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The Reaction of 8-Nitroquinoline with Thiophenol–Thiophenoxide Ion. An Example of Anionic Substitution[1]

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The reaction of 8-nitroquinoline with thiophenol and thiophenoxide ion results in reduction of the nitro group and anionic substitution of one or more phenylmercapto groups on the nucleus. Bromine atoms in 5,7-dibromo-8-aminoquinoline are displaced by chlorine during diazotization and deamination in hydrochloric acid.

In a previous communication[2] the reaction of 4-chloro-8-nitroquinazoline with thiophenoxide ion, during which not only the reactive chlorine but also the nitro group was displaced by phenylmercapto, was reported. Kremer[3] obtained preliminary evidence that, in the reaction of 5-bromo-6-methoxy-8-nitroquinoline with sodium methyl mercaptide in boiling methyl Cellosolve, the nitro group, in addition to the bromine atom, was displaceable by a methylmercapto or β-methoxyethoxy residue. In order to throw further light on this unexpected lability of a nitro group in the 8-position of quinazoline or quinoline toward anionic reagents we have investigated in detail the reaction of 8-nitroquinoline itself with thiophenol in the presence of thiophenoxide ion. No displacement of the nitro group was observed; rather the reaction took a different course.

The reactions of aromatic nitro compounds with organic and alkali metal sulfides and other basic reagents may be divided into three general types. (1) The familiar reduction of nitro groups to amines or intermediate reduction products. (2) Displacement of suitably activated nitro groups in polynitro compounds by the base during which the basic fragment may either take the position vacated by the nitro group or appear elsewhere in the molecule. (3) Direct substitution by the base accompanied by some reduction of the nitro groups. The third type of reaction is pertinent to the present work.

Bradley and Robinson[4] studied the addition of anionic reagents to aromatic systems and classified the ring systems capable of reacting with negatively charged fragments into four types: quinones, nitro compounds, phenols (or amines), such as resorcinol, which can display keto–enol tautomerism, and heterocyclic nitrogen compounds. In particular, they succeeded in adding piperidine in the presence of sodamide to the para position of nitrobenzene, the 4-position of 1-nitronaphthalene, and the 5-position of 8-nitroquinoline (*vide infra*). Bergstrom, Granara and Erickson[5] accomplished the addition of diphenylamine to the para position of nitrobenzene in the presence of sodamide in liquid ammonia. The reaction gave the best yield with excess nitrobenzene which they concluded reacted with the displaced hydride ion to form indefinite reduction products. The direct hydroxylation of nitrobenzene by solid potassium hydroxide[6] and the Piria reaction for the preparation of amino sulfonic acids from nitro compounds and alkali sulfites and bisulfites[7] are other examples of such substitutions.

8-Nitroquinoline fits two of the types in Bradley and Robinson's classification.[4] The nitro group is capable of inducing by resonance an electron de-

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[1] The material presented in this paper is taken from a dissertation submitted by Elizabeth F. Claflin in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Columbia University in June, 1951. A complete literature review of anionic substitutions will be found in the dissertation. After this manuscript was submitted, substantially the same general type of reaction with various nitro compounds and mercaptans was reported by H. R. Davis, Jr., J. W. Copenhaver, W. E. Hanford and H. F. Lederle (Abstracts of Papers Presented at the Spring Meeting of the American Chemical Society, Buffalo, N. Y., March 23-27, 1952, p. 46K).

[1a] University of Michigan, Ann Arbor, Mich.

[2] R. C. Elderfield, T. A. Williamson, W. J. Gensler and C. B. Kremer, *J. Org. Chem.*, **12**, 405 (1947).

[3] C. B. Kremer, unpublished work from these laboratories.

[4] W. Bradley and R. Robinson, *J. Chem. Soc.*, 1254 (1932).

[5] F. W. Bergstrom, I. M. Granara and V. Erickson, *J. Org. Chem*, **7**, 98 (1942).

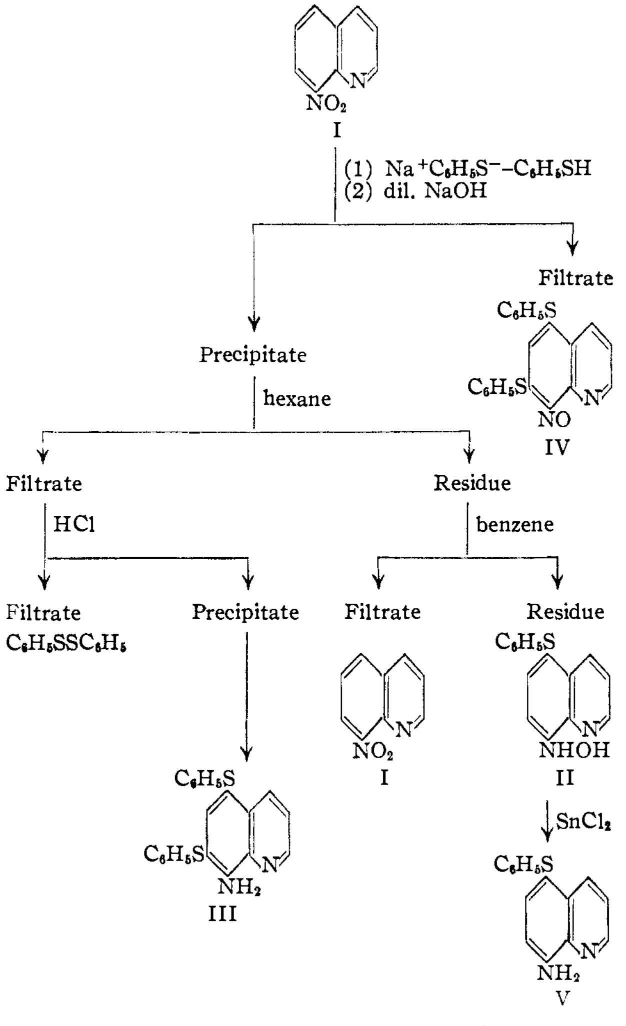
[6] A. Wohl, *Ber.*, **32**, 3486 (1899); O. C. Dermer and L. J. Druker, *Proc. Oklahoma Acad. Sci.*, **23**, 55 (1943); P. Hepp, *Ber.*, **13**, 2346 (1880), *inter alia*.

