# SYNTHESIS AND PROPERTIES OF 7,7-DIAMINOQUINONE METHIDES*

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Diaminoquinone methides *Xa*—*Xe* were prepared by aminolysis of the dicyanoquinone methide *IX*. From the isolated intermediates *XI* and *XIII* a four-step mechanism was deduced, involving addition and eliminatioon steps in the order Ad-E-Ad-E. Condensation of N,N,N′,N′-tetramethylchloroformamidinium chloride with 2,6-ditert-butylphenol afforded bis(dimethylamino)-quinone methide *Xc* which on transamination was converted to the diaminoquinone methides *Xa* and *Xb*. Analysis of physico-chemical data of diaminoquinone methides leads to the conclusion that their structure can be represented by the zwitterionic formula *XVII* rather than the quinonoid formula *X*.

The reactivity and physico-chemical properties of quinone methides are governed by substituents on the methide carbon atom rather than on the quinonoid ring. Particularly conspicuous changes are effected by strong electron donating or accepting substituents. Thus, *e.g.* 7,7-bis(alkylthio)quinone methides[1] are crystalline compounds which, unlike the unsubstituted quinone methide, are capable of existence even at room temperature. The stability of bis(alkylthio)quinone methides is undoubtedly due to a partial delocalization of the non-bonding electrons of the divalent sulfur into the $\pi$-electron system of the quinonoid ring, leading to a gain in resonance energy. In this respect, substituted 7,7-diaminoquinone methides could be of interest because one could expect an even greater tendency to aromatization as compared with the sulfur derivatives.

Unfortunately, the only hitherto described synthesis of 7,7-diaminoquinone methides from a dithiolane derivative is not quite straightforward and is apparently limited to primary amines[2]. In an attempted extension of this reaction to secondary amines, dithioquinone methide *I* in treatment with piperidine afforded the desired dipiperidinoquinone methide *Xa* in only negligible yield, the major product being the thiopiperidide *IV*. Addition of the second amine molecule to the intermediate *III* is obviously much slower than the thiolate ion assisted fragmentation of the C—S bond (Scheme 1).

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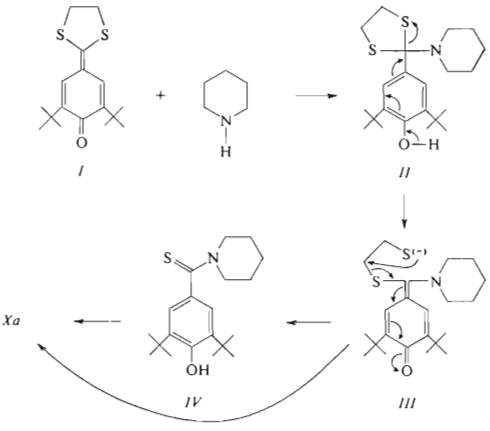
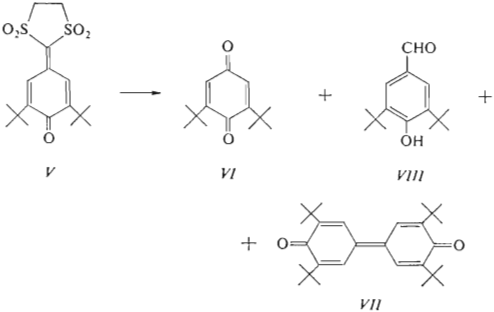



SCHEME 1

We therefore tried to elaborate a new synthesis of 7,7-diaminoquinone methides, based on the recently published synthesis of 7-piperidinoquinone methide[3]. We intended to use the disulfone *V* which is easily accessible from the corresponding dithiolane by oxidation with peroxy acids[4].

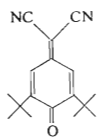



SCHEME 2

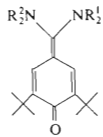
Although the disulfone *V* reacted instantaneously with piperidine, we were able to prove only traces of the desired quinone methide in the complex reaction mixture. The only isolated products were the quinone *VI*, diphenoquinone *VII* and 4-hydroxybenzaldehyde (*VIII*). The two latter compounds are probably products

of radical oxidation–reduction reactions[5] whereas the formation of *VI* can be ascribed to decomposition of the quinone methide π-bond system into the low-reactive dienone grouping and the very reactive vinylidene disulfone group which readily undergoes a Michael-type addition of water followed by a retroaldol reaction.

