($\sigma^{p}_{NO_2}$ = +0.78) electrons. Indeed, seven resonance forms can be drawn for 4-nitrochlorobenzene, for example, and five resonance forms can be drawn for 4-aminochlorobenzene. Thus, while the delocalization energy for conjugation of a substituent with an aromatic nucleus is proportional to σ,[16] it appears that the resonance energy of the substituted molecule should be proportional to σ^2.

A general relationship taking into account both Coulombic and resonance effects in the formation of a chelate is obtained by linearly combining σ and σ^2. The result is operationally equivalent to eq 16. Proper caution should be exercised in dealing with relations such as 16. While there are at least three arguments that can be advanced to explain a nonlinear dependance of biological activity on σ (ref 6 and the two already detailed) there is always the possibility that another parameter exists that is essentially independent of σ. Use of this parameter in combination with σ could cause an otherwise parabolic trend in σ to become linear.

With chelates as an active species, for example, a knowledge of the association constants for reactions A and B enables a calculation of the fraction of ionic chelate present at a specified pH. The observed activity could be "corrected" by multiplying the rate constants by the calculated fraction. The use of this corrected biological activity could then result in a linear dependence on σ. For the tetracyclines involved in this study, insufficient information is available to attempt this type of correction.

The basis for the precaution is essentially the same as for the linear free-energy approach taken by Hansch[17] in his account of electronic and lipophilic factors which influence biological activity. It must be concluded that correlations based on eq 16 are most probably physically significant, but the origin of σ^2 may take many forms.

(16) F. L. J. Sixma, *Rec. Trav. Chim.*, **72**, 673 (1953).

(17) C. Hansch in "Annual Review of Medicinal Chemistry," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966.

Antiprotozoal Quinones. II. Synthesis of 4-Amino-1,2-naphthoquinones and Related Compounds as Potential Antimalarials[1]

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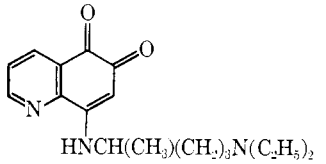
A wide variety of 4-amino-1,2-naphthoquinones, related to the presumed active metabolite of pamaquine, has been prepared and evaluated as potential antimalarials in *Plasmodium berghei* infected mice, *Plasmodium gallinaceum* infected chicks, and against the sexual phase of *P. gallinaceum* in mosquitoes. A few new 2-amino-1,4-naphthoquinones and 4-alkoxy-1,2-naphthoquinones have also been prepared and evaluated. None of the new quinones was curative but 4-(3-dipentylaminopropylamino)-1,2-naphthoquinone showed some activity in all three primary screens. In this series there seems to be a relationship between lipophilicity of the side chain and antimalarial activity as has been observed for other antiprotozoal quinones. Procedures for reaction of 1,2-naphthoquinones with enamines to give a new class of naphthalenediol derivatives are also described.

The supporting evidence for the postulate that the antimalarial action of 8-amino-6-methoxyquinolines such as pamaquine may be due to their *in vivo* oxidation to quinonoid products such as **1** has been detailed elsewhere.[2] The observation[3] that the presumed quinonoid metabolite of pamaquine has 16-fold greater *in vitro* activity than the parent drug against *Plasmodium gallinaceum* is in curious contrast to the report of Drake[2] of negligible *in vivo* activity of related 5,6-dihydroxy- and 5-hydroxy-6-methoxyquinolines in monkeys. These compounds were sensitive to oxidation and were expected to be converted to quinones *in vivo*. Our efforts have been directed toward a search for new quinones related to **1** which might possess *in vivo* antimalarial activity. This paper reports the investigation of a series of naphthoquinones **3a–c** and some related derivatives. Some 4-amino-1,2-naphthoquinones have been prepared previously by Fieser and others,[4] but the series has not been explored for possible antiprotozoal drugs.



1

Chemistry.—4-Ethoxy-1,2-naphthoquinone (**2**) was prepared from the Ag salt of 2-hydroxy-1,4-naphthoquinone[5] with EtI (Scheme I). The related 4-alkoxy-1,2-naphthoquinones **59** and **60** (Table I) were also prepared in this way. The orthoquinone structure was confirmed by the ready formation of phenazine derivatives.

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2880. This paper is Contribution No. 699 from the Army Research Program on Malaria, and was the subject of a preliminary report at the First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968.

(2) F. Schöenhöfer, *Z. Physiol. Chem.*, **274**, 1 (1942); K. C. Blanchard in F. W. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. I, J. W. Edwards, Ann Arbor, Mich., 1946, p 129 ff; B. B. Brodie and S. Udenfriend, *Proc. Soc. Exptl. Biol. Med.*, **74**, 845 (1950); N. L. Drake and Y. T. Pratt, *J. Am. Chem. Soc.*, **73**, 544 (1951); E. S. Josephson, J. Greenberg, D. J. Taylor, and H. L. Bami, *J. Pharmacol. Exptl. Ther.*, **103**, 7 (1951); R. R. Holmes, J. Conrady, J. Guthrie, and R. McKay, *J. Am. Chem. Soc.*, **76**, 2400 (1954); P. B. Russell in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 814.

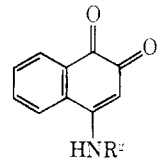
(3) E. S. Josephson, D. J. Taylor, J. Greenberg, and A. P. Ray, *Proc. Soc. Exptl. Biol. Med.*, **76**, 700 (1951).