[7] R. Piria, *Ann.*, **78**, 31 (1851); W. M. Lauer, M. M. Sprung and C. M. Langkammerer, THIS JOURNAL, **58**, 225 (1936), *inter alia*.

ficiency on the 5- and 7-carbon atoms making them attractive to anions, and the heterocyclic nitrogen exerts an attraction on the ring electrons leaving a partial positive charge on the 2- and 4-carbon atoms. If either set of effects can be extended to the other ring by resonance, the activation will be reinforced thereby increasing the reactivity of the compound toward anionic reagents at the 2-, 4-, 5- and 7-positions.

When 8-nitroquinoline (I) was heated with sodium thiophenoxide and excess thiophenol in boiling methanol according to the published procedure,[2] a mixture of products was obtained. This was separated into its components as shown in Chart 1.

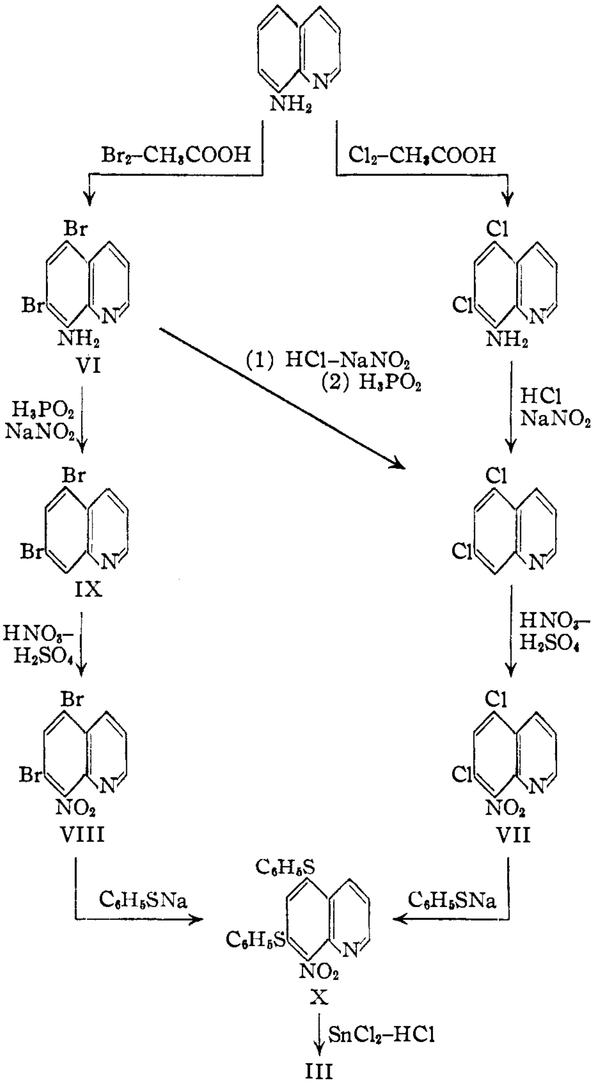
CHART 1



The reaction mixture was poured into dilute alkali and the insoluble material was washed thoroughly first with hexane and then with benzene. The insoluble residue was nearly pure 5-phenylmercapto-8-quinolylhydroxylamine (II) (50%). From the combined hexane washings the hydrochloride of 8-amino-5,7-bisphenylmercaptoquinoline (III) (5%) was obtained. Evaporation of the hexane filtrate from III gave an amount of diphenyl disulfide approximately equivalent to the combined yield of II and III. Extraction of the original alkaline filtrate with ether gave a small amount of brilliant orange needles to which the probable structure IV has been assigned. Unreacted I (about 25%) was recovered from the combined benzene washings on dilution with hexane.

II was very unstable and darkened in air or on recrystallization from most solvents in which it turned to a brown gum. It was soluble in hydrochloric acid with decomposition and gave a positive test with Tollens reagent. On this basis combined with elementary analyses, the compound was assigned structure III. It was reduced with stannous chloride to 8-amino-5-phenylmercaptoquinoline (V). V was synthesized independently for comparison by reaction of 5-bromo-8-nitroquinoline with one mole of sodium thiophenoxide and subsequent reduction of the nitro group. In order to remove all reasonable doubt as to the structure of V, 8-amino-7-phenylmercaptoquinoline was prepared similarly from 7-chloro-8-nitroquinoline.

CHART 2



If the theoretical considerations discussed above are valid, III should possess the structure assigned to it. That this was so was shown by synthesis of III as shown in Chart 2. However several points of interest were encountered during the course of this synthesis. 8-Aminoquinoline was brominated by a modification of the procedure of Claus and Setzer.[8] The product of this reaction had been shown by Claus and Setzer to be identical with the substance formed in the Skraup reaction with 2-nitro-3,5-dibromoaniline. Although repeated recrystallization of VI failed to raise the melting point to that reported by Claus and Setzer, the analytical data were satisfactory.

The behavior of VI when elimination of the amino group was attempted is interesting. When the diazotization was carried out in hydrochloric acid and the crude product was nitrated directly, the m.p. of the product could not be raised above 168°, the reported m.p. of 5,7-dichloro-8-nitroquinoline (VII) whereas 5,7-dibromo-8-nitroquinoline (VIII) melts at 198°. The identity of VII was established by comparison with an authentic sample prepared by the Skraup reaction,[9] and by conversion of material from both sources to 5,7-dimethoxy-8-nitroquinoline.[9]

The only source of chlorine in this exchange reaction was the hydrochloric acid present in the diazotization. Evidently there was reaction either with the conjugate acid of VI or with the diazonium salt. At first sight the former seemed to be more likely. Lauer[10] noted that 5-bromo-6-methoxy-8-acetaminoquinoline is converted to 7-bromo-6-methoxy-8-acetaminoquinoline in 85% yield when it is boiled with concentrated hydrochloric acid. A cationic exchange mechanism was postulated. However when 5,7-dibromo-8-aminoquinoline was warmed for two days on the steam-bath with hydrochloric acid—conditions more drastic than those obtained during the diazotization reaction—little, if any, exchange occurred. Therefore, the exchange must have taken place during the diazotization–deamination step.

