Aromatic nucleophilic substitution of hydrogen: mechanism of reaction of 6-nitroquinoline with cyanide ions, with and without participation of methyl cyanoacetate

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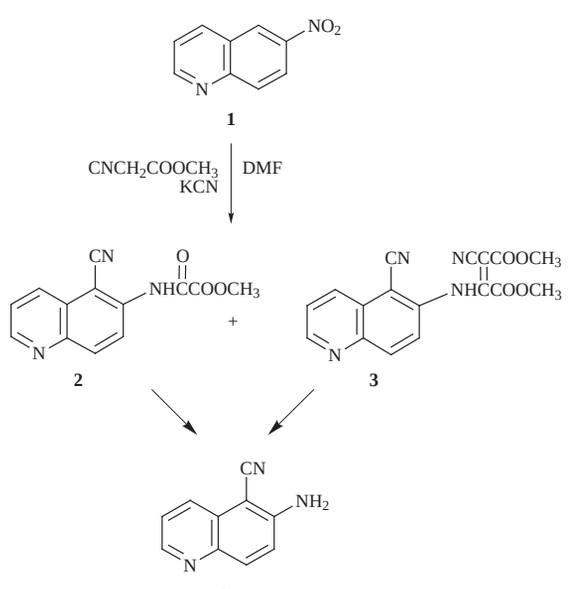
The mechanism of nucleophilic substitution of hydrogen (S_NAr^H) in 6-nitroquinoline **1** by action of cyanide ion in the presence or in the absence of methyl cyanoacetate in dimethyl sulfoxide has been studied by means of ^1H NMR. The main reaction products and some side products have been identified and their time–concentration dependences have been determined. An experiment with ^{13}C enriched potassium cyanide proved that the cyano group replaces hydrogen at the 5-position of the starting compound **1**. The two main products obtained from the reaction mixture of 6-nitroquinoline **1** and potassium cyanide are 6-hydroxyquinoline-5-carbonitrile **11** and 6,6′-azoquinoline-5,5′-dicarbonitrile **13**. On the basis of the data obtained, a mechanism has been suggested for aromatic nucleophilic substitution of hydrogen by cyanide ion in 6-nitroquinoline **1** involving a Meisenheimer adduct of 6-nitroquinoline **1** with cyanide ion and 6-nitrosoquinoline-5-carbonitrile **14** as unstable intermediates.

Introduction

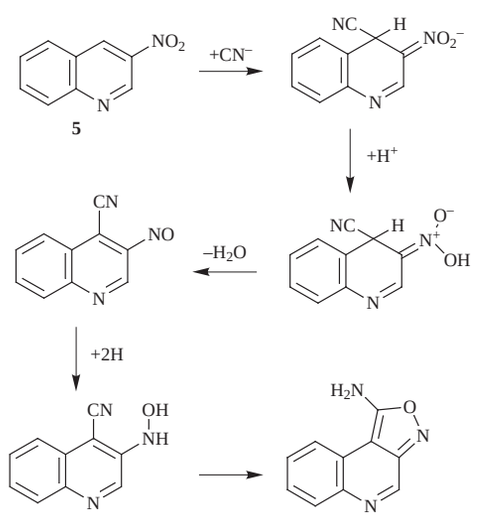
Tomioka and coworkers described products of reactions of some aromatic and heteroaromatic nitro compounds with active cyanomethylene compounds (methyl and ethyl cyanoacetates, malononitrile, cyanoacetamide, *p*-nitrophenylacetonitrile, ω-cyanoacetophenone, 1-cyanoacetylpyrrolidine) catalyzed by bases (KOH, t-BuOK or KCN) in polar aprotic solvents (DMF, DMSO, HMPA).[1–5] For instance, 6-nitroquinoline **1** undergoes a base catalyzed reaction with methyl cyanoacetate[1] to give 6-methoxalylaminoquinoline-5-carbonitrile **2** and dimethyl 2-cyano-3-(5-cyano-6-quinolylamino)-butenedioate **3**. The subsequent hydrolysis of compounds **2** and **3** produces 6-aminoquinoline-5-carbonitrile **4** (Scheme 1). The



Scheme 1

reaction is extraordinary in that methyl cyanoacetate (*i.e.* a derivative of propanedioic acid) is transformed in the products into an ethanedioic acid derivative (compound **2**) and butenedioic acid derivative (compound **3**). Analogous reactions are observed, beside 6-nitroquinoline **1**, with other substrates activated for nucleophilic substitution, *e.g.* 1- and 2-nitronapthalenes, 3-, 5-, 7- and 8-nitroquinolines, nitrobenzenes activated in the 3-position or also in the 5-position by electron acceptor substituents (CF_3, $COCH_3$, COC_6H_5).[1–5] Nitrobenzene itself does not undergo this reaction. The mechanism of these reactions has not been studied up to now.[6]

Similar features to those observed by Tomioka[1–5] can also be seen in the reactions with cyanides carried out in alcohols.[7,8] The reaction of 3-nitroquinoline **5** with cyanides in methanol in the presence of potassium ferricyanide[7] mainly produces 3-nitroquinoline-4-carbonitrile (62%) and 1-aminoisoxazolo-[3,4-*c*]quinoline **6** (30%).[7] Compound **6** is also formed by reduction of 3-nitroquinoline-4-carbonitrile with zinc in an aqueous methanolic solution of ammonium chloride,[7] *N*-(4-cyanoquinolin-3-yl)hydroxylamine being presumed as the intermediate. On the basis of these experiments, Okamoto[7] suggested a reaction mechanism (Scheme 2) involving the initial formation



Scheme 2

of a Meisenheimer adduct of the substrate and cyanide ion, subsequent protonation of the nitronate formed, and splitting off of a water molecule, which overall represents a reduction

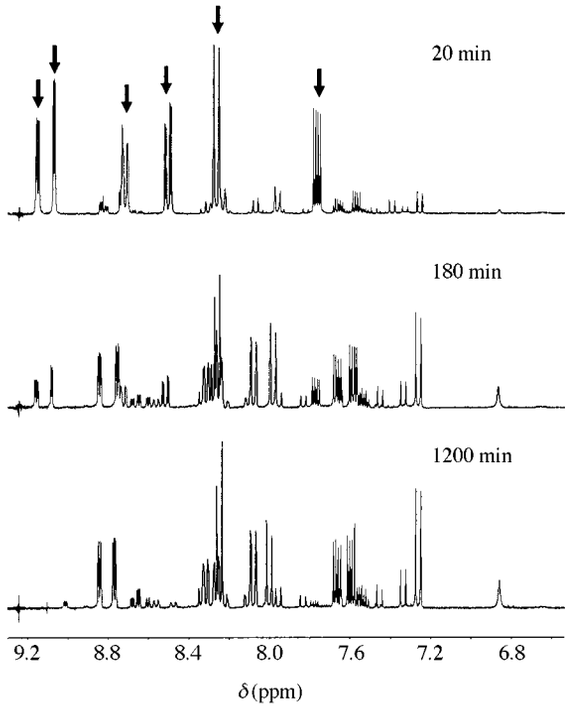


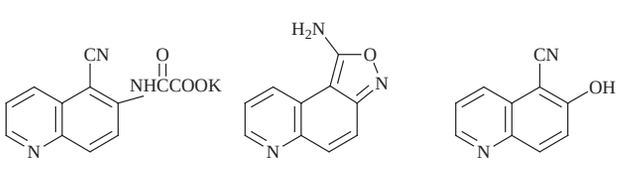
Fig. 1 ^{1}H NMR spectra of a reaction mixture of 20 mg 6-nitroquinoline **1**, 50 mg potassium cyanide, 0.3 ml methyl cyanoacetate, and 0.7 ml [$^2H_6$]dimethyl sulfoxide measured at the indicated time intervals from the point of mixing the starting reactants (expanded aromatic region is shown). The arrows denote the signals due to the starting compound **1**.