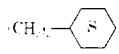
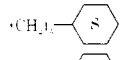
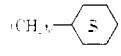
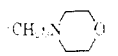
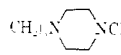
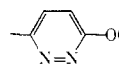
(4) (a) L. F. Fieser and M. Fieser, *J. Am. Chem. Soc.*, **57**, 491 (1935); (b) L. F. Fieser and J. L. Hartwell, *ibid.*, **57**, 1484 (1935); (c) L. F. Fieser and M. Fieser, *ibid.*, **61**, 596 (1939); (d) H. E. Fierz-David and E. Mannhart, *Helv. Chim. Acta*, **20**, 1024 (1937); (e) R. A. Henry and W. M. Dehn, *J. Am. Chem. Soc.*, **74**, 278 (1952); (f) W. Brackman and E. Havinga, *Rec. Trav. Chim.*, **74**, 937 (1955).

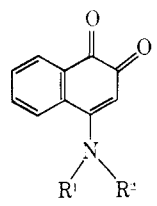
(5) L. F. Fieser, *J. Am. Chem. Soc.*, **48**, 2922 (1926).

TABLE I

4-AMINO-1,2-NAPHTHOQUINONES AND RELATED QUINONES

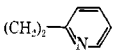
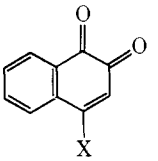
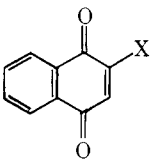
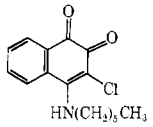


No.	R^2	Crysin solvent	Formula[a]	Mp, °C	Yield, %
16	$(CH_2)_8CH_3$[c]	EtOH	$C_{14}H_{15}NO_2$[c]	242.5–244	44
17	$(CH_2)_9CH_3$	EtOH	$C_{16}H_{19}NO_2$	236–237 dec	58
18	$(CH_2)_{10}CH_3$	HOAc	$C_{21}H_{29}NO_2$	233–235 dec	68
19	$(CH_2)_{11}CH_3$	HOAc	$C_{22}H_{31}NO_2$	233–235 dec	59
20	$(CH_2)_{13}CH_3$	EtOH-HOAc	$C_{24}H_{35}NO_2$	233–234 dec	33
21	$(CH_2)_{17}CH_3$	EtOH-HOAc	$C_{28}H_{43}NO_2$	225–226 dec	46
22	$CH(CH_3)(CH_2)_3CH(CH_3)_2$	MeOH-H_2O	$C_{15}H_{23}NO_2$	163–164	34
23		EtOH-HOAc	$C_{18}H_{21}NO_2$	248.5–250 dec	40
24		EtOH	$C_{20}H_{25}NO_2$	237–239 dec	45
25		EtOH	$C_{22}H_{29}NO_2$	233–234 dec	41
26	C_6H_{11}	EtOH	$C_{16}H_{17}NO_2$	232–234	27
27		EtOAc-EtOH	$C_{17}H_{17}NO_2$	223–224	41
28	$CH_2C_6H_5$[c]	EtOH	$C_{17}H_{13}NO_2$[c]	205–206	56
29	$CH_2C_6H_4O(CH_2)_5CH_3$-*p*[d]	EtOH-CH_3CN	$C_{24}H_{31}NO_3$	208–210 dec	42
30	$(CH_2)_5C_6H_4O(CH_2)_5CH_3$-*p*	CH_3CN	$C_{25}H_{33}NO_3$	226–228	46
31	$(CH_2)_5C_6H_4OCH(C_2H_5)_2$-*p*	EtOH	$C_{24}H_{37}NO_3$	212–213	37
32	$(CH_2)_5C_6H_4OCH_2CH(CH_3)(CH_2)_2CH_3$-*p*	EtOH	$C_{25}H_{39}NO_3$	219–220	43
33	$(CH_2)_4C_6H_3O(CH_2)_5CH_3$-*p*	CH_3CN	$C_{26}H_{31}NO_3$	228–230	44
34	$-C_6H_4OCH_3$-*p*	HOAc	$C_{17}H_{13}NO_3$	252–253 dec	63
35	$(CH_2)_2N(C_2H_5)_2$	EtOAc-EtOH	$C_{16}H_{20}N_2O_2$	204–205 dec	59
36	$(CH_2)_3N(CH_3)_2$		$C_{13}H_{16}N_2O_2$	184–187 dec	32
37	$(CH_2)_3N[(CH_2)_4CH_3]_2$[c]	$CHCl_3$-petr ether	$C_{24}H_{44}N_2O_2$	149–150	31
38	$(CH_2)_4N(C_2H_5)_2$	H_2O	$C_{18}H_{24}N_2O_2$	193–194 dec	33
39	$CH(CH_3)(CH_2)_2N(C_2H_5)_2$[f]	H_2O-EtOH	$C_{18}H_{24}N_2O_2$	156–157	21
40	$CH(C_2H_5)(CH_2)_2N(C_2H_5)_2$[g]	H_2O-EtOH	$C_{19}H_{26}N_2O_2$	155–156	27
41	$CH(CH_3)(CH_2)_3N(C_2H_5)_2$[h]	EtOAc-petr ether	$C_{19}H_{26}N_2O_2$	110–112	30
42	$CH(CH_3)(CH_2)_3\overset{+}{N}H(C_2H_5)_2$ pamoate		$C_{42}H_{42}N_2O_6$	222–224 dec	
43		EtOH	$C_{17}H_{20}N_2O_3$	224–225 dec	36
44		EtOH	$C_{18}H_{24}N_4O_2$	215.5–216 dec	30
45			$C_{13}H_{11}N_3O_3$	268–269 dec	54



