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Quinoline and Acridine Templates in Selective Steroid Chlorinations

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Abstract: Steroid esters of quinoline and acridine carboxylic acids can undergo template directed delivery of chlorine atoms to a particular steroid hydrogen even though chlorination selectivity studies with 2,3-dimethylbutane suggest that the bonding in the chlorine complex is probably different from that with pyridine templates.

We have described the radical-relay chlorination of steroids and of linear alkanols directed by attached templates.[1] Particularly interesting was the finding that pyridine rings of nicotinate ester groups, as in compound **1**, are able to direct chlorinations.[2] In **1** the C-9 position of the steroid is chlorinated with high selectivity. Since the effectiveness of this process depended on the position of the nitrogen atom, it was clear that the intermediate has a chlorine atom bonded to the nitrogen atom; this chlorine then abstracts the hydrogen at C-9. There were two obvious structures for such a chlorine-pyridine complex—a normal two-electron nitrogen-chlorine bond in a pyridine pi radical (**2**), or a three-electron bond between the chlorine and the nitrogen (**3**) with a normal pyridine pi system.

Our spectroscopic[3] and theoretical[3] studies made it clear that the latter model was correct, and this was confirmed by later ESR studies done by Symons.[4] However, in the balance between the structure **2**—that is characteristic of known[5] complexes of H· and CH_3· to pyridine—and the structure **3** of our pyridine/Cl· complexes, one of the factors is presumably the change in aromaticity of the pyridine system when an additional pi electron is added. Thus one might expect that the bonding situation with Cl· could change if fused rings, as in quinoline or acridine, are substituted for the pyridine system. Such ring fusion is well known to decrease the aromaticity of a ring, and lower the LUMO.

There are also practical reasons why these fused ring systems could be of interest as templates. For instance, the acridine ring is ideally constituted to permit the attachment of two linking or binding groups, so as to hold the substrate in a very well defined position. Thus we have examined the ability of fused ring pyridine derivatives to act as templates, and also looked for evidence on the nature of the intermediate Cl· complexes.

The quinoline ester **4** was prepared from the commercially available acid and 3α-cholestanol by coupling with N-ethyl-N'-dimethylaminopropylcarbodiimide. As the results in Table I indicate, it was able to direct chlorination into C-9 of the steroid just as the pyridine group in **1** does. Thus the extra ring fusion does not block this process.

We had found[6] that the N-oxide 5 of 1 also underwent template directed chlorination of the steroid at C-9. Models show that coordination by a three-electron bond of a chlorine atom to either the pyridine ring of 1 or to the oxygen atom of 5 puts the chlorine in a similar position. Thus we were also interested in the quinoline ester 6, whose nitrogen atom is in the same geometric position as is the oxygen of 5. Ester 6 was prepared from the known carboxylic acid by Mitsunobu reaction with 3β-cholestanol. As the Table indicates, it was also able to direct chlorination under radical relay conditions to the C-9 position of the steroid.

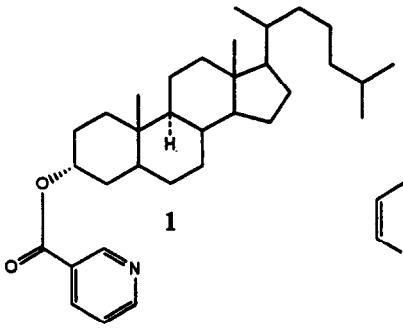
The nitrogen atom in acridine esters 7 and 8 is similarly located. The acridine acids needed for 7 and 8 were prepared in a standard fashion by cyclization of anilinoterephthalic acid—leading in a few steps to 7—or of the piperidine amide of 2-carboxy-3'-methyldiphenylamine[7]—leading to 8 after phenylation of the resulting acridone and NBS bromination to convert the methyl group to carboxyl. As the results in Table I show, both of these esters also underwent chlorination at the steroid C-9 position in yields similar to those with the other templates; however, the acridine ring in 7 also was chlorinated to some extent at its own carbon 9, a process blocked by the phenyl group in 8. Thus in all four of these esters—4, 6, 7, and 8—the nitrogen atom is able to direct chlorination to C-9 of the steroid.

We have also prepared the N-oxide 9. In this case insignificant steroid chlorination was seen under our standard conditions, presumably because—as models suggest—a chlorine atom bound to the oxygen of 9 would no longer be correctly located to attack a steroid hydrogen. Thus there is some geometric flexibility in the template used, seen in the results with 4, 6, 7 and 8, but not an unlimited amount.

