[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

Reactivity of 3,5-Dinitro-2-chlorobiphenyl

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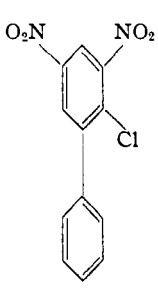
It is well known that 2,4-dinitrochlorobenzene is a halide sufficiently reactive to enter into many metathetical reactions. Of particular interest, condensation with sodio-malonic[1] and acetoacetic esters[2] may be readily accomplished.[3]

In view of this, we considered a study of the comparable system, 2-chloro-3,5-dinitrobiphenyl (I), to be interesting in that the condensation



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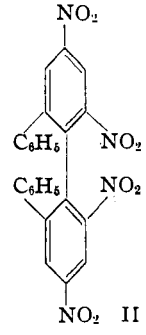

II

products might form useful intermediates in the synthesis of phenanthrene derivatives.

While 2-chloro-3,5-dinitrobiphenyl (I) has been described previously,[4] the reaction by which it was obtained (*p*-toluenesulfonyl chloride with 2-hydroxy-3,5-dinitrobiphenyl) was found to be without preparative value.[5] A more convenient route was afforded by the diazotization of 2-amino-3,5 dinitrobiphenyl[6] in nitrosyl sulfuric acid, followed by reaction with cuprous chloride. The resulting halide (I) shows a reactivity toward sodium methylate or ethylate comparable with that observed for 2,4-dinitrochlorobenzene,[7] and reacts readily with piperidine.[8] When heated with copper, it apparently underwent the Ullmann reaction to yield a tetranitrotetraphenyl (II).

When a solution of sodiomalonic ester in absolute alcohol was refluxed with the halide, the only product isolated was a 93% yield of 2-ethoxy-3,5-dinitrobiphenyl, and essentially the same result (74% yield) was obtained with sodio-acetoacetic ester.[9]

When the same reactions were repeated in the absence of alcohol using the sodio ester in benzene or dioxane and refluxing for even longer periods, there was no indication of reaction, that is to say the solution remained alkaline, gave no precipitate of sodium chloride and a considerable proportion of the starting materials could be recovered.

In our opinion, this great change brought about by the introduction of a phenyl group into the system of 2,4-dinitrochlorobenzene may be attributed to steric hindrance. The alkoxide anion is undoubtedly present to some extent in all cases in which sodio-esters are used in alcohol solution, but condensation takes place preferentially with the enolate anion. Here, however, the approach of the bulky ester anion is impeded or prevented altogether, while the smaller size of the alkoxide ion allows it to approach the reactive atom with a minimum of interference. Under these circumstances, alkoxylation, which is normally unimportant, becomes the predominant reaction.

Experimental

2-Chloro-3,5-dinitrobiphenyl.—On dissolving 186 g. of 2-(*p*-toluenesulfonamido)-biphenyl in 372 cc. of concentrated sulfuric acid and allowing the solution to stand at room temperature for one-half hour, the sulfate of the free amine was formed and was poured on ice and collected. This material was satisfactory for use in the diazotization.

Nitrosylsulfuric acid[10] was prepared by adding slowly 42.4 g. of sodium nitrate to 400 cc. of concentrated sulfuric acid at 0°. When the addition was complete, the solution was heated for four hours at 80°. After cooling the solution to room temperature, the amine sulfate prepared above was dissolved in 310 cc. of the nitrosylsulfuric acid solution and the solution stirred for two more hours at room temperature. At the end of this period, it was added slowly with stirring to an ice-cold solution of cuprous chloride prepared in the usual way from copper sulfate (72 g.), sodium chloride (30 g.), water (140 cc.), copper powder (32 g.) and hydrochloric acid (315 cc.). After stirring for an additional half-hour, the sparingly soluble diazonium compound was collected on a mat of glass wool, transferred to a flask and decomposed by refluxing for six hours with water. The chloride crystallized from methanol (small plates) or from acetic acid (prisms) and was yellow in color; m. p. 115–116° (lit.[4] 119°).

A sample prepared by the method of Borsche and Scholten[4] melted at the same temperature and gave no depression of melting point when mixed with our preparation.