	R^1	R^2				
46	C_2H_5	C_2H_5	$CHCl_3$-hexane	$C_{14}H_{15}NO_2$	132–135	55
47	CH_3	$(CH_2)_8CH_3$	$CHCl_3$-petr ether	$C_{15}H_{37}NO_2$	77–78 dec	17
48	CH_3	C_6H_{11}	CH_2Cl_2-petr ether	$C_{17}H_{19}NO_2$	172–173 dec	39
49	C_2H_5	C_6H_{11}	CH_2Cl_2-petr ether	$C_{18}H_{21}NO_2$	128–129 dec	9

TABLE I (*Continued*)

No.	R^1	R^2	Crystn Solvent	Formula[m]	Mp, °C	Yield, %
50	C_2H_5	CH_2CH_2OH	PrOH	$C_{14}H_{15}NO_3$	153–154 dec	19
51	CH_3	$(CH_2)_3N(CH_3)_2 \cdot 2H_2O$[i]	PrOH–MeCyhex	$C_{16}H_{20}N_2O_2 \cdot 2H_2O$[o]	75–80[j]	26
52	C_2H_5	$(CH_2)_2N(CH_3)_2$	CH_2Cl_2–petr ether	$C_{16}H_{20}N_2O_2$	83–84	13
53	CH_3		$CHCl_3$–petr ether	$C_{18}H_{16}N_2O_2$	123–124	62
54	$CH_2C_6H_5$	$(CH_2)_2N(CH_3)_2$	EtOAc	$C_{21}H_{22}N_2O_2$	136–137	36
55	C_6H_5	$(CH_2)_3N(CH_3)_2$[k]	Ether–hexane	$C_{21}H_{22}N_2O_2$	125	38
56			$CHCl_3$–CCl_4	$C_{14}H_{13}NO_2$	178–180 dec	35
57			$CHCl_3$–petr ether	$C_{15}H_{15}NO_2$	128–130 dec	54
58			$CHCl_3$–petr ether	$C_{18}H_{19}NO_2$	192–193.5	85
59	$O(CH_2)_5CH_3$		Hexane	$C_{16}H_{18}O_3$	86–87	27
60	$OCH_2CH(CH_3)(CH_2)_2CH_3$[l]			$C_{16}H_{18}O_3$	Oil	27
61	$OC_6H_4C(CH_3)_2CH_2C(CH_3)_3$-*p*		EtOH	$C_{24}H_{26}O_3$	200–203	80
62	$OC_2H_5 \cdot p\text{-}H_2NC_6H_4SO_2C_6H_4NH_2$-*p*			$C_{24}H_{22}SO_3$[p]	173–175	70
63	$NH(CH_2)_3N(CH_3)_2$		H_2O–EtOH	$C_{15}H_{18}N_2O_2$	79–80	70
64	$NH(CH_2)_3N[(CH_2)_4CH_3]_2$		Hexane (−70°)	$C_{23}H_{34}N_2O_2$	58–59	31
65	$CO(CH_2)_2C_6H_{11}$		EtOH	$C_{19}H_{20}O_3$	64–65	80
66			HOAc	$C_{16}H_{18}ClNO_2$[q]	229–230 dec	37

[a] See ref 4a for preparation. [b] The amine has been reported (C. G. Skinner, P. Gardner, and W. Shive, *J. Am. Chem. Soc.*, **79,** 2843 (1957)) but here was obtained by reduction of the amide (P. L. Pickard and C. W. Young, *ibid.*, **73,** 42 (1951)). [c] Amine prepared, T. L. Cairns, R. M. Joyce, and R. S. Schreiber, *ibid.*, **70,** 1689 (1958). [d] Amine prepared by LAH reduction of amide. [e] Amine prepared: W. F. Holcomb and C. S. Hamilton, *J. Am. Chem. Soc.*, **64,** 1309 (1942). [f] Amine described (O. Ya. Magidson and A. M. Grigorovskii, *Ber.*, **69B,** 396 (1936)), but here was obtained by lithium aluminum hydride reduction of the oxime of N,N-diethylamino-2-butanone. [g] Amine described (M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, **9,** 359 (1944)), but here was obtained by lithium aluminum hydride reduction of the oxime of diethylamino-3-pentanone. [h] Amine described (T. Sasa, *J. Soc. Org. Syn. Chem. Japan*, **12,** 132 (1954)), but here was obtained by lithium aluminum hydride reduction of the oxime of 5-diethylamino-2-pentanone (F. Giral and M. L. Cascaseras, *Ciencia* (Mex.), **5,** 105 (1944); *Chem. Abstr.*, **41,** 4891*i* (1947)). [i] This compound is a solid only as the hydrate. Drying over P_2O_5 *in vacuo* gave a red oil. [j] Taken in sealed melting point tube. [k] Amine reported (K. Kigasawa, *et al.*, *Yakugaku Zasshi*, **83,** 6961 (1963), *Chem. Abstr.*, **59,** 13847*g* (1963)), but here was prepared using a procedure similar to that of J. Walker, *J. Chem. Soc.*, 686 (1940). [l] 2-Methylpentyl iodide prepared according to G. Koller and E. Kandler, *Monatsh.*, **58,** 213 (1931). [m] All compounds were analyzed for C, H, N unless otherwise noted. [n] Not analyzed. [o] *Anal.* C, H, N, H_2O. [p] *Anal.* C, H, N, S. [q] *Anal.* C, H, N, Cl.

Reaction of a variety of primary amines with **2** proceeded smoothly to give **16–45**. Although substantial amounts of the quinone imines **4** are formed concomitantly,[6] separation of **3** and **4** is easily accomplished due to their very different solubility properties. A similar reaction of primary amines with 2-methoxy-1,4-naphthoquinone[5,7] and 3,4-dichloro-1,2-naphthoquinone[8] gave the quinones **63**, **64**, and **66**, respectively.