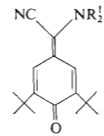
We turned therefore our attention to 7,7-dicyanoquinone methide *IX* which, according to our assumption, might react with amines similarly to tetracyanoquinodimethane[6]. Besides, our assumption is substantiated by a comparative study[7] on compounds in which the carbonyl oxygen has been replaced by a dicyanomethylene group. The reaction of dicyanoquinone methide *IX* with secondary amines is rather slow and a substantial part of the starting quinone methide *IX* is lost in competitive reactions. In order to suppress undesirable reactions of *IX*, we carried out the aminolyses with a substantial excess of the amine. Under these conditions almost all amines afforded directly the diaminoquinone methides *X*. Only the reaction with diethylamine was incomplete and stopped after one cyano group had been substituted. The arising aminocyanoquinone methide *XIa* did not react with the second molecule of diethylamine even under more drastic conditions. Since the nucleophilicity of diethylamine is comparable with that of other amines used[8], the anomalous behaviour of the compound could be ascribed to steric repulsion between the ethyl groups and the reaction center. This explanation is supported also by the fact that the diethylaminocyanoquinone methide *XIa* adds easily amines with lower steric demands (*e.g.* piperidine or morpholine) and affords the corresponding mixed diaminoquinone methides *Xd* and *Xe*.




*IX*




*X*



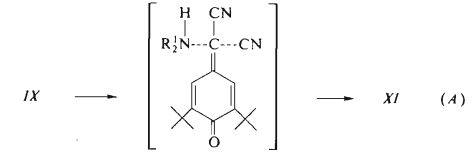

*XI*

*Xa*; $R_2^1 = R_2^2 = (CH_2)_5$
*Xb*; $R_2^1 = R_2^2 = (CH_2CH_2)O(CH_2CH_2)$
*Xc*; $R^1 = R^2 = CH_3$
*Xd*; $R^1 = C_2H_5$, $R_2^2 = (CH_2)_5$
*Xe*; $R^1 = C_2H_5$, $R_2^2 = (CH_2CH_2)O(CH_2CH_2)$

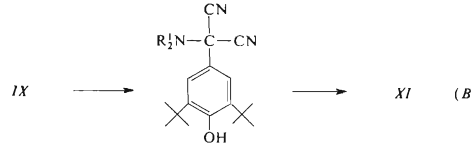
*XIa*; $R^1 = C_2H_5$
*XIb*; $R_2^1 = (CH_2CH_2)O(CH_2CH_2)$
*XIc*; $R_2^1 = (CH_2)_5$

From the results obtained it is obvious that the complete replacement of cyano groups by amino groups in the quinone methide *IX* involves at least one intermediate, *i.e.* aminocyanoquinone methide *XI*. From the mechanistic point of view, it would be of interest to decide whether the exchange of the cyano groups takes place by a direct substitution reaction on the methide $sp^2$ carbon (equation (*A*)) or by a two-step addition-elimination reaction (equation (*B*)). Intuitively, we can estimate that the

one-step process (*A*), involving the transition state *XII*, will be energetically more demanding than the two-step process (*B*), involving the $sp^3$ intermediate *XIII*.