Diazotization of VI in other acids was less satisfactory because of insolubility or formation of a by-product, m.p. 134°, which was not investigated further. Diazotization directly in 50% hypophosphorous acid gave about 40% of 5,7-dibromoquinoline (IX) which was nitrated to VIII.

5,7-Dichloro-8-aminoquinoline was prepared by direct chlorination of 8-aminoquinoline and diazotized, deaminated and nitrated to yield VII.

Either VII or VIII on reaction with sodium thiophenoxide gave 5,7-bis-phenylmercapto-8-nitroquinoline (X) which on reduction gave III, identical with the substance obtained from the reaction of I with thiophenoxide ion and thiophenol.

During the study of II, it was reduced with Raney nickel containing hydrogen according to the method of Mozingo[11] in order to remove the phenylmercapto group. The product was 8-amino-1,2-3,4-tetrahydroquinoline.

The action of methoxide and β-methoxyethoxide ions on 8-nitroquinoline was investigated. No evidence of displacement was noted. The reaction reported by Kremer[3] was repeated and, although a definite test for nitrite was given by the inorganic products of the reaction, no substances lacking the second nitrogen atom could be isolated. About 5% of 5-methylmercapto-6-methoxy-8-aminoquinoline was isolated. The formation of this indicates that methyl mercaptide ion acts as a reducing agent.

The reactions of several other nitro compounds with thiophenoxide ion under the conditions used with 8-nitroquinoline were investigated. 6-Nitroquinoline and nitrobenzene did not react. On the basis of Bradley and Robinson's observation,[4] and since it is electronically analogous to 8-nitroquinoline, *m*-dinitrobenzene might be expected to add thiophenoxide ion. Under the reaction conditions, *m*-dinitrobenzene was reduced to *m*,*m*′-dinitroazoxybenzene. No evidence of addition was found.

A few observations on the mechanism of the reaction of I with thiophenoxide ion and thiophenol may be made. The reaction is base catalyzed since only starting material was recovered from the products of an experiment with neutral thiophenol. It is also likely, from the observation of Bradley and Robinson[4] that the formation of the thio ether is an anionic reaction. If addition of an anion to an aromatic system occurs, a hydride ion must either be discharged or accounted for by an inter- or intramolecular reduction. Discharge of hydrogen gas from this reaction mixture was precluded by the fact that the reaction would then demand the formation of a larger amount of diphenyl disulfide than the one equivalent actually found and by the fact that no 5-phenylmercapto-8-nitroquinoline was isolated from the products. Treatment of 5-phenylmercapto-8-nitroquinoline with thiophenol–thiophenoxide ion under the usual conditions of the reaction resulted in the recovery of 70–90% of unchanged starting material, so that it seems unlikely that this substance would have been overlooked if it were present in significant amounts in the reaction products. 5-Phenylmercapto-8-nitroquinoline would also be expected among the reaction products. From these facts it may be concluded that the addition of one mole of thiophenoxide ion to I is accompanied by an intramolecular hydrogen transfer to the nitro (or nitroso) group, which could be accomplished by a shift of two electrons into the aromatic nitro system, and an exchange of protons with the solvent (thiophenol), (see chart). A similar scheme may be written for 8-nitroquinoline.

It is not likely that thiophenoxide ion adds to 8-quinolylhydroxylamine to give II. However, the possibility that II is an intermediate in the formation of III is not out of the question. When 8-quinolylhydroxylamine was treated with thiophenol–thiophenoxide ion under the usual conditions about 10% of III was obtained.

We believe that the formation of II is preceded by reduction of I to 8-nitrosoquinoline by thiophenol, rather than by addition of thiophenoxide ion to 8-nitroquinoline and subsequent reduction. Although it was not possible to demonstrate this experimentally because of our failure to prepare 8-nitrosoquinoline, certain observations in the literature support such a thesis.

The nitroso group has been reported to be para directing in aromatic substitution reactions such as

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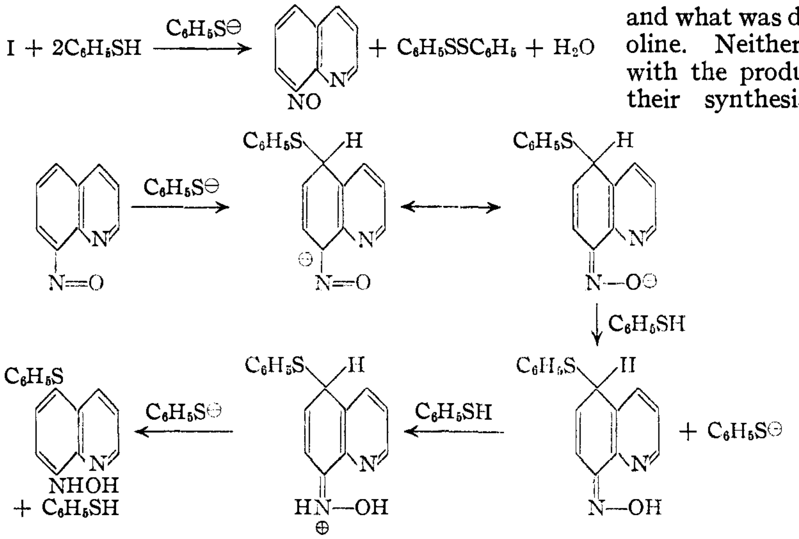
(8) A. Claus and E. Setzer, *J. prakt. Chem.*, [2] **53**, 401 (1896).

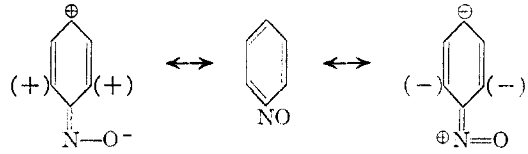
(9) R. C. Elderfield and G. L. Krueger, *J. Org. Chem.*, **17**, 358 (1952).

(10) Private communication from Dr. W. M. Lauer.

