ness, the oily residue was dissolved in a few ml. of hexane and developed with the same solvent on alumina–Celite (27 × 5.5 cm.). The *cis*-III zone was cut and eluted with benzene; the eluate was evaporated completely and the oily residue dissolved in optical grade hexane. *cis*-III-Diphenyloctatetraene could not be separated from traces of an impurity which absorbed light in the 220–300 mμ region (Fig. 4) but did not affect the main band. The molecular extinction values were determined as described for *cis*-II. In the absence of solvent the oily *cis*-III is very photosensitive and isomerizes spontaneously even at room temperature, in darkness. Much slower is the rearrangement in dilute hexane solutions (3 mg. per l.); under these conditions it amounted to 8% in a day. Insolation of dilute solutions yielded the all-*trans* form in 45 sec. The iodine catalysis induced a rearrangement in two distinct steps as shown in Figs. 5 and 6.

Methods of Isomerization and Estimation. (a) **Insolation.**—In order to determine the ratio of the stereoisomers formed a benzene solution of the all-*trans* compound (10 mg. per 25 ml.) was exposed in a Pyrex volumetric flask to bright sunshine (Table I), diluted with 4 vol. of hexane and developed on a 20 × 3.5 cm. magnesia–lime–Celite column with benzene–hexane 1:2. The following chromatogram is the result of insolation for 1 hr.

3 brownish yellow
1 blue fl.
15 green fl.; unchanged all-*trans*
4 somewhat weaker green fl.; *cis*-I
10 empty interzone
2 blue fl.
40 empty interzone
8 pale green fl.; *cis*-II
5 empty interzone
4 pale green fl.; *cis*-III
100 empty section

The *trans* and *cis*-I zones were cut out together, eluted, transferred to benzene-hexane 1:3 and developed on a 30 × 3.5 cm. column with pure benzene until the *cis*-I zone has separated from the upper (*trans*) zone. The *cis*-II and III zones were cut out separately, eluted and transferred to hexane. Each steric form was estimated photometrically after evaporating and re-dissolving in optical grade hexane.

(b) **Iodine Catalysis.**—A solution containing 1 mg. of all-*trans* form and 0.02 mg. of iodine in 100 ml. of hexane was exposed in a Pyrex flask to a fluorescent daylight lamp[4] from 60 cm. distance and developed with benzene–hexane 1:2 on an 18 × 2 cm. magnesia–lime–Celite column.

5 empty section
5 green fl.; unchanged all-*trans*
2 somewhat weaker green fl.; *cis*-I
30 empty interzone
6 pale green fl.; *cis*-II
10 empty interzone
7 pale green fl.; *cis*-III
110 empty section

The all-*trans* and *cis*-I forms had to be rechromatographed in order to obtain clear separation.

(c) **Refluxing.**—A hexane solution of 1 mg. of the all-*trans* form was refluxed in 100 ml. of hexane while nitrogen bubbled through. The solution was then chromatographed as just described. Solutions in benzene or xylene (1 mg. per 25 ml.) were diluted with 4 vol. of hexane before chromatography.

(d) **Irradiation.**—One mg. of the *trans* compound in 100 ml. of hexane, contained in a Pyrex volumetric flask, was illuminated by a Photoflood bulb No. 1 from 10 cm. distance while the flask was cooled with a stream of water, and then chromatographed.

(e) **Melting Crystals.**—A 10-mg. sample of the all-*trans* form, sealed in an evacuated tube, was immersed completely in an oil-bath at 255–260°, the contents were dissolved in benzene and, after the addition of 4 vol. of hexane, the solution was developed with benzene 1:2 on a 20 × 3.5 cm. magnesia–lime–Celite column. The combined all-*trans* and *cis*-I zones had to be rechromatographed before photometric estimation.

PASADENA, CALIFORNIA

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

Preparation of Some Imidazole Derivatives of 1,4-Naphthoquinone

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

RECEIVED MARCH 6, 1954

A series of 2-substituted-1H-naphthimidazole-4,9-diones has been synthesized as compounds having potential biological activity and their chemistry has been discussed.

