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Diels-Alder Reactions of 5,8-Quinolinedione

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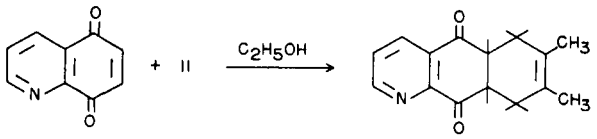
5,8-Quinolinedione (I) was first prepared in 1884 (2) and subsequent studies dealing with I have centered around the preparation of physiologically active substances for biological evaluation (3a-d, 4). Although the chemical reactivity of this quinone has been extensively investigated, the dienophilic properties of I have not been reported. We have investigated the reactions of I with dienes and found 5,8-quinolinedione to be a very reactive dienophile.

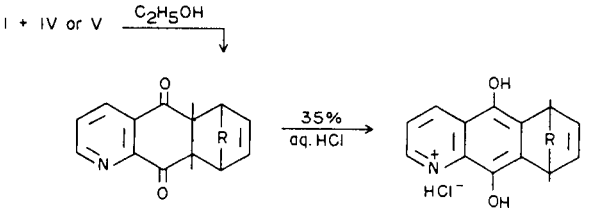
Several mechanisms have been proposed for the Diels-Alder reaction. The Alder rules (5) were first put forward to explain the favored *endo* configuration of the adducts which is consistent with a maximum accumulation of unsaturation centers in the transition state and minimal steric effects. This picture implies a one-step mechanism. Other authors (6) have postulated a two-step mechanism in which the first bond formation is rate-determining. Woodward and Katz (7) have reviewed the various mechanisms suggested and put forward a general mechanistic picture for Diels-Alder reactions. They postulated a primary bond formation between one end of the dienophile and one end of the diene. The electrons released in this process would be spread over the entire system and conjugating substituents would be expected to facilitate the reaction. After the formation of the first bond, the reaction would be completed with the relatively facile construction of a second full bond. Berson and coworkers (8) have shown that there is no difference between such a mechanism and a one-step four center reaction.

The reactions of I with 2,3-dimethyl-1,3-butadiene (II), cyclopentadiene (IV), cyclohexadiene (V) and anthracene (VIII) were found to proceed with considerable ease (Table I) and the adducts were formed in a shorter time than the corresponding adducts from 1,4-naphthoquinone (9,10,11,12). Since the 6-position in I has been shown by previous workers (4) to be more susceptible to nucleophilic attack, the greater reactivity of I is consistent with a picture in which the more positive 6 carbon atom of the 6,7-double bond would induce a faster polarization in the diene than if the 6 and 7 carbon atoms were equally charged. In addition, the electrons released would be stabilized by the presence of the more positive carbon atom of the 8-carbonyl group. Thus, the reactivity of I appears to support the Woodward and Katz mechanism although no definite proof or physicochemical data can be put forward to support this belief at this time.

An unusual feature of the Diels-Alder reactions of I was the enolization and oxidation of the adducts in the reaction mixture when the heating period was prolonged. For instance I and 2,3-dimethyl-1,3-butadiene yielded a quinhydrone in 78% yield after



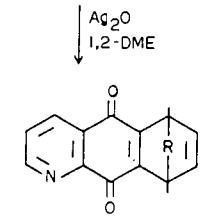
I III



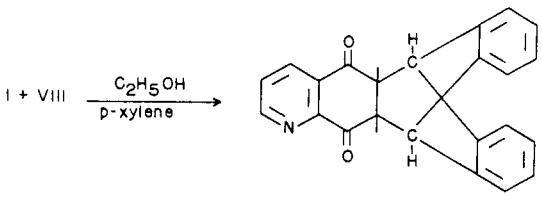
VI, R = CH_2

VII, R = CH_2CH_2

VIIa, R = CH_2CH_2



VIIb, R = CH_2CH_2



IX

TABLE I

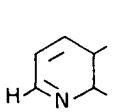
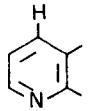
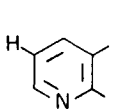
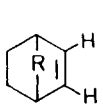
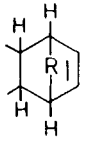
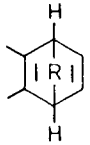
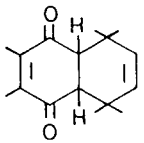
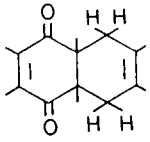
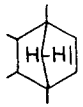
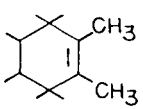
Diels-Alder Adducts of 5,8-Quinolinedione