Anal.[11] Calcd. for $C_{12}H_7O_4N_2Cl$: Cl, 12.72. Found: Cl, 12.40.

2-Ethoxy-3,5-dinitrobiphenyl.—To a solution prepared by dissolving 0.069 g. of sodium in 50 cc. of absolute ethanol, 0.8 g. of 2-chloro-3,5-dinitrobiphenyl was added, and the whole refluxed for fifteen minutes. Upon cooling,

(1) Dey and Doraiswami, *J. Ind. Chem. Soc.*, **10**, 309 (1933).

(2) Borsche, *Ber.*, **42**, 601 (1909).

(3) The comparable condensation reactions of 2,4-dinitro bromobenzene have been more extensively investigated; Heckmann, *Ann.*, **220**, 128 (1883); Richter, *Ber.*, **21**, 2470 (1888); see also ref. 2.

(4) Borsche and Scholten, *Ber.*, **50**, 596 (1917).

(5) In addition to the desired halide, the ester and a considerable amount of tar are produced.

(6) Bell, *J. Chem. Soc.*, 2770 (1928).

(7) A nearly quantitative yield of the ethers may be obtained by refluxing for only fifteen minutes. Dey and Doraiswami (ref. 1) observed that the corresponding reactions with 2,4-dinitrochlorobenzene could be accomplished in twenty to thirty minutes.

(8) Borsche and Scholten (ref. 4) demonstrated the reactivity of the chlorodinitrobiphenyl (I) by reaction with two other amines (aniline and phenylhydrazine), as well as with ammonia.

(9) The procedures used were modeled after those of Dey and Doraiswami for the preparation of dinitrophenylmalonic and acetoacetic esters (ref. 1).

(10) The diazotization technique is essentially that used by Holleman (*Rec. trav. chim.*, **35**, 1 (1916)) in the preparation of 2,3-dinitrochlorobenzene.

(11) Microanalyses by Dr. T. S. Ma, University of Chicago.

0.75 g. (93%) of colorless flat prisms (m. p. 114–115°) was obtained. The melting point was not changed by recrystallization from ethyl alcohol.

Anal. Calcd. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20. Found: C, 58.68; H, 4.08.

2-Methoxy-3,5-dinitrobiphenyl was obtained as above using absolute methanol instead of ethanol. A nearly quantitative yield of small white plates was obtained, m. p. 113.5–114°.[12]

Anal. Calcd. for $C_{13}H_{10}N_2O_5$: C, 56.93; H, 3.68. Found: C, 57.41; H, 3.67.

2-Piperidino-3,5-dinitrobiphenyl was prepared by refluxing 2-chloro-3,5-dinitrobiphenyl for three minutes in piperidine solution. On cooling, the piperidino compound crystallized out in almost quantitative yield. The compound crystallized from methanol as small yellow-orange needles, m. p. 184.5–185°.

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.23. Found: C, 62.13; H, 5.06.

2,2'-Diphenyl-4,4',6,6'-tetranitrobiphenyl (II).—A mixture of 2.8 g. of 2-chloro-3,5-dinitrobiphenyl and 3 g. of sand was heated to 215° and 2.8 g. of copper powder added over a period of about forty minutes. The mixture was stirred for two hours at 190° and then poured into 10–15 g. of sand. The sand was extracted repeatedly with hot acetic acid. After several recrystallizations, a small quantity of small yellow needles was obtained, m. p. 248–249°.

Anal. Calcd. for $C_{24}H_{14}N_4O_8$: C, 59.26; H, 2.90. Found: C, 59.27; H, 2.92.

Attempts to Condense 2-Chloro-3,5-dinitrobiphenyl with Sodio-malonic and Acetoacetic Esters in Ethanol Solution.—To a solution of approximately 0.23 g. of sodium in 75 cc. of absolute ethanol, 1.6 g. of ethyl malonate was added. To this, 3 g. of 2-chloro-3,5-dinitrobiphenyl was added with stirring and the mixture refluxed for eight hours. After evaporation of most of the alcohol, the residue was poured into cold dilute hydrochloric acid. The resulting product was recrystallized from ethanol, m. p. 114–115°. When mixed with the starting material, it melted below 95°, but it did not depress the melting point of 2-ethoxy-3,5-dinitrobiphenyl; yield 2.9 g. (93%).[13]

When the above reactions were repeated using an equimolecular quantity of acetoacetic ester instead of malonic ester, 2.3 g. (74%) of the ether was obtained.

