REACTIONS OF DERIVATIVES OF 4*a*,9-DIAZA-1,2,4*a*,9*a*-TETRAHYDRO-6H-FLUORENE WITH NUCLEOPHILIC REAGENTS AND BROMINE

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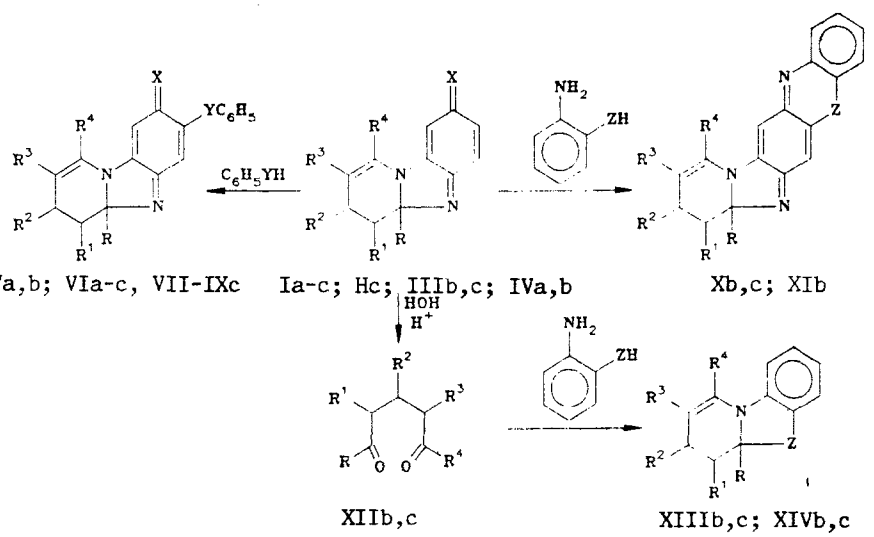
The reaction of quinone mono- and diimines of the 4a,9-diaza-12,4a,9a-tetrahydro-6H-fluorene series with aniline and thiophenol gives the corresponding 7-monosubstituted derivatives; with o-phenylenediamine and o-aminophenol the corresponding 6,7-annellated products are formed. Methylenequinone imines of this series, and also the 7,8-benzannellated analogs of diazahydrofluorenes, do not react with these nucleophiles. The bromination of diazahydrofluorene derivatives involves both the quinoid system and the enamine fragment.

The reactions of quinonoid compounds in general [1, 2, 3], and of heterocyclic quinone imines in particular [4], with nucleophilic and, to a lesser extent, with electrophilic reagents, are well-studied. On the other hand, almost no studies on the reactivity of enamino quinonoid compounds have been published.

We have synthesized polycyclic enamino quinonoid compounds of the 4*a*,9-diaza 1,2,4*a*,9*a*-tetrahydro-6H-fluorene series and studied the reactions of some of them with the nucleophilic reagents aniline, thiophenol, o-phenylenediamine, and o-aminophenol. We also describe their reactions with bromine. The compounds studied include the quinone monoimines Ia-c [5], the quinone diimines IIc, IIIb, c [6], and the methylenequinone imines IVa, b [7].

Scheme 1



I—XIV a R=R²=C₆H₅, R¹=R³=H; b R+R¹=(CH₂)₄, R²=R⁴=C₆H₅, R³=H; c R+R¹=R³+R⁴=(CH₂)₄, R²=H, I, V, VI X=O; II, VII, VIII X=NC₆H₅; III, IX X=N-*cyclo*-C₆H₁₁; IV X=C(CN)₂; V, VII Y=NH; VI, VIII, IX Y=S; X, XIII Z=NH; XI, XIV Z=O

