ible activity in this tumor is a $T/C \leqq 150\%$ at the optimal dose.[2e]

Conclusions

Tylocrebrine shows high activity against Lymphoid Leukemia L1210 in mice, and these tests indicate that best results are likely to be obtained at a dose level of about 10 mg./kg. The activity ascertained in these tests is sufficient for scheduling this compound for preclinical pharmacology and, in the absence of prohibitive toxicity, for large-scale clinical testing.

Acknowledgment.—The authors wish to express thanks to Dr. J. L. Hartwell, Chief of the Research Communications Branch, Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda 14, Md., for his interest in this project.

1,2-Disubstituted Naphth[2,3-*d*]imidazole-4,9-diones and Corresponding Quaternary Salts[1]

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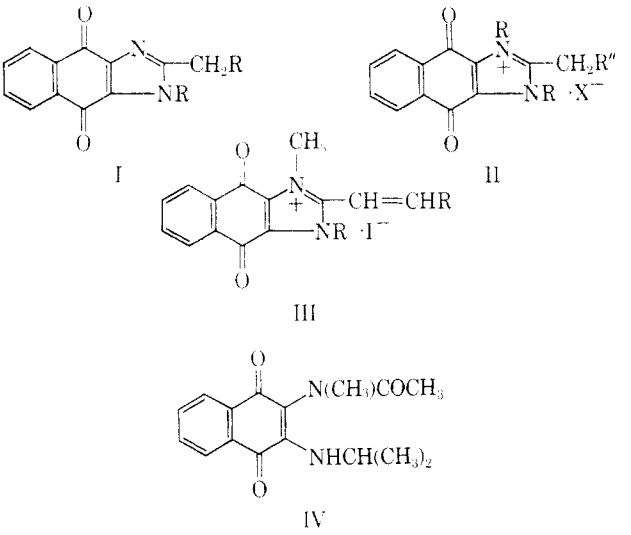
Hoover and Day[2] described the preparation and properties of a number of 2-alkyl-1H-naphth[2,3-*d*]-imidazole-4,9-diones. Some of these compounds were reported to have inhibitory activity against *Escherichia coli* 113-3 and B96.[2] The present work deals with the preparation of 1-alkyl- and 1-aryl-2-methylnaphth-[2,3-*d*]imidazole-4,9-diones (I), quaternary salts of these compounds, and a study of various properties of these substances.

2-Acetamido-3-alkyl- or -3-aryl-1,4-naphthoquinones were prepared according to the directions of Truitt, *et al.*[3] These compounds were converted to the imidazoles (I) by the action of 2 *N* sodium hydroxide as directed by Fries and Billig[4] and utilized by Hoover and Day.[2] It is interesting to note in our work that the expected 2-acetamido-3-anilino-1,4-naphthoquinone was obtained if an ethanol solution of aniline and 2-acetamido-3-chloro-1,4-naphthoquinone (2:1 mole ratio) was refluxed. However, if the reactants were used in a 1:1 mole ratio, 2-methyl-1-phenylnaphth-[2,3-*d*]imidazole-4,9-dione was produced in good yield. *p*-Bromoaniline and *p*-toluidine gave similar results but with lower yields. Alkyl amines did not give imidazoles under similar condition.

When the imidazoles (I) were heated with methyl iodide (or other reactive halides) the quaternary salts (II) were obtained. These compounds melted with vigorous evolution of a gas. The pyrolysis of II (R = isopropyl, R′ = methyl, R″ = H, and X = I) gave isopropyl iodide and methyl iodide in a 10:1 ratio, as determined by gas chromatography.



I II III IV

Although Hoover and Day[2] reported that 1H-2-methylnaphth[2,3-*d*]imidazole-4,9-dione would not react with aldehydes in the presence of bases, we found that the quaternary salts (II) gave the expected styryl derivatives (III) when refluxed with benzaldehyde in the presence of piperidine or pyrrolidine.

