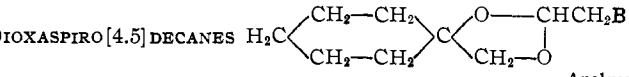
TABLE III

BASIC 1,3-DIOXASPIRO[4.5]DECANES 

Cpd. no.[a]	B	B.p., °C. base	Mm.	Yield, %	Salt	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
1	$N(CH_3)_2$	69–71	0.2	85	HCl	150–152	$C_{11}H_{22}O_2NCl$	56.04	55.87	9.41	9.27	5.94	6.10	15.04	14.86
2	$N(CH_3)_2$				CH_3Br	173–175	$C_{12}H_{24}O_2NBr$	48.98	49.40	8.22	8.46	4.76	4.75	27.16	26.89
3	$N(C_2H_5)_2$	68–71	.2	97	HCl	101–102	$C_{13}H_{26}O_2NCl$	59.18	58.97	9.94	9.50	5.31	5.35	13.44	13.39
4	$NHCH_2CH_2N(CH_3)_2$	104–106	.4	73	2HCl	152–153	$C_{14}H_{28}O_2N_2Cl_2$					8.88	8.79	22.49	22.68

[a] Compounds 1, 2 and 4 were recrystallized from ethanol–ether; 3 from toluene–ether.

was refluxed and about 500 cc. of xylene was added, dropwise, while the xylene was distilled from the mixture at the same rate that it was added. This operation required about 5 hours. The product was a red, amorphous solid. After the addition of 100 cc. of 10% sodium hydroxide solution, the mixture was heated until all of the material had dissolved. The layers were separated and the aqueous layer was extracted with ether. The solvents were removed from the combined extract and xylene layer, and the residue was fractionated; b.p. 168–178° (0.2 mm.), yield 44.0 g. (78%). In this instance, and in the case of the two spirodecanes described below, a sharp boiling point could not be obtained by further fractionation, therefore, the crude amine was converted into the hydrochloride by treatment with ethereal hydrogen chloride. The base, liberated from the pure salt, boiled at 175–178° (0.6 mm.); m.p. 72–75°.

Anal. Calcd. for $C_{20}H_{23}O_2N$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.50; H, 7.41; N, 4.49.

The hydrochloride was obtained by the use of ethereal hydrogen chloride.

The methobromide was prepared by the addition of excess methyl bromide at 0° to a solution of the base in methyl ethyl ketone; after 7 days the precipitate was filtered.

The allobromide and the butobromide were obtained in the same manner as the methobromide.

2,3-Diphenyl-8-ethyl-1,4-diox-8-azaspiro[4.5]decane.—1-Ethyl-4-piperidone hydrochloride[6] (42.0 g.) and 55.0 g. of hydrobenzoin were allowed to react in the manner described above for the 8-methyl homolog; b.p. 180–184° (0.7 mm.), m.p. 60–63°, yield 74.0 g. (89%).

Anal. Calcd. for $C_{21}H_{25}O_2N$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.86; H, 8.03; N, 4.35.

2,3,6-Triphenyl-8-methyl-1,4-diox-8-azaspiro[4.5]decane.—1-Methyl-3-phenyl-4-piperidone hydrochloride[7] (18.0 g.) and 21.3 g. of hydrobenzoin were treated in the described manner. However, in this instance, after the xylene had been added, the mixture was refluxed for 21 hours; b.p. 228–232° (0.5 mm.), m.p. 149–150°, yield 12.0 g. (39%).

Anal. Calcd. for $C_{26}H_{27}O_2N$: C, 81.00; H, 7.06; N, .63. Found: C, 81.01; H, 7.18; N, 3.67.

2-Bromomethyl-1,3-dioxaspiro[4.5]decane.—A mixture of 27.0 g. of 1-(hydroxymethyl)-cyclohexanol[8] and 41.0 g. of bromoacetal was heated at 130° until nearly the calculated amount of ethanol had distilled from the mixture, and the residue was then fractionated; b.p. 128–130° (14 mm.), yield 40.0 g. (82%).

Anal. Calcd. for $C_9H_{15}O_2Br$: C, 45.97; H, 6.43; Br, 33.99. Found: C, 45.64; H, 6.41; Br, 33.83.