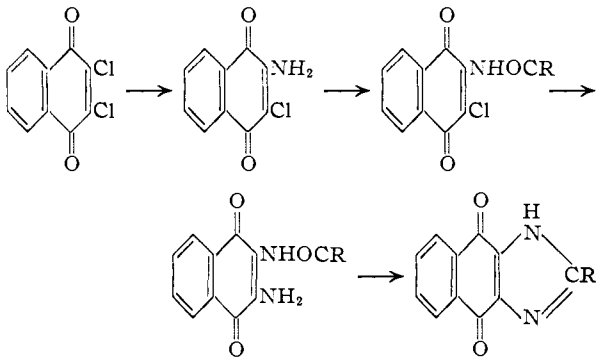
The work presented here represents a continuation of our efforts to synthesize compounds which would compete with essential metabolites. The present paper reports the synthesis of a number of 1H-naphthimidazole-4,9-diones. It was thought that such compounds might interfere with the normal utilization of vitamin K or of the purines since they contain groups common to these two classes of compounds.

A number of 1,4-naphthoquinones have been shown to be metabolite antagonists and their activity is neutralized by the addition of vitamin K or 3-methyl-1,4-naphthoquinone. 2,3-Dichloro-1,4-naphthoquinone is a powerful fungicide.[1] 2-Methoxy- and 2-chloro-1,4-naphthoquinone display some antibiotic activity toward certain organisms.[2] Certain 2-alkyl-3-hydroxy-1,4-naphthoquinones have considerable antimalarial activity.[3] Benzimidazole and 5(6)-aminobenzimidazole were found to exhibit a bacteriostatic action which could be reversed by the addition of guanine or adenine.[4]

In view of the above reports, as tudy of the preparation of a number of 1H-naphthimidazole-4,9-diones appeared desirable. Little work appears in the literature on the preparation of the linear imidazoles of 1,4-naphthoquinone. The preparation of 1H-naphthimidazole-4,9-dione and 2-methyl-1H-naphthimidazole-4,9-dione was effected earlier, by the chromic acid oxidation of naphth(2,3)imidazole and 2-methylnaphth(2,3)imidazole.[5] The last two compounds were obtained by heating 2,3-diaminonaphthalene with formic acid and acetic acid, respectively. This did not appear to be a good method for the present investigation for two reasons: (1) the diamine is not easily obtainable, and (2) the introduction of oxidizable groups into the molecule would not be feasible because of the oxidative step.

(1) D. W. Woolley, *Proc. Soc. Exptl. Biol. Med.*, **60**, 225 (1945).
(2) J. Guerillot-Vinet and Mme. J. Guerillot-Vinet, *Compt. rend.*, **227**, 03 (1948).
(3) L. F. Fieser, *et al.*, *Record Chem. Progress*, **7**, No. 314, 26 (1946); THIS JOURNAL, **70**, 3151 (1948).
(4) D. W. Woolley, *J. Biol. Chem.*, **152**, 225 (1944).
(5) K. Fries, R. Walter and K. Schilling, *Ann.*, **516**, 248 (1935).

The method finally adopted was an adaptation of a method first reported by Fries and Billig.[6] They observed that 2-acylamino-3-arylamino-1,4-naphthoquinones were converted to the corresponding imidazoles on treatment with acids or bases. After extensive study and many modifications, this procedure was used to prepare most of the imidazoles reported in this paper. The method involves several steps starting with 2,3-dichloro-1,4-naphthoquinone.



Amination of 2,3-dichloro-1,4-naphthoquinone proceeds very readily with the replacement of only one halogen atom.[6] The reaction has been carried out in hot nitrobenzene[7] and in aqueous alcohol.[8] The use of aqueous alcohol gives the best results.

Acylation of 2-amino-3-chloro-1,4-naphthoquinone was effected most readily by heating the amine with an acyl chloride in the presence of concentrated sulfuric acid or dry hydrogen chloride. The latter was the more effective catalyst. Two acyl chlorides, benzoyl chloride and carbobenzoxy chloride, failed to react. Attempts to acylate the amino compounds under basic conditions were unsuccessful.

