The Substitution of Aryl Iodides with Cuprous Acetylides. A Synthesis of Tolanes and Heterocyclics[1]

R. D. STEPHENS AND C. E. CASTRO

The Departments of Nematology and Chemistry, University of California, Riverside, California

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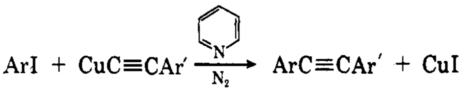
Diarylacetylenes are prepared conveniently in good yields by treating aryl iodides with cuprous acetylides in refluxing pyridine under a nitrogen atmosphere. Under these conditions, aryl iodides bearing an *ortho* nucleophilic substituent are converted exclusively to the corresponding heterocycle in high yields.

Diarylacetylenes have been prepared[2] by the dehydrohalogenation of dihalodibenzyls,[3] oxidation of the benzil dihydrazones with mercuric oxide,[4] rearrangement of 1,1-diaryl-2-haloethenes upon treatment with base,[5] and by the action of base upon 5,5-diaryl-3-nitroso-2-oxazolidones.[6]

In the course of studies of the reduction of multiple bonds by low valent transition metal ions,[7] we have had occasion to prepare a variety of tolanes. We have found that these substances are readily obtained in good yield by exposing aryl iodides to cuprous acetylides in refluxing pyridine.[8] Reaction 1 is carried out in



$$ArI + CuC\equiv CAr' \xrightarrow[N_2]{\text{pyridine}} ArC\equiv CAr' + CuI \qquad (1)$$

a nitrogen atmosphere to prevent coupling to the diacetylene.[9] The scope of the reaction is indicated by the results presented in Table I.

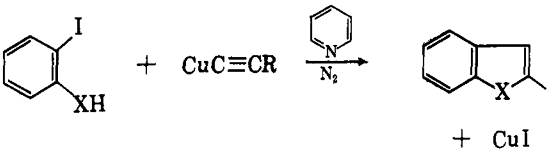
TABLE I

YIELDS OF TOLANES FROM ARYL IODIDES AND CUPROUS PHENYLACETYLIDE

Aryl halide	Product	Yield,[a] %
Iodobenzene	Diphenylacetylene	87
p-Methoxyiodobenzene	4-Methoxydiphenylacetylene	99
o-Methoxyiodobenzene	2-Methoxydiphenylacetylene[b]	91
p-Iodoaniline	4-Aminodiphenylacetylene	76
p-Iodobenzoic acid	4-Carboxydiphenylacetylene[b]	85
p-Iodophenol	4-Hydroxydiphenylacetylene[b]	82
p-Nitroiodobenzene	4-Nitrodiphenylacetylene	75
o-Nitroiodobenzene	2-Nitrodiphenylacetylene[b]	84

[a] Yields reported here and in Table II are for the purified product. [b] Not previously described.

When the aryl iodide bears an *ortho* nucleophilic substituent, tolanes are not obtained, but rather cyclization to the corresponding heterocycle occurs exclusively under the same reaction conditions (see eq. 2). This cyclization, while detracting from the generality of the tolane synthesis, provides a novel and convenient route to a variety of heterocyclic substances.



(2)

The results portrayed in Table II are indicative of the scope and usefulness of this reaction.

TABLE II

YIELDS OF HETEROCYCLICS FROM *o*-SUBSTITUTED ARYL IODIDES AND CUPROUS ACETYLIDES

Aryl iodide	Cuprous acetylide	Product	Yield, %
o-Iodobenzoic acid	$CuC\equiv CPh$	3-Phenylisocoumarin	91
o-Iodophenol	$CuC\equiv CPh$	2-Phenylbenzofuran	88
o-Iodoaniline	$CuC\equiv CPh$	2-Phenylindole	85
o-Iodoaniline	$CuC\equiv CPr\text{-}_n$	2-*n*-Propylindole	87

These reactions are similar to a series of transformations (eq. 3) that resemble the Rosenmund–von Braun

$$RX + CuY \longrightarrow RY + CuX \qquad (3)$$

nitrile synthesis.[10] Thus, the solvolysis of allylic halides has been shown to be catalyzed by cuprous salts.[11] Alkyl alcohols,[12] alkyl halides,[13,14] and aryl bromides[15] have been converted to the corresponding cyanides through the action of cuprous cyanide. Aryl and alkyl halides have been converted to thio ethers with cuprous mercaptides.[16] The exchange of aromatic halides has been effected with Cu(I) halides,[15] and the Cu(I)-catalyzed alkylation of acetylenic halides with acetylenes has been noted.[17]

