Quinoxalinediones. II. The Diels–Alder Reactions of 2,3-Dimethyl-5,8-quinoxalinedione[1]

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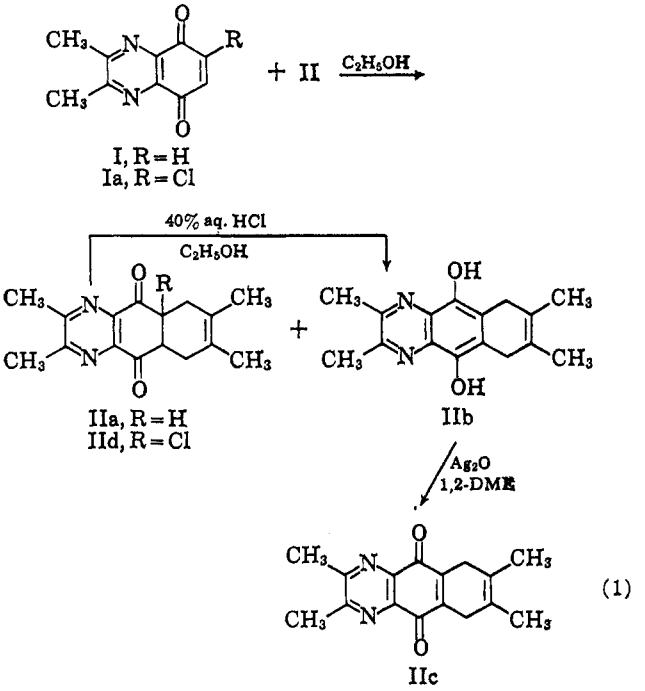
2,3-Dimethyl-5,8-quinoxalinedione has been shown to react easily with four dienes of varying reactivity and geometry. The Diels–Alder adducts were tautomerized to hydroquinones which were oxidized to new heterocyclic quinones. Infrared, ultraviolet, and n.m.r. spectroscopy were used to elucidate the structure and stereochemistry of the products obtained.

Although *p*-benzoquinone and 1,4-naphthoquinone have been extensively used as dienophiles in Diels–Alder reactions, similar reactions with heterocyclic quinones have not been explored. Since 2,3-dimethyl-5,8-quinoxalinedione (I) may be regarded as the pyrazine analog of 1,4-naphthoquinone, it seemed of interest to investigate the dienophilic nature of this heterocyclic quinone since the deactivating effect of the nitrogen atoms in the pyrazine ring should increase the electrophilic nature of the quinone double bond.

2,3-Dimethylbutadiene (II) was treated with 1,4-naphthoquinone in ethanol,[3] in nitrobenzene,[4] and in the absence of solvents using an excess of diene.[5] When nitrobenzene was used as a solvent, enolization, dehydrogenation, and oxidation of the primary adduct occurred to yield a substituted 9,10-anthraquinone. When I was refluxed with an excess of II, in ethanol, both 5a,6,9,9a-tetrahydro-2,3,7,8-tetramethylbenzo[*g*]-quinoxaline-5,10-dione (IIa) and 6,9-dihydro-2,3,7,8-tetramethylbenzo[*g*]quinoxaline-5,10-diol (IIb) were obtained, the product ratio being 46% of IIa to 7% of IIb after 6 hr. The adduct was tautomerized to the hydroquinone both at its melting point and also by treatment with 40% aqueous hydrochloric acid in ethanol. Compound IIb was oxidized to 6,9-dihydro-2,3,7,8-tetramethylbenzo[*g*]quinoxaline-5,10-dione (IIc) by oxidation with silver oxide in 1,2-dimethoxyethane, hereafter referred to as 1,2-DME.

The reaction of 2-chloro-6-methyl-*p*-benzoquinone with II gave an adduct which was chromatographed on an alumina column.[6] Elimination of hydrogen chloride occurred on the column and a quinone was formed. The same quinone was formed when the adduct was dried. The products formed in the reaction of 6-chloro-5,8-quinoxalinedione (Ia) with II, in ethanol, were similar to those obtained in the reaction of 2-chloro-1,4-naphthoquinone with II.[3] Only about 3% of the chloro adduct (IId) was isolated since elimination of hydrogen chloride occurred spontaneously to yield the quinone IIc in 82% yield. A quinhydrone was also formed. This product probably arose from the reduction of IIc to IIb and subsequent complex formation promoted by the alcoholic solvent and catalyzed by the acid present in solution. Braude has shown that quinones undergo such reactions in protic solvents.[7] The reactions of I and Ia with II are shown in eq. 1.