The preparation of 2-formamido-3-chloro-1,4-naphthoquinone originally appeared to be important for the synthesis of the unsubstituted 1H-naphthimidazole-4,9-dione. Although a number of standard procedures for the formylation of amines were tried, the formyl derivative was not obtained. In this case the imidazole was prepared by a special method.

The acylation of 2-amino-3-chloro-1,4-naphthoquinone increases the activity of the halogen atom so that it is easily replaced when treated with ammonia, amines, alkoxides and alkali. For the introduction of the second amino group, nitrobenzene proved to be the best solvent. In only one case, namely with 2-chloroacetamido-3-chloro-1,4-naphthoquinone, was it necessary to use a solvent other than nitrobenzene. In this case dioxane was employed.

The conversion of the 2-acylamino-3-amino-1,4-naphthoquinones to the corresponding imidazoles was readily accomplished by warming in alcohol containing 15% of 2 *N* sodium hydroxide. Contrary to the findings of Fries and Billig,[6] the conversion could not be effected under acidic conditions, except under reducing conditions.

(6) K. Fries and K. Billig, *Ber.*, **58**, 1128 (1925).
(7) F. Ullman and M. Ettish, *ibid.*, **54**, 270 (1921).
(8) K. Fries and P. Ochwat, *ibid.*, **56**, 1291 (1923).

1H-Naphthimidazole-4,9-dione was prepared by a special method. The imidazole ring was formed recently by the action of ethyl orthoformate on orthodiamines.[9] Although only the free diamines were known to react in this manner, the procedure was applied to 2-acetamido-3-amino-1,4-naphthoquinone using sulfuric acid as the catalyst and found to give the desired product.

2-Chloroacetamido-3-chloro-1,4-naphthoquinone when treated with ammonia gave 2-chloroacetamido-3-amino-1,4-naphthoquinone. The fact that the chlorine atom attached to the ring was replaced most readily was unexpected. The 2-chloroacetamido-3-amino compound is fairly readily converted to 2-dialkylaminoacetamido-3-amino-1,4-naphthoquinone by treatment with secondary amines in ethanol solution.

In the preparation of 2-dialkylaminomethyl-1H-naphthimidazole-4,9-diones from the corresponding 2-dialkylamino-acetamido-3-amino compounds, using base catalysts, considerable difficulty was experienced with purification of the products. Consequently, the possibility of ring closure under acid conditions was investigated. It was found that the cyclization could be effected by heating in acetic acid solution in the presence of zinc, followed by the oxidation of the hydroquinone form of the imidazole to the quinone structure. Better results were obtained when a catalytic hydrogenation method was used in place of the zinc and acetic acid. It was found most convenient to isolate the 2-dialkylaminomethyl imidazoles in the form of their hydrochlorides and to convert the latter to the free bases by passing an aqueous alcoholic solution of the hydrochloride over a weak-base ion exchange resin.

The 1H-naphthimidazole-4,9-diones are yellow compounds with relatively high melting points. The melting points of the 2-alkyl derivatives drop regularly as the size of the alkyl group increases. They are practically insoluble in water with the exception of the 2-dialkylaminomethyl derivatives which can be recrystallized from hot water. These compounds exhibit the amphoteric nature typical of imidazoles in general. They readily form sparingly soluble sodium salts on treatment with dilute sodium hydroxide. Salts with acids were formed less readily. The hydrochlorides can be hydrolyzed to the free bases by adding a large excess of water. The 2-dialkylaminomethyl derivatives of course exhibit the typical basic properties of an aliphatic amine.

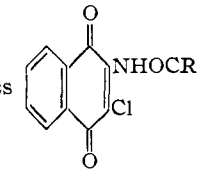
The imino hydrogen of the imidazole ring is readily replaced by an alkyl group. The 1-alkyl derivatives are more basic than the unsubstituted compounds. The free bases cannot be regenerated from the hydrochlorides by treatment with water alone.