of a nitronic acid to a nitroso compound. The latter is then reduced to the hydroxylamine and cyclized to give 1-aminoisoxazolo[3,4-*c*]quinoline **6**. This mechanism (Scheme 2) was only supported by the identification of reaction products,[7] but it does not contradict current ideas about S_NAr and S_NAr^H mechanisms (ref. 9).

Results and discussion

The course of the reaction of 6-nitroquinoline **1** with methyl cyanoacetate and potassium cyanide in dimethyl sulfoxide was monitored by means of NMR spectroscopy. This was made possible by a good separation of the signals of the aromatic hydrogens in the reaction mixture (Fig. 1) enabling parallel monitoring of the concentration changes of starting compound **1** and the reaction products at definite time intervals after mixing the reactants. The kinetic curves obtained from the concentrations thus measured are presented in Fig. 2. For unambiguous determination of the structure and assignment of the signals to the individual components, the respective compounds were either isolated from the reaction mixture or prepared by an independent synthesis; their ^{1}H NMR spectra were measured and compared with those of the reaction mixtures.

In total eight compounds, having at least 1 mol% concentration at some moment of measurement, were found in the reaction mixture. Six of them were identified, *viz.* 6-nitroquinoline **1**, 6-methoxalylaminoquinoline-5-carbonitrile **2**, dimethyl 2-cyano-3-(5-cyano-6-quinolylamino)butenedioate **3**, 6-aminoquinoline-5-carbonitrile **4**, potassium *N*-(5-cyano-6-quinolyl)oxamate **7**, and 1-aminoisoxazolo[4,3-*f*]quinoline **8**.



7 **8** **11**

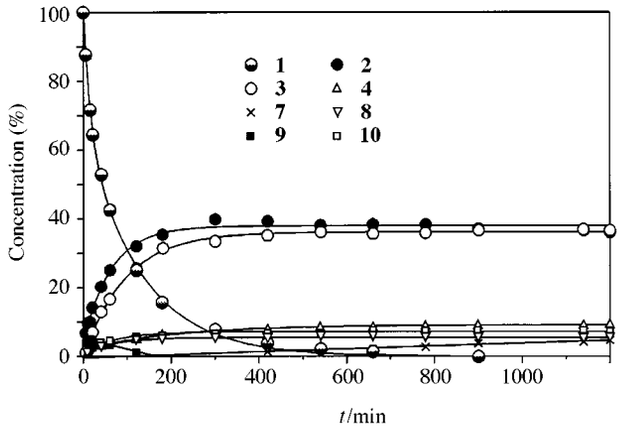


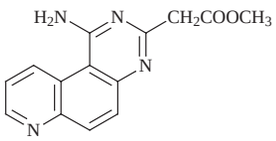
Fig. 2 Concentration–time dependences of compounds **1**–**4** and **7**–**10** in the reaction of 20 mg 6-nitroquinoline **1** with 50 mg potassium cyanide and 0.3 ml methyl cyanoacetate in 0.7 ml [$^2H_6$]dimethyl sulfoxide at 20 ± 1 °C.

The structures of the other two compounds, **9** and **10**, could not be determined, but the character of their NMR spectra indicates that they are 5,6-disubstituted quinolines. Futhermore, the reaction mixture contained a small amount of another compound, 6-hydroxyquinoline-5-carbonitrile **11**.

In accordance with the literature,[1] quinolines **2** and **3** represent the chief reaction products, their maximum contents being 39.9 mol% and 36.9 mol%, respectively. After the starting 6-nitroquinoline **1** is consumed, the content of both compounds **2** and **3** decreases. After a week from the start of reaction, the concentration of compound **2** dropped to zero and that of compound **3** to 34.5 mol%. Therefore it follows that the primary products, especially compound **2**, undergo consecutive reactions. From the course of the concentration–time dependences of the main products it can be concluded that both compounds are formed by competitive reactions from a common intermediate, compound **3** not being produced by a subsequent reaction from compound **2**. The remaining substances found are side products. At the moment when the starting material was exhausted their overall content was about 26 mol% of the reaction mixture. Potassium *N*-(5-cyano-6-quinolyl)oxamate **7** is formed by a base catalyzed hydrolysis of 6-methoxalylaminoquinoline-5-carbonitrile **2**. In the analyzed reaction mixture, compound **7** was only observed after 420 min and its highest concentration was found after one week from the start of the reaction.

We studied separately the reaction of compound **2** with potassium cyanide in [$^2H_6$]dimethyl sulfoxide. The ^{1}H NMR spectra exhibited signals of compounds **4** and **7**. The base catalyzed hydrolysis of compound **2** obviously proceeds both at the ester group to give carboxylate **7** and at the amide group to give amine **4**. 6-Aminoquinoline-5-carbonitrile **4** can also, to a small extent, be a product of base catalyzed hydrolysis of quinoline **3**. An interesting product (which was not isolated by the authors[1]) of the reaction investigated is 1-aminoisoxazolo-[4,3-*f*]quinoline **8**. This compound reached a maximum concentration of 5.8 mol% in the reaction mixture, and its content decreased only negligibly during the next phases of the reaction. Compound **9** (whose structure was not elucidated) is unstable, its kinetic curve showing a maximum (a content of 5.4 mol%) at 15 minutes after the mixing of the starting reactants. After that its concentration rapidly decreased to zero. The second compound with unknown structure (**10**) is relatively stable, being formed from the beginning of the reaction, and when the starting nitroquinoline **1** is consumed, its content in the reaction mixture varies about a value of 5.5 mol%. After a week from the start of reaction, however, compound **10** was not detected in the reaction mixture any more, on the other hand, the mixture contained 3.3 mol% of 1-aminopyrido[3,2-*f*]quin-

azoline-3-acetate **12** and 17.5 mol% of another 5,6-disubstituted quinoline of unknown structure. Compound **12** is probably formed from compound **2** and methyl cyanoacetate.



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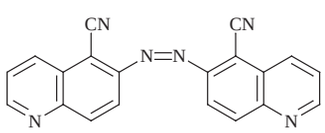
A ^{13}C NMR spectrum of the reaction mixture of compound **1**, methyl cyanoacetate and ^{13}C enriched potassium cyanide proved that the cyano group from the alkali cyanide replaces hydrogen at the 5-position of the starting compound **1**. This finding is important with regard to the fact that aromatic nitro compounds react with activated cyanomethylene compounds to give identical products in the presence of bases other than alkali cyanides (*e.g.* KOH).