(1)

Both 1,3-cyclohexadiene (III) and 1,3-cyclopentadiene (IV) yield adducts with 1,4-naphthoquinone. A cyclopentadiene adduct was obtained in benzene although the *endo* adduct was unstable and yielded 1,4-naphthohydroquinone diacetate with acetic anhydride.[8] A stable cyclohexadiene adduct was obtained in ethanol[9] and also in the absence of a solvent and with excess diene.[10] Air and an ethanolic alkali solution were used to dehydrogenate the *endo* adduct to the corresponding quinone.[10] The adduct, 5a,6,9,9a-tetrahydro-2,3-dimethyl-6,9-ethanobenzo[*g*]quinoxaline-5,10-dione (IIIa) was obtained in 74% yield when I and III were refluxed in ethanol for 17 hr. A small amount of thermally tautomerized 6,9-dihydro-2,3-dimethyl-6,9-ethanobenzo[*g*]quinoxaline-5,10-diol (IIIb) was also obtained. Compound IIIb was oxidized to IIIc.

When I was refluxed, in ethanol, with 1,3-cyclopentadiene (IV), 5a,6,9,9a-tetrahydro-2,3-dimethyl-6,9-methanobenzo[*g*]quinoxaline-5,10-dione (IVa) was obtained

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(2) Abstracted in part from the forthcoming Ph.D. thesis of W. F. Gum, Jr.

(3) I. G. Farbenind. A.-G., British Patent 320,375 (1928); *Chem. Abstr.*, **24**, 2757 (1930).

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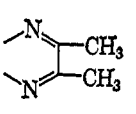
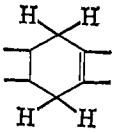
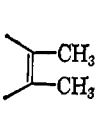
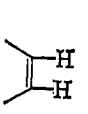
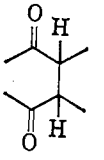
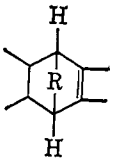
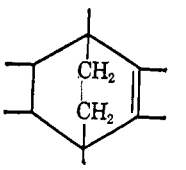
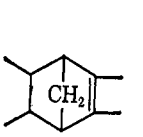
(10) O. Diels, K. Alder, G. Stein, P. Pries, and H. Winckler, *Ber.*, **62B**, 2337 (1929).

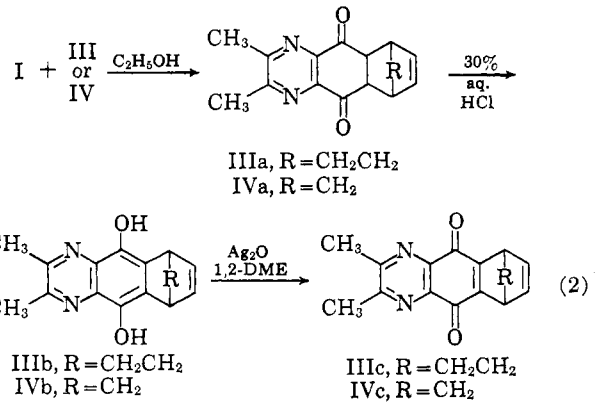
TABLE I

PROTON N.M.R. ASSIGNMENTS[a]

Compd.								
IIa	7.36(6)	7.84(4)	8.39(6)	...	6.67(2)	...	...	...
IId	7.25(6)	...	8.27(3), 8.48(3)	...	...	...	...	...
IIIa	7.39(6)	...	...	4.07(2)	6.79(4)		8.21, 8.61[b] (4)	...
IIIc	7.29(6)	...	...	3.52(2)	...	5.45(2)	8.47(4)	...
IVa	7.37(6)	...	...	4.22(2)	6.52(4)		...	8.46(2)
IVc	7.33(6)	...	...	3.16(2)	...	5.77(2)	...	7.66(2)
Va[c]	7.44(6)	...	...	...	6.60(2)	5.08(2)	...	...