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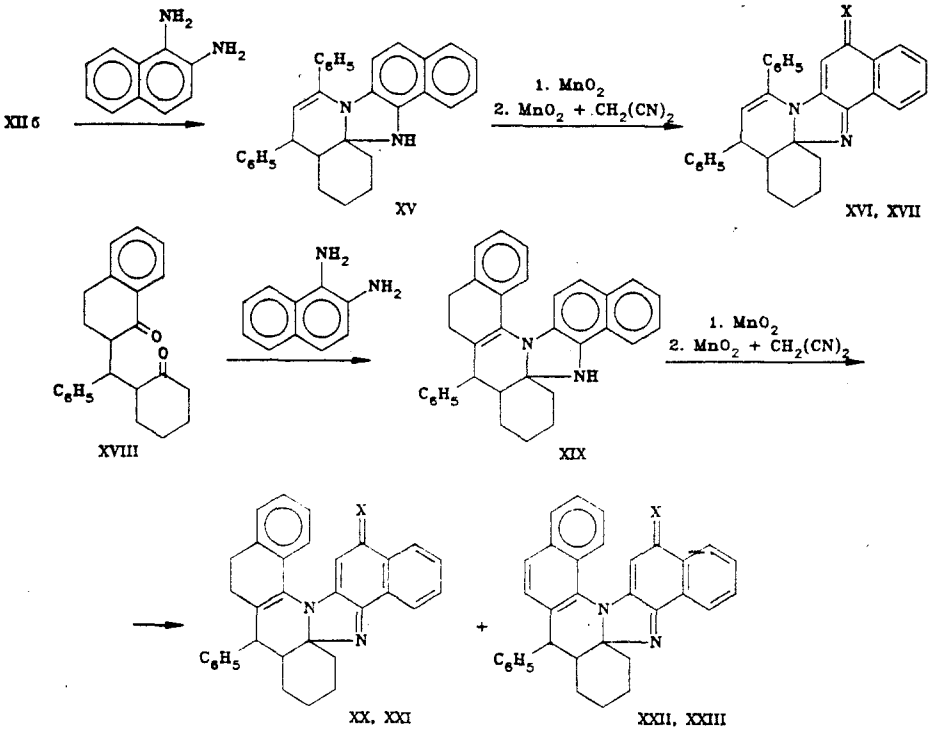
The reaction of quinone mono- and diimines I-III with aniline and thiophenol proceeded as a regioselective 1,4-addition across the conjugated C=C—C=N system and in the absence of oxidants led to the formation of the corresponding 7-monosubstituted quinone mono- (V, VI) and diimines (VII-IX). An acid activation of the substrate was required in the reactions with aniline, whereas a base activation of thiophenol had to be used in some cases (compounds Ia, b). The reactions of compounds I-III with o-phenylenediamine and o-aminophenol were carried out by heating in acetic acid and gave the 6,7-annellated compounds X and XI, which show a strong fluorescence in solution. With compounds II and III these reactions were accompanied by cleavage of the alkyl(aryl) imine fragment from position 6. Compounds X and XI were also formed when quinone monoimines I were reacted with these reagents in the presence of mineral acids, but here the reactions were complicated by a hydrolytic cleavage of the starting compounds I to the corresponding 1,5-diketones. The latter then reacted further with the bifunctional nucleophilic reagent present in the reaction mixture to give XIII and XIV. The diketone XIIc was isolated upon heating of quinone imine Ic in an acidic ethanol solution.

In contrast to compounds I-III, the methylenequinone imines IV do not react with these mono- and bifunctional nucleophiles under similar conditions. An attempt to carry out the reactions in strongly acidic media led to the decomposition of IV. This unreactivity of methylenequinone imines IV toward nucleophilic attack is most likely due to a significant charge transfer from N_{4a} to the dicyanomethylene group, which is a strong acceptor. As a result, a positive charge is localized at N_{4a}, which is a strong acceptor. As a result, a positive charge is localized at N_{4a}, which is inert toward a nucleophilic attack.

