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A FACILE ROUTE FOR THE PREPARATION OF 4-AMINOMETHYLACRIDINE AND ITS DERIVATIVES

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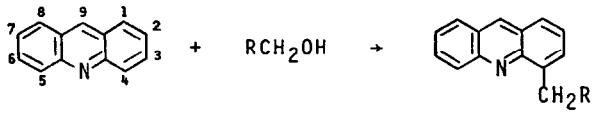
We were interested in the synthesis of 9-aminomethylacridine and derivatives thereof as potential pharmacological agents. A possible approach to such compounds is the conversion of 9-bromomethylacridine to the corresponding aminomethyl derivative using established methods.[1] Since this procedure requires several steps, a more convenient synthesis was considered. As an alternative approach we envisaged the use of N-hydroxymethylamides in strong sulfuric acid.

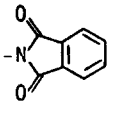
This process, known as the Tscherniac-Einhorn reaction[2] had previously been investigated by L. Monti.[3] Using acridine and N-hydroxymethyl benzamide and N-hydroxymethyl chloroacetamide respectively, the corresponding amidomethyl derivatives were obtained in unspecified yields. Monti postulated that substitution took place at the C-9 position of the acridine molecule. We have repeated this sequence under the conditions described by Monti. In the course of this work, we found that the reaction does not lead to the C-9 isomer as claimed earlier[3] but instead furnishes the corresponding 4-amidomethyl derivatives as the main products as shown below (Path a):

Path a



1 2 3

3a: R = -NHCOC$_6$H$_5$

3b: R = 

3c: R = -NHCOCH$_2$Cl

In the NMR spectrum, compounds 3a-c showed a one proton absorption peak at lowest field (Table 1). This was assigned to the C-9 proton on the

basis that the signal for this proton in acridine is shifted furthest downfield, well separated from the other signals in the spectrum![4] It was concluded therefore, that substitution did not take place at C-9 but elsewhere in the ring. Support for our assignment at C-4 was obtained unambiguously by a synthetic route (see below).

The amidoalkylating species employed in this sequence are powerful electrophilic reagents in strong sulfuric acid. Little is known about electrophilic substitutions in acridine. On the basis of nitration studies[5] we selected the 2-and/or 4-position where substitution was most likely to occur. Because of the experimental difficulties to obtain reasonable amounts of 2-aminomethylacridine,[6] we made the preparation of the 4-isomer our primary target.

The product from the reaction of 4-bromomethylacridine[7] with potassium phthalimide (4, Path b) was identical (M.p., IR, NMR and TLC) with 3b which resulted from the one-step reaction outlined above (Path a). The proton resonance spectra of these two samples are shown in Fig. 1. Furthermore, hydrolysis of 4-phthalimidomethylacridine 3b or 4, and of the benzamidomethyl derivative, 3a, gave the same aminomethylacridine (as dihydrochloride), 5. When the amine, 6, was in turn reacted with chloroacetyl chloride under standard conditions, the product which was isolated corresponded in all details to the compound from the Tscherniac-Einhorn reaction, 3c (Path c).

In addition to the 4-isomer, another monosubstituted phthalimidomethyl acridine, 7, was isolated during the Tscherniac-Einhorn reaction (Path a), albeit in much lower yield (5.3%). Its NMR spectrum is shown in Figure 2a. Using a similar procedure as that described in Path b, we prepared 2-phthalimidomethyl acridine, 8, which was identical in every detail with the above product, 7, cf. Figure 2b.

i. In summary, we have shown that the position of substitution has erroneously been assigned to the 9-position in the acridine ring and

ii. that the above sequence is a facile and economical route for the preparation of 4-aminomethylacridine and its derivatives.

The details of this work will be described elsewhere.