2-Dimethylaminomethyl-1,3-dioxaspiro[4.5]decane.—A mixture of 10.0 g. of 2-bromomethyl-1,3-dioxaspiro[4.5]-decane, 15 g. of dimethylamine, 24 g. of sodium iodide, 5 g. of sodium carbonate and 50 cc. of toluene was heated on a steam-bath in a pressure bottle for 6 days and then treated in the described manner; yield 7.2 g. (85%), b.p. 69–71° (0.2 mm.).

The bases of compounds 3 and 4 (Table III) were prepared by a process similar to that described above.

(6) This base was obtained in 52% yield from ethyl di-(β-carbethoxyethyl)-amine (A. Ziering, L. Berger, S. Heineman and J. Lee, *J. Org. Chem.*, **12**, 894 (1947)) and sodium hydride by a described method.[5]

(7) B. Barna, Dissertation, University of Michigan, 1952.

(8) Obtained as a by-product (3% yield) during the preparation of cycloheptanone (F. F. Blicke, N. J. Doorenbos and R. H. Cox, THIS JOURNAL, **74**, 2924 (1952)).

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Preparation of Some 1-Alkyl-1,2-dihydro-3-hydroxybenzo[g]quinoxaline-5,10-diones

BY JOHN R. E. HOOVER AND ALLAN R. DAY

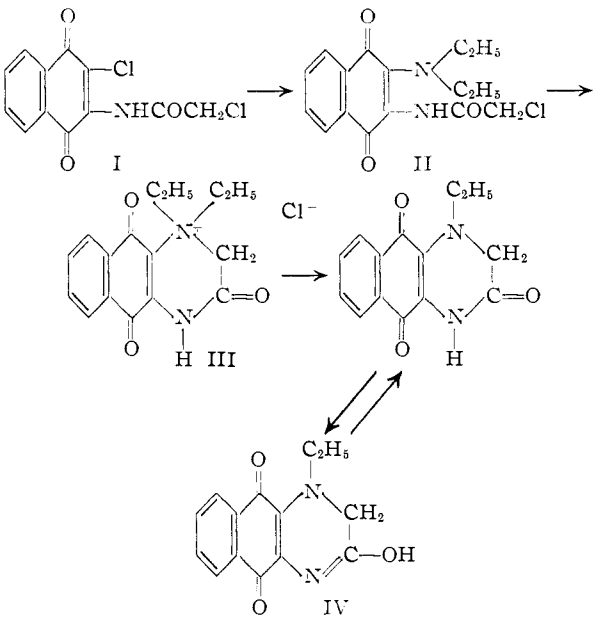
RECEIVED JUNE 9, 1954

It has been shown that aliphatic secondary amines react with 2-chloro-3-chloroacetamido-1,4-naphthoquinone to form 1-alkyl-1,2-dihydro-3-hydroxybenzo[g]quinoxaline-5,10-diones. Except in the case of diethylamine, the intermediate 2-dialkylamino-3-chloroacetamido derivatives can be isolated. Morpholine reacted in a similar manner to form 1-β-chloroethoxyethyl-1,2-dihydro-3-hydroxybenzo[g]quinoxaline-5,10-dione.

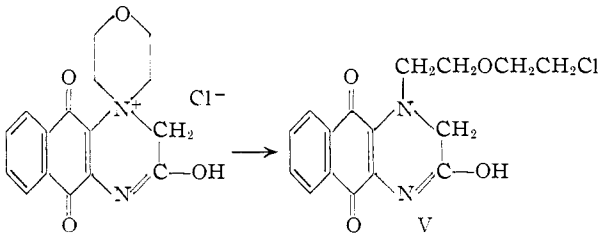
During the course of a recent study of 1-H-naphthimidazole-4,9-diones[1] it was observed that diethylamine reacted with 2-chloro-3-chloroacetamido-1,4-naphthoquinone in dry benzene solution in an anomalous manner. Instead of the expected replacement product, 2-diethylamino-3-chloroacetamido-1,4-naphthoquinone, a compound was obtained which contained no chlorine and whose physical properties were different from those expected of the normal replacement product. Repetition of this work and analysis of a carefully purified sample showed a difference in carbon, hydrogen and chlorine, from the expected product, equivalent to ethyl chloride. This suggested the intermediate formation of an intramolecular quaternary ammonium salt which subsequently lost a molecule of ethyl chloride according to the reaction shown.