(11) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers. THIS JOURNAL, **65**, 1015 (1943).



halogenation and nitration.[12] From the rule of Hammick and Illingworth[13] the nitroso group would be expected to be meta directing like the nitro group. However, nitrosobenzene can be expressed by resonance forms in which the ortho and para carbon atoms have either increased or decreased electron density.



XI

The strong activating effect of the nitroso group toward anionic reagents is evident from the ease with which substituents can be displaced from the para position by bases. Thus in the reaction of *p*-bromonitrosophenol with silver nitrate, the *p*-nitroso group has a labilizing effect far greater than that of two nitro groups in the 2- and 4-positions and comparable to, if not greater than, that of three nitro groups in picryl chloride or bromide.[14] Thus, toward anionic substitution in nitrosobenzene, the contribution of resonance form XI would be expected to be much greater than that of the analogous form of nitrobenzene, and there is no reason why a similar state of affairs should not exist with the 8-substituted quinolines. The anionic substitutions of Bradley and Robinson,[4] of Bergstrom and co-workers,[5] and the hydroxylation of nitrobenzene[6] were all accomplished under much more drastic conditions than the present or known substitutions on nitroso compounds and were not accompanied by reduction. The Piria reaction proceeds under milder conditions and is accompanied by reduction.

As previously mentioned, Bradley and Robinson[4] successfully added piperidine to 8-nitroquinoline in the presence of sodamide to form a piperidino-8-nitroquinoline. The position of the piperidino group was not determined. Based on the prediction that this would occupy the 2-, 4-, 5- or 7-position, they prepared 2-piperidino-8-nitroquinoline, and what was described as 5-piperidino-8-nitroquinoline. Neither of these substances was identical with the product of their reaction. However, in their synthesis of 5-piperidino-8-nitroquinoline, they proceeded from a chloronitroquinoline (m.p. 185°) to which the structure of 5-chloro-8-nitroquinoline had been erroneously assigned.[15] It was subsequently shown[16] that this is the 7-chloro compound and that the 5-chloro isomer melts at 138°. The 2- and 7-isomers had, therefore, been eliminated. We have synthesized 5-piperidino-8-nitroquinoline from 5-bromo-8-nitroquinoline and obtained a substance of the same m.p. as that obtained by Bradley and Robinson by addition of piperidine to 8-nitroquinoline. Attack by thiophenoxide ion as here reported is therefore consistent with the observations of Bradley and Robinson.

Experimental[17]

Reaction of 8-Nitroquinoline (I) with Thiophenol–Thiophenoxide Ion.—I was recrystallized from 3:1 ethanol–ether to a constant m.p. of 86–89°. A solution of 5 g. of I, 0.6 g. (1 equiv.) of sodium and 20 g. (6 equiv.) of thiophenol in 100 ml. of anhydrous methanol was refluxed for two hours under nitrogen, and then poured into one liter of water and cracked ice containing 6 g. of sodium hydroxide. After 20 minutes the precipitate had coagulated sufficiently to be filtered. The precipitate was sucked as dry as possible yielding 14.2 g. of a gummy yellow solid. It was washed twice with hexane by decantation and again filtered. The hexane washings were worked up as described below.

The hexane insoluble material (5.8 g.) was washed twice with cold benzene by decantation, the washings were filtered, diluted with hexane and allowed to stand. The benzene-insoluble material (II) (3.8 g., 50%), m.p. 96–100°, was repeatedly recrystallized from dry benzene to yield a microcrystalline substance, m.p. 99.8–100.2° (dec.).

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.2; H, 4.5; N, 10.5; S, 11.9. Found: C, 67.5; H, 4.5; N, 10.4; S, 11.8.

The compound decomposed very readily to a red or dark brown gum if it was allowed to stand in air for more than a few minutes before the washing with benzene was completed. It also decomposed on heating or on recrystallization from alcohol or wet benzene. The thoroughly washed compound was more stable. It is soluble in acid with decomposition and insoluble in base. The Tollens test, in alcoholic solution, was positive. From this observation taken together with its instability and the isolation of one equivalent of diphenyl disulfide from the hexane-soluble fraction, the structure of a hydroxylamine was assigned to the substance. The yield varied widely. It was lowered by use of less than 6 equiv. of thiophenol, by use of more than 1.4 equiv. of sodium, or by use of I of m.p. below 86°.

The hexane washings of the crude reaction product were combined and saturated with dry hydrogen chloride. The precipitate was shaken in a separatory funnel with ether and dilute ammonia solution. The dried ether solution on evaporation left a yellow oil. Two recrystallizations from hexane gave 0.35 g. of yellow solid, m.p. 80–85°. The remaining two-thirds of the oil could not be crystallized. Fur-

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(12) C. K. Ingold, *J. Chem. Soc.*, **127**, 513 (1925).

(13) D. L. Hammick and W. S. Illingworth, *ibid.*, 2358 (1930).

(14) R. J. W. Le Fevre, *ibid.*, 810 (1931).

(15) A. Claus and K. Junghanns, *J. prakt. Chem.*, [2] **48**, 253 (1893).

(16) (a) L. Bradford, T. J. Eliot and F. M. Rowe, *J. Chem. Soc.*, 437 (1947); (b) C. C. Price and D. B. Guthrie, THIS JOURNAL, **68**, 1592 (1946).

(17) Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill., and Schwarzkopf Microanalytical Laboratory, Middle Village, L. I., N. Y. All m.ps. are uncorrected except those reported to tenths of a degree.

ther recrystallization of the solid material from alcohol or hexane gave fine, greenish-white needles, m.p. 97.7–98.4°. The substance showed a strong blue-white fluorescence in ultraviolet light and gave a bright green color in concd. sulfuric acid when a drop of nitric acid was added. Analytical data corresponded to those demanded by III.

Anal. Calcd. for $C_{21}H_{16}N_2S_2$: C, 70.0; H, 4.4; S, 17.8. Found: C, 70.0; H, 4.6; S, 17.3.

The acetyl derivative of III was prepared by allowing it to stand overnight in acetic anhydride and collecting the precipitate. After recrystallization from alcohol it melted at 184.1–184.3°.