Scheme 2



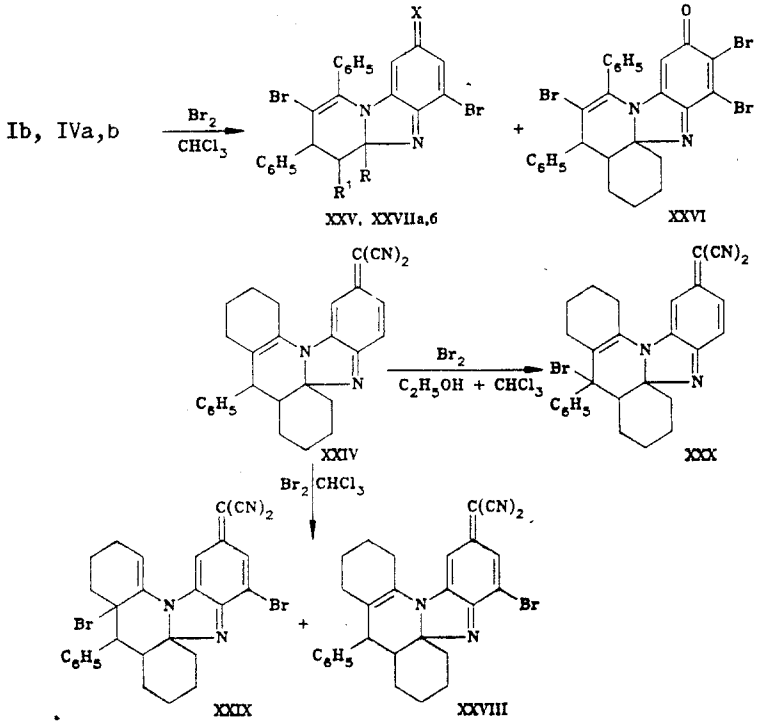
XVI, XX, XII X=O; XVII, XXI, XXIII X=C(CN)$_2$

We synthesized the 7,8-benzannellated analogs of diazatetrahydro-6H-fluorene, compounds XVI, XVII, and XX-XXIII, in which the 7-position is blocked. These compounds were prepared by reaction of 1,5-diketones XIIb and XVIII with 1,2-diaminonaphthalene, followed by an oxidative treatment (as described in [5, 7]) of the intermediates XV and XIX. The oxidations were carried out without the isolation and purification of the latter intermediates due to their instability. The reaction of the diketones with 1,2-diaminonaphthalene was found to be regioselective and in none of the cases was an isomeric 5,6-benzannellated analog isolated after oxidation. The oxidative conversions of XIX with activated MnO_2 gave a 10:1 mixture of XX and XXII, and a 5:1 mixture of XXI and XXIII (as determined by NMR). Pure XXI was obtained when the reaction was carried out with nonactivated MnO_2.

In contrast to compounds I-III, compound XVI did not react with aniline, thiophenol, o-phenylenediamine, and o-aminophenol, despite the use of harsher conditions and prolonged reaction times. Thus, the 5-position in the diazahydro-6H-fluorene system is inert toward nucleophilic attack.

A possible explanation for the selective nucleophilic attack at position 7 of the diazahydrofluorene system is the fact that in this case following a 1,4-addition of the nucleophile the resulting ionic intermediates still preserve the conjugation between the donor nitrogen (N_{4a}) and the acceptor group X, whereas this conjugation is disrupted in the intermediates if a nucleophilic attack takes place at positions 5 or 8.

Scheme 3



XXV R+R¹=$(CH_2)_4$, X=O; XXVII a R=C_6H_5, R¹=H, X=$(CN)_2$; b R+R¹=$(CH_2)_4$, X=$C(CN)_2$

TABLE 1. Electronic and IR Spectral Data of the Compounds Prepared

Compound	Electronic spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}
Va	384 (4,29), 465 (3,65)	3344, 1642, 1620, 1600, 1582
V b	386 (4,33), 472 (3,70)	3340, 1645, 1622, 1604, 1576
VI a	473 (3,46)	1647, 1603, 1577, 1547
VI b	476 (3,57)	1653, 1608, 1596, 1548
VI c	501 (3,69)	1670, 1612, 1582, 1540
VII c	388 (4,43), 491 (3,72)	3285, 1667, 1621, 1607, 1586
VIII c	508 (3,91)	1670, 1623, 1576, 1532
IX c	478 (3,82)	1668, 1623, 1589, 1538
X b	450 (4,43)	3460, 1643, 1596
X c	460 (4,45)	3455, 1668, 1592
XI b	468 (4,39)	1651, 1606, 1589
XV		3200, 1628
XVI	436 (4,01)	1650, 1610, 1590, 1550
XVII	525 (4,30)	2200, 1660, 1640, 1582, 1530
XIX		3200, 1620
XX	439 (3,95)	1628, 1600, 1580
XXI	438 (3,95)	2220, 1625, 1600, 1520
XXV	483 (3,90)	1640, 1600, 1588, 1560
XXVI	491 (3,84)	1643, 1605, 1572, 1541
XXVII a	408 (3,98), 574 (4,18)	2210, 1624, 1606, 1578, 1560
XXVII b	406 (3,89), 580 (4,20)	2208, 1631, 1612, 1578, 1563
XXVIII+XXIX	380 (3,95), 396 (3,62), 573 (4,18), 606 (4,12)	2207, 1620, 1595, 1575, 1561
XXX		2220, 1640, 1580