Although reaction with sodium 1,2-naphthoquinone-4-sulfonate (**5**) is the basis for a widely used colorimetric determination of amino acids (Folin[9]), our experience is that preparative use of this reaction with primary amines in attempts to prepare **3a** is inferior to the route beginning from **2**. However, reaction of **5** with secondary amines to give **3b** is quite satisfactory. The reaction probably proceeds through a bisulfite adduct of the product which presumably is decomposed by addition of base before attempted isolation of the product (see Experimental Section).

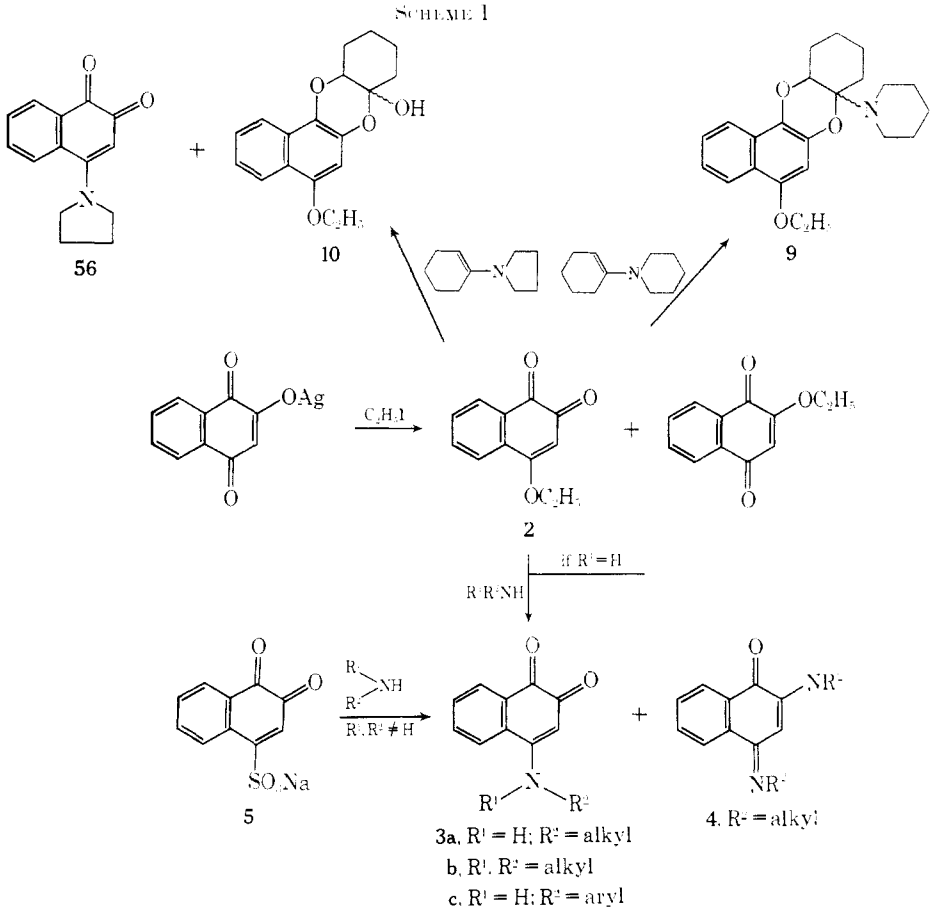
(6) Details have been described; see F. J. Bullock, J. F. Tweedie, and D. D. McRitchie, *J. Chem. Soc., C*, 1799 (1969).

(7) L. F. Fieser and E. L. Martin, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 465.

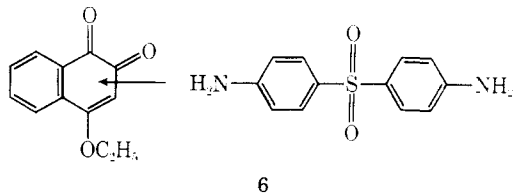
(8) Th. Zincke, *Ber.*, **19**, 2493 (1886); Th. Zincke and M. Engelhardt, *Ann.*, **283**, 341 (1894).

(9) R. J. Henry, "Clinical Chemistry, Principles and Techniques," Harper and Row, New York, N. Y., 1964, p 314.

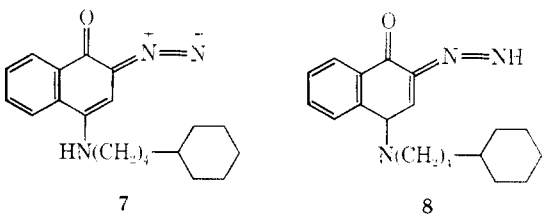
SCHEME I



Attempted reaction of 4,4′-diaminodiphenyl sulfone (DDS) with **2** gave a bright red material characterized by nmr as the molecular complex **6**. Molecular complexes of amines with quinones are well known[10] and in this case complex formation, rather than reaction, may be attributed to a decreased nucleophilicity of the amino group due to *p*-sulfonyl. A difference spectrum of **2** with tenfold excess of DDS relative to uncomplexed **2** had λ_{max}^{EtOH} 500 nm, but this is probably not a charge-transfer band.[11]



In an application of a procedure of Dutt,[12] **24** was converted to the α-diazo ketone **7** with *p*-toluenesulfonylhydrazine. Treatment of the intermediate hydrazone with base to accomplish its decomposition[13] was not necessary as decomposition occurred spontaneously. We assign the structure **7** rather than tautomer **8** on the basis of a characteristic band in the ir



(KBr) at 2078 cm^{-1} assigned to the stretching frequency of the $-^{+}N{=}N^{-}$ linkage. This absorption is similar to that observed in other azo ketones where tautomerism is not possible.[14]

The reaction of **2** with enamines gave an interesting pair of naphthalenediol derivatives. Although we have not extensively explored the scope of this reaction, the following observations are of interest. When 1-(1-cyclohexenyl)piperidine was used, the *p*-dioxin **9** was obtained, while with 1-(1-cyclohexenyl)pyrrolidine, the hemiketal **10** and the naphthoquinone **56** were formed (Scheme I). In a previous study[15] of the reaction of enamines with chloranil the formation of a hemiketal was not observed. Hydrolysis of a structure such as **9** to the ketone **11** and pyrrolidine, which in turn reacts

(10) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964.