Anal. Calcd. for $C_{23}H_{18}N_2OS_2$: C, 68.6; H, 4.5. Found: C, 68.8; H, 4.8.

The picrate of III came down as dark purple prisms from alcohol, m.p. 134–136°. Several recrystallizations from ethyl acetate gave thick orange needles, m.p. 140.5–141.5°. Intermediate recrystallizations gave both types of crystals.

Anal. Calcd. for $C_{27}H_{19}N_5O_7S_2$: C, 55.0; H, 3.2. Found: C, 54.7; H, 3.6.

Evaporation of the hexane filtrate from the hydrochloride of III left 4–6 g. of diphenyl disulfide, m.p. 57–60°.

The benzene wash liquors of the crude reaction product on dilution with hexane furnished 0.8 g. of unreacted I.

In an experiment in which 20 g. of I was added to 400 ml. of anhydrous methanol in which 40 g. of thiophenol (3 equiv.) and 5 g. of sodium (2 equiv.) had been dissolved, the mixture suddenly turned dark after two hours' heating. After pouring into ice and sodium hydroxide solution, the dark brown moist precipitate (39 g.) was washed three times with hexane and the residue (19 g.) was washed with benzene in which most of it dissolved. Treatment of the hexane soluble portion with hydrogen chloride gave 3.9 g. of the hydrochloride of III.

The basic filtrate from the crude product was extracted with ether. Concentration of the dried ether solution gave 1 g. of brilliant orange needles, m.p. 187–188° after recrystallization from acetone. The substance turned a brilliant red-violet in acid. In the diphenylamine test for nitroso compounds the solution first turned violet which faded to a pale blue-green on standing overnight. With Liebermann nitroso reagent it gave a grass-green color. When it was coupled with aniline in acetic acid solution, a deep crimson solution resulted. Analytical data agreed with those demanded by IV.

Anal. Calcd. for $C_{21}H_{14}N_2OS_2$: C, 67.4; H, 3.7; N, 7.5; S, 17.1. Found: C, 67.3; H, 3.7; N, 7.4; S, 17.5.

When the reaction was run without a solvent, no II was found. The product was almost exclusively III.

When I was heated with thiophenol in methanol in the absence of sodium no reaction occurred.

Reduction of II with Raney Nickel.—A suspension of 7–10 g. of Raney nickel prepared according to Mozingo, *et al.*,[11] in a solution of 0.76 g. of II in 15 ml. of absolute ethanol was refluxed for 45 minutes. After filtration from the catalyst and evaporation of the solvent a dark brown viscous oil remained. A picrate prepared from a filtered absolute alcoholic solution of the oil melted at 183–187° and did not depress the m.p. (182–184°) of a known sample of the picrate of 8-amino-1,2,3,4-tetrahydroquinoline.[18]

Further confirmation of the identity of the 8-amino-1,2,3,4-tetrahydroquinoline was provided by its conversion to 2,2-dimethyl-1,2,5,6-tetrahydro-4-imidazo[ij]quinoline, m.p. 139–141°, when it was warmed with acetone.[19]

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.6; H, 8.5. Found: C, 76.0; H, 8.3.

On thermal decomposition this was converted to 2-methyl-5,6-dihydro-4-imidazo[ij]quinoline, m.p. 127°; reported m.p. 128°.[18]

Reaction of 5-Bromo-6-methoxy-8-nitroquinoline with Sodium Methyl Mercaptide.—The procedure was a modification of that of Kremer[3] and of Gilman, *et al.*[20] To a solution of 29 g. of 5-bromo-6-methoxy-8-nitroquinoline (m.p. 203–206°) in 250 ml. of methyl Cellosolve was added a solution of 16 g. of sodium and 22 g. of methyl mercaptan in 180 ml. of methyl Cellosolve during 15 minutes. The mixture was refluxed for two hours and allowed to stand overnight. After removing the solvent under reduced pressure, the residue was taken up in boiling absolute alcohol and filtered from inorganic salts. The salts gave a strong test for nitrite ion with starch–potassium iodide test paper and a rough quantitative estimate showed the ratio of bromide to nitrite to be about 4:1. Nevertheless no quinoline derivatives in which the nitrogen in the 8-position was missing could be isolated.

The alcoholic filtrate on cooling deposited 8.2 g. of tan crystals, m.p. 124–129°. Recrystallization from alcohol gave 4.8 g. of brownish-gold plates, m.p. 130–134°; reported m.p. for 5-methylmercapto-6-methoxy-8-nitroquinoline, 136°.[3] The crude yield was 18%.

The mother liquor from the above compound was diluted with an equal volume of ether and filtered from black, hygroscopic, amorphous material. From the filtrate about 1 g. of yellow needles, m.p. 171–172° after recrystallization from dry benzene, was obtained; reported m.p. for 5-methylmercapto-6-methoxy-8-aminoquinoline, 166–167°.[3] The substance is readily absorbed on Norite and can be eluted with benzene.

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 60.0; H, 5.5; S, 14.7. Found: C, 59.9; H, 5.6; S, 14.9.

For comparison, a solution of 0.25 g. of 5-methylmercapto-6-methoxy-8-nitroquinoline, m.p. 135–137°,[3] in 2.5 ml. of concd. hydrochloric acid was added dropwise with vigorous stirring to a solution of 1 g. of stannous chloride in 8 ml. of concd. hydrochloric acid at 5°. The solution was stirred one hour in the ice-bath and for an additional hour at room temperature. After standing overnight it was diluted with 200 ml. of water and the precipitate dissolved. After cooling to 5°, concd. sodium hydroxide solution was added at 5–10° until the tin salts dissolved. From the solution, 0.20 g. of yellow micro plates, m.p. 170–171° after recrystallization from alcohol, were obtained. The mixture m.p. with the substance obtained above was 170–171°.

The acetyl derivative formed buff plates, m.p. 104–105°, from dilute alcohol.

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.5; H, 5.3. Found: C, 59.4; H, 5.2.

Reduction of II with Stannous Chloride (V).—The usual stannous chloride reduction procedure gave large amounts of tar. The following was satisfactory.

