

NOVEL N-10 TO C-4 OXYGEN MIGRATION IN THE ACRIDINE RING SYSTEM

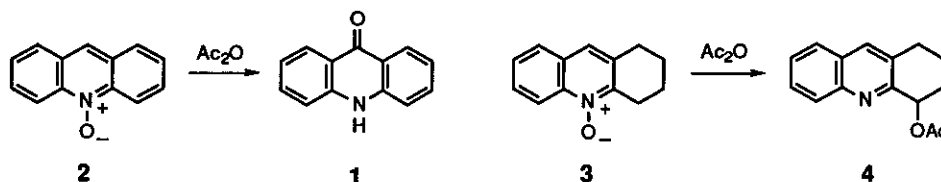
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Abstract - Treatment of 9-aryl-2,7-dimethoxyacridine-10-oxides with acetic anhydride results in a novel rearrangement to the corresponding 4-acetoxyacridines. The rearrangement offers a convenient synthetic route to poly-oxygenated acridines.

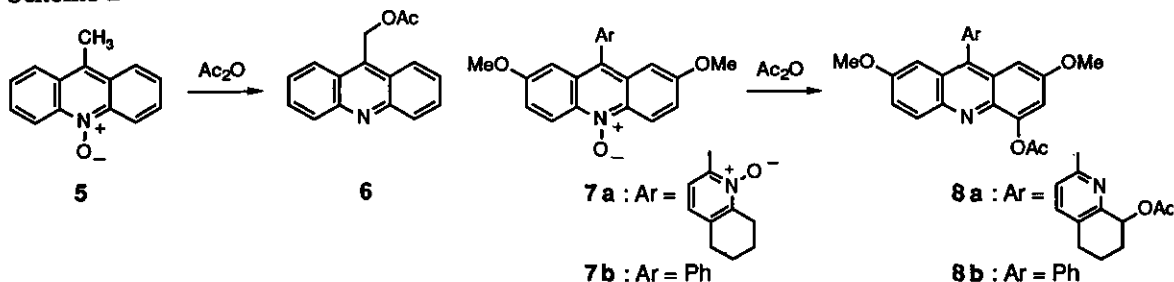
9-Acridones (e.g. 1) are formed when 9-unsubstituted acridine N-oxides (e.g. 2) are treated with acetic anhydride (Scheme 1).¹ In addition to being a useful method of preparing acridones, the reaction has received some mechanistic study.² Labelling studies showed the intermediate 9-acetoxyacridine to be formed *via* intramolecular transfer of acetate. A different course is followed with partially reduced acridines. For example, 1,2,3,4-tetrahydroacridine-10-oxide (3) undergoes oxygen transfer to 4-acetoxy-1,2,3,4-tetrahydroacridine (4).³ In a related reaction, we found that refluxing 9-methylacridine-10-oxide (5) in acetic anhydride produces 6 in 80% yield (Scheme 2).

Scheme 1



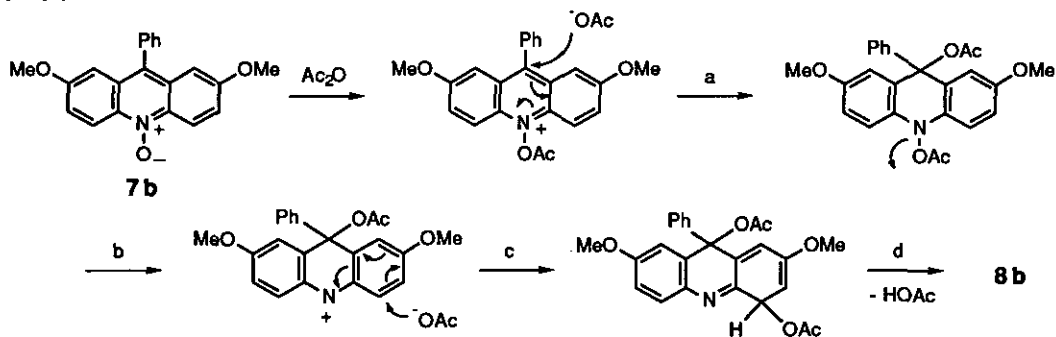
In the course of synthetic studies towards new "molecular tweezers" we required 8-acetoxy-2-(9-acridinyl)-5,6,7,8-tetrahydroquinolines.⁴ Given the precedent cited above, rearrangement of bis N-oxide (7a)⁵ was expected to occur only in the tetrahydroquinoline ring since the 9-position of the acridine is blocked. Instead, refluxing 7a in acetic anhydride produced a compound containing two acetoxy groups (62% yield) that was tentatively assigned structure (8a).

Scheme 2



To simplify spectral assignments, the rearrangement was carried out on the *N*-oxide derived from 2,7-dimethoxy-9-phenylacridine⁶ (7b). Compound (8b) was the sole product formed and was obtained in 87% yield. The acetoxy group was evident from the ir (1767 cm⁻¹), ¹H-nmr (δ 2.61), ¹³C-nmr (169.92), and the mass spectrum (M⁺ = 7b + COMe).⁷ The assignment of the regiochemistry as 8b was based on the following nmr data: (1) 17 aromatic carbons in the ¹³C-nmr indicated an unsymmetrically substituted acridine ring, (2) the ¹H-nmr indicated loss of one H-4 resonance, and (3) the ¹H-nmr splitting was consistent with a 2,4,7-trisubstituted acridine.

Scheme 3



A possible mechanism for this novel rearrangement is shown in Scheme 3.⁸ The addition of acetate at the 9-position (step a) allows a lateral transfer of acetate from N-10 to C-4 (steps b, c). A similar rearrangement occurs in *N*-aryl-*N,O*-diacylhydroxylamines⁹ and is believed to proceed through the intermediacy of a nitrenium ion,¹⁰ although we cannot rule out other mechanisms in our system (e.g. Claisen-type). If an ionic mechanism is operative, the 2,7-substituents may serve to control the regiochemistry of the migration. Loss of the 9-acetoxy group produces 8b. In conclusion, an N-10 to C-4 oxygen migration has been found to occur when 2,7-dimethoxy-9-arylacridine-10-oxides are treated with acetic anhydride. In addition to its mechanistic interest, this novel rearrangement may provide a convenient synthetic pathway to 4-hydroxyacridines.

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7. **8b**: $^1\text{H-nmr}$ δ : 8.10 (d, $J_{5,6} = 9.4$, 1H H-5), 7.61-7.56 (m, 3H, H-3', H-4', H-5'), 7.43 (dd, $J_{2',3'} = 4.8$, $J_{2',4'} = 1.9$, 2H, H-2', H-6'), 7.36 (dd, $J_{5,6} = 9.4$, $J_{6,8} = 2.7$, 1H, H-6), 7.18 (d, $J_{1,3} = 2.7$, 1H, H-3), 6.73 (d, $J_{6,8} = 2.7$, 1H, H-8), 6.69 (d, $J_{1,3} = 2.7$, 1H, H-1), 3.71 (s, 6H, OCH₃), 2.61 (s, 3H, CH₃CO₂); $^{13}\text{C-nmr}$ δ : 169.92, 157.34, 156.17, 148.45, 144.06, 142.47, 136.63, 131.97, 130.13, 130.74, 128.76, 128.26, 126.78, 126.71, 123.66, 115.00, 101.60, 100.38, 55.43, 55.23, 21.12; ms (EI, 70 eV) 373 (M⁺).
8. For a related mechanism in the quinoline ring system see: M. Hamana and S. Kumadaki, Chem. Pharm. Bull., 1973, **21**, 800.
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