TABLE 2. NMR Data of the Compounds Prepared

Compound	Chemical shift, ppm (J-Constant, Hz)					
	2-H	3-H, d	5-H	7-H, d	8-H	Other protons
Va	3,40*	5,64 (J=3,5)	5,00 s	—	6,55 s	1,65 q (J=−12,5; J=12), 1a-H, 3,40*, 1e-H
Vb	3,82 d.d (J=10; J=3,5)	5,60 (J=3,5)	4,86 s	—	6,62 s	
VIa	3,39 q.d (J=12; J=6; J=2,5)	5,61 (J=2,5)	5,04 s	—	6,25 s	1,62 q (J=−12,5; J=12), 1a-H, 3,24 t.q (J=−12,5; J=6), 1e-H
VIb	3,80 d.d (J=10; J=3,5)	5,56 (J=3,5)	4,85 s	—	6,32 s	
VIc	2,68 m	—	5,82 s	—	6,27 s	
VIIc	—**	—	5,60 s	—	6,57 s	
VIIIc	—**	—	5,62 s	—	6,25 s	
IXc	2,60 m	—	5,72 s	—	6,11 s	3,48 m (1H), CH—N=$C_{(6)}$
Xb	3,72 d.d (J=10; J=3,5)	5,59 (J=3,5)	6,14 s	—	6,93 s	
Xc	—**	—	6,71 s	—	6,97 s	
XIb	3,83 d.d (J=10; J=3,5)	5,50 (J=3,5)	5,15 s	—	6,45 s	
XVI	3,89 d.d (J=10; J=3,5)	5,60 (J=3,5)	4,95 s	—	—	7,65 m (2H), 2′-H, 3′-H, 8,24 m (2H), 1′-H, 4′-H
XVII	3,92 d.d (J=10; J=2,5)	5,65 (J=2,5)	5,60 s	—	—	7,67 m (2H), 2′-H, 3′-H, 8,70 m (2H), 1′-H, 4′-H
XX	3,58 d (J=10)	—	5,40 s	—	—	7,65 m (2H), 2′-H, 3′-H, 8,30 m (2H), 1′-H, 4′-H
XXI	3,63 d (J=10)	—	6,13 s	—	—	
XXII	4,35 d (J=10)	—	5,55 s	—	—	
XXIII	4,41 d (J=10)	—	6,25 s	—	—	
XXV	3,94 d (J=10)	—	4,36 s (J=1,5)	6,95 d (J=1,5)	—	
XXVI	3,93 d (J=10)	—	4,52 s	—	—	
XXVIIa	3,70 d.d (J=12; J=6)	—	4,89 d (J=1,5)	7,63 d (J=1,5)	—	
XXVIIb	4,00 d (J=10)	—	5,81 d (J=1,5)	7,67 d (J=1,5)	—	2,02 q (J=−12,5; J=12), 1a-H, 3,46 q (J=−12,5; J=6), 1e-H
XXVIII	3,40 d (J=10)	—	6,22 d (J=1,8)	7,78 d (J=1,8)	—	
XXIX	4,38 d (J=10,8)	—	6,70 d (J=1,5)	7,84 d (J=1,5)	—	5,44 t (J=3,2), $C_{(4)}$=C—H
XXX	—	—	6,60 уш. с	7,60 (J=10)	7,19 d (J=10)	

*The signals of H_{1e} and H_2 overlap.
**Overlaps with the signals of the CH_2 group.