A suspension of finely ground II (1.5 g.) in 25 ml. of water was added dropwise to a well cooled, stirred solution of 3 g. of stannous chloride in 28 ml. of concd. hydrochloric acid. After addition of 10 ml. of methanol, the mixture was allowed to come to room temperature. A fine orange precipitate formed. The solution was cooled below 10° and 20 g. of sodium hydroxide in the form of a 40% solution was added with stirring and cooling at such a rate that the temperature did not exceed 10°. Two more portions of 20 g. of sodium hydroxide were added and the solution was extracted with ether. The dried ether extract gave 1.3 g. of a yellow-brown oil. This was taken up in hexane, treated with charcoal, and cooled in a solid carbon dioxide-bath yielding 0.5 g. of crystalline material, m.p. 76–82°. Repeated recrystallization from hexane, at first from the carbon dioxide-bath, gave flat yellow needles, m.p. 88.9–90.1°; yield 30–35%.

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.4; H, 4.8; N, 11.1; S, 12.7. Found: C, 71.3; H, 4.8; N, 10.9; S, 12.3.

The acetyl derivative formed white needles from alcohol, m.p. 161–162°, and the mixture m.p. with a known sample was not depressed.

The *p*-toluenesulfonyl derivative formed pale greenish plates from alcohol, m.p. 155–156°, and the mixture m.p. with a known sample was not depressed.

5-Phenylmercapto-8-nitroquinoline.—To a hot solution of 11.5 g. of 5-bromo-8-nitroquinoline (m.p. 147–150°) in 450 ml. of alcohol was added a solution of 1 g. of sodium and 5 g. of thiophenol in 25 ml. of methanol. After refluxing for 1.5 hours, the mixture was evaporated to 200 ml. and poured into 800 ml. of water. The precipitate (12.4 g., 97%) melted at 140–143°. Recrystallization from alcohol gave yellow prisms, m.p. 142.3–143.4°.

Anal. Calcd. for $C_{15}H_{10}N_2O_2S$: C, 63.8; H, 3.6; S, 11.4. Found: C, 63.8; H, 3.5; S, 11.4.

The picrate, m.p. 138.2–139.1°, formed orange prisms from alcohol.

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[18] S. J. Hazlewood, G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 467 (1937–1938).

[19] *Cf.* H. J. Barber and W. R. Wragg, *J. Chem. Soc.*, 610 (1946); R. C. Elderfield and F. J. Kreysa, THIS JOURNAL, **70**, 44 (1948).

[20] H. Gilman, *et al.*, *ibid.*, **68**, 1578 (1946).

Anal. Calcd. for $C_{21}H_{13}N_5O_9S$: N, 13.7. Found: N, 13.6.

5-Phenylmercapto-8-aminoquinoline (V).—The above substance was reduced with stannous chloride and hydrochloric acid.[21] When the reaction mixture was diluted the tin complex did not dissolve. After filtering it and drying, the yield of tin complex was 75%. A suspension of 3.6 g. of the tin complex in ether and water in a separatory funnel was made alkaline with 10 g. of sodium hydroxide. From the ether 2.2 g. of V was obtained as long, yellow, iridescent needles, m.p. 85–87°. Recrystallization from hexane raised the m.p. to 90.4–90.7°. The mixture m.p. with V obtained as above was not depressed, nor were the mixture m.p.'s of the following derivatives.

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.4; H, 4.8; N, 11.1; S, 12.7. Found: C, 71.4; H, 5.0; N, 11.3; S, 12.2.

The *p*-toluenesulfonyl derivative formed pale greenish plates, m.p. 159.1–160.0° from alcohol.

Anal. Calcd. for $C_{22}H_{18}N_2O_2S_2$: C, 65.0; H, 4.5; S, 15.8. Found: C, 65.2; H, 4.5; S. 15.6.

The acetyl derivative formed white needles, m.p. 162.5–163.0°, from 70% alcohol.

Anal. Calcd. for $C_{17}H_{14}N_2OS$: C, 69.4; H, 4.8. Found: C, 69.3; H, 4.9.

7-Phenylmercapto-8-nitroquinoline.—This was prepared as was the 5-derivative except that it was necessary to reflux the mixture six hours. The crude yield was 97%. Recrystallization from alcohol gave yellow plates, m.p. 98.8–99.6°.

Anal. Found: C, 63.5; H, 3.6; S, 11.3.

The picrate formed short, deep yellow needles, m.p. 144.6–145.5°, from alcohol.

Anal. Found: N, 13.5.

7-Phenylmercapto-8-aminoquinoline, m.p. 68.2–69.4° after recrystallization from hexane, was prepared as was the 5-derivative.

Anal. Found: C, 71.6; H, 4.5; N, 10.9.

The *p*-toluenesulfonyl derivative, m.p. 197.0–197.8°, formed white plates from alcohol.

Anal. Found: C, 65.1; H, 4.4.

The acetyl derivative, m.p. 127.0–127.9°, formed hygroscopic white needles from 50% alcohol.

Anal. Found: C, 68.1; H, 5.2.

5,7-Dibromo-8-aminoquinoline (VI).—The method of Claus and Setzer[8] was used with certain necessary modifications. To a solution of 3.6 g. of 8-aminoquinoline in 30 ml. of glacial acetic acid and 8 ml. of water cooled to −15° was added dropwise with stirring a solution of 8 g. of bromine in 25 ml. of 80% acetic acid. After a portion of the bromine had been added, the mixture set to a thick mush. Filtration gave 1.25 g. of yellowish-gray powder, m.p. 114–117°. This was free VI. The filtrate was returned to the flask, cooled to −12°, and the remaining bromine solution was added. This gave a precipitate of 6.2 g. of the hydrobromide of VI. Dilution of the filtrate gave an additional 0.4 g. of free VI, m.p. 113–117°. The first two fractions were suspended in 50 ml. of concd. hydrochloric acid and the mixture was diluted to 2 l. yielding 5.3 g. of light gray powder, m.p. 116–118°. On recrystallization from hexane it formed long, flat, pale yellow needles, m.p. 120.3–120.6°. We were unable to raise the m.p. to 127° as reported by Claus and Setzer.[8]

Anal. Calcd. for $C_9H_6Br_2N_2$: C, 35.8; H, 2.0; Br, 52.9. Found: C, 36.3; H, 1.7; Br, 53.4.