We have not been able to do the spectroscopic study with quinoline systems that permitted us to support the structure 3 for the pyridine-chlorine complex. Furthermore, Professor Symons has unfortunately not been able to extend his ESR methodology to the quinoline system.[8] However, studies on chlorination selectivities indicate that the complex with quinoline probably has the pi radical structure 10 analogous to 2. These studies involve the effect of an added base, such as pyridine, on the selectivity of free radical chlorination of 2,3-dimethylbutane (DMB), a technique that we[3] and others[9-11] have used previously.

The general idea is that free Cl· is rather unselective between tertiary and primary hydrogens, but becomes more selective as the pyridine complex. The observed selectivities with various additives correlate with the stabilities of their Cl· complexes. We find that the quinoline ester 11 induces 30% more selectivity in DMB chlorination than does simple pyridine under the same conditions. Since even quinoline itself is less basic than is pyridine, and the ester 11 less basic still, this means that the less basic compound 11 forms a more stable complex with Cl·.

Simple Cl· coordination to the nitrogen unshared pair of electrons in a three-electron bond should be stronger when the nitrogen is more basic, and indeed we previously found[3] that selectivity in DMB chlorination was less with either nicotinate or isonicotinate esters as additives than it is with the more basic pyridine. Thus the greater selectivity in DMB chlorination with the even weaker base 11 is most consistent with the idea that its complex



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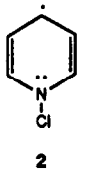

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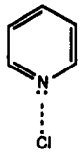

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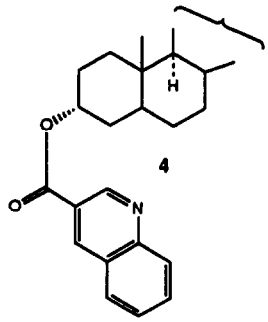

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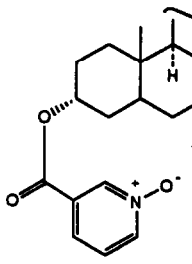

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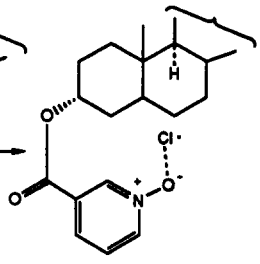

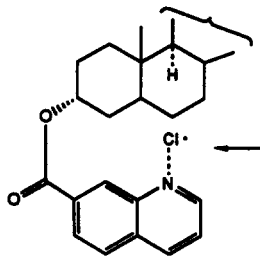

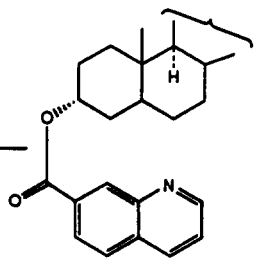

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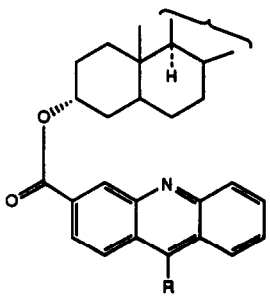
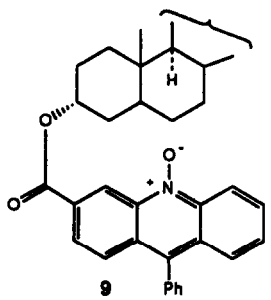


7 R = H
8 R = Ph



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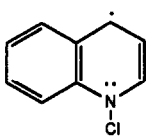

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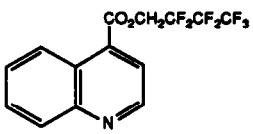

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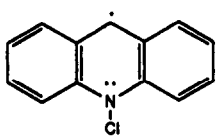

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with Cl· has a new structure, almost certainly **10**. If so, this apparently does not interfere with hydrogen abstraction from the steroid substrate by quinoline templates.

The acridine system was not stable under the DMB chlorination conditions, but acridine is even more likely to form the pi radical **12** when binding Cl·. In spite of this probable change in bonding, chlorine atoms complexed to these fused-ring heterocycles have proven to be still useful in template-directed chlorinations.

Table I
Selective Chlorinations under Standard Conditions[2]

Substrate	Equivalents $PhICl_2$	Yield of 9-Chlorosteroid	Recovered Starting Material
4	1.25	ca. 100%	0%
6	1.2	90%	7-9%
7	1.5	86%	9-10%
8	1.5	88%	ca. 10%

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