The mixture of reaction products from 6-nitroquinoline and potassium cyanide in [$^2H_6$]dimethyl sulfoxide was analyzed by means of ^1H NMR too, and it was found that after the starting material **1** was consumed the reaction mixture contained 40 mol% of 6-hydroxyquinoline-5-carbonitrile **11** and 18 mol% 6-aminoquinoline-5-carbonitrile **4**. None of the remaining reaction products reached a concentration of 5 mol%. The reaction was also carried out on a preparative scale to isolate 6-hydroxyquinoline-5-carbonitrile **11** and 6,6′-azoquinoline-5,5′-dicarbonitrile **13** in the yields of 21.4 and 21.6%, respectively.



13

The fact that the azo compound **13** was not observed in the spectra of the reaction mixture is probably due to its insolubility in dimethyl sulfoxide. Thus it is separated as a very fine precipitate during the reaction. The structure of compound **11** was established on the basis of ^1H and ^{13}C NMR, IR and mass spectra. For comparison with the spectrum of the reaction mixture, it was necessary to measure the ^1H NMR spectrum of compound **11** with the addition of potassium cyanide as a base. The formation of the conjugated base of compound **11** results in a considerable decrease of chemical shifts of the proton signals.

The structure of azo compound **13** was established on the basis of elemental analysis, ^1H, ^{13}C and ^{15}N NMR, IR, UV–VIS and mass spectra. The NMR spectra of azo compound **13** were measured in deuteriochloroform, in which compound **13** is somewhat soluble (about 10 mg in 1 ml). In order to assign unambiguously the chemical shifts of carbon signals of CH groups, we measured the heterocorrelated spectrum with inverse detection (Fig. 3). For the ^{15}N NMR spectral measurement to be possible, we prepared the isotopically labelled compound **13** from 6-nitroquinoline (10% $^{15}NO_2$). Detection of the signal at 129.5 ppm in the ^{15}N NMR spectrum of ^{15}N enriched compound **13** proves the presence of the azo group (the typical value for *E*-azobenzene is 129 ppm referenced to external nitromethane[10]). The IR spectrum exhibits an absorption band at 2231 cm^{-1} which is due to valence vibration of the cyano group. The mass spectrum gave the molecular weight of compound **13** (*M* 334).

Aromatic azo compounds are typical products of reactions of amines with aromatic nitroso compounds. Hence, in this context it can be presumed that 6-nitrosoquinoline-5-carbonitrile **14** is formed as an unstable intermediate. The reaction of compounds **14** and **4** at the given reaction conditions then

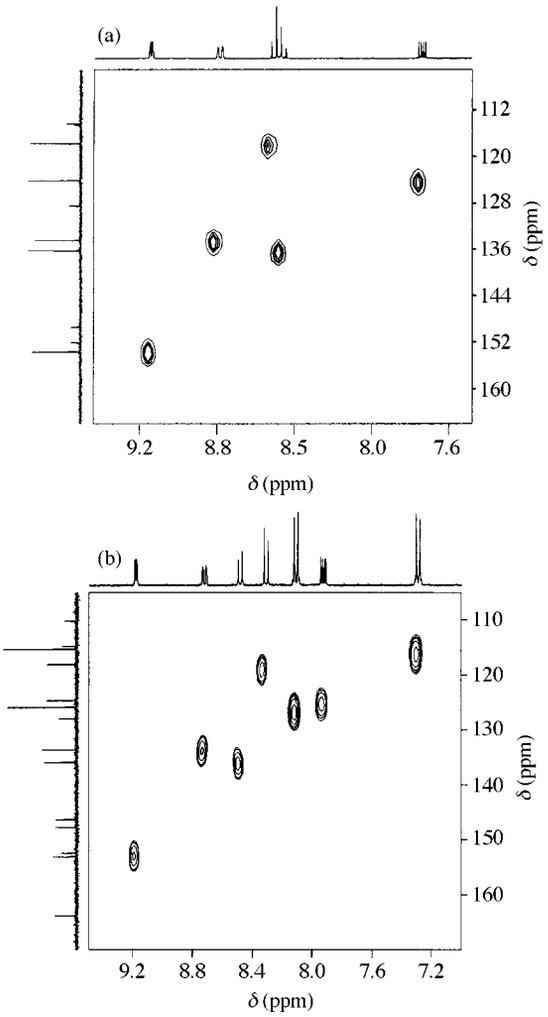
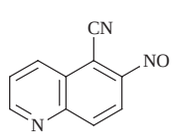


Fig. 3 (a) 2D ^1H–^{13}C reverse detected NMR spectrum of **13**; (b) 2D ^1H–^{13}C reverse detected NMR spectrum of **15**.



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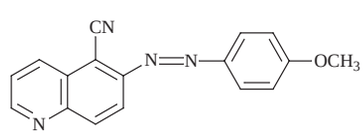
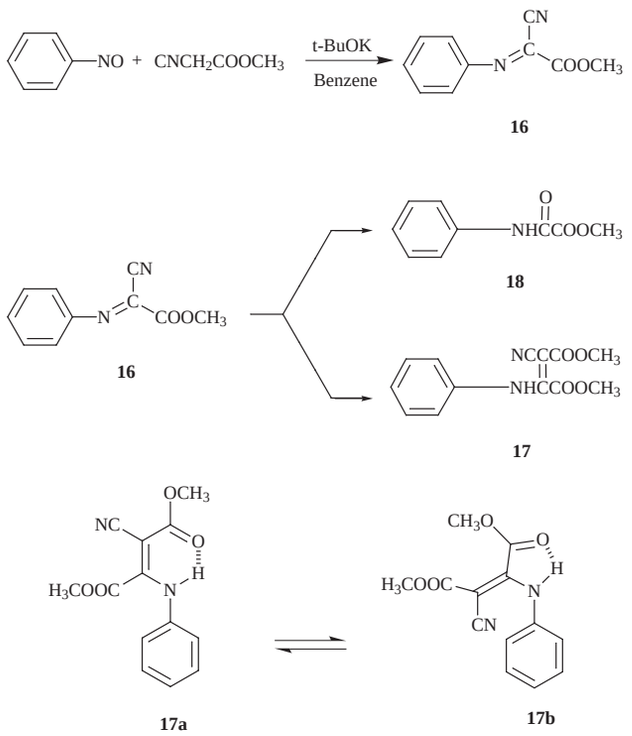


15

produces 6,6′-azoquinoline-5,5′-dicarbonitrile **13**. The reaction of compound **1** with potassium cyanide and excess *p*-anisidine gave 6-(4-methoxyphenylazo)quinoline-5-carbonitrile **15** as a side product which could be isolated. The formation of azo compound **15** confirms the correctness of the presumption that the nitroso compound **14** is formed as an unstable reaction intermediate. Compound **15** was identified by means of elemental analysis, ^1H and ^{13}C NMR, UV–VIS and mass spectra. In order to unambiguously assign the chemical shifts of the carbon signals of the CH groups, we measured the heterocorrelated spectrum with inverse detection (Fig. 3).