It is noteworthy that the following path has been proposed for the Rosenmund–von Braun nitrile synthesis[18] (eq. 4) conducted in the absence of solvent. A somewhat related sequence has been advanced to

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[1] Substitutions by Ligands of Low Valent Transition Metals. II. This work was supported in part by the National Science Foundation (G19145) and in part by the National Institutes of Health (AI 01532-01).

[2] For a summary of methods, see S. H. Harper in "Chemistry of Carbon Compounds," Vol. III, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1956, pp. 1157, 1158.

[3] L. I. Smith and M. M. Falkof, *Org. Syn.*, **22**, 50 (1942).

[4] A. C. Cope, D. S. Smith, and R. J. Cotter, *ibid.*, **34**, 42 (1954).

[5] G. H. Coleman, W. H. Holst, and R. D. Maxwell, *J. Am. Chem. Soc.*, **58**, 2310 (1936); D. Y. Curtin, E. W. Flynn, R. F. Nystrom, and W. H. Richardson, *Chem. Ind.* (London), 1453 (1957).

[6] M. S Newman and A. Kutner, *J. Am. Chem. Soc.*, **73**, 4199 (1951).

[7] C. E. Castro and R. D. Stephens, Abstracts of Papers, Organic Division, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 23.

[8] A preliminary account of this work has appeared: C. E. Castro and R. D. Stephens, *J. Org. Chem.*, **28**, 2163 (1963).

[9] C. Glaser, *Ann.*, **154**, 137, 159 (1870); K. Bowden, I. Heilbron, E. R. H. Jones, and K. H. Sargent, *J. Chem. Soc.*, 1579 (1947).

[10] D. T. Mowry, *Chem. Rev.*, **42**, 207 (1948).

[11] L. F. Hatch and R. R. Estes, *J. Am. Chem. Soc.*, **67**, 1730 (1945); L. F. Hatch, L. O. Morgan, and V. L. Tweedie, *ibid.*, **74**, 1826 (1952).

[12] C. C. Price and I. V. Krishnamerti, *ibid.*, **72**, 5324 (1950).

[13] N. Sperber and R. Frianco, *ibid.*, **72**, 2792 (1950).

[14] L. I. Zakharkin, *Chem. Abstr.*, **50**, 15492*a* (1956).

[15] (a) E. A. Lewton and D. D. Ritchie, *J. Org. Chem.*, **24**, 26 (1959); (b) M. S. Newman and D. K. Phillips, *J. Am. Chem. Soc.*, **72**, 3667 (1959); (c) R. G. R. Bacon and H. A. O. Hill, *Proc. Chem. Soc.*, 113 (1962).

[16] R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **83**, 3262 (1961).

[17] W. Chodkiewicz, *Ann. chim.* (Paris), [13] **2**, 819 (1957).

[18] C. F. Koelsch and A. G. Whitney, *J. Org. Chem.*, **6**, 795 (1941).

$$ArX + Cu^{++} \rightleftarrows [ArXCu]^{++} \xrightarrow{Cu^+} Cu^{++} + [ArXCu]^+$$
$$[ArXCu]^+ \longrightarrow Ar^+ + CuX$$
$$Ar^+ \xrightarrow{CN^-} ArCN \qquad (4)$$

explain the catalytic effect of Cu(I) on the solvolysis of allylic halides[11] (eq. 5).

$$[CH_2{=}CH{-}CH_2CuCl_2] \xrightarrow{OH^-} CH_2{=}CH{-}CH_2{-}OH + CuCl_2^- \qquad (5)$$