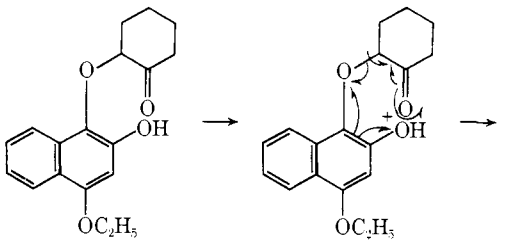
(11) For a discussion of the differences between a charge-transfer band and the bathochromic shifts frequently accompanying molecular complex formations, see F. J. Bullock in "Comprehensive Biochemistry," Vol. 22, M. Florkin and E. Stotz, Ed., Elsevier, Amsterdam, 1967, p 81.

(12) S. Dutt, *J. Chem. Soc.*, 2921 (1925).

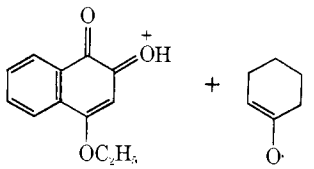
(13) M. P. Cava, R. L. Litle, and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2257 (1958), and references therein.

(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958, p 273.

(15) W. Reid and E. Torok, *Ann.*, **687**, 187 (1965).

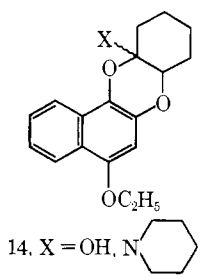


11 12, *m/e* 300

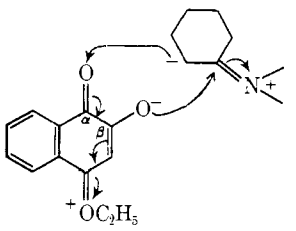


13, *m/e* 203

with starting quinone to give **56**, could account for these latter products. Structure **10** rather than the ketophenol **11** is assigned to our product based on the absence of carbonyl absorption and the presence of absorption due to OH in the ir (KBr). The mass spectral fragmentation of **10** is most conveniently interpreted in terms of **11**, however, since **12** provides a ready basis for accounting for the *m/e* 203 peak **13** as indicated. Structures **10** and **11** have not been rigorously proved but are assigned, rather than **14**, which is



14, X = OH, N



15

equally consistent with the physical data, on the basis of the following. In a previous study[6] we demonstrated that protonation of **3a–c**, as well as reaction with triethyloxonium tetrafluoborate, occurs at the β-carbonyl. This supports the expectation that the lone pair on nitrogen, and by analogy also that on oxygen, is partially delocalized onto the β-carbonyl. This would define the orientation of the incoming enamine group as indicated in **15**.

Other quinones reported here were prepared as follows. Quinone **61** was prepared by reaction of the appropriate phenolate with 4-chloro-1,2-naphthoquinone.[16] Quinone **65**, its synthetic precursors, and its derivatives were prepared by the route described by Cram.[17] New intermediates prepared during the course of this work are given in Table II.

Biological Results.—The naphthoquinones (Table I) and some of the intermediates (Table II) were evaluated against blood-induced *Plasmodium berghei* infections in mice[18] and many were also screened against *P. gallinaceum* in chicks[19] and *P. gallinaceum* in mosquitoes (*Aedes aegypti*)[20] as part of the Walter Reed Army Institute of Research malaria program. The use of the mosquito assay is based on the hypothesis that drugs which interfere with the development of sexual forms of the parasite in the mosquito may frequently be active against the tissue forms of the parasite in man.

The biological data may be summarized as follows. With few exceptions, none of the compounds tested (Tables I and II as well as **9** and **10**) possessed significant antimalarial activity in any of the screens. Generally, high toxicity at the 160–640-mg/kg level was observed for the quinones of Table I in the mouse and chick screen when one of the groups (R^1,R^2 or X) contained the dialkylaminoalkyl residue. A notable exception in this latter group is **37**. In the mouse screen the increase in mean survival time at 640 mg/kg was 3.5 days with no toxicity; in the chick at 480 mg/kg it was 2.9 days with no toxicity; and in the mosquito screen at a concentration of 0.01%, a 25% suppression of oocysts was observed. This indicates that lengthening the dialkyl group of the terminal amino in these side chains markedly decreases toxicity and enhances antimalarial activity. It also suggests a possible relationship between lipophilicity and antimalarial activity as has already been observed with other quinones.[21] The molecular complex **6** showed activity comparable with but not superior to that of DDS itself. The pamoate salt **42**, in contrast to the parent compound **41**, showed no toxicity at 640 mg/kg in mice or at 480 mg/kg in chicks but displayed no significant antimalarial activity.

In view of the numerous observations and reports[2] of antimalarial activity among certain orthoquinones and the weak activity found here, we were led to prepare a series of 5,6-quinolinediones more closely related to **1**. This work will be the subject of another communication.