Strong bases, such as NaOH, opened the imidazolium ring. For example, 4,9-dihydro-4,9-dioxo-1-dimethyl-3-(2-propyl)naphth[2,3-*d*]imidazolium iodide reacted with cold sodium hydroxide to give only 2-(*N*-methyl-acetamido)-3-(2-propylamino)-1,4-naphthoquinone(IV)

Physiological Acitivity.[5]—Compounds **15** and **16** (Table II) were not more than slightly active against pinworms in mice.[6] These results were insufficient to warrant further investigation. Two compounds (**4** and **10**, Table II) showed *in vitro* activity against *Mycobacterium tuberculosis* and *Streptococcus pyogenes*, respectively. *In vivo* tests in mice against the experimental infections failed to show chemotherapeutic activity. *In vitro* activity against *Endamoeba histolytica* was observed with **14** (Table III).[7] In view of the fact that this compound was amebicidal at only the highest concentration, *in vivo* tests were not carried out. Compound **14** (Table III) was also slightly active at cytotoxic levels against *Trypanosoma cruzi* in chick embryo tissue cultures.[8,9] No activity was observed against the experimental infection in mice.[10] Compound **4** (Table II) exhibited no action against convulsions produced by electroshock,[11] but did exhibit moderate activity against convulsions induced by pentylenetetrazole.[12] None of the compounds reported in the work showed significant antitumor activity.[13]

(1) Supported in part by a grant (CY3908) from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Md., a Faculty Grant from North Texas State University, and a Parke, Davis and Co. Fellowship.

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(3) P. Truitt, F. M. Wood, Jr., and R. L. Hall, *J. Org. Chem.*, **25**, 1460 (1960).

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(5) The physiological testings were arranged by Dr. E. Elslager of Parke, Davis and Company.

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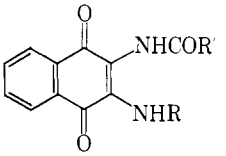
(12) G. M. Chen and C. R. Ensor, *Arch. Neurol. Psychiat.*, **63**, 56 (1950).

(13) The antitumor testings were arranged by Dr. Joseph Leiter of CCNSC and the complete results will be reported elsewhere.

TABLE I

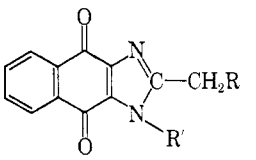
2-ACYLAMINO-3-SUBSTITUTED AMINO-1,4-NAPHTHOQUINONES



No.	R	R′	M.p., °C.	Yield, %	Formula	% N Calcd.	% N Found
1	CH_2=$CHCH_2$	H	180–181	80	$C_{15}H_{14}N_2O_3$	10.36	10.39
2	$CH_3O(CH_2)_3$	H	158–159	83	$C_{16}H_{18}N_2O_4$	9.27	9.45
3	$(CH_3)_2CH$	H	149–151	91	$C_{15}H_{16}N_2O_3$	10.29	10.36
4	$(CH_3)_2CHCH_2$	H	164–165	81	$C_{16}H_{18}N_2O_3$	9.78	9.77
5	$CH_3(CH_2)_3$	H	177–178	65	$C_{16}H_{18}N_2O_3$	9.78	9.48
6	$C_6H_5CH_2$	H	189–191	78	$C_{19}H_{16}N_2O_3$	8.74	8.84
7	2-$CH_3C_6H_4$	H	187–188	86	$C_{19}H_{16}N_2O_3$	8.74	8.89
8	4-$CH_3C_6H_4$	H	194–195	94	$C_{19}H_{16}N_2O_3$	8.74	9.11
9	4-Br-C_6H_4	H	200–201	90	$C_{18}H_{13}BrN_2O_3$	7.27	7.17
10	$HOCH_2CH_2$	H	174–176	62	$C_{14}H_{14}N_2O_4$	10.21	10.39
11	2-$CH_2OC_6H_4$	H	193–195	56	$C_{19}H_{16}N_2O_4$	8.33	8.42
12	$(CH_3)_2CH$	C_6H_5	150–151	78	$C_{21}H_{20}N_2O_3$	8.04	8.00
13	$CH_3(CH_2)_3$	C_6H_5	118–120	81	$C_{22}H_{22}N_2O_3$	7.73	7.98
14	$C_6H_5CH_2$	C_6H_5	172–175	70	$C_{25}H_{20}N_2O_3$	7.07	7.20
15	C_6H_5	C_6H_5	210–213	67	$C_{24}H_{18}N_2O_3$	7.33	7.47
16	2-$CH_3OC_6H_4$	C_6H_5	173–175	47	$C_{25}H_{20}N_2O_4$	6.80	6.76
17	CH_2=$CHCH_2$	C_6H_5	143–145	50	$C_{21}H_{18}N_2O_3$	8.09	7.91