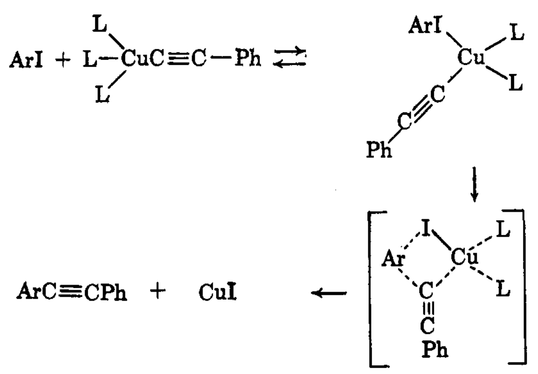
In the present work the ease of reaction of *para* substituted iodobenzenes with cuprous phenylacetylide is in the order p-NO$_2$ > p-H > p-CH$_3$O. A similar order of reactivity has been observed for the halogen exchange brought about by the action of Cu(I) halides on p-substituted aryl halides.[15c,19] Moreover, the kinetics for this latter process are reported to be first order in both aryl halide and Cu(I) halide.[15c] These findings are suggestive of a homolytic process (eq. 7).

$$ArX + CuY \longrightarrow Ar\cdot + CuXY \qquad (6)$$

$$Ar\cdot + CuXY \longrightarrow ArY + CuX \qquad (7)$$

Step 6 would be analogous to the cleavage of carbon–halogen bonds by Cr(II),[20] and 7 is in accord with the well documented efficiency of Cu(II) species to function as free-radical scavengers.[21]

Although the processes that might be depicted as eq. 3 could be accommodated by oxidation–reduction cycle such as eq. 6, 7, it would seem sterically difficult for an aryl radical to attack a Cu(II) acetylide complex in pyridine solution at the carbon adjoining copper. For this reason we prefer to describe a concerted path for these reactions (eq. 8).



(8)

In the heterocyclic synthesis both the substitution and cyclization would seem to occur within the same copper complex, since 2-aminodiphenylacetylene was not cyclized upon exposure to cuprous iodide and cuprous phenyl acetylide in refluxing pyridine.[22]

Experimental

Cuprous Phenylacetylide.[23]—An aqueous ammoniacal solution of 20.0 g. (0.105 mole) of cuprous iodide[24] was poured with stirring into a solution of 10.7 g. (0.105 mole) of phenylacetylene in 500 ml. of ethanol. The reaction mixture was allowed to stand for 15 min. The bright chartreuse precipitate was filtered off and washed five times each with water, ethanol, and ether. The bright canary yellow solid thus obtained was dried in a rotary evaporator at 50° (20 mm.) for 2 hr.; yield, 13.4 g. (77%).[25]

Cuprous *n*-Propylacetylide.—In a manner entirely analogous to that described previously for cuprous phenylacetylide, 19.40 g. (0.102 mole) of cuprous iodide and 6.95 g. (0.098 mole) of 1-pentyne provided after washing and drying 11.2 g. (0.086 mole, 88%) of bright yellow cuprous *n*-propylacetylide.

***p*-Methoxydiphenylacetylene.**—In a 300-ml. round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet, and a reflux condensor fitted to a mercury trap was placed 7.1 g. (0.030 mole) of *p*-iodoanisole and 100 ml. of dry pyridine. The flask was purged with nitrogen while stirring and 5.0 g. (0.030 mole) of cuprous phenylacetylide was added during the nitrogen flush. The contents were warmed in an oil bath at 120° for 10 hr. with stirring. Upon addition of the cuprous phenylacetylide a yellow slurry was formed which, after warming, slowly dissolved to give a yellow solution. As the reaction progressed, the color of the solution changed from a bright yellow to a clear reddish amber. Upon completion of the reaction the solution was cooled and diluted with 300 ml. of water. The mixture was extracted three times with ether, and the combined ether extracts were washed successively three times each with dilute hydrochloric acid, 5% sodium bicarbonate, and water, and dried over magnesium sulfate. The dried ethereal solution was concentrated *in vacuo* and the residue crystallized to yield an amber solid having m.p. 51–52°. This substance was decolorized with Norit in hot methanol and crystallized. There was obtained 6.2 g. (0.0298 mole, 98.5%) of small white plates of *p*-methoxydiphenylacetylene with m.p. 58–59° (lit.[26] m.p. 58–60°), $-C{\equiv}C-$ at 4.54 μ.

Anal. Calcd. for $C_{15}H_{12}O$: C, 86.54; H, 5.77; mol. wt., 208. Found: C, 86.46; H, 5.80; mol. wt. (Mechrolab osmometer), 206.