In a mixture of 6-nitroquinoline **1** with cyanide which also contains methyl cyanoacetate, it is likely that nitrosoquinoline **14** will preferentially react with its conjugated base. The initially formed azomethine can then undergo competitive reactions: hydration of compound **2**, and reaction with another molecule of methyl cyanoacetate to give compound **3**. Attempts at preparing nitroso compound **14** failed and for this reason the possibility of the above-mentioned reactions was verified with the use of a simpler and available substrate, namely nitrosobenzene. A new method has been developed for the preparation of imines from aromatic nitroso compounds which, in this particular case, consists of the reaction of nitrosobenzene with methyl

cyanoacetate in anhydrous benzene in the presence of potassium *tert*-butoxide as a heterogeneous catalyst. In this way, it was possible to isolate methyl 2-phenylimino-2-cyanoacetate **16** in the first reaction step, and dimethyl 2-(*N*-phenylamino)-3-cyanobut-2-ene-1,4-dioate **17** in the second step (Scheme 3).



Scheme 3

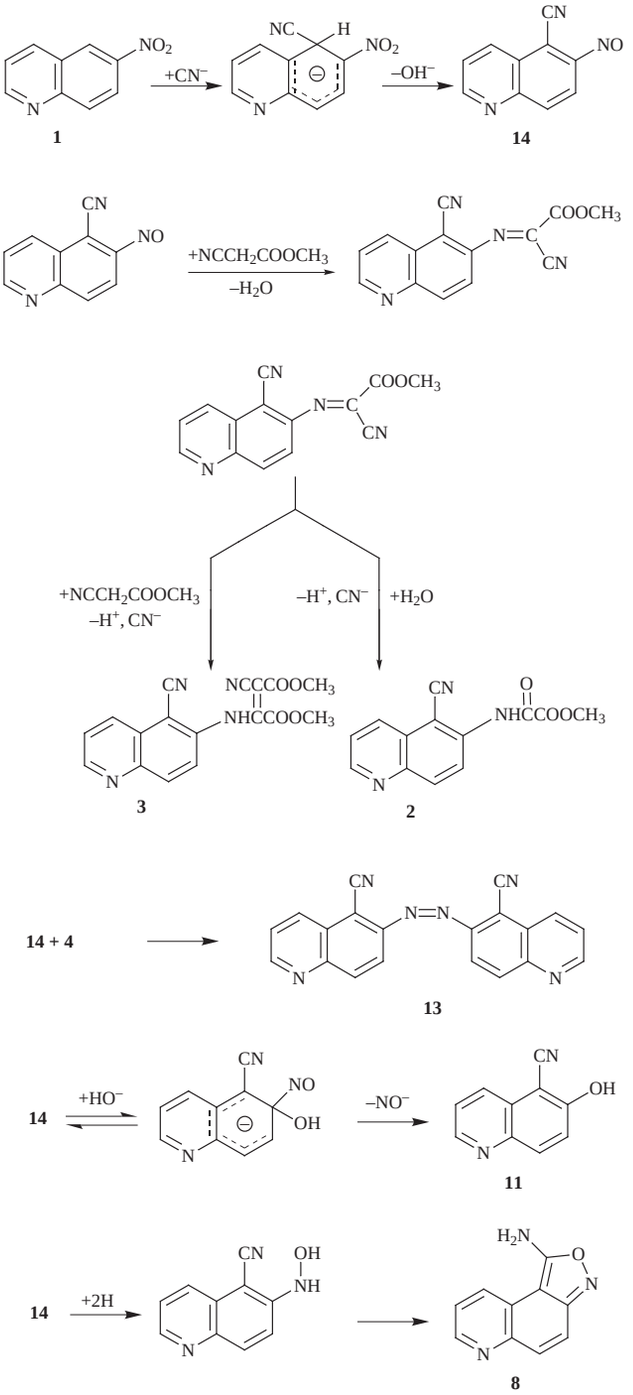
Compounds **16** and **17** were identified by means of elemental analyses, and ^{1}H and ^{13}C NMR spectra. In the case of imine **16**, we also measured the ^{15}N NMR spectrum and determined the chemical shifts δ_N for the imino group (10.8 ppm) and the cyano group (−106.9 ppm).

Interesting behavior was observed with butenedioate **17**, which can form a pair of isomers **17a** and **17b** due to the possibility of the presence of a hydrogen bond. These five- and six-membered rings are actually formed in dimethyl sulfoxide solutions, their ratio being 1:1. The evidence for this was provided by ^{1}H and ^{13}C NMR spectra of butenedioate **17** in [$^{2}H_6$]dimethyl sulfoxide which exhibit doubled numbers of signals. The 'doubling' of signals can be removed by addition of a base (KCN) to the solution. Obviously, the simplification is due to partial dissociation of the acidic proton in NH group. Butenedioate **17** exhibits simple spectra in deuteriochloroform solutions due obviously to a faster mutual interconversion of the two isomers. That is why the ^{1}H NMR spectrum measured in deuteriochloroform exhibits the signal of an NH group.

The base catalyzed (0.1 M NaOH) hydration of **16** in a water–dimethyl sulfoxide mixture (9:1) was studied with the help of UV spectroscopy. The electronic spectrum of the product was identical with that of methyl ester of *N*-phenylamide of ethanedioic acid **18** prepared by independent synthesis from methoxalyl chloride and aniline. The reaction of nitrosobenzene with methyl cyanoacetate in THF under otherwise the same reaction conditions gave the amide-ester **18** directly.

Conclusions

On the basis of experimental concentration–time dependences of reaction products, a mechanism has been suggested for the reaction of 6-nitroquinoline **1** with cyanides in the presence or in the absence of methyl cyanoacetate (Scheme 4). The mechanism suggested is in accordance with the mechanism of analo-



Scheme 4

gous reactions proceeding as vicarious S_NAr^H reactions (ref. 9, 11, 12), and it satisfactorily explains the formation of a number of products. In the first step, cyanide ion is added to the 5-position of the quinoline skeleton to give the Meisenheimer adduct. Thereafter, the proton adjacent to the cyano group and an oxygen atom of the nitro group are split off as a hydroxy ion. The splitting off of the vicarious nucleofuge results in the reduction of the nitro group to a nitroso group. It was impossible to isolate, or to identify in the reaction mixture, the unstable intermediates of this reaction which obviously proceed by the VS_NAr^H route, *viz.* the Meisenheimer adduct of 6-nitroquinoline **1** with cyanide ion and 5-cyano-6-nitrosoquinoline **14**. A deeper reduction of the nitro group and/or the subsequent condensation then lead to amine **4** and azo compound **13**. If methyl cyanoacetate is present in the reaction mixture, it reacts preferentially with nitroso compound **14** to give the chief reaction products—compounds **2** and **3**. The final reaction

product, amine **4**, is formed by subsequent hydrolysis of these compounds.

