as reaction intermediates is not a necessary condition for reactions proceeding by this mechanism. The greater or lesser degree of freedom of such ions must depend upon the organosilicon compound undergoing reaction, the attacking reagent, and the reaction medium, whereas the only essential requirement for reactions proceeding by the above mechanism is the creation of electron-deficiency at a carbon atom which is sufficiently close to the silicon so as to cause release of an electron-pair from silicon to carbon.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

6-Methoxy-8-nitroquinolines with Substituents in the 3- and 4-Positions[1]

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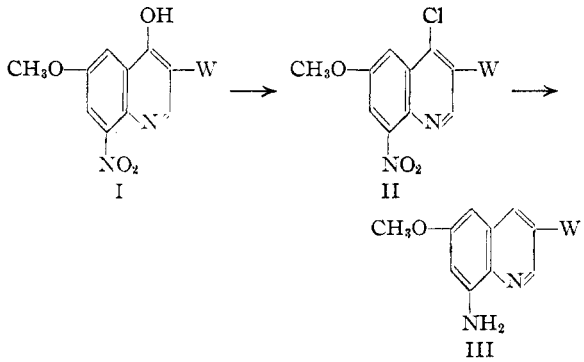
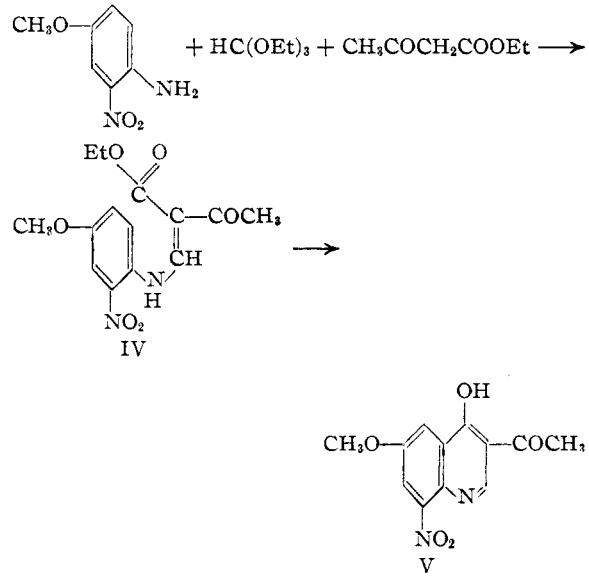
A common procedure for the replacement of hydroxyl by hydrogen in 4-quinolinols is conversion to the halide followed by reduction. Although this sequence of reactions had not been studied when other groups were in the 3-position, it appeared to be an attractive route to the 3-substituted-6-methoxy-8-aminoquinolines, III.



(W = CN, COOEt, C_6H_5 or CH_3CO)

The conversion to the halide, II, was difficult but could be accomplished with a mixture of phosphorus oxychloride and pentachloride.[2] However, none of a variety of conditions of hydrogenation over palladium, platinum or Raney nickel catalysts would effect reductive dehalogenation of II to III.

The preparation of 3-acetyl-6-methoxy-8-nitro-4-quinolinol (V) was accomplished by cyclization of the "anil" (IV) which in turn could be made by three methods. Direct combination of the nitroanisidine, ortho ester and keto ester is simpler but gives poorer yields than the reaction of the anisidine with ethoxymethyleneacetoacetic ester (formed by prior reaction of the latter two reagents). The third method involves reaction of the ortho ester and anisidine to give the substituted diphenylformamidine which in turn reacts with the keto ester.[3] Attempts were also made to produce ethoxymethylene-*m*-nitroanisidine which would be expected to be a useful intermediate but generally the diarylformamidine was the product.



Considerable difficulty has been encountered during "anil" formation in the use of α-formyl esters for quinolinol syntheses.[4] With formylphenylacetic ester and *m*-nitroanisidine, this difficulty is overcome by the use of zinc chloride to catalyze the reaction.

Successful attempts to prepare plasmochin-type drugs with blocking groups in the 3-position will be described in forthcoming publications.

