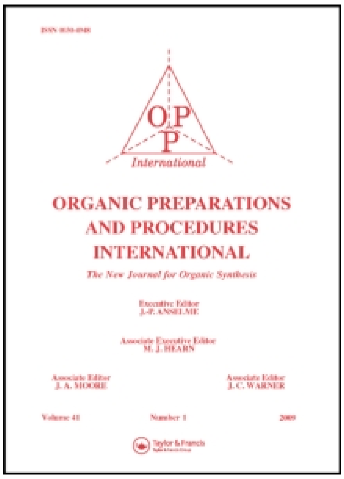

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Carroll, F. I. and Miller, H. Wayne(1970) 'THE REACTION OF 2,3-DICHLORO-1,4-NAPHTHOQUINONE WITH p-NITROBENZHYDRAZIDE1', Organic Preparations and Procedures International, 2: 4, 259 — 263

To link to this Article: DOI: 10.1080/00304947009458625

URL: http://dx.doi.org/10.1080/00304947009458625

ORGANIC PREPARATIONS AND PROCEDURES, 2(4), 259-263 (1970)

THE REACTION OF 2,3-DICHLORO-1,4-NAPHTHOQUINONE WITH p-NITROBENZHYDRAZIDE[1]

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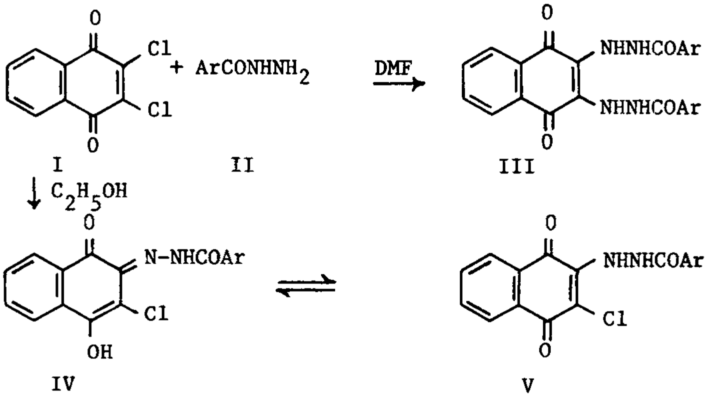
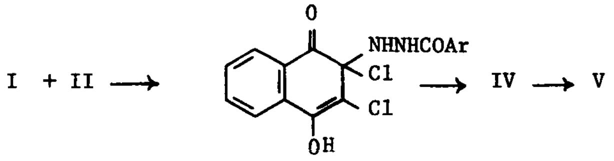
The reaction of 2,3-dichloro-1,4-naphthoquinone (I) with nitrogen nucleophiles is well documented.[2a,b] However, the reaction of I with aroylhydrazides has received little attention.[3,4,5] We have found that the reaction of I with p-nitrobenzhydrazide (II) in 1:2 or 2:1 ratios in DMF gave only the disubstituted product, bis-(p-nitrobenzhydrazino)-1,4-naphthoquinone (III). However, when an ethanolic solution of I and II was refluxed for 21 hr, only traces of III was obtained; the main product was a bright red precipitate that is apparently identical to a compound



Ar = p-NO$_2$C$_6$H$_4$

previously reported and assigned the structure, 2-(p-nitrobenzhydrazino)-3-chloro-1,4-naphthoquinone (V).[4] Based largely on the infrared spectrum which showed strong hydroxyl absorption at 3400 cm^{-1}, a weak N-H absorption at 3150 and 3125 cm^{-1}, a strong C=O peak at 1690 cm^{-1} and nitro peaks at 1535 and 1325 cm^{-1}, we have assigned the tautomeric structure, 4-hydroxy-3-chloro-1,2-naphthoquinone-2-p-nitrobenzhydrazone (IV) to this red compound. However, if this compound was recrystallized from a DMF and water mixture or an acetic acid and water mixture, the tautomeric form V was obtained as a beautiful yellow crystalline compound. The infrared spectrum which showed strong absorption at 3285 and 3250 cm^{-1} (NH), 1685 cm^{-1} (hydrazide C=O), 1670 and 1650 cm^{-1} (quinone C=O) and 1515 and 1340 cm^{-1} (NO_2) is in agreement with this assignment. Recrystallization of V from a dry DMF and anhydrous methanol mixture gave IV. The tautomerization of IV to V or V to IV was not appreciably affected by the addition of acidic or alkaline agents to a DMF solution of either tautomer. The use of dry solvents and crystallization at high concentration favored the formation of IV, whereas, the use of aqueous solvents and crystallization from dilute solution favored the formation of V.[6] In a brief study of the alkaline catalysis of the reaction of I with II, we found that the use of catalytic amounts of N,N-diethylaniline (DEA) increased the yield of IV from 50 to 66%. The use of one equivalent of DEA gave 47% of IV, and if two equivalents of DEA was used none of the products IV or V could be isolated.

The reaction of I and II in ethanol, with or without added DEA, always gave IV as the initial product. The formation of V apparently results solely from the tautomerization of IV. On the basis of this information and the fact that direct displacement of chloride from I would not be a very favorable reaction, we believe that IV is formed by an addition elimination reaction as shown on the next page.