*XII*

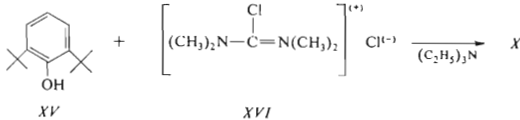



*XIII*

This assumption was proved by synthesis of the dicyanoaminophenol *XIIIa* (from piperidinocyanoquinone methide *XIc* and potassium cyanide in dimethyl sulfoxide) and its conversion into dipiperidinoquinone methide *Xa* under conditions of aminolysis of dicyanoquinone methide *IX*. Moreover, we isolated the phenol *XIIIb* in the reaction of dicyanoquinone methide *IX* with morpholine at low temperature. The complete reaction sequence, describing aminolysis of the quinone methide *IX*, lacks still an intermediate between the cyanoaminoquinone methide *XI* and the end product *X*. Although isolation of the intermediate *XIII* to a certain extent justifies the assumption of the existence of such species (*i.e. XIV*), we did not succeed to prove it experimentally. It is, however, very probable that, thanks to the presence of three electron donating substituents on the $sp^3$ carbon, the intermediate *XIV* is so labile that it cannot be isolated from the reaction medium. We assume that a similar tetrahedral intermediate must be involved also in transamination reactions of bis(dimethylamino)quinone methide *Xc* with piperidine and morpholine, leading to the diaminoquinone methides *Xa* and *Xb*, respectively.

The excellent yields of the transamination reactions were somewhat devaluated by the fact that the starting bis(dimethylamino)quinone methide *Xc* must be prepared from the not easily accessible[9] dicyanoquinone methide *IX*. We removed this disadvantage by working out a new synthesis of bis(dimethylamino)quinone methide *Xc*, consisting in the electrophilic substitution of 2,6-ditert-butylphenol (*XV*) with N,N,N′,N′-tetramethylchloroformamidinium chloride[10] (*XVI*) in the

presence of triethylamine (Scheme 3). This reaction can be extended to other tetrasubstituted chloroformamidinium chlorides[11]; however, its general applicability is limited by the competing C and O alkylation in the cases of sterically less hindered phenols.

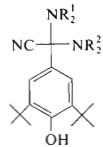



*XV* *XVI*

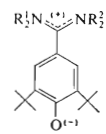
SCHEME 3

Physico-chemical properties of diaminoquinone methides *Xa*–*Xe* differ from those of other structurally related disubstituted quinone methides. The diamino derivatives are sparingly soluble in organic solvents and have high melting points. Whereas the experimentally determined dipole moments of quinone methides[1,12] range between 4·51 D (for 7,7-dimethyl-2,6-ditert-butylquinone methide) and 6·36 D (for the dithio derivative *I*), for the diaminoquinone methide *Xd* we found[13] an unusually high value (10·79 D). In the IR spectra of most of quinone methides we observed[12,14] a relatively large scatter of the carbonyl stretching vibration values (1 610 to 1 660 $cm^{-1}$) whereas for quinone methides *Xa*–*Xe* the corresponding bands are located at substantially lower wavenumbers in a narrow range (1 592–1 598 $cm^{-1}$). As a rule, UV spectra of quinone methides display only one solvent dependent absorption maximum[15], corresponding to the $\pi \rightarrow \pi^*$ transition. For most quinone methides it exhibits a positive solvatochromism, while in the case of diaminoquinone methides *Xa*–*Xe* the solvatochromism is negative.

The diamino derivatives have an exceptional position among the quinone methides hitherto investigated. They can be characterized as polar compounds with a developed negative center at oxygen with low carbonyl character and a positive center delocalized between the methide carbon and both the nitrogen substituents. The diaminoquinone methide *X* can thus be represented by the zwitterionic formula *XVII* rather than by the quinonoid structure *X*.




*XIV*




*XVII*

## EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Analytical samples were dried for 7 h at room temperature and 13 Pa. IR spectra were measured on an IR 20 spectrophotometer, UV spectra on a Specord UV-VIS instrument. Mass spectral measurements were carried out on an AEI MS 902 mass spectrometer (70 eV, source temperature 110—230°C).

### Reaction of Dithioquinone Methide *I* with Piperidine

A solution of the dithioquinone methide *I* (500 mg) in piperidine (3 ml) was heated for 8 h to 100°C. The mixture was poured in ice (50 ml) and extracted with ether (3× 15 ml). The ethereal extract was washed with water (5× 10 ml), dried over magnesium sulfate and taken down *in vacuo*. The residue was triturated with hexane and the insoluble material crystallized from dichloromethane, affording the diaminoquinone methide *Xa* (31 mg). The hexane extract gave 460 mg (85%) of 3,5-ditert-butyl-4-hydroxybenzothiopiperidide (*IV*), m.p. 142—143°C (ether–light petroleum). Found: $C_{20}H_{31}NOS$ (333·5) calculated: 72·02% C, 9·73% H, 4·19% N, 9·61% S; found: 72·00% C, 9·40% H, 4·20% N, 9·58% S. Mass spectrum: $M^+$ found: 333·2117, calculated for $C_{20}H_{31}NOS$: 333·2126.

