyl chloride is used as an alkylating agent. The ^{1}H NMR spectra of compounds 6f and 6g are gathered in Table III.

Table III

Compound	m.p.	Yield	Microanalysis C	H	N	^{1}H NMR Spectra ($CDCl_3$)
6f	140°C	6%	84.66 84.94	6.75 6.56	8.59 8.71	8.2 (m, 1H); 7.8 (m, 1H); 7.4 to 6.9 (m, 11H); 5.3 (s, 2H); 3.8 (t, 2H); 1.8 (m, 2H); 1.1 (t, 3H)
6g	180°C	45%	86.63 86.19	5.88 6.04	7.49 8.01	8.35 (m, 1H); 7.8 (m, 1H); 7.6 to 7.0 (m, 16H); 5.3 (s, 2H); 5.2 (s, 2H)

Since prices of commercial available starting compounds -N-phenyl anthranilic acid and 9-amino acridine- are close one with another, our one-step method would seem to be easier, more rapid as well as less expensive than the synthesis previously proposed.

General procedure: 9-Amino acridine (15 mmol), alkylating agent (37.5 mmol), TEBAC (7.5 mmol), 50% aqueous potassium hydroxyde (75 mmol) and toluene (150 ml) are mixed in a flask. This mixture is refluxed with stirring for two hours. Supernatant phase is water washed, then dried with anhydrous sodium sulphate. Afterwards toluene is evaporated. The viscous residue is taken up with ether. Finally a yellow precipitate is filtered.

If the viscous residue is dissolved in a slight amount of ethanol, and if a few ml of HCl (d = 1.38) is added, a mixture of hydrochlorides 4 and 5 is precipitated by addition of ether.

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