The 1H-naphthimidazole-4,9-diones are unchanged by prolonged heating with 2 *N* sodium hydroxide or 6 *N* hydrochloric acid. The imidazole ring is not opened by treatment with benzoyl chloride under Schotten and Baumann conditions. Attempts to acylate the imino group, using acetyl

(9) E. S. Schipper and A. R. Day, THIS JOURNAL, **73**, 5672 (1951); **74**, 350 (1952).

TABLE I

2-ACYLAMINO-3-CHLORO-1,4-NAPHTHOQUINONES



R	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3[e]	82[a] 79[b]	219						
C_2H_5	96[a] 80[b]	188.5–189.2	59.21	59.16	3.82	3.81	5.31	5.40
n-C_3H_7	85[c]	162–162.6	60.55	60.61	4.36	4.44	5.04	5.01
i-C_3H_7	84[d]	192.4–193.6	60.55	60.71	4.36	4.18	5.04	4.90
n-C_4H_9	82[b]	154.6–155.3	61.76	61.52	4.84	4.59	4.80	4.59
i-C_4H_9	56[d]	160.9–161.8	61.76	61.87	4.84	4.73	4.80	4.86
n-C_5H_{11}	75[c]	148–148.5	62.85	62.70	5.27	5.18	4.58	4.55
$(C_2H_5)_2CH$	86[d]	202.5–203.1	62.85	62.67	5.27	5.11	4.58	4.73
$C_6H_5CH_2$	79[c]	205–205.5	66.36	66.38	3.71	3.60	4.30	4.44
$ClCH_2$	86[d]	182–182.8	50.73	50.68	2.48	2.62	4.93	5.05

[a] Prepared by acid anhydride method. [b] Prepared by acyl chloride method 1. [c] Prepared by acyl chloride method 2. [d] Prepared by acyl chloride method 3. [e] Previously prepared by Fries and Ochwat, *Ber.*, **56**, 1291 (1923).

chloride, acetic anhydride or benzoyl chloride under a variety of conditions, failed also.

Reduction of the imidazolediones to the corresponding hydroquinones was accomplished with zinc and acetic acid, sodium hydrosulfite or with hydrogen and palladium black. The hydroquinones separated in colorless forms, but quickly turned deep blue in air.

The methyl groups in 2-methyl-4,9-naphth(2,3)-imidazoledione failed to react when heated with benzaldehyde in the presence of bases.

In preliminary tests some of the 1H-naphthimidazole-4,9-diones displayed pronounced inhibitory properties against *E. coli* 113-3 (vitamin B_{12} requiring) and *E. coli* B 96 (purine requiring). The more detailed study of the biological properties of this series will be included in a later communication.

Experimental

Preparation of 2,3-Dichloro-1,4-naphthoquinone.—A modification of the method of Ullman and Ettish[7] was used.[10] This compound is now available under the trade name of Phygon and can be obtained in sufficient purity to be used directly for the subsequent preparations.[11]

Preparation of 2-Amino-3-chloro-1,4-naphthoquinone.—A modification of the procedure reported by Fries and Ochwat[8] was used for this preparation. 2,3-Dichloro-1,4-naphthoquinone (150 g., 0.66 mole) was suspended in 3 l. of ethyl alcohol and 300 ml. of concentrated ammonium hydroxide. The mixture was gently refluxed for 90 minutes and during this period a slow stream of ammonia was passed into the solution. Nitrogen was then bubbled through the hot solution to remove the ammonia and the solution treated with decolorizing carbon and filtered. After standing overnight at 6°, the product was removed, washed with water and dried at 100°; yield 74%, m.p. 195–196°. This product was used without further purification.

Preparation of 2-Acylamino-3-chloro-1,4-naphthoquinones by the Acid Anhydride Method. 2-Acetamido-3-chloro-1,4-naphthoquinone.—Five drops of concentrated sulfuric acid was added to a cooled suspension of 51.9 g. (0.25 mole) of 2-amino-3-chloro-1,4-naphthoquinone in 75 ml. of acetic anhydride. After 15 minutes, the yellow precipitate was removed and washed free of acetic anhydride with ether. The product was recrystallized from ethyl alcohol.