### Reaction of Disulfone *V* with Piperidine

A solution of the disulfone *V* (500 mg) in piperidine (3 ml) was kept at 50°C for 1 h. The mixture was poured on ice (50 ml) and extracted with ether (3× 15 ml). The ethereal extract was taken down *in vacuo* and the residue chromatographed on silica gel (150 g, ether–light petroleum 1 : 9—1 : 1). affording the diphenoquinone *VII* (30 mg), m.p. 245—246°C, the quinone *VI* (120 mg), m.p. 66—67°C, and 4-hydroxybenzaldehyde (*VIII*) (95 mg), m.p. 188—189°C.

### Reaction of 2,6-Ditert-butyl-7,7-dicyanoquinone Methide (*IX*) with Amines

*A*) A solution of the dicyanoquinone methide *IX* (268 mg) in diethylamine (1 ml) was set aside at room temperature for 24 h. After evaporation the residue was chromatographed on silica gel (100 g, ether–light petroleum 1 : 5), affording 266 mg (72%) of 2,6-ditert-butyl-7-cyano--7-diethylaminoquinone methide (*XIa*), melting at 91—93°C (hexane). For $C_{20}H_{30}N_2O$ (314·4) calculated: 76·39% C, 9·61% H, 8·91% N; found: 76·22% C, 9·40% H, 9·05% N. UV spectrum (isooctane): 424 nm (log ε 4·47); IR spectrum ($CCl_4$): 1 604 $cm^{-1}$ (C=O). Mass spectrum; 314 ($M^+$). Elution with chloroform gave 2,6-ditert-butyltricyanovinylphenol (15 mg; 5%), m.p. 207·0—208·5°C (ether). UV spectrum (isooctane): 394 nm (log ε 4·27), 411 nm (log ε 4·33).

*B*) The dicyanoquinone methide *IX* (268 mg), dissolved at —5°C in dimethylamine (1 ml) was kept in a sealed ampoule at room temperature for 16 h. Dimethylamine was evaporated and the residue dissolved in dichloromethane (10 ml). The obtained solution was washed with water (3× 15 ml), dried over magnesium sulfate and concentrated *in vacuo*. Crystallization from dichloromethane–hexane yielded 106 mg (35%) of 2,6-ditert-butyl-7,7-bis(dimethylamino)-quinone methide (*Xc*). Its physical constants and spectral data were identical with those of an authentic sample.

*C*) A solution of the dicyanoquinone methide *IX* (268 mg) in piperidine (1 ml) was heated to 75°C for 2 h. The mixture was poured on ice (50 ml) and extracted with ether (5× 20 ml). The combined ethereal extracts were washed with water (5× 20 ml), dried over magnesium sulfate

and taken down *in vacuo*. The residue was triturated with ice-cold ether to remove 4-(tricyanovinyl)phenol. Crystallization from dichloromethane–hexane afforded 318 mg (83%) of 2,6-ditert-butyl-7,7-dipiperidinoquinone methide (*Xa*); m.p. 255—256°C. For $C_{25}H_{40}N_2O$ (384·6) calculated: 78·17% C, 10·48% H, 7·29% N; found: 77·85% C, 10·50% H, 7·05% N. UV spectrum, nm: (isooctane): 425 (log ε 4·55), (n-hexane): 425, (dichloroethane): 426, (acetone): 415, (dimethylformamide): 411, (dimethyl sulfoxide): 410, (acetonitrile): 404. IR spectrum ($CHCl_3$): 1 592 $cm^{-1}$ (C=O). Mass spectrum: 384 ($M^+$). The same procedure provided 2,6-ditert-butyl-7,7-dimorpholinoquinone methide (*Xb*) in 81% yield; m.p. 271—273°C. For $C_{23}H_{36}N_2O_3$ (388·5) calculated: 71·09% C, 9·34% H, 7·21% N; found: 70·17% C, 9·09% H, 7·20% N. UV spectrum (isooctane): 425 nm (log ε 4·49). IR spectrum ($CHCl_3$): 1 597 $cm^{-1}$ (C=O). Mass spectrum: 388 ($M^+$).