TABLE II

2,3-DISUBSTITUTED NAPHTH[2,3-*d*]IMIDAZOLE-4,9-DIONES



No.	R	R′	M.p., °C.	Yield, %	Formula	% N Calcd.	% N Found
1	H	CH_3	247–249	60	$C_{13}H_{10}N_2O_2$	12.39	12.57
2	H	CH_3CH_2	168–170	53	$C_{14}H_{12}N_2O_2$	11.66	11.69
3	H	$(CH_3)_2CH$	175–176	86	$C_{15}H_{14}N_2O_2$	11.02	10.97
4	H	$CH_3(CH_2)_3$	115–117	75	$C_{16}H_{16}N_2O_2$	10.44	10.26
5	H	$(CH_3)_2CHCH_2$	161–163	62	$C_{16}H_{16}N_2O_2$	10.44	10.50
6	H	$ClCH_2CH_2$	288–290	41	$C_{14}H_{11}ClN_2O_2$	10.20	10.17
7	H	$C_6H_5CH_2$	195–196	85	$C_{19}H_{14}N_2O_2$	9.27	9.06
8	H	C_6H_5	240–241[a]				
9	H	2-$CH_3OC_6H_4$	193–195	68	$C_{19}H_{14}N_2O_3$	8.80	8.99
10	H	2-$CH_3C_6H_4$	189–191	40	$C_{19}H_{14}N_2O_2$	9.27	9.41
11	C_2H_5	$CH_3(CH_2)_3$	144–145	66	$C_{18}H_{20}N_2O_2$	9.45	9.55
12	C_2H_5	$C_6H_5CH_2$	129–130	74	$C_{21}H_{18}N_2O_2$	8.48	8.51
13	C_2H_5	C_6H_5	174–175	84	$C_{20}H_{16}N_2O_2$	8.85	9.02
14	H	1-$C_{14}H_{29}$	72–73	72	$C_{26}H_{36}N_2O_2$	6.86	6.70
15	H	4-$CH_3C_6H_4$	260–263	40	$C_{19}H_{14}N_2O_2$	9.27	9.19
16	H	4-BrC_6H_4	242–244	82	$C_{18}H_{11}BrN_2O_2$	7.63	7.47
17	H	$CH_3(CH_2)_2$	145–147	78	$C_{15}H_{14}N_2O_2$	11.02	11.00
18	H	$CH_3(CH_2)_5$	128–129	38	$C_{18}H_{20}N_2O_2$	9.45	8.99
19	H	4-ClC_6H_4	236–238	73	$C_{18}H_{11}ClN_2O_2$	8.68	8.77
20	C_6H_5	$(CH_3)_2CH$	185–186	90	$C_{21}H_{18}N_2O_2$	8.48	8.30
21	C_6H_5	$CH_3(CH_2)_3$	178–179	70	$C_{22}H_{20}N_2O_2$	8.13	8.42
22	C_6H_5	$C_6H_5CH_2$	164–166	65	$C_{25}H_{18}N_2O_2$	7.40	7.28
23	C_6H_5	C_6H_5	177–180	50	$C_{24}H_{16}N_2O_2$	7.69	7.81
24	C_6H_5	2-$CH_3OC_6H_4$	224 226	85	$C_{25}H_{18}N_2O_3$	7.10	7.04
25	C_6H_5	CH_2=CHCH	156 158	60	$C_{21}H_{16}N_2O_2$	8.53	8.58

[a] Lit. m.p. 239–241°.[4]

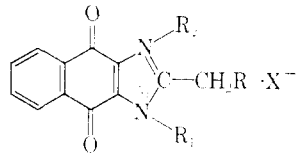
Experimental[14]

2-Acetamido-3-(2-propylamino)-1,4-naphthoquinone.—A mixture of 100 g. (0.40 mole) of 2-acetamido-3-chloro-1,4-naphthoquinone, 1 l. of ethanol, and 8 g. (0.80 mole) of isopropylamine was heated with stirring for 30 min. The reaction mixture was treated with charcoal, filtered, and cooled. The red precipitate weighed 71 g. (65%). The product was recrystallized from ethanol, m.p. 149–151°. This and other similar compounds are reported in Table I. They were readily recrystallized from ethanol or methanol.

(14) All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus.