Experimental

The ^{1}H, ^{13}C and ^{15}N NMR spectra were measured at 360.14, 90.57 and 36.51 MHz, respectively, using a Bruker AMX 360 apparatus. The chemical shifts δ_H and δ_C measured in [$^2H_6$]dimethyl sulfoxide solutions are referenced to the central signal of the solvent multiplet (δ_H 2.55 and δ_C 39.6). The chemical shifts of compounds measured in deuteriochloroform solutions are referenced to the central signal of the solvent triplet (δ_C 77.0). The signals in the ^{13}C NMR spectra were assigned by means of heterocorrelated 2D ^{1}H–^{13}C NMR spectra with inverse detection (HMQC) optimized to a one-bond interaction J(H,C) 155 Hz. J Values are given in Hz. The chemical shifts δ_N of azo compound **13** and imine **16** are referenced to external nitromethane (δ_N 0.0). The IR spectra of compounds **11** and **13** were measured with an ATI Unicam Genesis apparatus using the FTIR technique as KBr tablets. The mass spectra were measured with an LC MSVG-Platform spectrometer allowing the APCI or ESP ionization both in positive or negative mode. The electronic spectra of compounds **13** and **15** in methanolic solution and the spectra of a reaction mixture of compound **16** in water–dimethyl sulfoxide (9 : 1) with NaOH catalyst (0.1 M) were measured on an HP 8453 Diode Array spectrometer at 25 ± 0.1 °C.

NMR analysis of a reaction mixture of 6-nitroquinoline 1, methyl cyanoacetate and potassium cyanide

A solution of compound **1** (20 mg, 0.11 mmol) in 0.7 ml [$^2H_6$]dimethyl sulfoxide was placed in a 5 mm diameter NMR tube. A mixture of methyl cyanoacetate (0.3 ml, 3.4 mmol) and potassium cyanide (50 mg, 0.77 mmol) was added to that solution. At definite time intervals from mixing the reactants, ^{1}H NMR spectra of this mixture were measured while keeping the temperature within 20 ± 1 °C. The signals in the spectra were assigned with the help of spectra of standards. In a similar way were measured the ^{13}C NMR spectra of such a mixture with K^{13}CN (99.5% ^{13}C).

NMR analysis of a reaction mixture of 6-nitroquinoline 1 and potassium cyanide

A solution of compound **1** (10 mg, 0.06 mmol) in 0.6 ml DMSO-d_6 was placed in a 5 mm diameter NMR tube, and potassium cyanide (6 mg, 0.09 mmol) was added. After 1 day and 7 days from mixing the ^{1}H NMR spectra of this mixture were measured.

Preparation of 6-nitroquinoline 1

A mixture of 4-nitroaniline (15 g, 0.108 mol), glycerol (15 ml, 0.205 mol) and iodine (0.5 g, 2 mmol) was treated with 16 ml conc. sulfuric acid added dropwise with constant stirring. The reaction temperature increased to 80–90 °C and was maintained at this value by means of an oil bath for about 1 hour and then at 160–170 °C for about 2 hours. After cooling to room temperature, the mixture was treated with 250 ml water and neutralized by adding solid sodium carbonate. The separated solid was collected by suction and washed with water (about 500 ml portionwise). Yield 7.5 g raw product; after recrystallization from heptane 3.5 g (18.3%) 6-nitroquinoline **1**, mp 149–151 °C (ref. 13 gives mp 151 °C). δ_H((CD$_3$)$_2$SO) 7.76 (1H, dd, J 8.4 and 4.2, H-3), 8.23 (1H, d, J 9.2, H-8), 8.47 (1H, dd, J 9.2 and 2.6, H-7), 8.73 (1H, dd, J 8.4 and 1.8, H-4), 9.07 (1H, d, J 2.6, H-5), 9.14 (1H, dd, J 4.2 and 1.8, H-2); δ_C((CD$_3$)$_2$SO) 122.8 (C-7), 123.3 (C-3), 125.3 (C-5), 127.0 (C-4a), 131.0 (C-8), 138.5 (C-4), 145.1 (C-6), 149.7 (C-8a), 154.4 (C-2).

Preparation of 4-nitroaniline (10% $^{15}NO_2$)

The ^{15}N-labeled 4-nitroaniline was prepared from acetanilide (20 g, 0.15 mol) by nitration with a mixture of 17 g (0.17 mol) K^{15}NO$_3$ (10% ^{15}N) in 30 ml conc. sulfuric acid and subsequent hydrolysis of 4-nitroacetanilide (10% $^{15}NO_2$) in 10% hydrochloric acid. Yield 13.9 g (67%) 4-nitroaniline (10% $^{15}NO_2$), mp 150–151 °C.

Preparation of 6-nitroquinoline (10% $^{15}NO_2$)

A mixture of 4-nitroaniline (10% $^{15}NO_2$, 7 g, 0.05 mol), arsenic oxide hydrate ($As_2O_5 \cdot 3H_2O$; 15 g) and 50 ml 85% phosphoric acid was stirred and heated on an oil bath to 100 °C. Then it was treated with acrolein (5 ml, 75 mmol) added drop by drop with stirring. The rate of addition was regulated to keep the temperature of the reaction mixture within 98–102 °C. After adding the acrolein, the mixture was stirred for another 30 min at 100 °C, whereupon a second portion of 5 ml acrolein (75 mmol) was added and the mixture stirred at 100 °C again for 30 min. After cooling, the reaction mixture was poured onto 200 ml water, treated with a small amount of charcoal, and filtered. The filtrate was neutralized with ammonia; the separated solid was filtered off, washed and dried to give 5 g raw 6-nitroquinoline (10% $^{15}NO_2$); after recrystallization from heptane 3 g (34.4%) yellow needles, mp 149–151 °C.

Preparation of 6-methoxalylaminoquinoline-5-carbonitrile 2

A solution of 6-aminoquinoline-5-carbonitrile (0.5 g, 3 mmol) in 10 ml pyridine was treated with methoxalyl chloride (0.4 ml, 4 mmol), and the solution was left to stand at room temperature for about 2 hours. Then 50 ml water was added in one portion to the reaction mixture. The precipitate formed was collected by suction, washed with water and dried. After recrystallization from acetone, yield 0.4 g (60%), mp 171–174 °C (ref. 1 gives mp 175 °C). δ_H((CD$_3$)$_2$SO) 3.97 (3H, s, CH$_3$O), 7.85 (1H, dd, J 8.5 and 4.2, H-3), 8.03 (1H, d, J 9.2, H-7), 8.44 (1H, dd, J 9.2 and 0.7, H-8), 8.54 (1H, m, J 8.5, 1.6 and 0.7, H-4), 9.11 (1H, dd, J 4.2 and 1.6, H-2), 11.52 (1H, br, NH); δ_H((CD$_3$)$_2$SO, addition KCN) 3.70 (3H, s, CH$_3$O), 7.58 (1H, dd, J 8.5 and 4.2, H-3), 7.93 (1H, dd, J 9.4 and 0.8, H-8), 8.20 (1H, m, J 8.5, 1.7 and 0.8, H-4), 8.29 (1H, d, J 9.3, H-7), 8.72 (1H, dd, J 4.2 and 1.7, H-2); δ_C((CD$_3$)$_2$SO, addition KCN) 51.0 (CH$_3$O), 96.8 (C-5), 118.1 (CN), 122.8 (C-3), 128.8 (C-7), 129.2 (C-4a), 130.9 (C-4), 132.7 (C-8), 142.9 (C-8a), 147.4 (C-2), 158.6 (C-6), 163.1 (C=O), 167.2 (C=O); δ_C((CD$_3$)$_2$SO) 53.6 (CH$_3$O), 104.1 (C-5), 114.6 (CN), 124.4 (C-3), 127.4 (C-7), 127.6 (C-4a), 132.7 (C-4), 135.3 (C-8), 140.4 (C-6), 145.0 (C-8a), 151.9 (C-2), 156.0 (NHC=O), 160.6 (O-C=O).