*D*) A solution of the dicyanoquinone methide *IX* (268 mg) in morpholine (1 ml) was kept at room temperature for 6 h and then taken down. Chromatography of the residue on silica gel (100 g, ether–light petroleum 1 : 9—1 : 1) gave 60 mg of dicyano(morpholino)(3,5-ditert-butyl-4-hydroxyphenyl)methane (*XIIIb*), besides the unreacted quinone methide *IX*, diaminoquinone methide *Xb* and traces of 4-(tricyanovinyl)phenol. Physical constants and spectral data of *XIIIb* agreed completely with those of the authentic sample. Further isolated product was 2,6-ditert-butyl-7-cyano-7-morpholinoquinone methide (*XIb*) (70 mg), m.p. 133·5—134·0°C (hexane). For $C_{20}H_{28}N_2O_2$ (328·4) calculated: 73·13% C, 8·59% H, 8·54% N; found: 73·15% C, 8·60% H, 8·51% N. UV spectrum (isooctane): 416 nm (log ε 4·38); IR spectrum ($CCl_4$): 1 610 $cm^{-1}$ (C=O). Mass spectrum: 328 ($M^+$).

Dicyano(piperidino)(3,5-ditert-butyl-4-hydroxyphenyl)methane (*XIIIa*)

Potassium cyanide (40 mg) was added under argon in small portions to a solution of the methide *XIc* (163 mg) in dimethyl sulfoxide (3 ml) until the quinone methide band in the UV spectra disappeared. The mixture was poured on ice (10 ml) and extracted with pentane (5×10 ml). The combined pentane extracts were washed with water (10×5 ml) and dried over magnesium sulfate. The crystals, obtained after evaporation of the solvent, were repeatedly crystallized from hexane, affording thus the phenol *XIIIa* (127 mg, 78%); m.p. 122—125°C. For $C_{22}H_{31}N_3O$ (353·5) calculated: 74·75% C, 8·84% H, 11·89% N; found: 74·15% C, 8·50% H, 11·80% N. IR spectrum ($CCl_4$): 3 635 $cm^{-1}$ (OH). Mass spectrum: 353 ($M^+$). The quinone methide *XIb* (164 mg) was transformed analogously into dicyano(morpholino) (3,5-ditert-butyl-4-hydroxyphenyl)-methane (*XIIIb*; 142 mg; 80%), m.p. 138—139°C (hexane). For $C_{21}H_{29}N_3O_2$ (355·4) calculated; 70·95% C, 8·22% H, 9·00% N; found: 70·50% C, 8·15% H, 8·95% N. IR spectrum ($CCl_4$): 3 635 $cm^{-1}$ (OH). Mass spectrum: 355 ($M^+$).

2,6-Ditert-butyl-7-cyano-7-piperidinoquinone Methide (*XIc*)

A solution of 2,6-ditert-butyl-7-cyanoquinone methide (243 mg) in piperidine (1 ml) was kept at room temperature for 3 h, evaporated and the residue dissolved in ether (20 ml). The ethereal solution was washed with water (5×10 ml) and worked up as usual, affording cyano(piperidino)-(3,5-ditert-butyl-4-hydroxyphenyl)methane (249 mg; 76%), m.p. 108—110°C (hexane). IR spectrum ($CCl_4$): 3 640 $cm^{-1}$ (OH). Mass spectrum: 328 ($M^+$). This product (200 mg) was oxidized under argon with manganese dioxide (1 g) at 10°C to give 182 mg (92%) of 2,8-ditert-butyl-7-cyano-7-piperidinoquinone methide (*XIc*), m.p. 100—107°C (hexane). For $C_{21}H_{30}N_2O$ (326·5) calculated: 77·25% C, 9·26% H, 8·58% N; found: 77·40% C, 9·02% H, 8·72% N. UV spectrum (isooctane): 416 nm (log ε 4·31); IR spectrum ($CCl_4$): 1 608 $cm^{-1}$ (C=O). Mass spectrum: 326 ($M^+$).