[a] Chemical shifts (τ) observed in deuteriochloroform solution; τ values are given in p.p.m. relative to tetramethylsilane (10.00). [b] These figures refer to the center of the doublets resulting from two nonequivalent protons. [c] Aromatic protons (8) appear as a multiplet with center at τ 2.98.

in 95% yield. A tautomerized product was not isolated as in the previous reactions because IVa dissociated into its component parts at its melting point. However, tautomerization was accomplished in 30% aqueous hydrochloric acid to yield 6,9-dihydro-2,3-dimethyl-6,9-methanobenzo[*g*]quinoxaline-5,10-diol (IVb) which was oxidized to 6,9-dihydro-2,3-dimethyl-6,9-methanobenzo[*g*]quinoxaline-5,10-dione (IVc). The reactions of I with III and IV are illustrated in eq. 2.



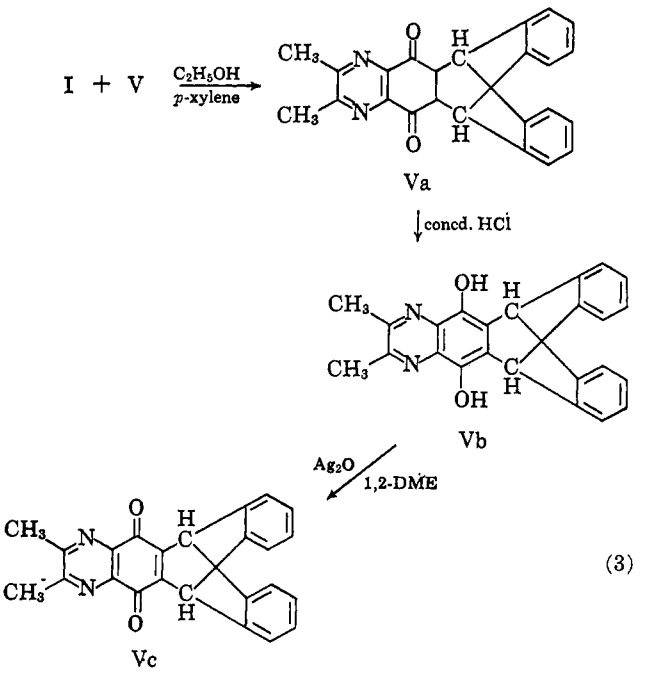
IIIa, R = CH_2CH_2
IVa, R = CH_2

IIIb, R = CH_2CH_2
IVb, R = CH_2

IIIc, R = CH_2CH_2
IVc, R = CH_2

(2)

1,4-Naphthoquinone has not been shown to undergo a Diels–Alder reaction with anthracene (V) although *p*-benzoquinone has been reported to give an adduct in xylene.[11] The reaction of I with V, the least reactive diene in this series was accomplished in a 50:50 mixture of ethanol and *p*-xylene. When I and V are mixed, a deep red solution is formed which is probably due to the formation of a complex between the quinone portion of I and anthracene. When this solution was heated 5a,6,11,11a-tetrahydro-2,3-dimethyl-6,11-*o*-benzenonaphtho[2,3-*g*]quinoxaline-5,12-dione (Va) was formed. This compound was tautomerized in concentrated hydrochloric acid to yield 6,11-dihydro-2,3-dimethyl-6,11-*o*-benzenonaphtho[2,3-*g*]quinoxaline-5,12-diol (Vb) which can be viewed as a 2,3-dimethylpyrazino derivative of triptycene. Compound Vb was oxidized to 6,11-dihydro-2,3-dimethyl-6,11-*o*-benzenonaphtho[2,3-*g*]quinoxaline-5,12-dione (Vc). These reactions are shown in eq. 3.



Va

Vb

Vc

(3)

Although the mechanistic pathway of the Diels-Alder reaction is still uncertain, the stereochemistry of adduct formation has been investigated extensively.[12] Since n.m.r. spectroscopy has been used successfully to determine the stereochemistry of quinone–diene Diels-Alder adducts,[6,13] we attempted to use this method to ascertain the configurations of IIa, IIIa, and IVa.

The probable *cis* configuration of adduct IIa could not be confirmed by its n.m.r. spectrum since the *cis* and *trans* forms of IIa have the same sets of dihedral angles for vicinal protons on the ring junction and methylene carbons. Thus, identical vicinal coupling constants would be obtained for the two forms. The proton n.m.r. assignments of IIa, the other adducts, and some quinones are shown on Table I.

The main difference between adducts IIa and IId is the splitting of the olefinic methyl groups in IId. This splitting can be attributed to the angular chloro group which exerts a deshielding effect on one of the methyl groups across space.