Preparation of dimethyl 2-cyano-3-(5-cyano-6-quinolylamino)-butenedioate 3

A solution of **1** (4 g, 0.023 mol) in 100 ml dimethyl sulfoxide was added to a mixture of methyl cyanoacetate (60 ml, 0.68 mol) and potassium cyanide (6 g, 0.092 mol). The reaction mixture was left to stand at room temperature for one day and then diluted with water to a volume of 500 ml. The solution was neutralized by gradual addition of 10% hydrochloric acid. At pH about 7, the solution separated to give a very fine suspension which was collected by suction, washed with 100 ml water and dried. Yield 2.9 g (37.4%) compound **3**, mp 192–193 °C (Found: C, 60.5; H, 3.6; N, 16.5. $C_{17}H_{12}N_4O_4$ requires C, 60.7; H, 3.6; N, 16.7%); δ_H(CDCl$_3$) 3.90 (3H, s, CH$_3$O), 3.94 (3H, s, CH$_3$O), 7.40 (1H, d, J 9.2, H-7), 7.66 (1H, dd, J 8.5 and 4.2, H-3), 8.30 (1H, dd, J 9.2 and 0.7, H-8), 8.49 (1H, m, J 8.5, 1.6 and 0.7, H-4), 9.02 (1H, dd, J 4.2 and 1.6, H-2), 11.83 (1H, br, NH); δ_H((CD$_3$)$_2$SO, addition KCN) 3.53 (3H, s, CH$_3$O), 3.54 (3H, s, CH$_3$O), 7.23 (1H, d, J 9.1, H-7), 7.68 (1H, dd, J 8.4 and 4.2, H-3), 8.07 (1H, dd, J 9.1 and 0.5, H-8), 8.29 (1H, m, J 8.4, 1.6 and 0.5, H-4), 8.85 (1H, dd, J 4.2 and 1.6, H-2);

δ_C((CD$_3$)$_2$SO, addition KCN) 50.1 (CH$_3$O), 51.3 (CH$_3$O), 97.7 (C-5), 116.5 (CN), 120.9 (CN), 123.5 (C-3), 126.0 (C-7), 128.4 (C-4a), 131.3 (C-4), 134.0 (C-8), 142.9 (C-8a), 143.5 (C-6), 148.9 (C-2), 156.8 (C=C), 161.6 (C=C), 166.0 (C=O), 167.6 (C=O).

Preparation of 6-aminoquinoline-5-carbonitrile 4

A suspension of butenedioate **3** (2.6 g, 7.7 mmol) in 500 ml 10% hydrochloric acid was boiled for 3 hours. Then it was cooled to room temperature and neutralized by addition of 10% sodium hydroxide to adjust the final pH to 8. The separated solid was collected by suction and dried. Yield 1.1 g (84.4%) pale yellow crystals, mp 182–184 °C (ref. 1 gives mp 181 °C). δ_H((CD$_3$)$_2$SO) 6.98 (2H, br, NH$_2$), 7.31 (1H, d, *J* 9.3, H-7), 7.57 (1H, dd, *J* 8.4 and 4.3, H-3), 7.96 (1H, dd, *J* 9.3 and 0.4, H-8), 8.08 (1H, m, *J* 8.4, 1.6 and 0.4, H-4), 8.65 (1H, dd, *J* 4.3 and 1.6, H-2); δ_C((CD$_3$)$_2$SO) 82.7 (C-5), 116.8 (CN), 121.7 (C-7), 123.6 (C-3), 129.1 (C-4a), 129.8 (C-4), 135.4 (C-8), 141.5 (C-8a), 146.4 (C-2), 152.7 (C-6).

Preparation of *N*-(5-cyano-6-quinolylamino)oxamic acid 7

Compound **7** was prepared by base catalyzed hydrolysis (NaOH) of compound **2** in DMF medium according to a published procedure,[4] yield 24.5%, mp 245–247 °C with decomp. (ref. 1 gives mp 197 °C with decomp.) (Found: C, 59.6; H, 2.9; N, 17.2. C$_{12}$H$_7$N$_3$O$_3$ requires C, 59.8; H, 2.9; N, 17.4%); δ_H((CD$_3$)$_2$SO) 7.85 (1H, dd, *J* 8.5 and 4.1, H-3), 8.11 (1H, d, *J* 9.2, H-7), 8.43 (1H, d, *J* 9.2, H-8), 8.52 (1H, dd, *J* 8.5 and 1.4, H-4), 9.10 (1H, dd, *J* 4.1 and 1.4, H-2), 11.34 (1H, s, COOH); δ_H((CD$_3$)$_2$SO, addition KCN) 7.79 (1H, dd, *J* 8.5 and 4.2, H-3), 8.37 (1H, d, *J* 9.4, H-8), 8.43 (1H, dd, *J* 8.5 and 1.4, H-4), 8.71 (1H, d, *J* 9.4, H-7), 9.00 (1H, dd, *J* 4.2 and 1.4, H-2).

Preparation of 1-aminoisoxazolo[4,3-*f*]quinoline 8

Compound **8** was obtained by chromatographic separation (alumina, chloroform) of the product mixture obtained from the reaction of **1** (2 g, 11 mmol) with potassium cyanide (1.5 g, 23 mmol) in 140 ml methanol (ref. 8). The first fraction contained 1.4 g (66%) 6-methoxyquinoline-5-carbonitrile, mp 175–176 °C after recrystallization from methanol (ref. 8 gives mp 178–179 °C). δ_H((CD$_3$)$_2$SO) 4.16 (3H, s, CH$_3$O), 7.76 (1H, dd, *J* 8.5 and 4.2, H-3), 7.90 (1H, d, *J* 9.5, H-7), 8.36 (1H, m, *J* 8.5, 1.6 and 0.6, H-4), 8.40 (1H, dd, *J* 9.5 and 0.6, H-8), 8.95 (1H, dd, *J* 4.2 and 1.6, H-2); δ_C((CD$_3$)$_2$SO) 57.3 (CH$_3$O), 93.3 (C-5), 114.8 (CN), 116.9 (C-7), 124.3 (C-3), 128.3 (C-4a), 131.5 (C-4), 136.8 (C-8), 142.5 (C-8a), 149.8 (C-2), 161.8 (C-6).