TABLE 3. Characterization of the Compounds Prepared

Compound	Molecular formula	mp, °C	Recrystallization solvent	Yield, %
Va	$C_{29}H_{23}N_3O$	241...243	Hexane/ether	60
Vb	$C_{33}H_{29}N_3O$	245...247	Hexane/ether	64
VIa	$C_{29}H_{22}N_2OS$	256...257	Hexane/chloroform	81
VIb	$C_{33}H_{28}N_2OS$	246...248	Propanol	86
VIc	$C_{25}H_{26}N_2OS$	211...213	Propanol	88
VIIc	$C_{31}H_{32}N_4$	248...250	Hexane/acetone	80
VIIIc	$C_{31}H_{31}N_3S$	216...218	Ethanol	85
IXc	$C_{31}H_{37}N_3S$	219...221	Ethanol	89
Xb	$C_{33}H_{28}N_4$	280...282 (decomp.)	Ethyl acetate/acetone	11
Xc	$C_{25}H_{26}N_4$	180...182 (decom.)	Ethyl acetate/acetone	46*
XIb	$C_{33}H_{27}N_3O$	282...283	Hexane/acetone	49
XVI	$C_{31}H_{26}N_2O$	284...286	DMF	64
XVII	$C_{34}H_{26}N_4$	246...248	Hexane/acetone	88
XX	$C_{32}H_{28}N_2O$	356...358	DMF	82**
XXI	$C_{35}H_{28}N_4$	274...276	Hexane/acetone	52***
XXV	$C_{27}H_{22}Br_2N_2$	220...222	Hexane/chloroform	79
XXVI	$C_{27}H_{21}Br_3N_2$	244...246	Hexane/chloroform	16
XXVIIa	$C_{32}H_{20}Br_2N_4$	240...242	Hexane/benzene	98
XXVIIb	$C_{30}H_{22}Br_2N_4$	237...239	Hexane	97
XXX	$C_{28}H_{25}BrN_4$	209...211 (not recrystallized)		84

*From compound IIc; yield from Ic: 40%.
**Contaminated with XXII.
***Contaminated with XXIII.

Only a few examples of bromination of quinone imines are known [8]. The only reported bromination of a methylenequinone imine is that of tetracyanoquinodimethane [2], which proceeds as a 1,6-addition. The bromination of methylenequinone imines has not been studied.

We have now studied the bromination of some enamino quinonoid compounds, namely of quinone monoimine Ib and of methylenequinone imines IVa, b and XXIV. When the bromination was carried out in chloroform, both the quinonoid system and the enamine bond reacted. Quinone monoimine Ib gave a mixture of 3,8-dibromo- and 3,7,8-tribromo-substituted compounds (XXV and XXVI, respectively). Under the same conditions, a selective bromination of the methylenequinone imines IVa, b is observed, leading to the corresponding 3,8-dibromides XXVIIa, b. The bromination of methylenequinone imine XXIV in chloroform led to an inseparable mixture of the 8-monobromo-substituted XXVIII and the 3,8-dibromo-substituted XXIX, in a ratio of 7:5 (determined by NMR). Surprisingly, when carried out in a chloroform—ethanol mixture, the same reaction gave the 2-monobromo-substituted compound XXX, a product of allylic bromination. Although the results are somewhat ambiguous, it seems that bromination takes place predominantly at position 8 of the quinonoid ring of the compounds studied. In the case of methylenequinone imines, this corresponds to a 1,4-addition across conjugated system $C_{10}=C_6-C_7=C_8$, followed by dehydrobromination, and this is in contrast with the reported 1,6-bromination of quinodimethanes mentioned above.

The structure of all compounds prepared was confirmed by spectral data. In particular, a strong NH absorbance peak is seen in the IR spectra (Table 1) of compounds V, VII, and X. Also, the strong absorbance peaks in the region above 1550 cm^{-1} due to the quinonoid structure [5, 6] are absent from the spectra of compounds X because of the formation of an aromatic phenazine system. The NMR spectral data are given in Table 2. A comparison of the NMR spectra of the 7-substituted diazahydrofluorenes with that of their corresponding starting compounds [5, 6] shows the disappearance of the signal due to the H_7 proton. Also, the signals of H_5 and H_8 become singlets. In the spectra of the bromo derivatives XXV-XXIX, the signal of H_8 disappears: in XXV-XXVII the signal of a vinyl hydrogen disappears, which is present in the spectra of compounds I-IV [5, 7]. In contrast, there is such a signal in the spectrum of XXIX. The presence of a singlet for H_5 (shifted upfield due to the shielding effect of the phenyl substituent in position 4 [5]) in the spectra of compounds XVI, XVII, and XX-XXIII is an indication that these compounds are indeed the 7,8- and not the 5,6-benzannellated diazahydrofluorene analogs. The molecular weights of all compounds prepared, as determined by mass spectroscopy, correspond to the calculated values. The mass spectra of compounds Xb and XIb show main peaks at $[M-193]^+$ and $[M-195]^+$, respectively, which indicates a fragmentation with loss of the phen(ox)azine part of the molecule.