2-Propionamido-3-chloro-1,4-naphthoquinone.—This compound was prepared by the same procedure, using propionic anhydride. The product was recrystallized from ethyl alcohol. All of the acylamino-chloro compounds were yellow to orange in color.

Preparation of 2-Acylamino-3-chloro-1,4-naphthoquinones by the Acyl Chloride Method (see Table I). **(1). 2-Acetamido-3-chloro-1,4-naphthoquinone.**—2-Amino-3-chloro-1,4-naphthoquinone (10.4 g., 0.05 mole) was suspended in 60 ml. of acetyl chloride followed by the addition of 5 drops of concentrated sulfuric acid. The reaction mixture was protected from strong light and heated under reflux with vigorous stirring until a dark yellow solution was obtained. This required about two hours. After cooling overnight, the product was removed by filtration, washed with ether and recrystallized from ethyl alcohol.

(2) 2-*n*-Butyramido-3-chloro-1,4-naphthoquinone.—*n*-Butyryl chloride was used in this case. In place of sulfuric acid, hydrogen chloride was bubbled through the suspension for five minutes prior to heating and the mixture was then refluxed for four hours.

(3) 2-Isobutyramido-3-chloro-1,4-naphthoquinone.—Isobutyryl chloride and hydrogen chloride were used for this preparation and xylene was added to raise the reflux temperature of the reaction mixture.

2-Chloroacetamido-3-chloro-1,4-naphthoquinone.—The hydrogen chloride–xylene modification was used for this preparation. The product was precipitated by the addition of an equal volume of ether. Long standing with ether was necessary for maximum yields.

Preparation of 2-Acylamino-3-amino-1,4-naphthoquinones. 2-Acetamido-3-amino-1,4-naphthoquinone. General Procedure.—The procedure described below was used, with certain modifications, for all of these compounds except 2-chloroacetamido-3-amino-1,4-naphthoquinone.

Dry ammonia was passed into a solution of 42.8 g. (0.17 mole) of 2-acetamido-3-chloro-1,4-naphthoquinone in 300 ml. of nitrobenzene for one hour while the temperature was kept at 145–150°. The ammonium chloride was removed and the filtrate on cooling deposited red needles. All of the compounds in this series (Table II) were red to reddish-violet. The product was recrystallized from ethyl alcohol and had the same properties as reported by Fieser and Martin.[12]

2-Chloroacetamido-3-amino-1,4-naphthoquinone.—The general method gave very poor results so the following procedure was adopted. Dry ammonia was passed into a boiling solution of 28.4 g. (0.1 mole) of 2-chloroacetamido-3-chloro-1,4-naphthoquinone in 125 ml. of dioxane. After 30 minutes, the ammonium chloride was removed and the filtrate cooled overnight. The product obtained by cooling was recrystallized from dioxane and finally from ethyl alcohol.

Preparation of 2-Dialkylaminoacetamido-3-amino-1,4-naphthoquinones. 2-Diethylaminoacetamido-3-amino-1,4-naphthoquinone.—2-Chloroacetamido-3-amino-1,4-naphthoquinone (26.5 g., 0.1 mole) was suspended in 600 ml. of

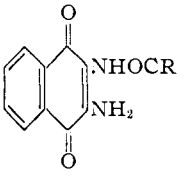
(10) John R. E. Hoover, Ph.D. Thesis, University of Pennsylvania, 1953.

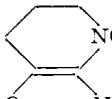
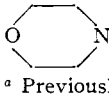
(11) Naugatuck Chemical Division, U. S. Rubber Company.

(12) L. F. Fieser and E. L. Martin, THIS JOURNAL, **57**, 1844 (1935).