Compound No.	Yield	Time (a)	M.p., °C (b)	Formula (c)	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Main Infrared Absorption Bands ν max ($CHCl_3$) in cm^{-1}
III	77	45	150-153 207-209 254-256	$C_{15}H_{15}NO_2$	74.67	74.54	6.27	6.34	5.80	6.01	2992, 1704-1696, 1573, 1281, 995
VI	73	60	130-132 174-177	$C_{14}H_{11}NO_2$	74.64	74.54	4.92	5.10	6.23	6.01	2998, 1684-1679, 1580, 1270, 971
VII	40	60	128-130 202-203	$C_{15}H_{13}NO_2$	75.16	75.06	5.48	5.66	5.85	5.81	2995, 1683-1680, 1580 1270, 1009
IX	59	540	180-183 250-253	$C_{23}H_{15}NO_2$ (d)	81.88	82.00	4.48	4.30	4.15	4.25	3040, 1667-1655, 1459, 1300, 902 (e)

(a) In minutes. (b) All compounds melted, resolidified and remelted with decomposition. (c) All compounds were recrystallized from chloroform-petroleum ether (b.p. 30-60°) unless otherwise stated. (d) Recrystallized from ethanol-*p*-xylene. (e) As potassium bromide disc.

TABLE II

Proton N.m.r. Assignments (a,b)

Compound No.											
III	1.38(1)	2.44(1)	2.84(1)	----	----	----	6.85(2)	7.81(4)	----	----	8.5(6)
VI	1.66(1)	2.41(1)	2.96(1)	4.43(2)	6.63(4)	----	----	----	8.37(2)	----	----
VII	1.44(1)	2.17(1)	2.75(1)	4.13(2)	6.87(4)	----	----	----	----	8.46(4)	----
VIIIb	0.97(1)	1.53(1)	2.31(1)	3.53(2)	----	5.43(2)	----	----	----	8.48(4)	----

(a) Chemical shifts (τ) observed in deuteriochloroform solution relative to tetramethylsilane (10.00). (b) The number in parentheses represents the number of protons.

heating the reaction mixture for 7 hours. However, I and cyclopentadiene yielded only the enol form of the adduct under the same conditions. Compound I and cyclohexadiene also yielded a quinhydrone after heating the reaction mixture for 36 hours. The quinhydrones were identified by their analytical data and infrared spectra. While all of the adducts showed split carbonyl bands, the quinhydrones showed one carbonyl band typical of a quinone carbonyl and quinoid double bond absorption in addition to absorption in the hydroxyl stretching region. Extensive work has been carried out to determine the structural features of quinhydrones (13, 14, 15). In the present work, we are assuming a 1:1 ratio of quinone to hydroquinone although we have no evidence for such a combination and this may well be an oversimplified picture of these molecules.

The adduct formed from I and cyclohexadiene, 5a, 6, 9, 9a-tetrahydro-6, 9-ethanobenzo[*g*]quinoline-5, 10-dione (VII) was enolized with aqueous hydrochloric acid to the hydrochloride of 6, 9-dihydro-6, 9-ethanobenzo[*g*]quinoline-5, 10-diol (VIIa) which was oxidized with silver oxide to the corresponding 6, 9-dihydro-6, 9-ethanobenzo[*g*]quinoline-5, 10-dione (VIIb). The other adducts could also be enolized and oxidized under similar conditions.