Experimental Section[22]

General Preparation of 4-Amino-1,2-naphthoquinones. 4-Alkylamino-1,2-naphthoquinones (16–33, 43, 44).—The amine (10 mmol) was added rapidly to a stirred solution of 1 g (5 mmol) of 4-ethoxy-1,2-naphthoquinone[5] in 100 ml of EtOH at 25°. The solution quickly changed from yellow-orange to red-orange with the reaction going to completion within 1 hr. At this point either of two procedures may be followed. (a) The solvent was evaporated, the residue was triturated with petroleum ether (30–60°), and quinone **3a** was filtered and purified by recrystallization. The petroleum ether filtrate contained the quinone imine **4**. (b) Quinone **3a**, frequently with **4**, may separate directly from solution when the mixture was chilled at 0° for 15 hr. Filtration and thorough washing of the filter cake with petroleum ether gave **3a** as an insoluble residue.

(16) L. F. Fieser and J. T. Dunn, *J. Am. Chem. Soc.*, **59**, 1016 (1937); W. I. Awad and M. S. Hafez, *ibid.*, **80**, 6057 (1958).

(17) D. J. Cram, *ibid.*, **71**, 3953 (1949).

(18) Testing was carried out by Dr. L. Rane of University of Miami; see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(19) This test was conducted by Dr. L. Rane. Chicks (9–12 days old) were infected (intravenously) with a standard inoculum to produce a consistently uniform disease fatal to 100% of untreated controls within 3–4 days. Candidate compounds were dissolved or suspended in peanut oil and administered either subcutaneously or *per os* immediately after infection. A 100% increase in survival time was considered to be the minimum effective response to the antimalarial activity of the drug. Chicks that survived for 30 days were recorded as cured.

(20) E. J. Gerberg, L. T. Richard, and J. B. Poole, *Mosquito News*, **26**, 359 (1966).

(21) (a) L. F. Fieser, J. P. Schirmer, S. Archer, R. L. Lorenz, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967), and references therein; (b) F. J. Bullock, *ibid.*, **11**, 419 (1968), particularly footnote 14.

(22) Melting points were determined on a Mel-Temp or Fisher-Johns apparatus. The ir and uv spectra were obtained on Perkin-Elmer Model 137 and Bechman DK instruments, respectively. The nmr spectra were taken in $CDCl_3$ on a Varian A-60 instrument using TMS as internal standard. Mass spectra were determined with a CEC Model 111 instrument. Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn., or Dr. S. M. Nagy at M. I. T. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The ir, uv, and nmr spectra were as expected for the assigned structures.

TABLE II
NEW INTERMEDIATES AND DERIVATIVES

No.	R	Bp (mm) or mp, °C	Recrystn solvent	Formula	Yield, %	Analyses
		$CH_3(CH_2)_5O$–C$_6$H$_4$–R				
67	$(CH_2)_4CO_2H$	45.5–46.5	Petr ether	$C_{16}H_{24}O_3$	47	C, H
68	$(CH_2)_3CONH_2$	118–119	EtOH-H_2O	$C_{16}H_{24}NO_2$	83	C, H, N
69	$(CH_2)_4NH_2$	138 (0.3)		$C_{16}H_{27}NO$	72	
69	*p*-Nitrobenzamide	96.5–97.5				C, H, N
70	$(CH_2)_2CO_2H$	74–75	Petr ether	$C_{15}H_{22}O_3$	72	C, H
71	$(CH_2)_2CONH_2$	133–134	C_2H_5OH–H_2O	$C_{15}H_{23}NO_2$	85	C, H, N
72	$(CH_2)_3NH_2$	136 (0.6)		$C_{15}H_{25}NO$	80	
72	Benzamide	48–48.5				
		$CH_3(CH_2)_2CH(CH_3)O$–C$_6$H$_4$–R				
73	$(CH_2)_2CO_2H$	30–32, 181–183 (0.6)		$C_{15}H_{22}O_3$	43	C, H
74	$(CH_2)_2CONH_2$	105–107	EtOH-H_2O	$C_{15}H_{23}NO_2$	90	C, H, N
75	$(CH_2)_3NH_2$	116 (0.2)		$C_{15}H_{25}NO$	80	
75	*p*-Nitrobenzamide	67–68				C, H, N
76	$(CH_2)_3CO_2H$	195–197 (0.3)		$C_{18}H_{24}O_3$	35	C, H
		$(C_2H_5)_2CHO$–C$_6$H$_4$–R				
77	$(CH_2)_2CO_2H$	130 (4×10^{-4})		$C_{14}H_{20}O_3$	31	C, H
78	$(CH_2)_2CONH_2$	82–83	MeOH-H_2O	$C_{14}H_{21}NO_2$	72	C, H, N
79	$(CH_2)_3NH_2$[a]	122 (0.2)		$C_{14}H_{23}NO$	80	
		C$_6$H$_4$(SO$_2$NHR)				
80	$CH(CH_3)(CH_2)_2N(C_2H_5)_2$	78–79	EtOH-H_2O	$C_{14}H_{24}N_2O_2S$		C, H, N
81	$CH(C_2H_5)(CH_2)_2N(C_2H_5)_2$	64–65	H_2O	$C_{15}H_{26}N_2O_2S$	40	C, H, N
82	$O(CH_2)_5CH_3$	61–62	EtOH-H_2O	$C_{13}H_{23}NO_3S$	40	C, H, N

[a] Characterized only by preparation of the corresponding 4-amino-1,2-naphthoquinone.