The work has now been extended to reactions with di-*n*-propylamine, di-*n*-butylamine and morpholine under similar conditions. These amines reacted with 2-chloro-3-chloroacetamido-1,4-naphthoquinone to form the corresponding 2-dialkylamino-3-chloroacetamido derivatives. The di-*n*-propylamino and di-*n*-butylamino derivatives when heated in a polar solvent, such as ethylene glycol or nitrobenzene, rapidly changed color and products were isolated which corresponded to that ob-

(1) J. R. E. Hoover and A. R. Day, THIS JOURNAL, **76**, 4148 (1954).



tained from diethylamine. When 2-morpholino-3-chloroacetamido-1,4-naphthoquinone was heated in ethylene glycol, a similar change in color took place, but the product which was isolated gave the same analytical results as the starting compound. Since the color change during the reaction was the same as noted in the other cases and since the chlorine in the final product was not present as chloride ion, as shown by the lack of a reaction with silver ions, it appears that the final product is 1β-chloroethoxyethyl-1,2-dihydro-3-hydroxybenzo[g]quinoxaline-5,10-dione.



In this case ring opening occurred in place of the elimination of an alkyl group.

The statement that the secondary amines, which were used, replaced the chlorine atom directly attached to the ring rather than the one in the side chain is based on two observations. When 2-chloro-3-acetamido-1,4-naphthoquinone was treated with ammonia, a monoamino compound was obtained which still contained one chlorine atom. When this compound was treated with a secondary amine, under somewhat more vigorous conditions, the remaining chlorine was replaced. The resulting compound when subjected to ring closure formed a 2-alkylaminomethyl-1H-naphthimidazole-4,9-dione.[1] This product could only have been formed providing the ammonia had replaced the nuclear chlorine atom and the secondary amine had replaced the chlorine atom in the side chain. Secondly, the high reactivity of the chlorine atom in 2-chloro-3-acylamino-1,4-naphthoquinones is shown by the ease with which it can be replaced. Thus 2-morpholino-3-acetamido-1,4-naphthoquinone can be prepared from 2-chloro-3-acetamido-1,4-naphthoquinone under the same conditions used for the preparation of the type II compound.

Experimental

Preparation of 1-Ethyl-1,2-dihydro-3-hydroxybenzo[g]-quinoxaline-5,10-dione.—A solution of 10 g. (0.018 mole) of 2-chloro-3-chloroacetamido-1,4-naphthoquinone (I) and 8 ml. of diethylamine in 600 ml. of benzene was boiled for five minutes and the benzene removed under reduced pressure. The residue was dried, washed with water and recrystallized from alcohol; dark violet needles, m.p. 207.2–207.9°, yield 73%.

Anal. Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.61; H, 4.72; N, 10.93. Found: C, 65.63; H, 4.73; N, 10.76.

Preparation of 2-Di-*n*-propylamino-3-chloroacetamido-1,4-naphthoquinone.—To a boiling solution of 7.1 g. (0.025 mole) of 2-chloro-3-chloroacetamido-1,4-naphthoquinone in 150 ml. of benzene was added 7.5 ml. (0.055 mole) of di-*n*-propylamine. The solution, which became dark red immediately, was refluxed for 20 minutes. The di-*n*-propylamine hydrochloride was removed from the cooled mixture and the benzene was removed *in vacuo*. The red residue was washed with water and dried over phosphorus pentoxide, yield 98%. After successive recrystallizations from ethanol, toluene and ethanol, orange-red needles were obtained which melted at 123.2–124.3°, yield 60%.

Anal. Calcd. for $C_{18}H_{21}O_3N_2Cl$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.80; H, 5.90; N, 7.94.

Preparation of 2-Di-*n*-butylamino-3-chloroacetamido-1,4-naphthoquinone.—The above procedure was used with di-*n*-butylamine, yield 93%. Red-violet needles were obtained by successive recrystallizations from toluene and alcohol, yield 70%, m.p. 104–104.9°.

Anal. Calcd. for $C_{20}H_{25}O_3N_2Cl$: C, 63.74; H, 6.69; N, 7.43. Found: C, 63.58; H, 6.58; N, 7.31.

Preparation of 2-Morpholino-3-chloroacetamido-1,4-naphthoquinone.—The above procedure was repeated with morpholine, yield 98%. The crude product was recrystallized from alcohol, bright red needles, yield 70%, m.p. 185–185.5°.