Attempts to Condense 2-Chloro-3,5-dinitrobiphenyl with Sodio-esters in the Absence of Alcohol.—The sodio-esters were prepared in the usual way by the action of powdered sodium on the esters in an inert solvent. The halide was added and refluxed for a period after which the mixture was poured on ice and hydrochloric acid. The solvent layer was separated, the solvent distilled off, the ester recovered by distillation and the halide by crystallization of the residue. The results are reported in the accompanying table.

ATTEMPTED CONDENSATION WITH 2-CHLORO-3,5-DINITROBIPHENYL IN THE ABSENCE OF ALCOHOL

Sodio-ester	Solvent	Time of refluxing, hr.	Ester recovered, %	Chloride recovered, %
Malonic	Benzene	24	[a]	66[b]
Malonic	Dioxane	60	75	28
Aceto-acetic	Benzene–xylene (1:1)	72	0	50

[a] No attempt made to recover ester. [b] When this experiment was repeated using sodio-desoxybenzoin, 66% of the chloro compound was recovered.

Summary

In contrast to 2,4-dinitrochlorobenzene which is reported to undergo condensation with sodio-esters even in the presence of alcohol, 2-chloro-3,5-dinitrobiphenyl has been found to undergo ethoxylation under these conditions.

This difference in behavior has been attributed to steric hindrance.

(12) Hill and Hale (*Am. Chem. J.*, **33**, 1 (1905)) apparently obtained the same product, m. p. 114–115°, by methylation of 2-hydroxy-3,5-dinitrobiphenyl.

(13) The yield was calculated from the halide rather than from the sodium which was not weighed so accurately.

DURHAM, N. C. RECEIVED MAY 1, 1944

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Dialkylaminoalkyl Derivatives of Substituted Quinolines and Quinaldines

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Inasmuch as only four dialkylaminoalkyl derivatives of 4-amino-6-methoxyquinoline have been described,[1,2] it was decided to extend this series to include a representative group of dialkylaminoalkyl side chains to determine whether any suitably active compound could be evolved for use in the treatment of malaria. Several of these derivatives were demethylated to the corresponding 6-hydroxy derivatives since no compounds of this type had ever been described. In the course of the investigation, two substituted quinaldines were also prepared, since Holcomb and Hamilton[3] have reported recently that substituted quinaldines were active in avian malaria in contrast to the findings of early investigators.[4]

Accordingly, we have prepared the series of substituted 4-amino-6-methoxy- and 4-amino-6-hydroxyquinolines and the two quinaldines given in Table I.

Experimental Part

4-(γ-Diethylaminopropyl)-amino-6-methoxyquinoline Dihydrochloride.—A mixture of 9.5 g. (0.05 mole) of 4-chloro-6-methoxyquinoline[1] and 7 g. (0.06 mole) of γ-diethylaminopropylamine in 50 cc. of *p*-cymene was refluxed in an oil-bath for eight hours. The mixture was then cooled, shaken with about 100 cc. of water containing a little hydrochloric acid and extracted twice with ether. The aqueous layer was made alkaline and the 4-(γ-diethylaminopropyl)-amino-6-methoxyquinoline which separated as an oil was taken up in 200 cc. of ether, dried

(1) O. Y. Magidson and M. V. Rubtsov, *J. Gen. Chem.* (U. S. S. R.) **7**, 1896 (1937).

(2) E. P. Hal'perin, *Med. Parasitol. Parasitic Diseases* (U. S. S. R.) **9**, 44 (1940).

(3) W. F. Holcomb and C. S. Hamilton, THIS JOURNAL, **64**, 1309 (1942).

(4) I. L. Krichevskii, E. Y. Sternberg and E. P. Hal'perin, *J. Microbiol. Expidemiol. Immunobiol.* (U. S. S. R.) **14**, 642 (1935).