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

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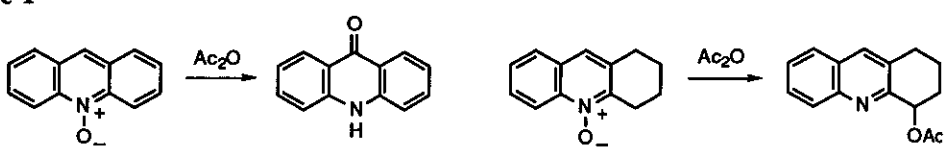
Abstract - Treatment of 9-aryl-2,7-dimethoxyacridine-10-oxides with acetic anhydride results in a novel rearrangement to the corresponding 4-acetoxy-acridines. The rearrangement offers a convenient synthetic route to poly-oxygenated acridines.

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).

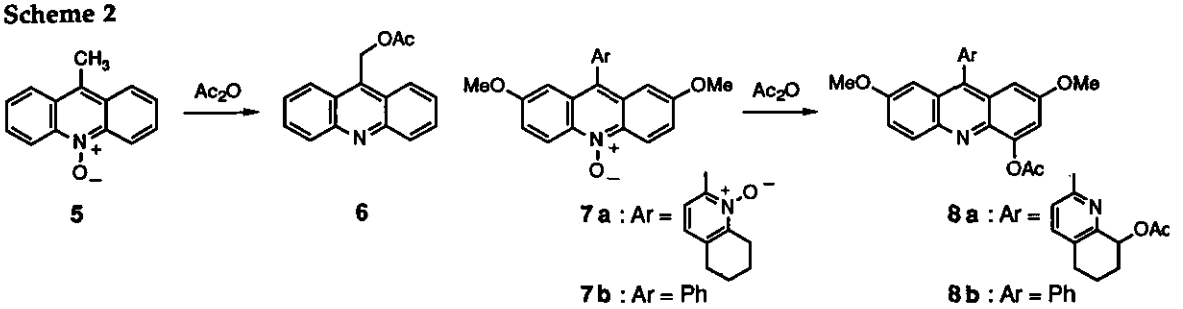
Scheme 1



2 **1** **3** **4**

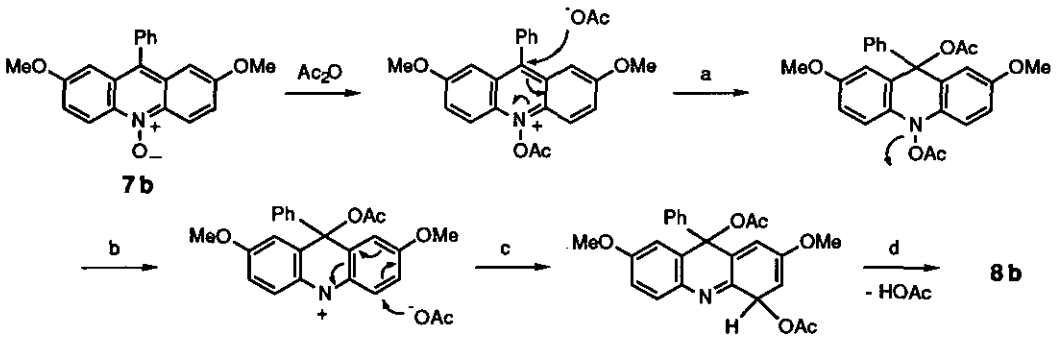
In the course of synthetic studies towards new "molecular tweezers" we required 8-acetoxy-2-(9-acridinyl)-5,6,7,8-tetrahydroquinolines.[4] Given the precedent cited above, rearrangement of bis *N*-oxide (**7a**)[5] was expected to occur only in the tetrahydroquinoline ring since the 9-position of the 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-phenylacridine[6] (**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}), ^{1}H-nmr (δ 2.61), ^{13}C-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 ^{13}C-nmr indicated an unsymmetrically substituted acridine ring, (2) the ^{1}H-nmr indicated loss of one H-4 resonance, and (3) the ^{1}H-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*-diacylhydroxylamines[9] 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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REFERENCES AND NOTES.

1. A. Kliegel and A. Fehrle, Ber. , 1914, **47**, 1629; A R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic N-Oxides,' Academic, New York, 1971.
2. J. H. Markgraf and C. G. Carson, J. Org. Chem., 1964, **29**, 2806; J. H. Margraf and M.-K. Ahn, J. Am. Chem. Soc., 1964, **86**, 2699. S. Oae, S. Kozuka, Y. Sakaguchi, and K. Hiramatsu, Tetrahedron, 1966, **22**, 3143.
3. E. Hayashi and T. Nagao, Yakugaku Zasshi, 1964, **84**, 198.
4. S. C. Zimmerman, Z. Zeng, W. Wu, and D. E. Reichert, J. Am. Chem. Soc., 1991, **113**, 183.
5. Z. Zeng and S. C. Zimmerman, Tetrahedron Lett., 1988, **29**, 5123.
6. H. Lund, P. Lunde, and F. Kaufmann, Acta Chem. Scand., 1966, **20**, 1631.
7. **8b**: ^{1}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, OCH_3), 2.61 (s, 3H, CH_3CO_2); ^{13}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.
9. R. M. Coates and I. M. Said, J. Am. Chem. Soc., 1977, **99**, 2355; L. Horner and H. Steppan, Liebigs Ann. Chem., 1957, **606**, 24.
10. C. Nicolaou and G. R. Underwood, Tetrahedron Lett., 1989, **30**, 1479.

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