Diphenylacetylene.—In the manner described for *p*-methoxydiphenylacetylene, 6.40 g. (0.039 mole) of cuprous phenylacetylide reacted with 7.94 g. (0.039 mole) of iodobenzene in 100 ml. of pyridine. The crude product was recrystallized from ethanol to yield 6.0 g. (0.034 mole, 87%) of long white needles of diphenylacetylene having melting point and mixture melting point with an authentic sample of 60–61°. The infrared spectrum of this product was identical with that of an authentic sample.

***o*-Methoxydiphenylacetylene.**—In similar fashion 8.5 g. (0.036 mole) of *o*-iodoanisole and 6.0 g. (0.036 mole) of cuprous phenylacetylide in 100 ml. of pyridine provided 10.3 g. of a brown oil giving upon fractionation through a small Vigreux column 7.8 g. (0.033 mole, 91%) of *o*-methoxydiphenylacetylene. The clear colorless oil had b.p. 144–145° (0.2 mm.), n^{22}_{D} 1.6567, $-C{\equiv}C-$ at 4.56 μ.

Anal. Calcd. for $C_{15}H_{12}O$: C, 86.54; H, 5.77; mol. wt., 208. Found: C, 86.74; H, 5.95; mol. wt., 211.

***p*-Nitrodiphenylacetylene**—A mixture of 7.0 g. (0.028 mole) of *p*-nitroiodoiodobenzene, 4.7 g. (0.028 mole) of cuprous phenylacetylide, and 100 ml. of pyridine warmed at 80° for 10 hr. afforded 5.0 g. of crude tolane. The material was recrystallized from petroleum ether to yield 4.8 g. (0.021 mole, 75%) of long amber needles of *p*-nitrodiphenylacetylene having m.p. 119–120°, $-C{\equiv}C-$ at 4.57, NO$_2$ at 6.53 and 7.55 μ.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.04; N, 6.28; mol. wt., 223. Found: C 75.45; H, 4.10; N, 6.29; mol. wt., 228.

***o*-Nitrodiphenylacetylene.**—A mixture of 4.0 g. (0.017 mole) of *o*-iodonitrobenzene, 2.74 g. (0.016 mole) of cuprous phenylacetylide, and 100 ml. of pyridine warmed at 100° for 8 hr. yielded a

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[19] If path 4 were operative in these reactions the converse order of reactivity would be expected since the rate-determining step would be the heterolytic scission of the proposed copper complex to an aryl cation. In keeping with exhaustive studies of electrophilic aromatic substitution, p-CH$_3$O is more capable of stabilizing such an entity than is p-NO$_2$.

[20] C. E. Castro and W. C. Kray, Jr., *J. Am. Chem. Soc.*, **85**, 2768 (1963); C. E. Castro, *ibid.*, **83**, 3262 (1961).

[21] H. E. De La Mare, J. K. Kochi, and F. F. Rust, *ibid.*, **85**, 1437 (1963), and references therein.

[22] On the contrary, cyclization of 1,4-di-*o*-hydroxyphenyl-1,3-butadiyne to α,α-dibenzofuranyl is reported to occur upon treatment with base: F. Toda and M. Nakagawa, *Bull. Chem. Soc. Japan*, **34**, 1000 (1961).

[23] This preparation is adopted from the procedure of N. Ya. Kronvod, *et. al.*, *Zh. Obshch. Khim.*, **26**, 1876 (1956); *Chem. Abstr.* **51**, 4981c (1957).

[24] G. B. Kauffman and R. P. Pinnell, *Inorg. Syn.*, **6**, (1960).

[25] It should be noted that distinctly lower yields of tolanes and heterocycles than those reported here were obtained when the acetylide was not adequately washed free of ammonia or not sufficiently dried. The acetylide containing traces of ammonia had a greenish yellow color.

[26] A. R. Katritzky, A. J. Boulton, and D. J. Short, *J. Chem. Soc.*, 1519 (1960).

reddish crystalline solid. This substance was decolorized with Norit in methanol and crystallized to provide 3.0 g. (0.013 mole, 83.5%) of pale yellow needles of *o*-nitrodiphenylacetylene with m.p. 43–44°, $-C\equiv C-$ at 4.57, NO_2 at 6.55 and 7.50μ.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.34; H, 4.04; N, 6.28; mol. wt., 223. Found: C, 75.43; H, 4.36; N, 6.85; mol. wt., 217.