EXPERIMENTAL

Electronic spectra were recorded in chloroform, on a Perkin—Elmer instrument; IR spectra in chloroform on a Specord IR-75; NMR spectra in $CDCl_3$ with TMS as an internal standard, on a Bruker WM-250 (250 MHz). Mass spectra were obtained on a LKB-9000, at 70 eV, and with direct inlet. The reactions were monitored by TLC on Silufol plates.

Satisfactory elemental analysis data (for C, H, and N) were obtained for the compounds prepared.

Table 3 lists the characteristic data of the compounds synthesized.

7-Phenylamino-6-Oxo(phenylimino)-9*a*-R-1-R^1-2-R^2-3-R^3-4-R^4-4*a*,9-diaza-1,2,4*a*,9*a*-tetrahydro-6H-fluorenes (Va, b and VIIIc). To a 2% solution of the quinonoid compound (Ia and Ib in DMF; IIc in CH_3COOH) was added freshly distilled aniline. The molar ratio quinone imine/aniline was 1:2 for compounds Ia, b and 1:1.5 for IIc. In the case of compounds Ia, b several drops of concentrated HCl were added to the solution. The mixtures were then heated on a boiling water bath for 1.5-2 h, diluted with water, neutralized with a Na_2CO_3 solution, and extracted with ether. The extracts were dried over Na_2SO_4, the solvent removed, and the residues purified by column chromatography on silica gel using hexane/ethyl acetate as the eluant.

7-Phenylthio-6-oxo(phenylimino, cyclohexylimino)-9*a*-R-1-R^1-2-R^2-3-R^3-4-R^4-4*a*,9-diaza-1,2,4*a*,9*a*-tetrahydro-6H-fluorenes (VIa-c, VIIIc, and IXc). Thiophenol was added to a 2% solution of one of the quinonoid compounds I-III in ethanol. The molar ratio quinone imine/thiophenol was 1:4 for compounds Ia, b and 1:2 for Ic, IIc, and IIIc. With compounds Ia, b an equimolar amount (with respect to the thiophenol used) of NaOH in ethanol was added. The reaction was then stirred at room temperature (Ia, b and IIIc) or refluxed (Ic and IIc) for 2-4 h, cooled to 0°C, and the virtually pure reaction product filtered off.

Reaction of Compounds I-III with o-Phenylenediamine and o-Aminophenol. A. A 50% molar excess of the reagent was added to a 2% solution of the quinone imine in CH_3COOH. The mixture was heated on a boiling water bath for 2-3 h (in the reaction with o-phenylenediamine), or for 7 h (with o-aminophenol), cooled, diluted with water, neutralized with a Na_2CO_3 solution, the precipitate collected by filtration, washed with water, dried, and chromatographed on silica gel. The elution was carried out with hexane/ethyl acetate. After chromatography, the solvent was removed either in vacuum (compound Xc) or at atmospheric pressure (all other compounds). Compounds Xb and XIb, respectively, were obtained when Ib was reacted with o-phenylenediamine and o-aminophenol. The reaction of o-phenylenediamine with Ic and IIc led to the formation of Xc, which was also formed by reaction of IIIc with o-phenylenediamine. In the former case, compound Xc was not isolated, but its formation detected by TLC in three different solvent systems, using an authentic sample as a standard.