The acetyl derivative formed white needles, m.p. 212.6–213.6°, from dilute alcohol.

Anal. Calcd. for $C_{11}H_8Br_2N_2O$: C, 38.4; H, 2.3. Found: C, 38.6; H, 2.5.

Diazotization and Deamination of VI.—A suspension of 5.7 g. of VI in 75 ml. of concd. hydrochloric acid was diazotized at 0° with the calculated amount of sodium nitrite. After addition of 25 ml. of 50% hypophosphorous acid the solution was left for one day in the ice-box and for an additional day at room temperature and then poured into 1.5 l. of water. After filtration from some 1.5 g. of pinkish solid, m.p. 133–135°, which was not investigated further, the filtrate was made basic and 4.2 g. of white solid separated. This was recrystallized repeatedly from alcohol yielding white needles, m.p. 114.8–115.2°. Claus and Setzer[8] report m.p. 112° for 5,7-dibromoquinoline, and m.p. 116° for 5,7-dichloroquinoline.

Anal. Calcd. for $C_9H_5Br_2N$: C, 37.7; H, 1.7. Calcd. for $C_9H_5Cl_2N$: C, 54.6; H, 2.5. Found: C, 55.5; H, 3.1.

Although the analytical data are not good, they suffice to show that exchange of bromine for chlorine had occurred. The best yield was 60%. Subsequent runs, worked up by subliming the material precipitated by base, gave a product melting at 109–111° which was nitrated directly since the impurities were oxidized during nitration.

In view of the above result, deamination of VI in acids other than hydrochloric was investigated. A solution of 0.50 g. of VI in 20 ml. of 50% hypophorous acid, 4 ml. of concd. sulfuric acid and 6 cc. of water was diazotized with 0.12 g. of sodium nitrite and allowed to stand for two days in the ice-box and one day at room temperature. The crude product isolated as above was sublimed *in vacuo* yielding 0.19 g. of impure IX, m.p. 96–98°, which, however, was satisfactory for nitration. Diazotization in sulfuric acid gave primarily the by-product, m.p. 135°.

Nitration of 5,7-Dichloroquinoline (VII).—The crude product of the deamination of VI, m.p. 102–109° (0.6 g.) was added to a mixture of 3 ml. of concd. sulfuric acid and 3 ml. of fuming nitric acid cooled in an ice-bath. After standing several hours at room temperature, the mixture was heated on the steam-bath. The course of the reaction was followed by diluting a drop of the mixture with water and noting the m.p. of the precipitate. After eight hours at room temperature this was 150–161° and, after three hours on the steam-bath, it was constant at 163–168°. After pouring the mixture into 100 ml. of water, the precipitate was recrystallized from alcohol. The m.p. and mixture m.p. with a known sample of VII[9] was 164–167°. Further recrystallization from alcohol raised the m.p. to 168.1–169.2°. Claus and Ammelburg[22] report m.p. 168.5° for VII.

Anal. Calcd. for $C_9H_4Cl_2N_2O_2$: C, 44.5; H, 1.6. Calcd. for $C_9H_4Br_2N_2O_2$: C, 32.6; H, 1.2. Found: C, 44.9; H, 1.8.

5,7-Diphenylmercapto-8-nitroquinoline.—A solution of 0.46 g. of VII in 30 ml. of anhydrous methanol was added to a solution of 0.11 g. of sodium and 0.42 g. of thiophenol in 5 ml. of methanol. After refluxing the mixture for 45 minutes, the heavy yellow precipitate, m.p. 184–188°, was collected. A further amount was obtained on dilution of the mother liquor. The yield was 90%. Recrystallization from alcohol raised the m.p. to 190–191°.

Anal. Calcd. for $C_{21}H_{14}N_2O_2S_2$: C, 64.6; H, 3.6; S, 16.4. Found: C, 64.5; H, 3.9; S, 16.2.

5,7-Dichloro-8-aminoquinoline.—Chlorine was passed into a solution of 0.5 g. of 8-aminoquinoline in 2.5 ml. of acetic acid until the weight increased 0.5 g. The red precipitate (0.5 g.) was shaken with ether and dilute sodium hydroxide solution. From the ether layer, after drying over anhydrous magnesium sulfate, 0.23 g. (31%) of crude 5,7-dichloro-8-aminoquinoline, m.p. 113–116°, was obtained. Repeated recrystallization from hexane raised the m.p. to 121.3–121.6°; reported m.p. 124°[22] and 119–120°.[16(b)]

Anal. Calcd. for $C_9H_6Cl_2N_2$: C, 50.7; H, 2.8; Cl, 33.3. Found: C, 50.9; H, 2.9; Cl, 32.8.

The chlorination proceeded better at or above room temperature than in an ice-bath. At low temperatures there was considerable blackening. At high temperatures the rate of chlorination exceeded the rate of decomposition.

5,7-Diphenylmercapto-8-aminoquinoline (III).—A hot suspension of 0.3 g. of X in 25 ml. of concd. hydrochloric acid was added dropwise with vigorous stirring to a solution of 1.2 g. of stannous chloride in 4 ml. of concd. hydrochloric acid cooled to 3–5°. The mixture was allowed to stand for three days and diluted with 200 ml. of water. The tin complex (0.6 g.) was filtered off and shaken with ether and dilute sodium hydroxide solution. From the ether layer 0.16 g. (58%) of III, m.p. 97.5–98.1° after recrystallization from hexane was obtained. The mixture m.p. with III isolated from the reaction of I and thiophenol was undepressed.

Anal. Found: C, 70.2; H, 4.7; N, 7.7; S, 17.6.

The picrate, m.p. 134–137°, and the acetyl derivative,

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[21] R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1586 (1946).

[22] A. Claus and A. Ammelburg, *J. prakt. Chem.*, [2] **51**, 418 (1895).

m.p. 179–180°, also did not depress the m.p.'s of the corresponding derivatives of III obtained as above.