The n.m.r. spectra of IIIa and III care shown in Figure 1. The n.m.r. spectrum of IIIa resembles that of the *endo* epoxide of benzobicyclo[2.2.2]octene which also shows the ring junction and bridgehead hydrogens

(11) E. Clar, *Ber.*, **64B**, 1676 (1931).

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(13) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

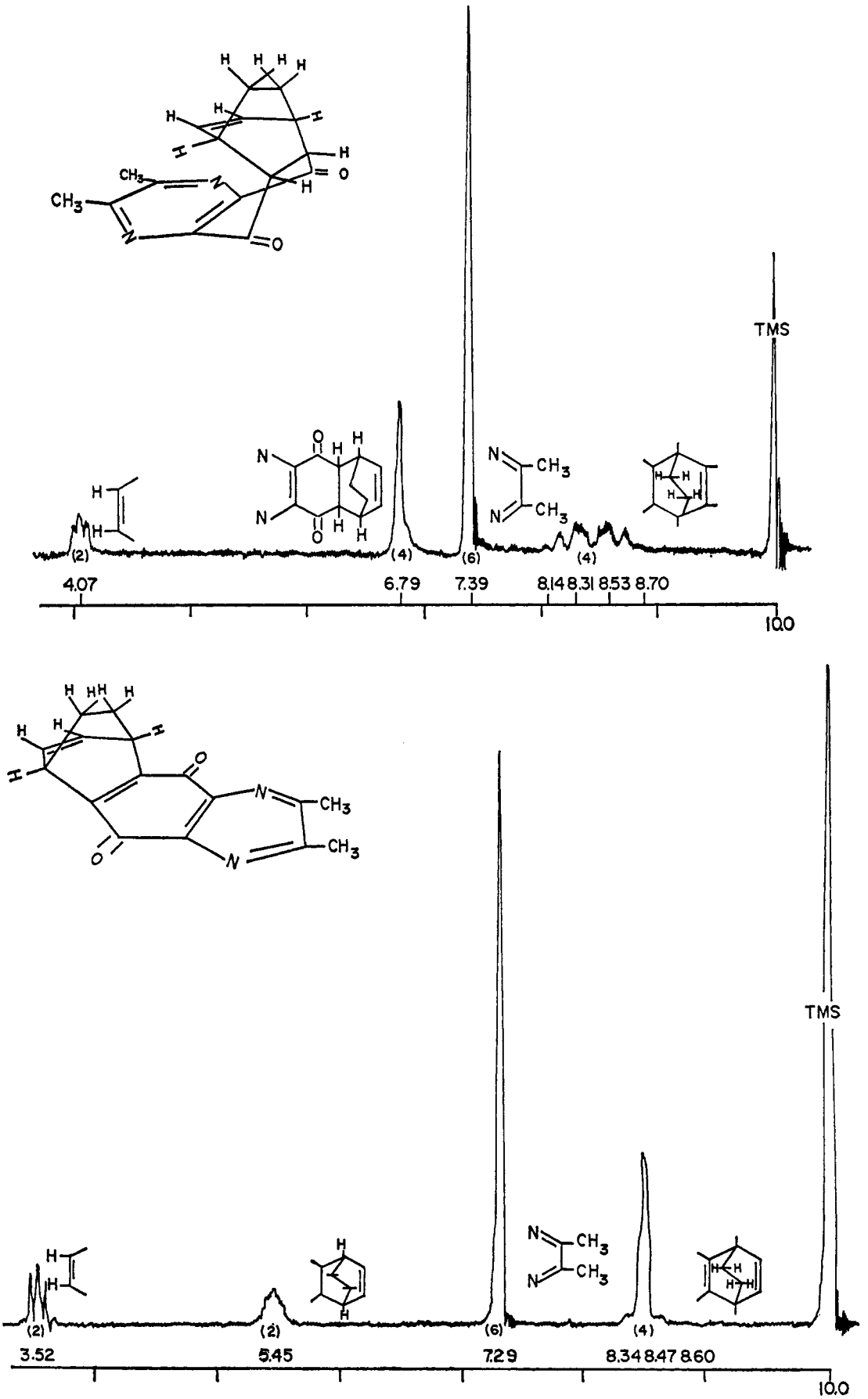

Figure 1.—N.m.r. spectra of IIIa and IIIc in deuteriochloroform.