2,6-Ditert-butyl-7,7-bis(dimethylamino)quinone Methide (*Xc*)

A solution of N,N,N′,N′-tetramethylchloroformamidinium chloride (1·71 g) in acetonitrile (8 ml) was added dropwise under nitrogen to a mixture of 2,6-ditert-butylphenol (*XV*) (205 mg) and triethylamine (2·8 ml). The mixture was refluxed for 3 h, cooled, poured on ice (100 ml) and extracted with dichloromethane (3× 20 ml). The combined extracts were washed with water (5× 10 ml), dried over magnesium sulfate and taken down *in vacuo*. The residue was triturated with pentane and the residue crystallized from a dichloromethane–hexane mixture to give the quinone methide *Xc* (121 mg; 40%), m.p. 246—247°C. For $C_{19}H_{32}N_2O$ (304·4) calculated: 74·95% C, 10·60% H, 9·20% N; found: 74·00% C, 10·25% H, 9·05% N. UV spectrum (isooctane): 417 nm (log ε 4·41); IR spectrum ($CHCl_3$): 1 597 $cm^{-1}$ (C═O). Mass spectrum: 304 ($M^+$).

2,6-Ditert-butyl-7-diethylamino-7-piperidinoquinone Methide (*Xd*)

Piperidine (85 mg) was added to a solution of the quinone methide *XIa* (314 mg) in chloroform (5 ml) and the mixture was refluxed for 4 h. The usual work-up procedure afforded *Xd* (305 mg; 72%), m.p. 139—142°C (dichloromethane–hexane). For $C_{24}H_{40}N_2O$ (372·6) calculated: 77·36% C, 10·82% H, 7·52% N; found: 77·52% C, 11·00% H, 7·49% N. UV spectrum (isooctane): 425 nm (log ε 4·78); IR spectrum ($CHCl_3$): 1 594 $cm^{-1}$ (C═O). Mass spectrum: 372 ($M^+$). 2,6-Ditert-butyl-7-diethylamino-7-morpholinoquinone methide (*Xe*) (295 mg; 79%) was prepared analogously; m.p. 201—204°C (dichloromethane–hexane). For $C_{23}H_{38}N_2O_2$ (374·6) calculated: 73·75% C, 10·23% H, 7·48% N; found: 74·09% C, 9·87% H, 7·55% N. UV spectrum (isooctane): 425 nm (log ε 4·54); IR spectrum ($CHCl_3$): 1 598 $cm^{-1}$ (C═O). Mass spectrum: 374 ($M^+$).

Reaction of Dicyano(piperidino)(3,5-ditert-butyl-4-hydroxyphenyl)methane (*XIIIa*) with Piperidine

A solution of dicyanopiperidinophenol *XIIIa* (100 mg) in piperidine (1 ml) was heated to 75°C for 2 h. The mixture was poured on ice (20 ml) and extracted with ether (5× 10 ml). The combined ethereal extracts were washed with water (5 . 20 ml). dried over magnesium sulfate and taken down *in vacuo*. Crystallization from dichloromethane-hexane gave the dipiperidinoquinone methide *Xa* in 85% yield. Its physical constants and spectral data were identical with those of the authentic sample.

Transamination of Bis(dimethylamino)quinone Methide *Xc*

A solution of the bis(dimethylamino)quinone methide *Xc* (200 mg) in piperidine (1 ml) was heated to 50°C for 2 h. The mixture was worked up as usual and the dipiperidinoquinone methide *Xa* was obtained in 93% yield by crystallization from dichloromethane–hexane. The dimorpholinoquinone methide *Xb* was prepared by the same procedure in 89% yield. Their physical constants and spectral data were identical with those of authentic samples.

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