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o-Chloranil Oxidation of Azlactones

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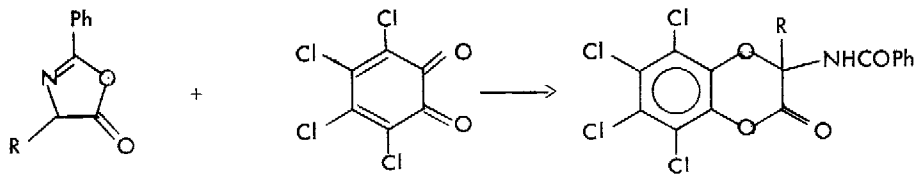
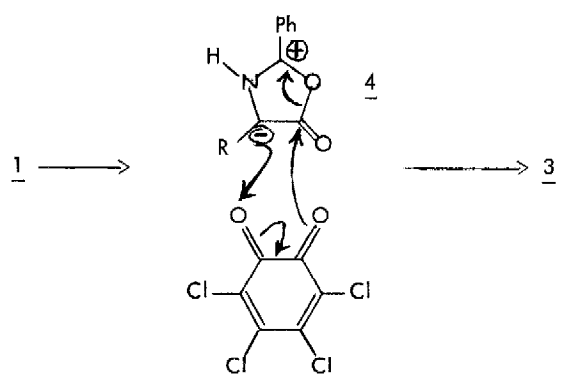
In our continuing study[2] of the oxidation of azlactones (1), we had occasion to examine their reaction with o-chloranil (2). Instead of the expected unsaturated azlactones, benzodioxinones (3), were



1 + 2 → 3

a, R = $PhCH_2$ d, R = H
b, R = $(CH_3)_2CH$ e, R = Ph
c, R = CH_3 f, R = $(CH_3)_2CHCH_2$

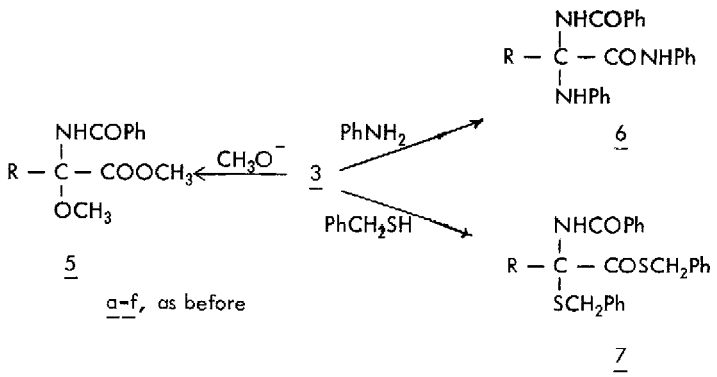
formed in excellent yields. The formation of "quinone adducts" is not unprecedented[3] since olefins, ketenes, keteninines, enamines and strained hydrocarbons[4] form dioxins with o-quinones. The presence of a high electron density at the azlactone C-4, due either to deprotonation leaving a C-4 carbanion[5] or to the dipolar "Munchnone" character[6] (4) of azlactones, is probably responsible for initiating the reaction. The adducts (3a-f) crystallized from solution[7] in 60-95% yields when the appropriate N-benzoyl amino acids were treated at room temperature with one equivalent of o-chloranil in acetic anhydride



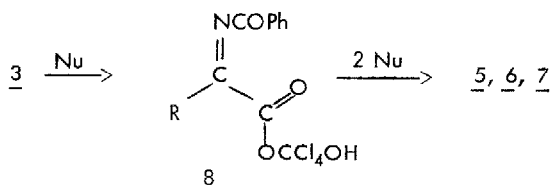
1 → 4 → 3

solution. Off-resonance ^{13}C nmr spectra of 3a and 3d were examined in order to confirm the dioxinone structures. The key absorption peak of C-3 in both of these compounds showed the required splitting; i.e 88.6 ppm, singlet for 3a and 75.2 ppm, doublet for 3d. Also 3a showed its benzyl carbon absorption as a triplet at 45.1 ppm.

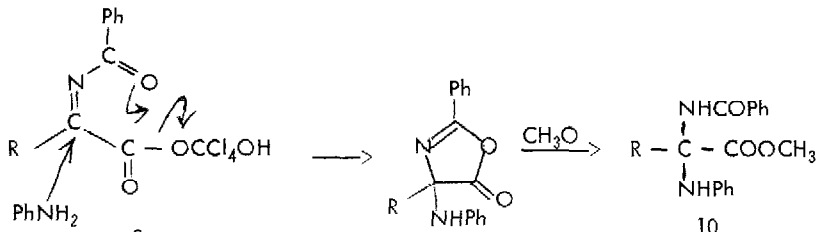
The chemistry of the adducts (3) was then investigated to see if they might be useful intermediates in the synthesis of amino acid derivatives. We found that 3 reacted rapidly with nucleophiles such as



methoxide, aniline and benzyl mercaptan to form α-substituted esters (5 and 7) and amides (6) in 60-85% yields[7]. The decoupled ^{13}C nmr spectra of 5a and 5d again confirmed these structures by showing a singlet for the α-carbon of 5a (43.8 ppm) and a doublet for that of 5d (78.9 ppm). Since this reaction occurred under basic to neutral conditions, the mechanism might be envisioned as a deprotonation of the amide nitrogen atom followed by formation of a phenoxy ester (8) which then reacted with two moles of