TABLE III

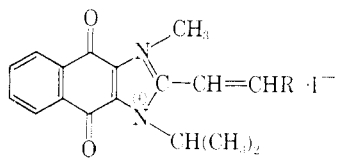
NAPHTH[2,3-*d*]IMIDAZOLIUM SALTS



No.	R	R_1	R_2	X	M.p., °C.	Yield, %	Formula	%N Calcd.	%N Found	%I Calcd.	%I Found
1	H	C_2H_5	CH_3	I	247–250	85	$C_{15}H_{15}IN_2O_2$	7.33	7.27	33.21	33.51
2	H	C_2H_5	$CH_3(CH_2)_2$	I	177–181	60	$C_{17}H_{19}IN_2O_2$	6.83	6.78	30.93	31.30
3	H	$(CH_3)_2CH$	CH_3	I	249–251	92	$C_{16}H_{17}IN_2O_2$	7.07	6.93	32.04	32.38
4	H	$(CH_3)_2CH$	$CH_3(CH_2)_2$	I	211–214	81	$C_{18}H_{21}IN_2O_2$	6.60	6.90	29.91	30.48
5	H	$CH_3(CH_2)_3$	CH_3	I	224–226	91	$C_{17}H_{19}IN_2O_2$	6.83	6.89		
6	H	$CH_3(CH_2)_3$	C_2H_5	I	127–129	35	$C_{18}H_{21}IN_2O_2$	6.60	6.51		
7	H	$CH_3(CH_2)_3$	$C_6H_5CH_2$	Cl	179–181	30	$C_{23}H_{23}ClN_2O_2$	7.09	7.19		
8	H	$CH_3(CH_2)_3$	$4\text{-}O_2NC_6H_4CH_2$	Br	235–236	83	$C_{23}H_{22}BrN_3O_4$	8.68	8.72		
9	H	$CH_3(CH_2)_3$	$4\text{-}O_2NC_6H_4COCO_2$	Br	224–225	75	$C_{24}H_{22}BrN_3O_5$	8.20	8.18		
10	H	$CH_3(CH_2)_3$	$C_6H_5CH_2CH_2$	Br	203–206	75	$C_{24}H_{25}BrN_2O_2$	6.18	6.11		
11	H	$C_6H_5CH_2$	CH_3	I	210 dec.	87	$C_{20}H_{17}IN_2O_2$	6.31	6.22	28.57	28.97
12	H	C_6H_5	CH_3	I	273–275	60	$C_{19}H_{15}IN_2O_2$	6.52	6.63	29.50	30.30
13	H	$2\text{-}CH_3OC_6H_5$	CH_3	I	277–280	50	$C_{20}H_{17}IN_2O_3$	6.10	6.23	27.63	27.93
14	H	C_6H_5	$4\text{-}O_2NC_6H_4CH_2$	Br	234–236	74	$C_{23}H_{18}BrN_3O_4$	8.34	8.30		
15	H	$(CH_3)_2CHCH_2$	CH_3	I	226–227	62	$C_{17}H_{19}IN_2O_2$	6.83	6.72	30.93	31.30
16	H	$(CH_3)_2CHCH_2$	$4\text{-}O_2NC_6H_4COCH_2$	Br	230–231	86	$C_{24}H_{22}BrN_3O_5$	8.20	8.27		
17	C_6H_5	$CH_3(CH_2)_3$	CH_3	I	135–136	71	$C_{23}H_{23}IN_2O_2$	5.76	5.69		

TABLE IV

STYRYL DERIVATIVES OF NAPHTH[2,3-*d*]IMIDAZOLIUM SALTS



No.	R	M.p., °C.	Yield, %	Formula	%N Calcd.	%N Found
1	C_6H_5	218–219.5	90	$C_{23}H_{21}IN_2O_2$	5.79	6.22
2	$2\text{-}ClC_6H_4$	214–215	13	$C_{23}H_{20}ClIN_2O_2$	5.40	5.69
3	$4\text{-}(CH_3)_2NC_6H_4$	212–214	31	$C_{25}H_{26}IN_3O_2$	7.97	8.01
4	$4\text{-}CH_3OC_6H_4$	210–211	30	$C_{24}H_{23}IN_2O_3$[a]	5.45	5.59
5	$4\text{-}HOC_6H_4$	245–247	36	$C_{23}H_{21}IN_2O_3$[b]	5.60	5.87

[a] *Anal.* Calcd.: I, 24.70. Found: I, 25.03. [b] *Anal.* Calcd.: I, 25.36. Found: I, 25.39.