TABLE II

2-ACYLAMINO-3-AMINO-1,4-NAPHTHOQUINONES

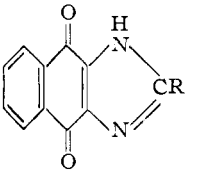


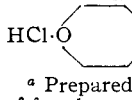
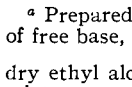
R	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	91	233–234[a]						
C_2H_5[b]	75	193	63.92	63.77	4.95	4.59	11.47	11.67
n-C_3H_7	72	169.5–169.9	65.10	64.98	5.46	5.26	10.85	11.00
i-C_3H_7	86	209–210	65.10	65.08	5.46	5.48	10.85	10.66
n-C_4H_9	86	157.2–158	66.16	66.10	5.92	5.78	10.29	10.27
i-C_4H_9	66	164–165	66.16	66.06	5.92	5.90	10.29	10.35
n-C_5H_{11}	94	139.4–140.1	67.13	66.96	6.34	6.18	9.79	9.70
$(C_2H_5)_2CH$	91	151.4–152.2	67.13	67.20	6.34	6.39	9.79	9.92
$C_6H_5CH_2$[d]	79	183.2–184.8[c]	70.57	70.49	4.61	4.65	9.14	9.08
$ClCH_2$	69	204–205.3	54.45	54.44	3.43	3.36	10.59	10.53
$(C_2H_5)_2NCH_2$[e]	70	87.8–88.5	63.77	63.97	6.36	6.40	13.94	14.11
	85	149–149.5	65.16	65.26	6.11	6.05	13.41	13.40
	91	211.6–212.2	60.94	60.92	5.44	5.33	13.32	13.32

[a] Previously prepared by L. Fieser and E. L. Martin, THIS JOURNAL, **57**, 1844 (1935). [b] Temperature of the reaction was kept at the boiling point of the solution. [c] Marked sintering at about 165°. [d] Reaction time reduced to 35 minutes. [e] Prepared from the 2-chloroacetamido-3-amino derivative.

TABLE III

2-SUBSTITUTED 1H-NAPHTHIMIDAZOLE-4,9-DIONES



R	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	95	370 uncor.	66.67	66.46	3.02	3.02	14.14	13.93
CH_3	63	368 uncor.	67.91	67.88	3.80	3.81	13.20	13.10
C_2H_5	70	304.4–305	69.01	68.90	4.45	4.34	12.39	12.23
n-C_3H_7[a]	65	221.8–222.2	69.98	69.98	5.03	4.90	11.66	11.66
i-C_3H_7[b]	83	260.1–261.3	69.98	69.87	5.03	5.07	11.66	11.52
n-C_4H_9[b]	74	232–232.8	70.84	70.79	5.55	5.48	11.02	11.06
i-C_4H_9[a]	57	250–251.4	70.84	71.01	5.55	5.46	11.02	11.15
n-C_5H_{11}[a]	68	182.3–183.5	71.61	71.34	6.01	5.99	10.44	10.51
$(C_2H_5)_2CH$[a]	81	240.7–242	71.61	71.57	6.01	6.06	10.44	10.59
$C_6H_5CH_2$[a]	62	279–280.3	74.99	75.00	4.20	4.28	9.72	9.88
$HCl\cdot(C_2H_5)_2NCH_2$[c]	76	264.2–265.4	60.09	60.02	5.67	5.75	13.14	13.15
	42	310 dec.	61.53	61.50	5.47	5.58	12.67	12.68
	80	317 dec.	57.75	57.56	4.54	4.71	12.63	12.59

[a] Prepared by method used for the 2-ethyl derivative. Prepared by method used for the 2-methyl derivative. [c] M.p. of free base, 190–191.5°. [d] M.p. of free base, 240.6–241.5°. [e] M.p. of free base, 213°.

dry ethyl alcohol containing 75 ml. of diethylamine. The mixture was refluxed until the suspended solid dissolved (4 hr.). The dark red solution was concentrated to 100 ml. *in vacuo*, four volumes of water added and the mixture cooled. The product so obtained was recrystallized from 50% ethyl alcohol.

2-Piperidinoacetamido-3-amino-1,4-naphthoquinone.—Piperidine was used in place of diethylamine and the solution was refluxed for only 30 minutes. On cooling, the product separated. It was recrystallized from dioxane and subsequently from dry ethyl alcohol.