Anal. Calcd. for $C_{16}H_{15}N_2O_4Cl$: C, 57.40; H, 4.53; N, 8.37. Found: C, 57.56; H, 4.63; N, 8.41.

Preparation of 1-*n*-Propyl-1,2-dihydro-3-hydroxybenzo-[g]quinoxaline-5,10-dione.—A solution of 4 g. (0.011 mole) of 2-di-*n*-propylamino-3-chloroacetamido-1,4-naphthoquinone in 40 ml. of ethylene glycol was heated to 190–195° for ten minutes. During this time the color of the solution changed from deep red to blue. The hot solution was poured into 400 ml. of cold water and the dark violet needles which separated were removed by filtration, washed with water and dried. One recrystallization from alcohol followed by two recrystallizations from 50% aqueous dioxane gave a product melting at 201–202.3°, yield 70%.

Anal. Calcd. for $C_{15}H_{14}O_3N_2$: C, 66.65; H, 5.22; N, 10.36. Found: C, 66.63; H, 5.30; N, 10.27.

Preparation of 1-*n*-Butyl-1,2-dihydro-3-hydroxybenzo-[g]quinoxaline-5,10-dione.—The above procedure was used starting with 5 g. of 2-di-*n*-butylamino-3-chloroacetamido-1,4-naphthoquinone in 25 ml. of ethylene glycol. The conversion required several minutes longer than the previous preparation. The product was purified by successive recrystallizations from toluene, 50% aqueous dioxane and alcohol; yield 40%, m.p. 197–198° (sample inserted at 190°, $\Delta t = 2°$ per minute).

Anal. Calcd. for $C_{16}H_{16}O_3N_2$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.70; H, 5.76; N, 9.94.

Preparation of 1β-Chloroethoxyethyl-1,2-dihydro-3-hydroxybenzo[g]quinoxaline-5,10-dione.—The procedure for the preparation of the 2-*n*-propyl derivative was applied to 2.5 g. of 2-morpholino-3-chloroacetamido-1,4-naphthoquinone. The solution changed color from red to blue. After successive recrystallizations from toluene, ethanol and 50% aqueous dioxane, the product was obtained as deep violet, irregular plates or as dark greenish-violet needles, yield 40%, m.p. 155.5–156°.

Anal. Calcd. for $C_{16}H_{15}O_4N_2Cl$: C, 57.40; H, 4.52;

N, 8.37; Cl, 10.59. Found: C, 57.50; H, 4.56; N, 8.32; Cl, 10.48.

Preparation of 2-Morpholino-3-acetamido-1,4-naphthoquinone.—Five grams of 2-chloro-3-acetamido-1,4-naphthoquinone and 3.2 ml. of morpholine in 200 ml. of benzene were heated under reflux for 20 minutes. The precipitated morpholine hydrochloride was removed and washed with 50 ml. of warm benzene. The filtrate and washings were combined and concentrated in vacuo to about one-fourth the original volume. Dark red needles separated on cooling. The product was recrystallized from toluene, dioxane and finally from 50% alcohol; yield 60%, m.p. 203.4–204.5°.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.11; H, 5.49; N, 9.33.

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Quinolinequinones. II. N-Substituted 6-Amino-5,8-quinolinequinones[1]

BY YOLANDA T. PRATT WITH NATHAN L. DRAKE

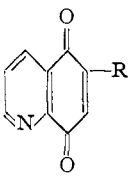
RECEIVED JUNE 25, 1954

6-Methoxy-5,8-quinolinequinone (I) has been synthesized and hydrolyzed to 6-hydroxy-5,8-quinolinequinone (II). The methoxyquinolinequinone, like the corresponding methoxynaphthoquinone is the vinylog of an ester and reacts with both primary and secondary amines to yield N-substituted 6-amino-5,8-quinolinequinones (III). The methoxyquinone readily transetherifies with ethanol to form the corresponding ethoxyquinone.

The quinolinequinones (dihydroquinolinediones) are of potential biological interest because of the physiological activities of both quinolines and quinones. In the first paper of this series[2] certain 8-amino-5,6-quinolinequinone derivatives were prepared to test the theory that such compounds are the active metabolites of the 8-aminoquinoline antimalarials. In the present work some of the isomeric N-substituted 6-amino-5,8-quinolinequinones (III) which are related to physiologically active compounds have been prepared for biological evaluation.