Reaction of *m*-Dinitrobenzene with Thiophenol and Thiophenoxide Ion.—The reaction was carried out as was done with 8-nitroquinoline. From 2 g. of *m*-dinitrobenzene 1.05 g. of fluffy white needles separated when the reaction mixture was poured into 250 ml. of water containing 2 g. of sodium hydroxide. Recrystallization from alcohol or benzene gave *m,m'*-dinitroazoxybenzene, m.p. 147.9–148.5°; reported m.p. 143°.[23]

Anal. Calcd. for $C_{12}H_8N_4O_5$: C, 50.0; H, 2.8. Found: C, 50.0; H, 2.9.

From the alkaline mother liquor, 3.3 g. of diphenyl disulfide was obtained.

Reaction of 8-Quinolylhydroxylamine and Thiophenol–Thiophenoxide Ion.—A solution of 0.6 g. of 8-quinolylhydroxylamine[24] in 6 ml. of anhydrous methanol was added to 10 ml. of methanol containing 0.13 g. of sodium, and 3 g. of thiophenol was heated under reflux for 1.5 hours and poured into 50 ml. of water and ice containing 0.8 g. of sodium hydroxide. The gummy precipitate dissolved almost completely in hexane. The hexane solution yielded a mixture of 0.9 g. of white needles and a yellow oil which was again taken up in hexane and treated with hydrogen chloride. The precipitated red hydrochloride (0.39 g.) was filtered. Evaporation of the hexane gave 0.6 g. of diphenyl disulfide. The hydrochloride was shaken with dilute ammonia and ether. Evaporation of the dried ether extract left 0.26 g. of a yellow gum which gave a small amount of II, m.p. 86–89° after crystallization from hexane. The mixture m.p.'s of this with II and of the acetyl derivatives were not depressed.

5-Piperidino-8-nitroquinoline.—5-Bromo-8-nitroquinoline (1 g.) was heated for four hours in 10 ml. of piperidine. The heavy yellow gum which separated when the mixture was poured into water slowly crystallized; yield 1 g. After recrystallization from alcohol, yellow prisms, m.p. 131.2–132.3°, were obtained. The product obtained by Bradley and Robinson[4] from 8-nitroquinoline and piperidine in the presence of sodamide is reported as melting at 131.5–132.5°.

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.4; H, 5.9; N, 16.3. Found: C, 65.4; H, 5.6; N, 16.0.

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[23] C. A. Lobry de Bruyn, *Rec. trav. chim.*, **20**, 115 (1901).

[24] L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **62**, 1648 (1940).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY]

The Single-Stage Conversion of 1-(3',4',5'-Trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline to 2-(3',4',5'-Trimethoxybenzoyl)-4,5-methylenedioxystyrene[1,2]

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Evidence is presented for the reaction path in the formation of 2-(3',4',5'-trimethoxybenzoyl)-4,5-methylenedioxystyrene by treatment of 1-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline with methyl sulfate and alkali.

We have recently described a method of converting 1-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (I) directly to 2-(3',4',5'-trimethoxybenzoyl)-4,5-methylenedioxystyrene (VII) by treating the dihydroisoquinoline with methyl sulfate and alkali.[3] This transformation had suggested itself originally on considering a sequence of separate reactions dealing with hydrastinine and related compounds.[4] In terms of the present compounds, the sequence is given in formulations I to VII. Now evidence is adduced for this as the path actually followed in the one-stage process. The mode of attack consisted in the preparation of intermediates and test of their behavior with methyl sulfate and with alkali.

That alkali alone was ineffective in the conversion of the dihydroisoquinoline (I) to the vinyl ketone (VII) was shown by the resistance of the former compound to the action of hot sodium hydroxide solution. The dihydroisoquinoline was recovered unchanged after long boiling with 20% aqueous alkali.

The quaternary dihydroisoquinolinium methosulfate (II methosulfate) was prepared by allowing the dihydroisoquinoline (I) to react with methyl sulfate in inert solvent; the iodide of II was formed using methyl iodide. The corresponding chloride was obtained by reaction of the carbinolamine (III) with hydrochloric acid. Treatment of the quaternary dihydroisoquinolinium salts (II) with aqueous alkali produced the carbinolamine (III) in a virtually instantaneous reaction; but the latter compound remained unchanged even after long exposure to alkali. On the other hand, when the carbinolamine (III) was warmed with alkali *and* methyl sulfate, the vinyl ketone (VII) was produced in 84% yield.

No attempt was made to isolate the two forms III and IV of the carbinolamine. Judging from the absence of any carbonyl peak in the infrared absorption curve of the solid (as a mull with mineral oil) structure III is preferred to IV for the crystalline material.[5]

In experiments directed to the preparation of the dimethylamino ketone (V) it was found that the action of methyl sulfate in toluene on the carbinolamine produced the quaternary methosulfate of compound VI as the only isolated material. Methyl iodide in chloroform solution transformed the carbinolamine into a mixture from which the iodides of quaternary salts II and VI could be isolated; but

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[2] A summary of the material in this paper was presented in Boston, Mass., on April 3, 1951, before the Division of Organic Chemistry of the American Chemical Society.

[3] W. J. Gensler and C. M. Samour, THIS JOURNAL, **72**, 3318 (1950): **73**, 5555 (1951).

[4] (a) H. Becker, *et al.*, *Ann.*, **395**, 299, 321 (1913); M. Freund, *Ber.*, **22**, 2329 (1889); (b) W. Roser, *Ann.*, **249**, 156 (1888): M. Freund and F. Becker, *Ber.*, **36**, 1521 (1903); H. Decker and P. Becker, *Ann.*, **395**, 328 (1913); (c) W. H. Perkin, Jr., *J. Chem. Soc.*, **109**, 815 (1916).

[5] This is not necessarily the case for *solutions* of the carbinolamine. A preliminary study of the infrared absorption in solvents such as chloroform, dihydrofuran and dioxane indicates that the relative amount of the carbinolamine (III) and of the monomethylamino ketone (IV)—the latter form being detected by an absorption peak at 6.0μ—depends on the nature of the solvent.