The second fraction contained 0.3 g (14.2%) 1-aminoisoxazolo[4,3-*f*]quinoline **8**, mp 200 °C with decomp. (ref. 8 gives mp 199–200 °C). δ_H((CD$_3$)$_2$SO) 7.47 (1H, d, *J* 9.6, H-4), 7.54 (1H, dd, *J* 8.1 and 4.6, H-8), 7.67 (1H, dd, *J* 9.6 and 0.6, H-5), 8.10 (2H, br, NH$_2$), 8.56 (1H, m, *J* 8.1, 1.6 and 0.6, H-9), 8.61 (1H, dd, *J* 4.6 and 1.6, H-7); δ_C((CD$_3$)$_2$SO) 89.4 (C-9b), 118.0 (C-4), 122.8 (C-8), 124.3 (C-9a), 129.0 (C-9), 135.0 (C-5), 145.7 (C-7), 145.8 (C-5a), 156.9 (C-3a), 166.8 (C-1).

Preparation of methyl 1-aminopyrido[3,2-*f*]quinazoline-3-acetate 12

Quinazolineacetate **12** was prepared by reaction of compound **2** with methyl cyanoacetate in DMF according to a published procedure,[14] yield 22.4%, mp 225–227 °C (ref. 14 does not give any mp). δ_H((CD$_3$)$_2$SO) 3.70 (3H, s, CH$_3$O), 3.91 (2H, s, CH$_2$), 7.74 (1H, dd, *J* 8.6 and 4.3, H-9), 7.82 (2H, br, NH$_2$), 7.90 (1H, d, *J* 9.2, H-5), 8.25 (1H, d, *J* 9.2, H-6), 8.97 (1H, dd, *J* 4.3 and 1.3, H-8), 9.19 (1H, d, *J* 8.6, H-10); δ_C((CD$_3$)$_2$SO) 44.8 (CH$_2$), 51.9 (CH$_3$), 107.0 (C-10b), 122.2 (C-5), 124.0 (C-10a), 130.4 (C-9), 132.8 (C-10), 135.3 (C-6), 146.9 (C-6a), 148.9 (C-8), 152.4 (C-4a), 160.8 (C-1), 162.4 (C-3), 170.2 (C=O).

Preparation of 6,6′-azoquinoline-5,5′-dicarbonitrile 13 and 6-hydroxyquinoline-5-carbonitrile 11

A solution of **1** (2 g, 11 mmol) in 120 ml dimethyl sulfoxide was treated with potassium cyanide (1.2 g, 18.5 mmol). The mixture was stirred at room temperature for 24 hours, then it was diluted with 1 l cold water and neutralized with 10% hydrochloric acid. The separated fine precipitate was filtered off and redissolved in about 300 ml hot chloroform. The solution was filtered, and the filtrate was extracted with water (2 × 50 ml); the organic phase was dried with anhydrous sodium sulfate. Then part of the chloroform (about 250 ml) was distilled off, and the residue was treated with 20 ml aqueous acetone. The separated orange–brown solid was collected by suction and dried. Yield 0.4 g (21.6%) 6,6′-azoquinoline-5,5′-dicarbonitrile **13**, which sublimes above 250 °C (Found: C, 72.0; H, 3.0; N, 25.0. C$_{20}$H$_{10}$N$_6$ requires C, 71.8; H, 3.0; N, 25.1%); δ_H(CDCl$_3$) 7.74 (1H, dd, *J* 8.5 and 4.2, H-3), 8.46 (1H, dd, *J* 9.3 and 0.6, H-8), 8.50 (1H, d, *J* 9.3, H-7), 8.78 (1H, m, *J* 8.5, 1.7 and 0.6, H-4), 9.14 (1H, dd, *J* 4.2 and 1.7, H-2); δ_C(CDCl$_3$) 114.3 (C-5), 114.6 (CN), 117.7 (C-7), 124.0 (C-3), 128.5 (C-4a), 134.4 (C-4), 136.2 (C-8), 149.4 (C-8a), 152.1 (C-6), 153.6 (C-2); δ_N(CDCl$_3$) 129.9 (N=N); λ_{max} 354 nm; ν_{max}(KBr)/cm^{-1} 2231, 1605, 1492, 1321, 848; *m*/*z* 335 (MH$^+$, 100%).

The aqueous phase (left after precipitation and removal of the fine precipitate of the azo compound by filtration) was extracted with 150 ml chloroform. The extract was dried with anhydrous sodium sulfate, the chloroform was evaporated, and the evaporation residue was washed with water (2 × 50 ml) and dried to give 0.4 g (21.4%) raw 6-hydroxyquinoline-5-carbonitrile; mp 280–282 °C after recrystallization from acetic acid (ref. 15 gives mp 293 °C). δ_H((CD$_3$)$_2$SO) 7.56 (1H, d, *J* 9.3, H-7), 7.71 (1H, dd, *J* 8.5 and 4.2, H-3), 8.21 (1H, dd, *J* 9.3 and 0.7, H-8), 8.29 (1H, m, *J* 8.5, 1.6 and 0.7, H-4), 8.87 (1H, dd, *J* 4.2 and 1.6, H-2), 12.05 (1H, br, OH); δ_H((CD$_3$)$_2$SO, addition KCN) 6.73 (1H, d, *J* 9.6, H-7), 7.25 (1H, dd, *J* 8.4 and 4.2, H-3), 7.53 (1H, d, *J* 9.6, H-8), 7.68 (1H, m, *J* 8.4, 1.6 and 0.5, H-4), 8.21 (1H, dd, *J* 4.2 and 1.6, H-2); δ_C((CD$_3$)$_2$SO) 91.0 (C-5), 115.2 (CN), 121.4 (C-7), 123.9 (C-3), 128.5 (C-4a), 131.2 (C-4), 136.3 (C-8), 142.2 (C-8a), 148.7 (C-2), 161.5 (C-6); ν_{max}(KBr)/cm^{-1} 2220, 1620, 1502, 1333, 810; *m*/*z* 171 (MH$^+$, 100%).

Preparation of 6-(4-methoxyphenylazo)quinoline-5-carbonitrile 15

A solution of **1** (2 g, 11 mmol) and *p*-anisidine (10 g, 81 mmol) in 40 ml dimethyl sulfoxide was treated with potassium cyanide (2 g). The mixture was stirred at room temperature for 4 hours. Then the solid portion was filtered off, and the filtrate was evaporated *in vacuo*. The evaporation residue was extracted with chloroform (5 × 50 ml). The insoluble residue contained about 250 mg (12.8%) raw 6-hydroxyquinoline-5-carbonitrile. The chloroform extract was washed with water (2 × 50 ml) and concentrated *in vacuo*. The residue was steam distilled to remove *p*-anisidine. The suspension remaining in the distillation flask was extracted with chloroform (5 × 50 ml). The extract was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was separated by column chromatography (alumina, chloroform–hexane 1:1) to give 135 mg (4.1%) azo compound **15**, mp 209–211 °C (Found: C, 70.5; H, 4.4; N, 19.4. C$_{17}$H$_{12}$N$_6$O requires C, 70.8; H, 4.2; N, 19.4%); δ_H((CD$_3$)$_2$SO) 3.97 (3H, s, CH$_3$O), 7.27 and 8.10 (2 × 2H, AA′XX′, H-10 and H-11), 7.93 (1H, dd, *J* 8.5 and 4.2, H-3), 8.31 (1H, d, *J* 9.2, H-7), 8.46 (1H, dd, *J* 9.2 and 0.6, H-8), 8.71 (1H, m, *J* 8.5, 1.6 and 0.6, H-4), 9.16 (1H, dd, *J* 4.2 and 1.6, H-2); δ_C((CD$_3$)$_2$SO) 56.1 (CH$_3$O), 110.2 (C-5), 114.8 (CN), 115.3 (C-11), 118.1 (C-7), 124.7 (C-3), 125.9 (C-10), 128.0 (C-4a), 133.7 (C-4), 135.9 (C-8), 146.4 (C-9), 147.8 (C-8a), 152.5 (C-2), 153.2 (C-6), 163.9 (C12); λ_{max} 378 nm; *m*/*z* 289 (MH$^+$, 100%).