2-Morpholinoacetamido-3-amino-1,4-naphthoquinone.—Morpholine was used in this case and the solution refluxed for one hour. The product began to crystallize from the solution after 30 minutes. After cooling, it was removed by filtration. It was recrystallized from toluene and finally from ethyl alcohol.

Preparation of 1H-Naphthimidazole-4,9-diones. 1H-Naphthimidazole-4,9-dione.—Concentrated sulfuric acid was added dropwise to a hot solution of 4.6 g. (0.02 mole) of 2-acetamido-3-amino-1,4-naphthoquinone in 100 ml. of ethyl orthoformate until the color of the solution changed from bright red to a light orange. Vigorous bubbling followed each addition of the acid (several ml. were required). Yellow needles separated on cooling. The product was dissolved in warm dilute sodium hydroxide, treated with de-

colorizing carbon and filtered. The imidazole was precipitated from the filtrate by neutralizing with 6 *N* hydrochloric acid. It was then recrystallized from nitrobenzene following which the crystals were warmed with toluene and then petroleum ether and dried.

Preparation of 2-Substituted-1H-naphthimidazole-4,9-diones. Base-catalyzed Ring Closures. 2-Methyl-1H-naphthimidazole-4,9-dione.—To a hot solution of 4 g. of 2-acetamido-3-amino-1,4-naphthoquinone (0.017 mole) in 160 ml. of ethyl alcohol was added 20 ml. of 2 *N* sodium hydroxide. The mixture was heated for 15–20 minutes until the violet coloration changed to a brownish-orange. The solution was poured into 600 ml. of water containing 20 ml. of 2 *N* hydrochloric acid. The mixture was heated and alcohol gradually added until the imidazole, which had separated, redissolved. The hot solution was treated with decolorizing carbon, filtered and cooled. The product separated as yellow needles and was recrystallized from ethyl alcohol. All of the imidazoles in this series were yellow, crystalline compounds.

2-Ethyl-1H-naphthimidazole-4,9-dione.—A solution of 12 g. (0.049 mole) of 2-propionamido-3-amino-1,4-naphthoquinone in 480 ml. of alcohol and 60 ml. of 2 *N* sodium hydroxide was distilled *in vacuo* to 200 ml. and the solution was acidified with 6 *N* hydrochloric acid. The product was dissolved in warm dilute sodium hydroxide and reprecipitated, after treating with decolorizing carbon, with hydrochloric acid. The product was recrystallized from ethyl alcohol.

Preparation of 2-Substituted-1H-naphthimidazole-4,9-diones. Acid-catalyzed Ring Closure. 2-Methyl-1H-naphthimidazole-4,9-dione. (a).—Two grams of 2-acetamido-3-amino-1,4-naphthoquinone in 50 ml. of glacial acetic acid was boiled with an excess of zinc turnings until the red color changed to yellow (about 10 minutes). Additional acetic acid was added to dissolve the blue precipitate which had formed. The hot solution was treated with decolorizing carbon, filtered and poured into four volumes of water whereupon yellow needles separated. More product was obtained from the filtrate by adjusting to a *p*H of 8, bubbling air through the solution until the color became orange and acidifying, total yield 65%. It was recrystallized from ethyl alcohol, m.p. 368°.

(b).—Hydrogen was passed into a boiling solution of 2 g. of 2-acetamido-3-amino-1,4-naphthoquinone in 50 ml. of glacial acetic acid, in the presence of 100 mg. of palladium black, until the solution became dark yellow. The palladium was removed and the acetic acid removed under reduced pressure. The residue was suspended in 200 ml. of water and allowed to stand with occasional shaking for 24 hours, or until the suspended solid became yellow. Sodium hydroxide (12 *N*) was added to dissolve the imidazole. The solution was treated with decolorizing carbon and acidified, yield 71%. The product was recrystallized from ethyl alcohol, m.p. 368°.