Experimental[5]

3-Acetyl-6-methoxy-8-nitro-4-quinolinol.—Equimolar quantities of *m*-nitroanisidine and ethyl ethoxymethyleneacetoacetate were heated at 150° for fifteen minutes, cooled and the "anil" crystallized from ethanol in quantitative yield, m. p. 153–154°. This material was added to fifteen times its weight of boiling Dowtherm (a mixture of biphenyl and diphenyl ether). Eighteen minutes of

(1) This work was supported by a grant from the National Institute of Health, U. S. Public Health Service.

(2) C. C. Price, N. J. Leonard and H. F. Herbrandson, THIS JOURNAL, **68**, 1251 (1946), used thionyl chloride for this conversion on simpler compounds but we were unable to use it in this work.

(3) These combinations of reactants were previously studied by H. R. Snyder and R. E. Jones, *ibid.*, **68**, 1253 (1946).

(4) Because of this, we have previously used the α-oxalyl esters and subsequent decarboxylation, R. H. Baker and R. M. Dodson, *ibid.*, **68**, 1283 (1946); B. Riegel, C. J. Albisetti, Jr., G. R. Lappin and R. H. Baker, *ibid.*, **68**, 2685 (1946).

(5) Microanalyses by Jane Gibbs, Rosalind Guy and Virginia Hobbs.

heating was found to be the optimum time for 5 g. of "anil." The quinolinol was precipitated from the cooled reaction mixture by addition of Skellysolve "C" (petroleum ether, b. p. 85–100°). Crystallized from methanol the maximum yield was 40% of yellow plates. These change to needles at 180°, m. p. 232.5–235°.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: N, 10.68. Found: N, 10.72.

3-Acetyl-4-chloro-6-methoxy-8-nitroquinoline.—The corresponding 4-quinolinol was covered with a large excess of freshly distilled phosphorus oxychloride and heated on the steam-bath for an hour. Fresh oxychloride was added and the solution refluxed for another hour. The excess phosphorus oxychloride was distilled at reduced pressure and the residue cooled in an ice-bath. This was slowly poured with vigorous stirring into a slurry of shaved ice. The acid was partially neutralized at 0° with sodium hydroxide. The precipitate was removed by filtration and crystallized from isopropyl alcohol (decolorized by Norit) to give fibrous white crystals, m. p. 118–119°. The yield varies greatly from run to run and has never exceeded 15%.

Anal. Calcd. for $C_{12}H_9ClN_2O_4$: N, 10.0. Found: N, 9.94.

2,2′-Dinitro-4,4′-dimethoxydiphenylformamidine.—A solution of 4.2 g. (0.025 mole) of *m*-nitroanisidine and 3.7 g. (0.025 mole) of ethyl orthoformate in 50 ml. of xylene was distilled slowly through a short distilling column until 3 ml. of alcohol and xylene had been collected. On cooling, 3 g. (69%) of red needles was obtained, m. p. 165–166°. Occasionally the product was long yellow needles, m. p. 41–42°, which appeared to be **ethoxymethylene-*m*-nitroanisidine,** but the preparation of this compound was unreliable.[6]

The formamidine was also prepared by the method of Lander.[7] 2-Nitro-4-methoxyformanilide, m. p. 142–143°, was prepared in 88% yield by refluxing 16.8 g. (0.10 mole) of the amine in 50 ml. of 50% formic acid for twelve hours and cooling to produce crystals. To a solution of 3.3 g. (0.027 mole) of the formanilide in 12.5 g. (0.08 mole) of ethyl iodide was added portionwise 10 g. of freshly prepared dry silver oxide. During the addition the mixture was diluted with 50 ml. of dry ether, and when it had all been added, the mixture was refluxed for two hours. After filtration, the solvent was evaporated and the residue crystallized from acetone, 1 g. (22%), m. p. 163–164°. Mixed with the material from the ortho ester preparation there was no depression in m. p.

Anal. Calcd. for $C_{15}H_{14}N_4O_6$: N, 16.2. Found: N, 16.1.