Taylor and Greenberg[3] have shown that certain 6-hydroxyquinolines with diethylaminoalkylamino side chains at the 8-position are effective amebicides against *E. histolytica* in guinea pigs. The hydroquinone of 8-isopropylaminoamylamino-5,6-quinolinequinone, which is rapidly converted to the quinone by air,[2] is slightly active despite the fact that the quinone is not stable and is probably rapidly destroyed *in vivo*. It was therefore of interest to synthesize the more stable isomeric types such as VI, VII and VIII (Table I) for the determination of their amebicidal activities. Certain 6-amino-5,8-quinolinequinones (*e.g.*, IX and X) are related to the 8-hydroxyquinoline amebicides[4] in that 5,8-quinolinequinone is an oxidation product of 8-hydroxyquinoline.[5] These compounds will also be tested as antibacterial agents since this type of activity is displayed by some quinolines and many quinones.[6]

Although the parent 5,8-quinolinequinone[7] was first prepared in 1884, very little research on this compound or its derivatives has been reported.[8] The starting material for the present work was 6-methoxy-5,8-quinolinequinone (I), readily obtained



I, R = $-OCH_3$
II, R = $-OH$
III, R = $-NR'R''$

by oxidizing the 5,8-diamine formed from 6-methoxy-8-aminoquinoline *via* the diazonium coupling product.[9] Despite the instability of the methoxyquinone I in aqueous acid, it could be prepared satisfactorily by oxidizing the diamine with acidic dichromate solution. Since the product is a very weak base it could be extracted into chloroform[10] as it was formed, thus minimizing acid hydrolysis. The over-all yield of pure methoxyquinone (I) from 6-methoxy-8-aminoquinoline was 57%.

Like 2-methoxy-1,4-naphthoquinone,[11] 6-methoxy-5,8-quinolinequinone (I) is the vinylog of an ester. It is hydrolyzed rapidly by dilute alkali at room temperature forming a red salt. Pure 6-hydroxy-5,8-quinolinequinone (II) is obtained in quantitative yield upon neutralization. In related work now in progress it is planned to convert this hydroxyquinone II to various types of analogs of physiologically active 2-hydroxy-1,4-naphthoquinones and hydroxyquinolines. Like the corresponding naphthoquinone, compound II appears to be a stronger acid than acetic acid since it dissolves in sodium acetate solution. It may be reconverted to the methoxy compound I by heating with methanol in the presence of acid catalysts, but the yields are only about 60% because of decomposition. Although the hydroxyquinone II, by analogy with the related naphthoquinone,[11] may exist predominately in the *p*-quinone form, as written, the facility with

(1) This investigation was supported by a research grant (PHS E-665) from the National Microbiological Institute of the National Institutes of Health, Public Health Service.

(2) N. L. Drake and Y. T. Pratt, THIS JOURNAL, **73**, 544 (1951).

(3) D. J. Taylor and J. Greenberg, *Am. J. Hyg.*, **56**, 58 (1952).

(4) J. H. Burckhalter and W. H. Edgerton, THIS JOURNAL, **73**, 4837 (1951), and references therein.

(5) The oxidation of 8-hydroxyquinoline to 5,8-dihydroxyquinoline by means of persulfate has been described by V. J. Dalvi, R. B. Desai and S. Sethna, *J. Ind. Chem., Soc.*, **28**, 366 (1951).

(6) For example, see Buu-Hoi, *Bull. soc. chim. France*, [5] **11**, 578 (1944), for tuberculostatic 2-amino-1,4-naphthoquinones, and T. Urbanski, S. Slopek and J. Venulet, *Nature*, **168**, 29 (1951), for tuberculostatic quinoline derivatives.

(7) O. Fischer and E. Renouf, *Ber.*, **17**, 1644 (1884).

(8) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 192–197.

(9) K. N. Campbell, *et al.*, THIS JOURNAL, **68**, 1561 (1946).

(10) Fischer and Renouf[7] had found that the parent 5,8-quinolinequinone can be extracted from the oxidizing mixture by means of chloroform.

(11) L. F. Fieser, THIS JOURNAL, **48**, 2922 (1926); **50**, 439 (1928).