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REACTIONS OF AZIDOQUINONES WITH NUCLEOPHILES. SYNTHESIS OF HETEROCYCLIC QUINONES

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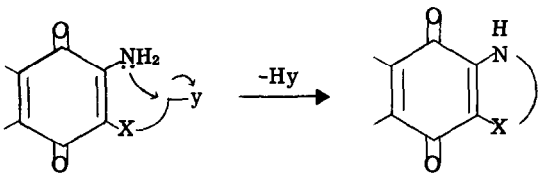
A potentially general synthetic route to a large variety of heterocyclic quinones is formally outlined below. Specifically, generation of an adequately substituted aminoquinone (1) followed by its intramolecular ring closure would provide a versatile pathway to a number of heterocyclic ring systems (2).

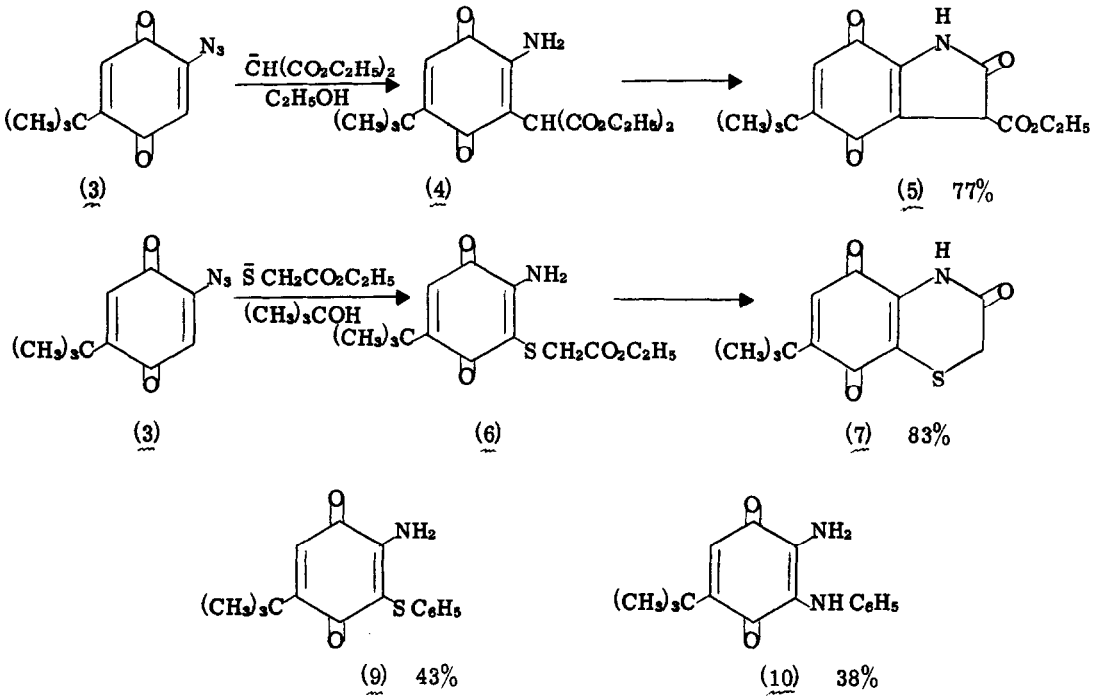


(1) (2)

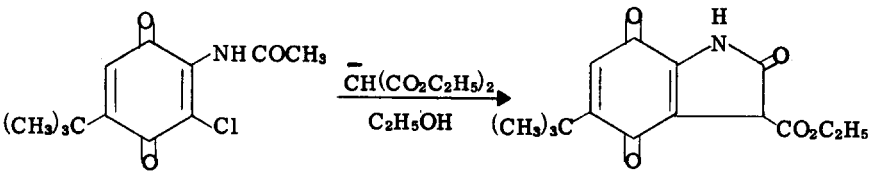
Until now, the above approach has been ignored since no good method was known for the generation of the key substituted aminoquinone intermediates (1). That is, classical methods of introducing substituents on the quinone nucleus, such as 1,4-additions and nucleophilic displacements, are untenable for aminoquinones since the amino group effectively inhibits nucleophilic attack on the double bond to which it is attached.