Ar = p-$NO_2C_6H_4$-

Aryl hydrazones derivatives of simple ketones are theoretically capable of existing as imine-enamine tautomers similar to IV and V. However, no valid evidence for the existence of simple enehydrazines have been reported except in cases where the enamine carbon-carbon double bond has additional stabilization.[7,8] In the present case structure V is stabilized by the 1,4-naphthoquinone system.

EXPERIMENTAL[9]

The Reaction of 2,3-Dichloro-1,4-naphthoquinone (I) with p-Nitrobenzhydrazide (II).

a) In N,N-Dimethylformamide

A solution of 1.0 g (4.4 mmoles) of 2,3-dichloro-1,4-naphthoquinone (I) and 1.60 g (8.8 mmoles) of p-nitrobenzhydrazide (II) in 20 ml of dry N,N-dimethylformamide (DMF) was heated on the steam bath for 1/4 hr. On cooling and dilution with methanol, 1.0 g (44%) of 2,3-bis-(p-nitrobenzhydrazino)-1,4-naphthoquinone (III) separated, m.p. 272-274° (dec.). The analytical sample prepared by further recrystallization from a DMF and methanol mixture had m.p. 274-277° (dec). ν_{max}^{KBr} 1708 (broad C=O peak) and 1650 cm^{-1} (weak C=O peak).

Anal. Calc'd for $C_{24}H_{16}N_6O_8$: C, 55.82; H, 3.12; N, 16.28. Found: C, 55.74; H, 3.00; N, 16.24.

If 4.4 and 2.2 mmoles of II was used in place of 8.8 mmoles the yield was reduced to 31 and 20%, respectively.

b) In Ethanol

A mixture of 1.0 g (4.4 mmoles) of I and 0.8 g (4.4 mmoles) of II in

50 ml of absolute ethanol was refluxed for 21 hr. The hot reaction mixture was filtered. The red crystals obtained were washed with ethanol and dried to give 0.80 g (50%) of 4-hydroxy-3-chloro-1,2-naphthoquinone-2-p-nitrobenzhydrazone (IV), m.p. 200° (dec). The analytical sample prepared by two recrystallizations from a DMF and methanol mixture had m.p. 205° (dec), lit[4] m.p. 222 (dec). The mass spectrum showed M^+ at m/e 371 and 373.

Anal. Calc'd for $C_{17}H_{10}ClN_3O_5$: C, 54.92; H, 2.71; N, 11.30, Cl, 9.54. Found: C, 55.29; H, 2.85; N, 11.33; Cl, 9.68.

In a separate experiment the initially formed red crystals were recrystallized from an acetic acid and water mixture to give 47% of 2-(p-nitrobenzhydrazino)-3-chloro-1,4-naphthoquinone (V), m.p. 199-204°. The analytical sample prepared by further recrystallization from the same solvent system had m.p. 203-206°. The mass spectrum showed M^+ at m/e 371 and 373.

Anal. Calc'd for $C_{17}H_{10}ClN_3O_5$: C, 54.92; H, 2.71; N, 11.30; Cl, 9.54. Found: C, 54.73; H, 2.84; N, 11.42; Cl, 9.43.

c) In Ethanol Containing N,N-Diethylaniline

If the reaction of I and II was carried out in the same manner as described in (b) but with 0.25 g of N,N-diethylaniline (DEA) added, 1.06 g (66%) of V, m.p. 199° (dec) was obtained.

If 0.65 g (4.4 mmoles) of DEA was used, 0.77 g (47%) of V was obtained, m.p. 197° (dec).

References

1. This investigation was carried out under Contract No. DA-49-193-MD-2862 with the Department of the Army and the U.S. Army Research and Development Command. This paper is contribution number 590 from the Army Research Program on Malaria.
2. See a) J. A. Van Allan and G. A. Reynolds, J. Org. Chem., 28, 1019

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3. S. Petersen, W. Gauss and E. Urbschat, Angew. Chem., 67, 217 (1955).
4. M. Akatsuka, Yakugaku Zasshi, 83, 440 (1963); C. A. 59, 7443 (1963).
5. In 1955 Petersen, Gauss and Urbschat[3] mentioned in a footnote that the reaction of I with benzhydrazide in N,N-dimethylformamide (DMF) gave 2,3-dibenzoylhydrazino-1,4-naphthoquinone and Akatsuka[4] reported the reaction of I with several hydrazides. To our knowledge these are the only reports concerning the reaction of I with aroylhydrazides.
6. The almost complete insolubility of IV and V in all common solvents at room temperature prevented the use of UV and n.m.r. techniques to study this tautomerization.
7. N. D. Heindel, P. D. Kennewell and M. Pfau, J. Org. Chem., 35, 80 (1970).
8. Heindel, Kennewell and Pfau[7] found that the addition of arylhydrazine to dimethyl acetylenedicarboxylate gave stable enehydrazine. Stabilization in this case is due to conjugation of the enamine double bond with the two carbomethoxy groups.
9. Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. Ir spectra were measured with a Perkin Elmer 221 Spectrophotometer; samples were prepared in the form of pressed KBr disks. Mass spectra were measured on an AEI MS-902 spectrometer. Thin layer plates were prepared using silica gel HF. The plates were eluted with benzene-ethanol-acetic acid (9:1:1). Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois.

Acknowledgement

We thank Dr. Monroe E. Wall, Director of this Laboratory, for his kind encouragement and support of this work.

(Received April 30, 1970)