***p*-Carboxydiphenylacetylene.**—A mixture of 4.5 g. (0.0183 mole) of *p*-iodobenzoic acid, 3.0 g. (0.018 mole) of cuprous phenylacetylide and 100 ml. of pyridine warmed at 110° for 8 hr. yielded a brown crystalline solid. The substance was decolorized with Norit in methanol and recrystallized from chloroform–petroleum ether to give 3.4 g. (0.0153 mole, 85%) of white needles of *p*-carboxydiphenylacetylene having m.p. 221–222° (lit.[27] m.p. 220.5–221°), $-C\equiv C-$ at 4.55 μ.

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 81.08; H, 4.51; mol. wt., 222. Found: C, 80.70; H, 4.71; mol. wt., 219.

***p*-Hydroxydiphenylacetylene.**—A mixture of 4.0 g. (0.018 mole) of *p*-iodophenol, 3.4 g. (0.0206 mole) of cuprous phenylacetylide, and 160 ml. of pyridine warmed at 125° for 8 hr. provided 3.4 g. of a reddish oil. The substance was decolorized with Norit in methanol and crystallized from petroleum ether to yield 2.9 g. (0.015 mole, 82%) of white needles of *p*-hydroxydiphenyl acetylene having m.p. 83–84°, $-C\equiv C-$ at 4.58, OH at 2.9–3.1 μ.

Anal. Calcd. for $C_{14}H_{10}O$: C, 86.60; H, 5.15. Found: C, 86.43; H, 5.03.

***p*-Aminodiphenylacetylene.**—A mixture of 5.35 g. (0.025 mole) of *p*-iodoaniline, 4.0 g. (0.024 mole) of cuprous phenylacetylide, and 100 ml. of pyridine warmed at 125° for 24 hr. upon work-up.[28] afforded a red oil. This substance was decolorized with Norit in methanol and recrystallized from chloroform–petroleum ether to yield 3.6 g. (0.0185 mole, 76%) of fine pale yellow needles of *p*-aminodiphenylacetylene. A further recrystallization gave 2.7 g. of white needles with m.p. 128–129° (lit.[29] m.p. 126–127°), $-C\equiv C-$ at 4.55, NH_2 at 2.95 and 3.05 μ.

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.05; H, 5.70; N, 7.25. Found: C, 87.02; H, 5.85; N, 7.14.

2-Phenylbenzofuran.—A mixture of 4.03 g. (0.0183 mole) of *o*-iodophenol, 3.0 g. (0.0184 mole) of cuprous phenylacetylide, and 100 ml. of pyridine warmed at 125° for 7 hr. provided 3.8 g. of a brown crystalline solid. The substance was decolorized with Norit in methanol and recrystallized from petroleum ether to yield 3.4 g. (0.0175 mole, 85%) of white platelets of 2-phenylbenzofuran having melting point and mixture melting point with an authentic sample of 120–121°. The infrared spectrum of the product was identical with that of an authentic sample.

This reaction was carried out in other solvents, but in no case did the yield exceed that in pyridine. The solvents[30] employed and the yields of of 2-phenylbenzofuran obtained were dimethyl sulfoxide, 79%; dimethylformanide, 81%; ethylene glycol, 70%; and acetic acid, 83%.

3-Phenylisocoumarin.—A mixture of 4.5 g. (0.204 mole) of *o*-iodobenzoic acid, 3.0 g. (0.0182 mole) of cuprous phenylacetylide, and 100 ml. of pyridine warmed at 125° for 6 hr. provided a tan solid which was recrystallized from methanol–water to yield 3.8 g. (0.0171 mole, 94%) of colorless 3-phenylisocoumarin with m.p. 90–91° (lit.[31] m.p. 91–92°), C=O at 5.70 μ.

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 81.09; H, 4.50; mol. wt., 222. Found: C, 80.88; H, 4.69; mol. wt., 222.

2-Phenylindole.—A mixture of 4.0 g. (0.0175 mole) of *o*-iodoaniline, 3.0 g. (0.0182 mole) of cuprous phenylacetylide, and 100 ml. of pyridine at 125° for 8 hr. afforded a brownish solid. The substance was recrystallized from petroleum ether to yield 3.0 g. (0.0155 mole) of small white plates of 2-phenylindole having melting point and mixture melting point with an authentic sample of 189°. The infrared spectrum of the product was identical with an authentic sample.