B. A 50% molar excess of the reagent was added to 0.5 g of Ib or Ic in 10 ml of ethanol. Concentrated HCl, 3-5 drops, was added and the mixture refluxed for 2-3 h. Workup was carried out as described in **A**. The reaction of o-phenylenediamine with Ib gave compounds Xb and XIIIb in 21 and 24% isolated yields. The reaction of o-aminophenol with Ic gave compounds XIb and XIVb in 28 and 25% isolated yields. Finally, the reaction of Ic with o-phenylenediamine gave compounds Xc (21%) and XIIIc (24%). Compounds XIIIb, c and XIVb were identified by determination of their mixed melting points with authentic samples and by their IR spectra.

Hydrolytic Cleavage of Compound Ic. To a solution of 0.2 g of compound Ic in 5 ml of ethanol were added three drops of concentrated HCl. The mixture was refluxed for 2 h, cooled, diluted with water, neutralized with Na_2CO_3, and extracted with ether. The ether was evaporated and the residue purified by column chromatography on silica gel using hexane/ethyl acetate as the eluant. Yield of diketone XIIc: 0.10 g (71%). The product was identified as diketone XIIc by comparison of its IR spectrum with that of an authentic sample of this compound.

Reaction of Diketones XIIb and XVIII with 1,2-Diaminonaphthalene. To a suspension of 3.3 g (9.3 mmoles) of 1,2-diaminonaphthalene sulfate in 50 ml of water was added concentrated ammonia solution to pH 9. The resulting mixture was stirred 5 min, the separated amine filtered off, washed with water until neutral, and added to a suspension of an equimolar amount of the diketone in 30-40 ml of ethanol. p-Toluenesulfonic acid, 50 mg, was added, the mixture refluxed under Ar for 6-7 h, cooled under a stream of Ar, and the separated compounds XV or XIX filtered off in 70 and 49% yields, respectively. These products were used without further purification for the subsequent oxidative transformations.

Synthesis of Compounds XVI, XX, and XXII by Oxidation of XV and XIX. To a solution of 1 g of compound XV or XIX in 20 ml of acetone was added 2-2.3 g (approximately 15-fold molar excess) of activated MnO_2. The mixture was stirred for 15-30 min, the MnO_2 filtered off, and washed with acetone and chloroform until the filtrate was colorless. The combined filtrates were then concentrated to dryness. Compound XVI was thereby obtained virtually pure by oxidation of XV; the oxidation of XIX resulted in a 10:1 mixture of XX and XXII, which upon recrystallization gave pure XX.

Synthesis of Compounds XVII, XXI, and XXIII by Oxidative Coupling of Compounds XV and XIX with Malononitrile. To a solution of 1 g of compound XV or XIX in 20 ml of $CHCl_3$ containing a threefold molar excess of malononitrile was added 2-2.3 g of MnO_2 (nonactivated in the case of compound XV; activated in the case of XIX). The resulting mixture was stirred for 45 min (compound XV) or 15 min (compound XIX), MnO_2 was filtered

off, washed with $CHCl_3$, and the filtrate concentrated. Compound XVII was purified by preparative TLC using hexane/ethyl acetate as the eluant. The mixture of compounds XXI and XXIII (5:1) was separated by column chromatography with hexane/chloroform as the eluant.

Bromination of Quinone Monoimine Ib and of Methylenequinone Imines IVa, b and XXIV. A. A solution of bromine in chloroform was added to 0.5 g of the quinonoid compound in 15 ml of chloroform. The molar ratio substrate/bromine was 1:2 in the case of compounds Ib and IVa, b and 1:5 for compound XXIV. With compounds Ib and XXIV, the bromine solution was added dropwise in the course of 30 min to 1 h. Excess bromine was removed after 1 h of reaction by extracting the reaction mixture with an aqueous Na_2CO_3 solution. The products of bromination of IVa, b and compounds XXVIIa, b were then obtained virtually pure by evaporation of the chloroform, whereas the products of bromination of Ib, namely compounds XXV and XXVI, were separated by preparative TLC using chloroform/hexane as the eluant. The crude product of bromination of compound XXV comprised a 7:5 mixture of XXVIII and XXIX, which could not be separated because of their identical R_f values. The ratio of these compounds in the mixture was determined by integration of the NMR signals of the H_2 and H_5 protons.

B. To a solution of 0.5 g of compound XXV in 15 ml of ethanol was added a solution of 0.4 g of bromine in 5 ml of chloroform. Compound XXX precipitated and was obtained virtually pure by filtration after 2 h of reaction.

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