under one peak (τ 6.59) and the bridge methylene hydrogens as two doublets with centers at τ 8.25 and 8.61.[14] The n.m.r. spectrum of IIIc is only slightly but significantly different. The bridge methylene protons are no longer split since the anisotropic shielding of these protons is more nearly equal because of the introduction of the quinoid double bond. The bridgehead protons are shifted downfield because they are now allylic to two double bonds. Also a large downfield or paramagnetic shift (33 c.p.s.) is observed for the olefinic protons. Although the introduction of the quinoid double bond into the bicyclic system would be expected to produce a shift of this type, the magnitude of this shift appears greater than expected. The introduction of a benzene ring into the bicyclo[2.2.2]-octene system has been shown to cause a paramagnetic shift of 13.8 c.p.s. in the position of absorption of the olefinic protons.[15] While there is no data on the shift caused by the introduction of a quinoid double bond into this system, there is no reason to expect this shift to be more than twice that caused by a benzene ring. A possible explanation for this shift may be obtained if one examines the Dreiding model of the *endo* configuration of IIIa. It is seen that in this configuration long-range diamagnetic anisotropic shielding of the olefinic protons by the pyrazine ring is possible. This is supported by the fact that the olefinic protons in IIIa are found at higher field (τ 4.22) than the corresponding protons in bicyclo[2.2.2]octene (τ 3.75).[15] Conversion of the adduct into the quinone swings the pyrazine ring out of position to exert a long-range shielding effect on the olefinic protons. Thus, these protons should shift downfield to their more usual position for a bicyclo[2.2.2]octene system. If IIIa existed in the *exo* configuration the pyrazine ring would be in no position to exert shielding effect on the olefinic protons. Thus the n.m.r. data appear to support the *endo* configuration for IIIa.

The fact that the adduct obtained from I and III, in 1,2-DME, at room temperature was found to be identical with IIIa by comparing the infrared and n.m.r. spectra of these compounds also supports the *endo* configuration.

The most striking difference between the n.m.r. spectra of IIIa and IVa is the lack of geminal splitting of the methylene bridge protons. This has also been observed for similar compounds having a methylene bridge.[13,16]

A large paramagnetic shift (64 c.p.s.) in the position of absorption of the olefinic protons is also observed when IVa is converted to IVc (Figure 2). The introduction of a benzene ring into norbornene has been reported to cause a shift of 47 c.p.s. in the position of absorption of the olefinic protons. The larger shift observed for these protons in going from IVa to IVc may also be attributed to the long-range diamagnetic anisotropic shielding effect of the pyrazine ring on the olefinic protons in the *endo* configuration of IVa and the disappearance of this effect in IVc. If IVa existed in the *exo* configuration this long-range effect would not be possible. The fact that the olefinic protons in IVa absorb at higher field (τ 4.22) than those of norbornene (τ 4.02)[15] also support the existence of such an effect. Long-range shielding of olefinic protons by a benzene ring has been observed in other adducts of known configuration.[16]

The ultraviolet maxima for the new quinone systems prepared in this investigation are shown in Table II.

TABLE II

ULTRAVIOLET SPECTRA OF QUINONES

Compd.	λ_{CH_3CN}, mμ (log ϵ)
I	290 (4.00), 282 (3.91), 248 (4.31), 227 (4.27)
IIc	285 (4.48)
IIIc	292 (4.24), 276 (4.46), 252 (4.45), 220 (4.76)
IVc	292 (4.37), 282 (4.52), 251 (4.60), 220 (4.96)
Vc	292 (4.46), 273 (4.59), 251 (4.65)

Experimental[17]

The yields, melting points, and analytical data for all of the compounds prepared are shown in Tables III, IV, and V.

Diels–Alder Adducts.—The Diels–Alder adducts were prepared by treating I with the appropriate diene, in ethanol, and refluxing the mixture for several hours. The length of the refluxing period varied between 6.5 and 17 hr. In the case of anthracene, this compound was previously dissolved in *p*-xylene. The general procedure will be illustrated with the preparation of IIa. 2,3-Dimethyl-5,8-quinoxalinedione (I, 2 g., 0.011 mole) was suspended in 50 ml. of absolute ethanol. Freshly distilled 2,3-dimethyl-1,3-butadiene (II, 2.0 g., 0.024 mole) was added to the mixture and the reaction refluxed for 6.5 hr. The solid formed (0.2 g.) was removed by filtration from the warm solution. It was shown to be the enol form of the Diels–Alder adduct (IIb). From the cooled filtrate another solid (0.8 g.) was obtained which was shown to be the keto form of the Diels–Alder adduct (IIa). An additional 0.5 g. of this product was obtained by concentrating the filtrate and by treating it with anhydrous ether. The only other example in which the enol form was isolated from solution was the reaction of I and III.