The last fraction taken from the column contained 0.41 g (21.3%) azo compound **13**.

Preparation of methyl 2-phenylimino-2-cyanoacetate 16

A solution of nitrosobenzene (0.5 g, 4.6 mmol) and methyl cyanoacetate (0.4 ml, 4.5 mmol) in 30 ml benzene was treated with potassium *tert*-butoxide (0.2 g, 1.8 mmol), and the mixture was refluxed 2 hours. The salts were removed by filtration and the benzene by evaporation. The raw product was purified by column chromatography (silica gel, chloroform) and vacuum sublimation to give 0.33 g (36.3%) methyl 2-phenylimino-2-cyanoacetate **16**, mp 76–79 °C (Found: C, 64.0; H, 4.3; N, 14.8. $C_{10}H_8N_2O_2$ requires C, 63.8; H, 4.3; N, 14.9%); $\delta_H(CDCl_3)$ 4.05 (3H, s, CH_3O), 7.41 (2H, m, H-*o*), 7.46 (1H, m, H-*p*), 7.51 (2H, m, H-*m*); $\delta_C(CDCl_3)$ 54.3 (CH_3O), 110.2 (CN), 121.8 (C-H_o), 129.3 (C-H_m), 129.9 (C=N), 130.6 (C-H_p), 146.1 (C *ipso*), 159.7 (C=O); $\delta_N(CDCl_3)$ 10.8 (C=N), −106.9 (C≡N).

Preparation of dimethyl 2-(*N*-phenylamino)-3-cyanobut-2-ene-1,4-dioate 17

A solution of compound **16** (0.19 g, 1 mmol) and methyl cyanoacetate (0.3 g, 3 mmol) in 25 ml dry benzene was treated with potassium *tert*-butoxide (0.1 g, 1.25 mmol), and the mixture was refluxed 8 hours. The solids were filtered off and the filtrate was concentrated *in vacuo*. The raw product was purified by column chromatography (silica gel, chloroform–hexane 9 : 1) and recrystallization from benzene–hexane mixture (1 : 1) to give 100 mg (38%) butenedioate **17**, mp 83–84 °C (Found: C, 60.1; H, 4.7; N, 10.6. $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.7; N, 10.8%); $\delta_H((CD_3)_2SO)$ 3.71 (6H, s, 2 × CH_3O), 3.74 (3H, s, CH_3O), 3.84 (3H, s, CH_3O), 7.26 (4H, m, 2 × H-*o*), 7.38 (2H, m, 2 × H-*p*), 7.46 (4H, m, 2 × H-*m*); $\delta_H((CD_3)_2SO$, addition KCN) 3.41 (3H, s, CH_3O), 3.48 (3H, s, CH_3O), 6.67 (2H, m, H-*o*), 6.89 (1H, m, H-*p*), 7.17 (2H, m, H-*m*); $\delta_H(CDCl_3)$ 3.79 (3H, s, CH_3O), 3.85 (3H, s, CH_3O), 7.09 (2H, m, H-*o*), 7.28 (1H, m, H-*p*), 7.37 (2H, m, H-*m*); $\delta_C((CD_3)_2SO)$ 52.1, 52.4, 53.2 and 53.9 (4 × CH_3O), 73.2 (C_q), 115.3 and 116.2 (CN), 123.7 and 124.7 (C-H_o), 127.5 and 127.6 (C-H_p), 129.2 and 129.6 (C-H_m), 137.2 and 137.6 (C *ipso*), 158.4 (C_q), 158.8 (C_q), 161.8 (C_q), 162.4 (C_q), 164.2 (C_q), 166.1 (C_q); $\delta_C((CD_3)_2SO$, addition KCN) 49.5 and 50.6 (CH_3O), 114.0 (CN), 121.2 (C-H_o), 121.4 (C-H_p), 122.8 (C *ipso*), 128.2 (C-H_m), 152.3 (C_q), 160.5 (C_q), 166.2 (C_q), 168.0 (C_q); $\delta_C(CDCl_3)$ 52.5 and 53.7 (CH_3O), 74.6 (C_q), 115.8 (CN), 122.8 (C-H_o), 127.6 (C-H_p), 129.7 (C-H_m), 137.1 (C *ipso*), 158.8 (C_q), 161.4 (C_q), 168.1 (C_q).

Preparation of methyl ester of *N*-phenylamide of ethanedioic acid 18

Procedure A. With cooling at −60 °C, methyl cyanoacetate (0.8 ml, 9.2 mmol) was added to a mixture of sodium hydride (0.22 g, 9.2 mmol) and 80 ml THF, followed by nitrosobenzene (1 g, 9.2 mmol) again with cooling. The mixture gradually changes color from green through orange to intense red. After 1 hour stirring at the above-mentioned temperature, the mixture was left so that the temperature slowly increased to 20 °C, and the solution was evaporated on a rotary evaporator *in vacuo*. The evaporation residue was separated by column chromatography (silica gel, chloroform) to give 0.9 g (54.6%) compound **18**, mp 108–112 °C after vacuum sublimation (ref. 16 gives mp 111–112 °C). $\delta_H((CD_3)_2SO)$ 3.90 (3H, s, CH_3O), 7.19 (1H, m, H-*p*), 7.41 (2H, m, H-*m*), 7.79 (2H, m, H-*o*), 10.86 (1H, br, NH); $\delta_C((CD_3)_2SO)$ 53.3 (CH_3O), 120.6 (C-H_o), 124.9 (C-H_p), 128.9 (C-H_m), 137.6 (C *ipso*), 155.4 (NH–C=O), 161.2 (O–C=O).

Procedure B. A solution of aniline (0.58 ml, 6.3 mmol) in 20 ml dichloromethane was treated with methoxalyl chloride (0.25 ml, 3 mmol) added drop by drop. The solution was left to stand at room temperature 30 min. The separated solid was filtered off, and the filtrate was evaporated *in vacuo* to give 0.25 g (46.5%) product (**18**), mp 112–113 °C after recrystallization from heptane (ref. 16 gives mp 111–112 °C) (Found: C, 60.4; H, 5.1; N, 7.8. $C_9H_9NO_3$ requires C, 60.3; H, 5.1; N, 7.8%). The NMR spectra of products from procedures A and B are identical.

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