The stereochemistry of adduct formation has been extensively investigated (16). Since n.m.r. spectroscopy has been used successfully to determine the stereochemistry of quinone-diene Diels-Alder adducts (17, 18, 19), we have examined the n.m.r. spectra of the adducts prepared. The proton n.m.r. assignments for the adducts from 2, 3-dimethyl-1, 3-butadiene (III), cyclopentadiene (VI), cyclohexadiene (VII) and its corresponding quinone (VIIb) are shown in Table II. The 2- and 4-protons of the quinoline ring absorbed as doublets while the 3-proton appeared as a quartet. The olefinic protons exhibited a large downfield or paramagnetic shift (36 c.p.s.) in going from the adduct (VII) to the corresponding quinone (VIIb). Although the introduction of the quinoid double bond would be expected to produce a shift of this type, the magnitude of this shift is greater than expected and similar to the one observed in the quinoxaline series (19) for related systems. This shift may also be attributed to the *endo* arrangement of the adduct in which the pyridine ring may exert a long range diamagnetic anisotropic shielding on the olefinic protons. In the corresponding quinone the pyridine ring is no longer in a position to exert this shielding effect.

EXPERIMENTAL (20)

5, 8-Quinolinedione (I).

Compound I was obtained in 45% overall yield by the procedure of Pratt and Drake (3d), m.p. 121-122° dec. (sintered at 113°), lit. (2) m.p. 110-120°; ν (KBr), C=O, 1669 cm^{-1}.

Preparation of Diels-Alder Adducts (Table I). Reaction of I with 2, 3-Dimethyl-1, 3-butadiene (II). Typical Procedure.

Compounds I (1 g., 0.0063 mole), II (1.3 ml., 0.013 mole) and 20 ml. of absolute ethanol were placed in a round-bottomed flask fitted with a reflux condenser and a calcium chloride tube and heated for 45 minutes. Some decomposed solid was removed by filtration from the hot reaction mixture. The filtrate was cooled and colorless needles of 5a, 6, 9, 9a-tetrahydro-7, 8-dimethylbenzo[*g*]quinoline-5, 10-dione (III) were obtained. Compound III was collected by filtration and recrystallized from chloroform and petroleum ether (b.p. 30-60°). Adducts VI (5a, 6, 9, 9a-tetrahydro-6, 9-methanobenzo[*g*]quinoline-5, 10-dione) and VII (5a, 6, 9, 9a-tetrahydro-6, 9-ethanobenzo[*g*]quinoline-5, 10-dione) were obtained by a similar procedure. The adduct, 5a, 6, 11, 11a-tetrahydro-6, 11-*o*-benzonaphtho[2, 3-*g*]quinoline-5, 12-dione, (IX) was obtained by using a 50-50 mixture of absolute ethanol and *p*-xylene as the solvent.

Quinhydrone Formation. Reaction of I with II Under Prolonged Reflux Time. Typical Procedure.

When I and II were mixed as described above and the reaction mixture heated for 7 hours, wine-red needles were obtained (2.32 g., 73%). This compound, believed to be a quinhydrone, was recrystallized from absolute ethanol. The product melted at 190-193°, resolidified melted at 209-210°, resolidified and melted again at 256-257°. The main infrared bands were found at ν max (KBr), 3400, 1664, 1640, 1595, 1572 cm^{-1}.

Anal. Calcd. for $C_{30}H_{28}N_2O_4$: C, 74.97; H, 5.87; N, 5.83. Found: C, 74.95; H, 5.69; N, 5.83.

When I and V were mixed as described and heated for 36 hours, dark red needles were obtained (1.45 g., 98%). This product, believed to be a quinhydrone, was recrystallized from absolute ethanol and melted at 173°, resolidified and melted at 275-277°. The main infrared bands were found at ν max (KBr), 3410, 1663, 1655, 1615, 1589, 1577 cm^{-1}.

Anal. Calcd. for $C_{30}H_{24}N_2O_4$: C, 75.62; H, 5.08; N, 5.88. Found: C, 76.00; H, 4.81; N, 5.90.