2-*n*-Propylindole.—A mixture of 7.55 g. (0.0344 mole) of *o*-iodoaniline, 4.50 g. (0.0346 mole) of cuprous *n*-propylacetylide, and 100 ml. of pyridine was warmed at 125° for 6 hr. The work-up was like that described for *p*-methoxytolane except that the ether extracts were washed rapidly with cold very dilute (1%) hydrochloric acid followed immediately by the sodium bicarbonate and water washings. The dried (potassium carbonate) ether extracts upon concentration afforded 6 g. of a dark oil. This substance was fractionated through a small Vigreux column to yield 4.9 g. (0.0308 mole, 89%) of 2-*n*-propylindole having b.p. 93° (0.3 mm.). The material could not be induced to crytsallize.[32] The infrared spectrum of ths product was very similar to authentic 2-methylindole. The ultraviolet was characteristic of indoles, λ_{max} 219 and 260 mμ (weak, broad). A pine splint test was positive.

Anal. Calcd. for $C_{11}H_{13}N$: C, 83.02; H, 8.18; N, 8.80. Found: C, 82.90; H, 8.18; N, 8.80.

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[27] K. Koch and G. S. Hammond, *J. Am. Chem. Soc.*, **75**, 3443 (1953).

[28] The ether extracts were washed six times with water only.

[29] L. M. Litvinenko, *et. al.*, *Zh. Obshch. Khim.*, **28**, 2046 (1958); *Chem. Abstr.*, **53**, 2154*a* (1959).

[30] The work-up in these solvents was the same as that described for *p*-methoxytolane except that before ether extraction the solution was diluted with 400 ml. of water and the ether extracts were washed with water only.

[31] S. Gabriel, *Ber.*, **18**, 2445(1885).

[32] A melting point of 34° has been reported: A. Verley and J. Beduwe, *Bull. soc. chim. France*, **37**, 189 (1925).

Synthesis of Unsymmetrical Diarylphosphinous Chlorides and Their Conversion to Secondary Phosphine Oxides[1,2]

LOUIS D. QUIN AND RONALD E. MONTGOMERY

Department of Chemistry, Duke University, Durham, North Carolina

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The reduction with aluminum of six aryldiazonium fluoroborate–arylphosphonous dichloride reaction products (presumably $Ar_2PCl_2{}^+BF_4{}^-$) has produced diarylphosphinous chlorides in roughly 30–50% yield. This reaction offers a new route to unsymmetrical diarylphosphinous chlorides, which have remained relatively obscure up to the present study. It also was found that the phosphinous chlorides can be hydrolyzed on addition to water to produce diarylphosphine oxides in good yield and purity. Unsymmetrical diaryl phosphine oxides have not hitherto been available.

Recent reports from this laboratory[3] have described a new synthesis of arylphosphonous dichlorides, based on reactions 1 and 2. Reaction 1, conducted in dry solvents, was first observed by Doak and Freedman.[4] Structure I has been suggested,[5] but not established, for the product. This intermediate, which is not isolated, has been widely used[6] as a precursor of phosphonic acids which are formed on hydrolysis. The occurrence of reaction 2 was anticipated because of the resemblance of I to other structures capable of under-

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[1] A portion of this work was presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, and was the subject of a preliminary communication [L. D. Quin and R. E. Montgomery, *J. Org. Chem.*, **27**, 4120 (1962)]; taken from the Ph.D. dissertation of R. E. Montgomery, Duke University, 1963.

[2] Supported by Research Grant CY-5507 from the National Cancer Institute, Public Health Service.

[3] L. D. Quin and J. S. Humphrey, Jr., *J. Am. Chem. Soc.*, **82**, 3795 (1960); **83**, 4124 (1961).

[4] G. O. Doak and L. D. Freedman, *ibid.*, **73**, 5658 (1951).

[5] P. C. Crofts, *Quart. Rev.* (London), **12**, 341 (1958).

[6] L. D. Freedman and G. O. Doak, *Chem. Rev.*, **57**, 479 (1957).