Tautomerization of Diels–Alder Adducts.—Tautomerization was accomplished by treating the keto form with 30 or 40% hydrochloric acid. Concentrated hydrochloric acid was used in the case of adduct Va. The general procedure is described for compound IIc. Compound IIa (0.36 g., 0.001 mole) was treated with 30 ml. of 40% aqueous hydrochloric acid. Absolute ethanol (5 ml.) was added to partially dissolved IIa, and the mixture was heated on a steam bath while the reaction was stirred. A light red flocculent precipitate formed, and the solution was neutralized with 10% potassium carbonate solution until the color of the precipitate changed from red to yellow. The yellow solid was removed by filtration, dried, and recrystallized.

Oxidation of the Enol Form of the Diels–Alder Adducts.—The enol forms of the Diels–Alder adducts were oxidized with silver oxide, Fisher reagent. The general method will be described for the preparation of IIc. Compound IIb (1.1 g., 0.004 mole) was suspended in 150 ml. of 1,2-DME. Silver oxide (3.0 g., 0.013 mole) was added to the suspension and the mixture stirred in the dark at room temperature for 4 hr. The mixture was treated with decolorizing carbon, the carbon was removed by filtration, and the filtrate was concentrated under reduced pressure to yield a yellow solid which was shown to be the desired quinone. More solid could be obtained by further concentration of the filtrate.

(14) K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Letters*, **No. 11**, 559 (1964).

(15) K. Tori, Y. Hata, R. Muneyuki, Y. Takano, T. Tseyi, and H. Tanida, *Can. J. Chem.*, **42**, 926 (1964).

(16) H. E. Simmons, *J. Am. Chem. Soc.*, **83**, 1657 (1961).

(17) All melting points were taken on a Thomas–Hoover capillary melting point apparatus. The infrared spectra were determined on a Perkin-Elmer double-beam 521 recording spectrophotometer as potassium bromide disks or in 0.211-mm. sodium chloride cells using chloroform as a solvent. The ultraviolet spectra were obtained in Eastman Spectrograde acetonitrile on a Cary Model 14 recording spectrophotometer using 1-cm. quartz cells. Microanalysis were carried out by Galbraith Laboratories, Knoxville, Tenn., and Dr. A. Bernhardt, Max Planck Institute, 433 Mülheim (Ruhr), West Germany. The n.m.r. spectra were determined at 60 Mc./sec. on a Varian Associates n.m.r. spectrometer (Model HR-60) for 5–10% solutions in $CDCl_3$ with tetramethylsilane as internal standard, and the line positions are expressed in Tiers notation. Line positions were measured by the conventional side-band technique using a Hewlett-Packard audio oscillator (Model 200 CD).