When I and IV were mixed as described and heated for 7 hours, the only product isolated was found to be the hydroquinone (6, 9-dihydro-6, 9-methanobenzo[*g*]quinoline-5, 10-diol). This compound was purified by sublimation at 120° (0.5 mm.), m.p. 175-177°. The main infrared bands were found at ν max (KBr), 3350, 1607, 1509, 1216, 1080 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.64; H, 4.92; N, 6.23. Found: C, 74.61; H, 5.02; N, 6.42.

Enolization of Diels-Alder Adducts. Reaction of 5a, 6, 9, 9a-tetrahydro-6, 9-ethanobenzo[*g*]quinoline-5, 10-dione (VII) with 35% Aqueous Hydrochloric Acid. Typical Procedure.

Adduct VII (1 g., 0.0042 mole) was placed in a 25 ml. Erlenmeyer flask and 8 ml. of 35% aqueous hydrochloric acid was added to it and the mixture warmed on a steam bath for 10 minutes. The reaction mixture was treated with 10 ml. of water and cooled. The yellow solid formed was collected by filtration to give 0.82 g. (71%) of the hydrochloride of 6, 9-dihydro-6, 9-ethanobenzo[*g*]quinoline-5, 10-diol, m.p. 182-183°, resolidified and remelted at 275-277°. The main infrared bands were found at ν max (KBr), 3450-3100 (broad), 1621, 1581, 1540, 1070, 780 cm^{-1}.

Anal. Calcd. for $C_{15}H_{14}ClNO_2$: C, 65.33; H, 5.11; N, 5.08. Found: C, 65.68; H, 4.92; N, 5.02.

Adducts III and VI could be enolized by the same procedure.

Oxidation of Hydroquinones. Oxidation of 6, 9-Dihydro-6, 9-ethanobenzo[*g*]quinoline-5, 10-diol Hydrochloride (VIIa). Typical Procedure.

6, 9-Dihydro-6, 9-ethanobenzo[*g*]quinoline-5, 10-diol hydrochloride (1.1 g., 0.004 mole) was placed in a 100 ml. one-necked, round-bottomed flask fitted with an air condenser, calcium chloride tube and treated with silver oxide (3 g., 0.004 mole) and 90 ml. of 1, 2-dimethoxyethane. The mixture was stirred with a magnetic stirrer, at room temperature, in the dark for 4 hours. The black solid formed was removed by filtration and the filtrate evaporated to dryness on a rotary evaporator. The residue was dissolved in a minimum amount of chloroform and 200 ml. of petroleum ether (b.p. 30-60°) added to the solution. The mixture was chilled and the solid formed collected by filtration to yield 0.6 g. (70%) of 6, 9-dihydro-6, 9-ethanobenzo[*g*]-quinoline-5, 10-dione as light yellow needles. The solid melted at 180-183°, resolidified and melted again at 275-277°. The main infrared bands were found at ν max ($CHCl_3$), 2997, 1663-1652, 1624, 1581, 1570, 1325, 1305 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.83; H, 4.81; N, 6.10.

6, 9-Dihydro-7, 8-dimethylbenzo[*g*]quinoline-5, 10-dione was prepared by a similar procedure, (70% yield), m.p. 194-196°, resolidified and

remelted at 257-258°. The main infrared bands were at ν max ($CHCl_3$), 2990, 1670, 1639, 1582, 1309 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.50; H, 5.53; N, 5.82.

The same conditions were used to prepare 6,9-dihydro-6,9-methano-[*g*]quinoline-5,10-dione (44% yield), m.p. 180-182° dec. The main infrared bands were at ν max ($CHCl_3$), 2995, 1671-1661, 1601, 1581, 1310 cm^{-1}.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.29; H, 4.05; N, 6.16.

Acknowledgment.

This investigation was supported by a grant (AM 07684-02) from the National Institutes of Health, U. S. Public Health Service. The authors wish to thank Mr. W. Marmer for technical assistance.

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Received August 23, 1966 Philadelphia, Pennsylvania 19104