2-Methyl-1-phenylnaphth[2,3-*d*]imidazole-4,9-dione. A.—A mixture of 30.6 g (0.10 mole) of 2-acetamido-3-phenyl-1,4-naphthoquinone[4] and 500 ml. of ethanol was heated to reflux and 50 ml. of 2 *N* NaOH was added. The mixture was heated 30 min., diluted with 500 ml. of hot water, 50 ml. of 2 *N* HCl added, filtered, and cooled. The yellow needles were recovered and dried yielding 25 g. (80%), m.p. 240–241°.

Other imidazoles were prepared in the same manner and when necessary they were recrystallized from dioxane. The data for these compounds are recorded in Table II.

B.—A solution of 24.95 g. (0.10 mole) of 2-acetamido-3-chloro-1,4-naphthoquinone in 200 ml. of ethanol was heated to reflux and a solution of 9.3 g. (0.10 mole) of aniline in 25 ml. of ethanol was added. The mixture was refluxed for 6 hr., diluted with 100 ml. of water, and cooled. The yellow precipitate was collected and dried, m.p. 238–240°. Recrystallization gave 21 g. (73%) of bright yellow needles of the imidazole, m.p. 239–241°.

4,9-Dihydro-1,2-dimethyl-4,9-dioxo-3-(2-propyl)naphth[2,3-*d*]imidazolium Iodide.—A solution of 25.4 g. (0.10 mole) of 2-methyl-1-(2-propyl)naphth[2,3-*d*]imidazole-4,9-dione, 200 ml. of Methyl Cellosolve, and 19 g. of methyl iodide was refluxed for 4 hr., cooled, and a reddish powder recovered. Recrystallization from methanol gave 35 g. (88.5%), m.p. 249–251° dec., of the quaternary salt (see Table III).

The other quaternary salts were prepared and purified in the same manner and all the data for these compounds are included in Table III.

4,9-Dihydro-4,9-dioxo-1-methyl-1-(2-propyl)-2-(β-styryl)naphth[2,3-*d*]imidazolium Iodide.—A mixture of 5 g. (0.0126 mole) of 4,9-dihydro-1,2-dimethyl-4,9-dioxo-3-(2-propyl)naphth[2,3-*d*]imidazolium iodide, 3 g. (0.028 mole) of benzaldehyde, 60 ml. of dioxane, and 1 ml. of piperidine was refluxed for 2 hr. The mixture was cooled, filtered, and the orange product (5.5 g., 90%) was recrystallized from methanol, m.p. 218–219.5° dec.

Other styryl derivatives were prepared in the same manner and are included in Table IV.

2-Chloro-3-(N-methylacetamido)-1,4-naphthoquinone.—A mixture of 8 g. (0.0362 mole) of 2-methylamino-1,4-naphthoquinone (m.p. 117–119°), 5 ml. of acetic anhydride, and 2 drops of H_2SO_4 was stirred and warmed on a steam bath for 2 hr. The thick paste was washed with ether and water and finally recrystallized from methanol. Nine grams (94.7%) of yellow-orange crystals was obtained, m.p. 123–125°.

Anal. Calcd. for $C_{13}H_{10}ClNO_3$: N, 5.31. Found: N, 5.69.[15]

2-(N-Methylacetamido)-3-(2-propylamino)-1,4-naphthoquinone. (VI).—A mixture of 2.6 g. (0.01 mole) of 2-chloro-3-(N-methylacetamido)-1,4-naphthoquinone, 2 g. of isopropylamine, and 50 ml. of ethanol was warmed on a steam bath for 2 hr. Isolation and recrystallization of the orange crystals from methanol gave 1.5 g. (50%) of product, m.p. 198–199.5° dec.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: N, 9.78. Found: N, 9.68.

Hydrolysis of 4,9-dihydro-1,2-dimethyl-4,9-dioxo-3-(2-propyl)naphth[2,3-*d*]imidazolium Iodide (V).—A mixture of 1 g. of V and 100 ml. of ethanol was stirred with 10 ml. of 2 *N* sodium hydroxide for 10 min. The orange solid was removed and recrystallized from methanol, m.p. 198–199°. The infrared spectrum of this product was identical with 2-(N-methylacetamido)-3-(2-propyl)-1,4-naphthoquinone (IV).

(15) All nitrogen determinations were made with a Coleman Model 99 nitrogen analyzer.

Pyridylurethanes of Pharmacological Interest

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Although urethanes of the pyridyl group have occasionally been prepared and their chemical properties investigated, their pharmacological potentialities have not, to our knowledge, yet been explored. In view of the interesting biological activity of certain urethanes,