2-(N-Diethylaminomethyl)-1H-naphthimidazole-4,9-dione.—A boiling solution of 15.07 g. (0.05 mole) of 2-diethylaminoacetamido-3-amino-1,4-naphthoquinone in 100 ml. of glacial acetic acid, in the presence of 300 mg. of palladium black was treated with hydrogen as above. After removing the acetic acid *in vacuo*, the residue was dissolved in excess of warm 2 *N* sodium hydroxide and diluted to 500 ml. Oxygen was passed into the solution for 15 minutes. The solution was decolorized, acidified with hydrochloric acid and cooled, yield of hydrochloride 76%. The product was recrystallized from water and dried at 120° *in vacuo*.

The hydrochloride was converted to the free base by passing a solution in 50% alcohol through a column of anion exchange resin, IR4B(OH). The resulting solution, which was free of chloride ion, was distilled *in vacuo* and the yellow residue recrystallized from toluene, yield 72%.

2-Piperidinomethyl-1H-naphthimidazole-4,9-dione.—The above procedure was applied to 2-piperidinoacetamido-3-amino-1,4-naphthoquinone.

2-Morpholinomethyl-1H-naphthimidazole-4,9-dione.—2-Morpholinoacetamido-3-amino-1,4-naphthoquinone was subjected to the above procedure.

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

Researches on Substituted 5-Phenylhydantoins[1]

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Twelve new 5-(substituted phenyl)- or 5,5-di-(substituted phenyl)-hydantoins have been synthesized. Catalytic hydrogenation of 5-(4-methylphenyl)-5-phenylhydantoin attacks only the unsubstituted phenyl grouping.

While numerous 5-phenyl-5-substituted hydantoins have been tested for pharmacological activity,[3] very little has been learned concerning the activities of 5-(substituted phenyl)-hydantoins.[4] It was of interest, therefore, to prepare other substituted-phenyl hydantoins so that their anticonvulsant activities, if any, might be compared with that of the potent 5,5-diphenylhydantoin or 5-ethyl-5-phenylhydantoin.

The first group of hydantoins, synthesis of which is reported in this paper, is monosubstituted derivatives of 5,5-diphenylhydantoin and were obtained through utilization of appropriate ketones, namely: $C_6H_5COC_6H_4$–X(*para*) where X = amino, hydroxy or methoxy. Another group illustrated disubstituted types derived from (*p*)-X–$C_6H_4COC_6H_4$–X-(*p'*), where X = amino or chloro. The third class, related to 5-ethyl-5-phenylhydantoin, was prepared from ketones of the type $C_2H_5COC_6H_4$–X, where X = bromo, hydroxy or methoxy. Of the various individual derivatives prepared, that produced from 4,4'-diaminobenzophenone, namely, 5,5-di-(4-aminophenyl)-hydantoin, possessed added interest. The parent ketone had been shown to possess a sulfonamide-like action in that it inhibits the growth of bacteria, this inhibition being overcome by *p*-aminobenzoic acid.[5] Obviously, testing of this hydantoin derivative would be desirable in order to ascertain whether this inhibition was retained in the hydantoin.

The replacement of one or both of the phenyl groups in 5,5-diphenylhydantoin with an equal number of cyclohexyl groups apparently causes

(1) From the Ph.D. dissertation of A. F. Isbell, June, 1943.

(2) University Advanced Research Fellow, The University of Texas, 1942–1943.

(3) H. H. Merritt and T. J. Putnam, *Epilepsia*, **3**, 51 (1945). Although many 5-phenyl-5-substituted hydantoins have been shown to possess some degree of anticonvulsant activity, an increasing number of such compounds is being found to be devoid of such activity. Moreover, several 5,5-disubstituted hydantoins having no phenyl substituent are known to be active anticonvulsants.

(4) J. W. Melton and H. R. Henze, THIS JOURNAL, **69**, 2018 (1947), have reported on the preparation of 5-(*meta*-substituted phenyl)-hydantoins; without exception, these compounds have been found to lack anticonvulsant activity.

(5) R. Kuhn, E. F. Moller, G. Wendt and H. Binert, *Ber.*, **75B**, 711 (1942).