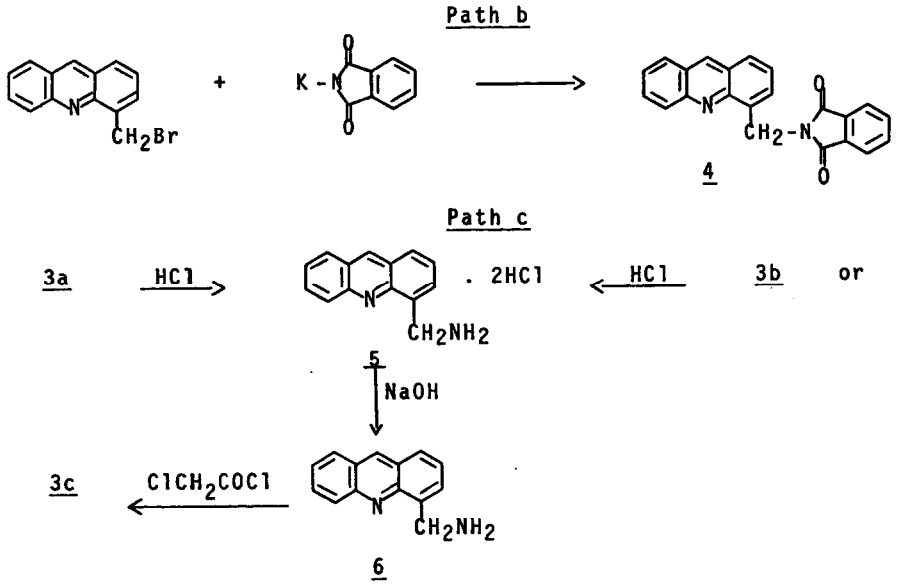


Table 1

Cpd.	% Yield* (% Acridine recovered)	M.P., °C**	τ (multiplicity) - 60 MHz§§ C9-H	ArH	ArCH2N	COCH2Cl	Solvent
3a	29.6 (35.5)	160-163*** [Lit.(3)162-164]	0.8(s)	1.5-2.6(m)	4.6(d)	-	DMSO-d_6
3b	59.5 (10.6)	199-201§	1.1(s)	1.5-2.7(m)	4.1(s)	-	$CDCl_3$
3c	59.2 (13.8)	178-180 [Lit.(3)172-174]	0.9(s)	1.6-2.7(m)	4.9(d)	5.8(s)	DMSO-d_6

* After chromatography (silica gel)-TLC one spot-and one recrystallization.

** All melting points are corrected.

*** M.P. for 9-benzamidomethylacridine was reported as 118°C.(8)

§ Mixed M.P. of 3b and 4 : 199-201°.

§§ TMS as internal standard.

All compounds gave satisfactory elemental analyses.

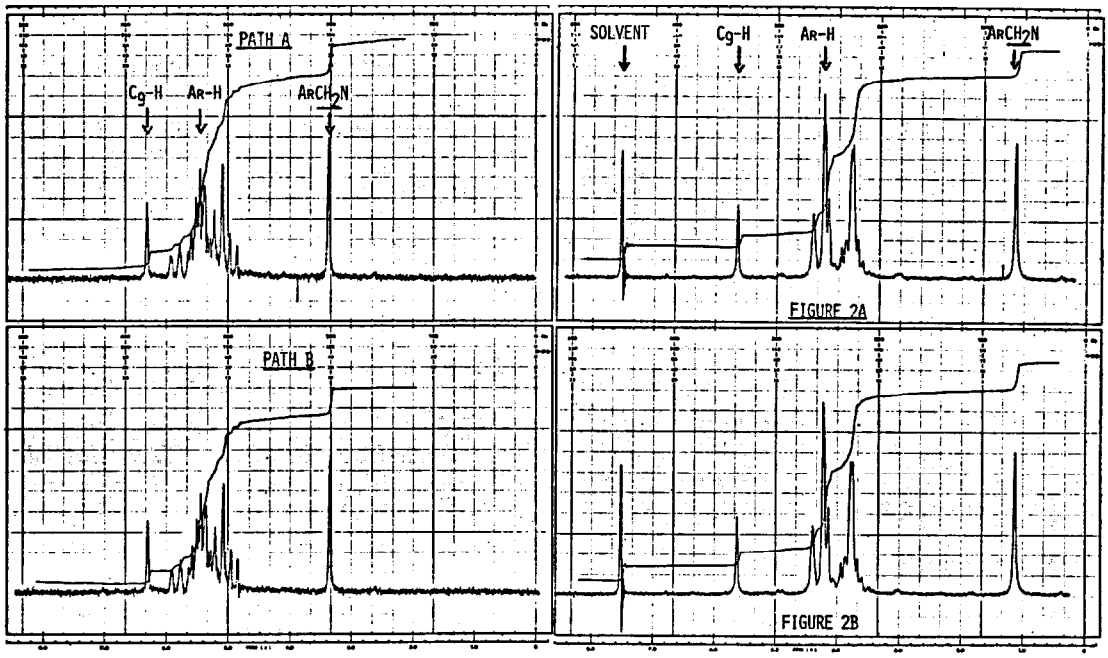


FIGURE 1. -PARTIAL NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 4-PHTHALIMIDOMETHYL ACRIDINE (60 MHz, $CDCl_3$).

PARTIAL NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 2-PHTHALIMIDOMETHYL ACRIDINE (60 MHz, CF_3COO-d).

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