We have taken advantage of the fact that azidohydroquinones, which can be generated by Michael addition reactions to azidoquinones, readily disproportionate to the corresponding aminoquinones.[2] In this way the key intermediate (1) can be generated and thus the heterocyclic quinone can be obtained in effectively a one step laboratory operation. 2-Azido-5-tert-butyl-1,4-benzoquinone (3) was chosen as the azidoquinone for initial investigations since the bulky tert-butyl group would sterically inhibit nucleophilic attack at position-6. Electronic inhibition is, of course, also conceivably possible for those quinones having strong electron donating

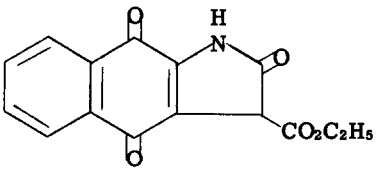
groups at positions -5 and/or -6. The reactions of (3) with a series of C-, S-, and N- nucleophiles were studied and the results are outlined below. The azidoquinone (3) reacts immediately with sodium diethylmalonate in ethanol to give a 77% isolated yield of 5-tert-butyl-3-carboethoxy-indole-2, 4, 7-trione (5). Similarly, ethyl mercaptoacetate reacts with (3) in the presence of potassium tert-butoxide/tert-butanol to give an 83% yield of (7). The respective aminoquinones (4) and (6) were not isolated or detected. However, since 2-azido-5-tert-butyl-1, 4-benzoquinone (3) reacts with thiophenol and aniline to give respectively 2-amino-5-tert-butyl-3-thiophenyl- (9) and 2-amino-3-anilino-5-tert-butyl-1, 4-benzoquinone (10), their intermediacy is likely.



The recent observation[3] that 2-aminoquinones can be selectively chlorinated at position-3 using tert-butyl hypochlorite suggested still another route to intermediates of general structure (1) and thus to heterocyclic quinones. That is, nucleophilic displacement of chloride ion from the acylated aminoquinone derivative followed by hydrolysis would give the desired aminoquinone derivative (1) and subsequently the ring closed product (2). Indeed, 2-acetamino-3-chloro-5-tert-butyl-1, 4-benzoquinone (11) reacts with sodium diethylmalonate in ethanol to give the indolequinone (5) in 90% yield. In an analogous way (12) was prepared (96%) from 2-acetamido-3-chloro-1, 4-naphthoquinone.



(11) (5) 90%



(12) 96%

Table I

Properties of New Compounds[4]

Compound	mp	yield	ir (cm^{-1})	nmr (ppm)
(5)	95-100°	77	3230, 1725, 1650, 1610,	1.28 s (9), 1.31 t (3) J = 7Hz, 4.26 q (2) J = 7Hz, 6.30 s (1)
(7)	164-166°	83	3210, 1720, 1675, 1650,	1.30 s (9), 3.47 s (2) 6.58 s (1), 8.18 b (1)
(9)	-------	43	3450, 3330, 1680, 1610	1.27 s (9), 5.71 b (2) 6.55 s (1), 7.18 m (5)
(10)	135-138°	38	3460, 3250, 1660, 1625	1.3 s (9), 4.42 b (2) 6.06 b (1), 6.44 s (1) 6.90 m (5)
(12)	199-200°	96	3210, 1680, 1645, 1610	1.33 t (3) J = 7Hz, 4.29 (2) J = 7Hz, 7.92 m (4)

References

1. The authors are grateful to the National Cancer Institute for Grant No. CA 11890-03 which provided financial support of this project.

2. H.W. Moore and H.R. Shelden, J. Org. Chem., 33, 4019 (1968).

3. H.W. Moore and G. Cajipe, Synthesis, (1), 49 (1973).

4. Combustion analysis of the compounds reported are in agreement with their formulations