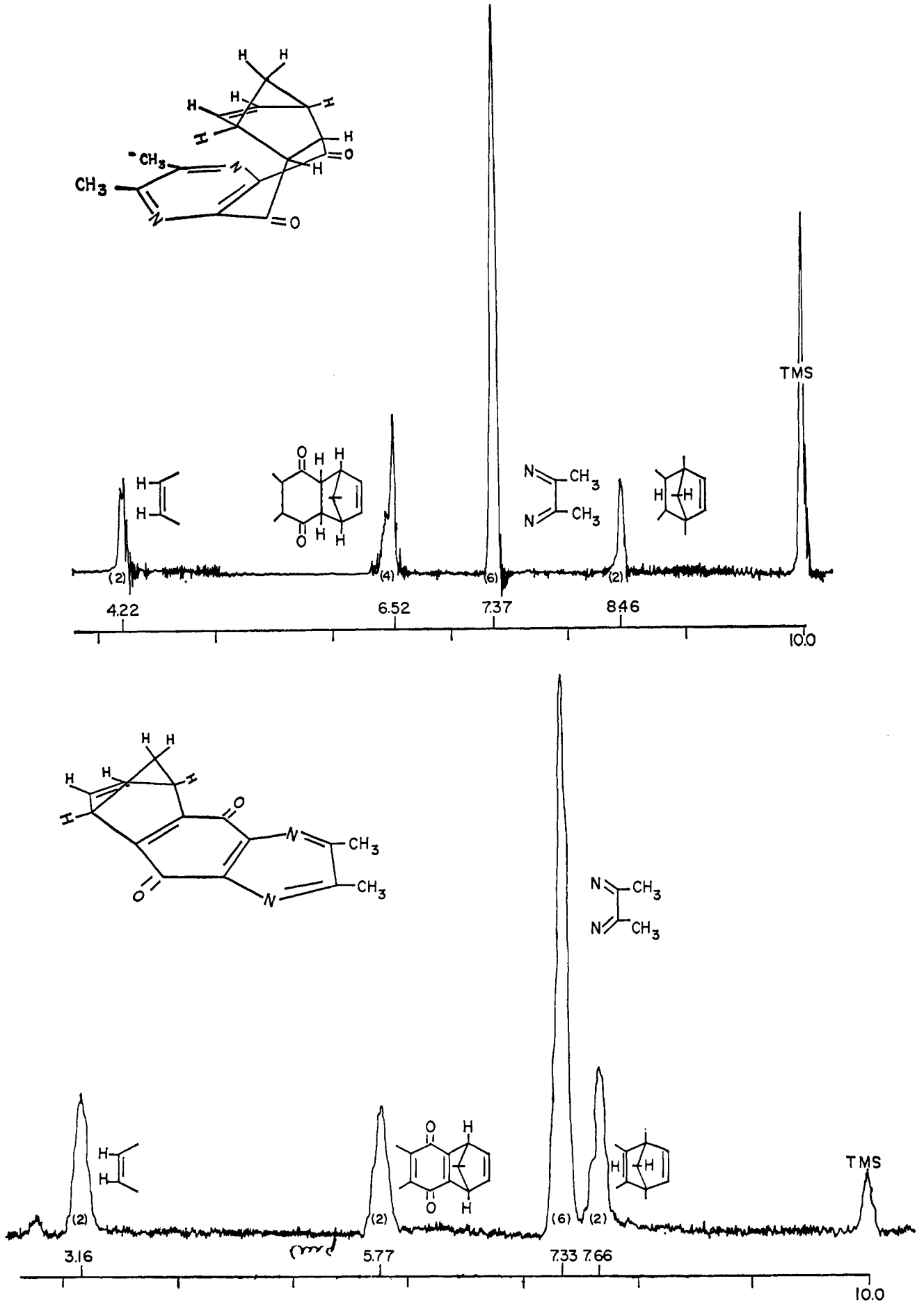

Figure 2.—N.m.r. spectra of IVa and IVc in deuteriochloroform.

TABLE III

DIELS–ALDER ADDUCTS OF 2,3-DIMETHYL-5,8-QUINOXALINEDIONE (KETO FORM)

Compd.	Yield, %	Recrystn. solvent[a]	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIa	53,[b] 69[c]	A	173–174	$C_{16}H_{18}N_2O_2$[d]	71.09	6.71	10.37	70.94	6.58	10.49
IIIa	74	A	171–173	$C_{16}H_{16}N_2O_2$[e]	71.62	6.01	10.44	71.67	5.90	10.45
IVa	95	B	169–170 dec.	$C_{15}H_{14}N_2O_2$[f]	70.85	5.55	11.02	70.87	5.45	10.97
Va	69	C	256–257 dec.	$C_{24}H_{18}N_2O_2$[g]	78.67	4.95	7.64	78.50	5.01	7.62

[a] A = 1,2-DME, B = ethanol, C = chloroform–ether. [b] After 6 hr. [c] After 16 hr. [d] $\nu_{C=O}^{CHCl_3}$ 1704 cm.$^{-1}$. [e] $\nu_{C=O}^{CHCl_3}$ 1688 cm.$^{-1}$. [f] $\nu_{C=O}^{CHCl_3}$ 1686 cm.$^{-1}$. [g] $\nu_{C=O}^{CHCl_3}$ 1687 cm.$^{-1}$.