3-Carbethoxy-4-chloro-6-methoxy-8-nitroquinoline.—The corresponding 4-quinolinol[8] was covered with phosphorus oxychloride and heated at 100° for six hours. After cooling and pouring into a slurry of ice, the product was crystallized from Skellysolve "C" to give yellow needles, m. p. 108–109°, in 20% yield.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_5$: N, 9.34. Found: N, 9.11.

(6) Compare the preparation of ethoxymethyleneaniline, H. W. Post, "The Chemistry of the Aliphatic Ortho Esters," Reinhold Publishing Corp., New York, N. Y., 1943, pp. 87–88.

(7) H. Lander, *J. Chem. Soc.*, **83**, 414 (1903).

(8) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson and R. H. Baker, THIS JOURNAL, **68**, 1264 (1946).

Ethyl α-Phenyl-β-(2-nitro-4-methoxyanilino)-acrylate.—An equimolar mixture of *m*-nitroanisidine and ethyl formylphenylacetate[9] was heated in an oil-bath to 165–170° and then freshly fused and powdered zinc chloride (one part per ten parts of mixture) was carefully added.[10] After maintaining the temperature for twenty-five minutes, the solution was cooled, diluted with chloroform and filtered. The filtrate was evaporated and the residue crystallized from ethanol to give two crystalline modifications of red needles. The higher melting, 138–139°, was the one most readily purified.

Anal. Calcd. for $C_{18}H_{18}N_2O_5$: N, 8.19. Found: N, 8.15.

The lower melting isomer, 114–115°, was obtained by repeated crystallization from ethanol. A mixture of the two forms melted at 100°, but both forms gave the same cyclization products described below.

3-Phenyl-6-methoxy-8-nitro-4-quinolinol.—The "anil," 3.5 g., was added to 50 ml. of refluxing Dowtherm and heated for twenty-five minutes. Addition of Skellysolve "C" to the cooled solution precipitated an amorphous product which was very difficult to crystallize due to gel formation. Brown prisms, m. p. 178–180°, were produced by slow evaporation of a dilute methanol solution.

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: N, 9.46. Found: N, 9.58.

3-Phenyl-4-chloro-6-methoxy-8-nitroquinoline.—The procedure described for the 3-acetyl derivative was used on the amorphous 4-quinolinol. The product was crystallized from isopropyl alcohol in white fibrous needles, m. p. 166–167°. The yield based on "anil" was 56%.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_3$: N, 8.91. Found: N, 8.33.

3-Cyano-4-chloro-6-methoxy-8-nitroquinoline.—According to the method of Snyder and Jones[3] 0.25 mole each of *m*-nitroanisidine, 42 g., ethyl orthoformate, 37 g., and ethyl cyanoacetate, 28 g., were mixed and heated at 160–165° until no more ethanol distilled. The "anil," m. p. 160–164°, was cyclized by refluxing for four hours in ten times its weight of Dowtherm. The product obtained by dilution with Skellysolve "C" was crystallized from acetic acid to give 8 g., 13%, of yellow needles, m. p. about 320°. This crude quinolinol was covered with an excess of a 3:1 mixture of phosphorus oxychloride and pentachloride and refluxed for five hours. The product worked up as previously described and crystallized from ethanol gave yellow needles, m. p. 194–195°, in 80% yield.

Anal. Calcd. for $C_{11}H_6ClN_3O_3$: N, 15.9. Found: N, 15.6.

Summary

6-Methoxy-8-nitro-4-quinolinols with cyano, carbethoxy, acetyl and phenyl groups in the 3-position have been described. These have been converted into the corresponding 4-chloro derivatives. Reductive dehalogenation of the chloro derivatives was unsuccessful.

EVANSTON, ILLINOIS RECEIVED APRIL 13, 1949

(9) Prepared by the method of W. Wislicenus, *Ber.*, **20**, 2930 (1887), in 76% yield, b. p. 96–97° at 3 mm.

(10) This is the method of G. Reddelien, *ibid.*, **43**, 2476 (1910); **47**, 1364 (1914).