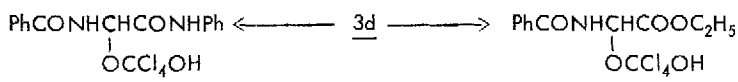


nucleophile giving the product.[8] Initial nucleophilic attack at the carbonyl function of 3 is quite sterically hindered, since the α-carbon atom is trisubstituted. When 3b was treated with one equivalent of aniline, an intermediate having carbonyl absorption at 1825 cm^{-1} was formed. On treatment with methanol in situ, this substance was converted into the α-anilino methyl ester[7] (10) very rapidly. The high carbonyl frequency of the intermediate indicated to us that it was very probably[9] an α-anilino azlactone (9). The formation of 9 can be explained by assuming that addition of aniline to 8 occurred with concommitant ring closure, facilitated by the fact that the tetrachlorophenoxide ion is an excellent leaving group.



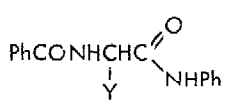
8 9 10

The adducts 3 (R>H) did not react at all with methanol or ethanol in the absence of a basic catalyst However, 3d (R=H) reacted rapidly with ethanol without catalysis to give the α-tetrachlorophenoxy ester[7] (11) and with aniline to form the corresponding anilide[7] (12). Both of these products obviously resulted from initial attack at the carbonyl group of 3d. We found that 12 could then be converted into



12 11

the α-substituted anilides[7] (13a, b, c) on treatment with the appropriate nucleophiles in the presence of triethylamine. It seems clear that, with careful development of reaction conditions, any combination of



a, Y = CH_3O
b, Y = $PhCH_2S$
c, Y = PhNH

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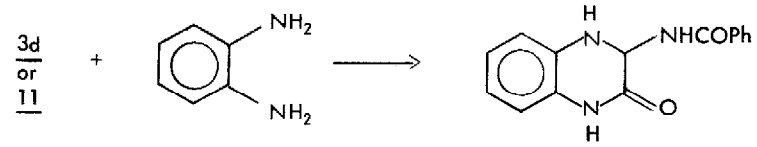
nucleophile residues might be placed on the α-and carbonyl carbon atoms of an amino acid residue using these dioxinone intermediates.

Since the dioxinones react with two equivalents of nucleophiles and the sites of reaction are adjacent, heterocycles should be formed when a bifunctional nucleophile is used. Indeed, when either 3d or 11 was treated with o-phenylenediamine, the tetrahydro quinoxaline derivative 14 was formed[7] in 81% and 75% yields, respectively. Compound 14 was readily oxidized with DDQ to the known[10] 2-hydroxy-3-benzamidoquinoxaline.[11] We are investigating the further use of benzodioxinones (3) as intermediates in heterocycle synthesis.



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References

1) Extracted from the Ph.D. Dissertation of James M. Riordan which was submitted to the University of Georgia Graduate School, February, 1976. Presented to the Fifth International Congress of Heterocyclic Chemistry, Ljubljana, Yugoslavia, July, 1975.

2) a) J. M. Riordan and C. H. Stammer, Tetrahedron Lett., 4969 (1971); b) James M. Riordan and C. H. Stammer, J. Org. Chem. 39, 654 (1974); c) Edward G. Breitholle and Charles H. Stammer, Tetrahedron Lett., 2381 (1975).

3) a) W. M. Horspool, Quart. Rev., 23, 228 (1969); b) P. DeMayo, Adv. in Org. Chem., Methods and Results, R.A. Raphael Ed., Interscience Pub., Inc. New York, N.Y., Vol. 2, p. 383 (1960).

4) W. Friedrichsen, E. Buldt and R. Schmidt, Tetrahedron Lett., 1137 (1975).

5) It is well known that the proton at C-4 in the azlactone ring has enhanced acidity, this being responsible for the rapid racemization of optically active azlactones.

6) F. Texier and O. Yebdri, Tetrahedron Lett., 855 (1975).

7) All new compounds had acceptable C, H and N analyses and showed the expected infrared and ^{1}H nmr spectra.

8) α-Substituted amino acid esters have recently been shown to undergo exchange of the α-substituent with other nucleophiles, N-acylimines being postulated as intermediates; c.f. R. K. Olsen and A. J. Kolar, Tetrahedron Lett., 3579 (1975).

9) If the intermediate were a tetrachlorophenyl ester, it might be expected to have a carbonyl absorption in the same range as the dioxinones; i.e., 1765-1805 cm^{-1}.

10) D. Shiho and S. Tagami, Chem. Pharm. Bull, 5, 45 (1957).

11) This reaction was carried out by Dr. M. Sato in our laboratories.