TABLE IV

DIELS–ALDER ADDUCTS OF 2,3-DIMETHYL-5,8-QUINOXALINEDIONE (ENOL FORM)

Compd.	Yield, %	Recrystn. solvent[a]	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIb	95	A	294–296	$C_{16}H_{18}N_2O_2$[b]	71.09	6.71	10.37	71.34	6.68	10.57
IIIb	90	B	247–249	$C_{16}H_{16}N_2O_2$[c]	71.62	6.01	10.44	71.55	6.08	10.51
IVb	89	A	241–243 dec.	$C_{15}H_{14}N_2O_2$[d]	70.85	5.55	11.02	70.62	5.68	10.88
Vb	92	C	375–380 dec.	$C_{24}H_{18}N_2O_2$[e]	78.67	4.95	7.64	78.74	5.01	7.80

[a] A = 1,2-DME, B = absolute ethanol, C = dimethylformamide. [b] $\nu_{OH}^{1,2\text{-DME}}$ 3520, 3585 cm.$^{-1}$. [c] $\nu_{OH}^{1,2\text{-DME}}$ 3475 cm.$^{-1}$. [d] $\nu_{OH}^{1,2\text{-DME}}$ 3470 cm.$^{-1}$. [e] $\nu_{OH}^{1,2\text{-DME}}$ 3400, 3550 cm.$^{-1}$.

TABLE V

QUINONES FROM OXIDATION OF ENOL FORMS OF DIELS–ALDER ADDUCTS

Compd.	Yield, %	Recrystn. solvent[a]	M.p., °C. dec.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIc	79	A	310–312	$C_{16}H_{16}N_2O_2$[b]	71.62	6.01	10.44	71.72	5.87	10.62
IIIc	61	B	244–245	$C_{16}H_{14}N_2O_2$[c]	72.17	5.30	10.52	72.11	5.41	10.71
IVc[d]	37	..	183–184	$C_{15}H_{12}N_2O_2$[e]	71.41	5.12	11.11	71.41	4.91	11.21
Vc	66	C	266–267	$C_{24}H_{16}N_2O_2$[f]	79.11	4.43	7.69	79.08	4.59	7.75

[a] A = 1,2-DME and anhydrous ether, B = 1,2-DME, C = ethyl acetate. [b] $\nu_{C=O}^{CHCl_3}$ 1682, 1677 cm.$^{-1}$; $\nu_{C=C}^{CHCl_3}$ 1598 cm.$^{-1}$. [c] $\nu_{C=O}^{CHCl_3}$ 1669 cm.$^{-1}$; $\nu_{C=C}^{CHCl_3}$ 1590 cm.$^{-1}$. [d] Purified by sublimation. [e] $\nu_{C=O}^{CHCl_3}$ 1669 cm.$^{-1}$; $\nu_{C=C}^{CHCl_3}$ 1596 cm.$^{-1}$. [f] $\nu_{C=O}^{CHCl_3}$ 1669 cm.$^{-1}$; $\nu_{C=C}^{CHCl_3}$ 1610 cm.$^{-1}$.

Reaction of 6-Chloro-2,3-dimethyl-5,8-quinoxalinedione (Ia) and 2,3-Dimethylbutadiene (II).—Compound Ia[18] (1.0 g., 0.004 mole) was added to a solution of freshly distilled II (1.5 g., 0.018 mole) in 80 ml. of absolute ethanol. The mixture was refluxed for 8 hr. in a dry atmosphere and then allowed to stand overnight. A precipitate was formed (0.33 g.) which was separated into two fractions by 1,2-DME. The fraction insoluble in 1,2-DME (0.13 g.) which consisted of light purple prisms was thought to be a quinhydrone. This compound started to melt at 173° and decomposed from 288–310°.

Anal. Calcd. for $C_{32}H_{34}N_4O_4$: C, 71.35; H, 6.36; N, 10.40. Found: C, 71.48; H, 6.28; N, 10.49.

The fraction soluble in 1,2-DME was found to be identical with IIc. Further concentration of the original filtrate yielded another fraction (0.81 g.) of which 0.76 g. was also identified as IIc, m.p. 306–307 dec., by comparison of its infrared spectrum with that of a known sample of IIc. Only a very small sample (0.05 g.) of a beige solid, m.p. 153.5–155°, could be isolated. This material decomposed at its melting point into a red liquid, and gas was expelled. A sodium fusion test showed that this compound contained chlorine. Although no analytical data could be obtained, the n.m.r. spectrum of this compound showed it to be the expected Diels–Alder adduct (IId).

(18) The preparation of this compound will be reported elsewhere.

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