4-[(ω-Dialkylamino)alkylamino]-1,2-naphthoquinones (35–41).—A solution of 7 mmol of the ω-dialkylaminoalkylamine in 10 ml of EtOH was added rapidly to a stirred solution of 1 g (5 mmol) of 4-ethoxy-1,2-naphthoquinone in 100 ml of EtOH. The mixture which gradually turned dark red was stirred for 1 hr at 25°. If cooling to 0° for 15 hr did not yield the desired quinone, the solvent was evaporated *in vacuo* without application of heat to a volume of about 10 ml. Trituration of the separated material with 15–25 ml of Et_2O (cold) or addition of 10 ml of petroleum ether followed by 150–200 ml of Et_2O gave, after filtration and recrystallization, the bright red quinone.

4-{[3-(Diethylamino)-1-methylbutyl]amino}-1,2-naphthoquinone Pamoate (42).—Exactly 6 mmol of a standardized solution of HCl in absolute EtOH was added to a solution of 4-{[3-(diethylamino)-1-methylbutyl]amino}-1,2-naphthoquinone (1.95 g, 6.2 mmol) in 100 ml of $CHCl_3$. After evaporation of solvent a sticky solid was obtained. Trituration with dry Et_2O gave the hydrochloride as a filterable hydroscopic red solid (*ca.* 2 g) which was quickly collected and protected from the air in a desiccator.

The hydrochloride (1.84 g) was dissolved in 10 ml of DMF and poured into a solution of 2.04 g of monosodium pamoate in 10 ml of DMF. After addition of 2 ml of H_2O, the red precipitate obtained by filtration was washed thoroughly with DMF, then H_2O. For additional purification, the pamoate was extracted with 20 ml of hot DMF, chilled, collected, and washed with H_2O to yield 3.5 g, mp 222–224° dec.

4-Arylamino- and 4-Dialkylamino-1,2-naphthoquinone (34, 45–58).—A solution of 22 mmol of the amine in 5 ml of EtOH was rapidly added to a solution of 5.2 g (20 mmol) of sodium 1,2-naphthoquinone-4-sulfonate in 400 ml of H_2O. After stirring the reaction mixture for 2 hr at 25°, solid Na_2CO_3 was added until the solution was slightly basic. The desired quinone separated either as a solid which was filtered and recrystallized or as an oil which was extracted with $CHCl_3$ or CH_2Cl_2 and dried (Na_2SO_4). Evaporation of solvent gave the product which was recrystallized.

4-Alkoxy-1,2-naphthoquinones[a] (59, 60).—A suspension of 10 g (35 mmol) of the Ag salt of 2-hydroxy-1,4-naphthoquinone[a] and 40 mmol of the alkyl halide in 100 ml of C_6H_6 was refluxed for 2 hr. The reaction mixture was cooled and filtered to remove the Ag salts. The yellow-brown oil obtained by evaporation of the filtrate was treated with 100 ml of warm 10% aqueous $NaHSO_3$. Any insoluble oil was removed by extraction with Et_2O. If the bisulfite adduct separated from the aqueous layer on cooling (**59**) it was collected by filtration, then suspended in 100 ml of H_2O. After addition of K_2CO_3 (2 g) and stirring for 15 min, the quinone was collected and recrystallized. If the bisulfite adduct did not separate from the aqueous solution on cooling (**60**), K_2CO_3 was added until the solution was weakly basic. Extraction of the separated oil with $CHCl_3$ and evaporation of solvent followed by reextraction of the residual dark oil with hexane gave the quinone as a yellow oil after evaporation of the hexane.

The phenazine derivatives were prepared by refluxing 5 mmol of the quinone with 5.5 mmol of *o*-phenylenediamine in 50 ml of EtOH for 1 hr. Careful dilution (H_2O) gave, from **59**, a green-yellow solid (EtOH) [mp 108–109°. *Anal.* ($C_{22}H_{22}N_2O$) C, H, N] and, from **60**, a yellow solid (EtOH) [mp 57–65°. *Anal.* ($C_{22}H_{22}N_2O$) C, H, N].

4-[*p*-(1,1,3,3-Tetramethylbutyl)phenoxy-1,2-naphthoquinone (61).—*p*-(1,1,3,3-Tetramethylbutyl)phenol (2.60 g, 10 mmol) dissolved in a solution of Na (0.23 g, 10 g-atoms) in 50 ml of absolute EtOH was added slowly to a vigorously stirred solution of 4-chloro-1,2-naphthoquinone[16] (1.92 g, 10 mmol) in 300 ml of a 2:1 EtOH–C_6H_6 mixture at −30°. After the reaction mixture had warmed to 25°, it was diluted with CH_2Cl_2, washed with H_2O,

dried (Na_2SO_4), and evaporated. The residue was recrystallized from EtOH to give 2.9 g (80%) of quinone as glistening yellow plates, mp 200–203°.

4-Ethoxy-1,2-naphthoquinone–4,4′-Diaminodiphenyl Sulfone Molecular Complex (62).—A solution of 4,4′-diaminodiphenyl sulfone (1.3 g, 5 mmol) and 4-ethoxy-1,2-naphthoquinone in a mixture of toluene (100 ml), EtOH (100 ml), and H_2O (50 ml) was refluxed while the solvents were allowed to evaporate continuously, EtOH being added as needed to keep H_2O from separating. After it appeared that only toluene was present, the solution was cooled and the product collected (1.05 g). Evaporation of filtrate and repetition of the EtOH–H_2O treatment produced an additional 0.5 g of the complex, mp 173–175° (total 70%). The complex as obtained was a hydrate (nmr) but drying *in vacuo* over P_2O_5 gave the anhydrous material. We were unable to obtain the complex directly in anhydrous solvents, always finding it necessary to first isolate it as its hydrate.

4-(4-Cyclohexylbutylamino)-2-diazo-1(2H)-naphthalenone (7).—*p*-Toluenesulfonylhydrazine (2.0 g, 11 mmol) was added to a stirred solution of 2.8 g (9 mmol) of 4-(4-cyclohexylbutylamino)-1,2-naphthoquinone (**24**) in 200 ml of MeOH and 100 ml of $CHCl_3$ at 40° under N_2. After 15 hr at 25°, evaporation of solvent and trituration of the residue with petroleum ether gave a brown solid. Several recrystallizations from EtOH (charcoal) gave 1.4 g (48%) of product as glistening orange plates, mp 157–159° dec, with darkening at 140°. *Anal.* ($C_{22}H_{25}N_3O$) C, H, N.

Reaction of Enamines with 4-Ethoxy-1,2-naphthoquinone. 7-Ethoxy-1,2,3,4,4a-12a-hexahydro-4a-(1-piperidinyl)benzo[*b*]naphtho[1,2-*e*]*p*-dioxin (9).—A solution of 1-(1-cyclohexenyl)-piperidine[23] (4 ml) in 10 ml of EtOH was added dropwise to a stirred solution of 4-ethoxy-1,2-naphthoquinone (2 g, 10 mmol) in 200 ml of EtOH at 25°. After the mixture was cooled at −10° for 15 hr, the precipitate was collected and recrystallized several times from CCl_4–MeOH (charcoal) to give 1.36 g (39%) of **10** as a white solid, mp 124–125°. *Anal.* ($C_{23}H_{29}NO_3$) C, H, N.

7-Ethoxy-1,2,3,4,4a,12a-hexahydro-4a-hydroxybenzo[*b*]naphtho[1,2-*e*]-*p*-dioxin (10).—A solution of 1-(1-cyclohexenyl)pyrrolidine (5 ml) of EtOH was added to a stirred solution of 4-ethoxy-1,2-naphthoquinone (3 g, 15 mmol) in 300 ml of EtOH at 25°. After 1 hr, evaporation and trituration of the residue with warm MeOH gave a tan solid, collected after the mixture had cooled. Several recrystallizations from EtOH–H_2O (charcoal) yielded 0.97 g (21%) of **10** as a white solid, mp 149–150°. *Anal.* ($C_{18}H_{20}O_4$) C, H.

(23) G. Opitz, A. Griesinger, and H. W. Shubert, *Ann.*, **665**, 91 (1963).

When the residue obtained by evaporation of the reaction mixture above was dissolved in EtOH, addition of some Et_2O gave 0.5 g of 4-(1-pyrrolidinyl)-1,2-naphthoquinone (**56**), mp 175–180°. It is identical (ir, mmp) to the compound prepared from sodium 1,2-naphthoquinone-4-sulfonate by reaction with pyrrolidine.

2-Substituted 1,4-Naphthoquinones (63, 64).—The amine (14 mmol) was added rapidly to a stirred solution of 2.2 g (12 mmol) of 2-methoxy-1,4-naphthoquinone[5,7] in a mixture of $CHCl_3$ (50 ml) and EtOH (50 ml) at 25°. After 12 hr the reaction mixture was evaporated and the quinone was isolated directly by recrystallization of the residue.

2-(3-Cyclohexylpropionyl)-1,4-naphthoquinone (65).—The following were prepared by procedures analogous to those described by Cram.[17] **2-(3-Cyclohexylpropionyl)-1-naphthol** was obtained as pale yellow needles, mp 75–76° (36%), from EtOH. *Anal.* ($C_{19}H_{22}O_2$) C, H. **2-(3-Cyclohexylpropionyl)-4-nitro-1-naphthol** was obtained from the above compound as glistening yellow plates, mp 109–111° (65%), from EtOH. *Anal.* ($C_{19}H_{21}NO_4$) C, H. Quinone **65** was obtained from the nitronaphthol as a yellow solid, mp 64–65° (80%), from EtOH.

2-(3-Cyclohexylpropionyl)-3,4-diacetoxy-1-naphthol was prepared using the procedure described by Cram[17] from the BF_3 complex of the naphthol (mp 180–182° dec) and obtained as small yellow needles, mp 122–123° (61%), from EtOH. *Anal.* ($C_{23}H_{26}O_6$) C, H.

2-(4-Cyclohexylbutyryl)-3,4-diacetoxy-1-methoxynaphthalene was prepared as a yellow solid, mp 96–96.5° (41%), from EtOH by a procedure analogous to Cram's using CH_2N_2. *Anal.* ($C_{25}H_{30}O_6$) C, H.

3-Chloro-4-hexylamino-1,2-naphthoquinone (66).—Hexylamine (4.6 g, 45 mmol) was added rapidly to a stirred solution of 3,4-dichloro-1,2-naphthoquinone[8] in $CHCl_3$ (50 ml) and EtOH (50 ml) at −25°. After the reaction mixture had warmed to 25° (1 hr), the solution was evaporated and the residue was triturated with EtOH, then recrystallized from AcOH to give 1.4 g (37%) of deep red solid, mp 229–230° dec.

Intermediates of Table II.—The acids **67**, **70**, **73**, **76**, and **77** were prepared by alkylation of the ethyl esters of 4-(*p*-hydroxyphenyl)butyric or propionic acid and subsequent ester hydrolysis essentially as we have described previously.[21b] The amides **68**, **71**, **74**, and **78** were prepared from the acid chloride ($SOCl_2$) with concentrated NH_4OH, separating as solids. Reduction of the amides with LAH (Et_2O) gave the amines **69**, **72**, **75**, and **79**. Preparation of benzamides and benzenesulfonamides was similarly carried out by standard methods.