Synthesis of Potential Antineoplastic Agents. XIV. Some 2-Substituted 2,3-Dihydro-1H-perimidines[1,2]

WILLIAM WASULKO, ADRIA CATALA NOBLE, AND FRANK D. POPP

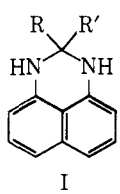
Department of Chemistry, Clarkson College of Technology, Potsdam, New York

Received January 14, 1966

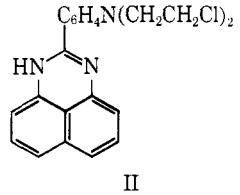
A variety of aldehydes and cyclic ketones have been treated with 1,8-diaminonaphthalene to give the title compounds. Screening data are included on these compounds as well as on some related dihydroperimidines prepared earlier. Only a few of these compounds exhibited any appreciable antineoplastic action.

Some time ago we reported[3] the condensation of a variety of aromatic aldehydes with 1,8-diaminonaphthalene to give a series of 2-aryl-2,3-dihydro-1H-perimidines (I, R = aryl groups; R′ = H). At the same time we prepared the related perimidine II. We further reported that both II and I (R = *p*-$(ClCH_2CH_2)_2NC_6H_4$; R′ = H) were inactive against the nitrogen mustard sensitive Dunning leukemia but that I (R = *p*-$(ClCH_2CH_2)_2NC_6H_4$; R′ = H) was active (T/C = 34% at 250 mg/kg) against Adenocarcinoma 755 while II was inactive. We now wish to report the screening data on the other dihydroperimidines (I) previously prepared[3] and these results are included in Table I. In addition to the nitrogen mustard listed above, only the compound from 3,4-dichlorobenzaldehyde exhibited any appreciable activity. Despite this lack of promise it was decided on the basis of these two active examples to prepare additional compounds to see if further active compounds could be obtained.

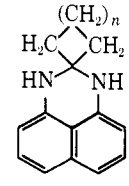
Eight additional aldehydes were condensed with 1,8-diaminonaphthalene to give compounds of the type I included in Table II. In this case aliphatic and heterocyclic aldehydes were used in addition to aromatic ones. An attempt was made to extend this reaction to ketones and although acetone (see also Table II) gave I (R = R′ = CH_3) a number of aromatic ketones such as benzophenone, 4,4′-dinitrobenzophenone, and 3,4-dichloroacetophenone failed to give under our conditions any product of the type I. As can be seen from Table III a number of these new products show some activity such as I (R = 3,4,5-$(CH_3O)_3C_6H_2$; R′ = H) against Sarcoma 180, I (R = 3-BrC_6H_4; R′ = H) against Lewis lung carcinoma, and I (R = $CH_3CH_2CH_2$; R′ = H) against cell culture (KB).



I

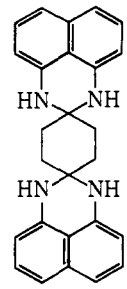


II

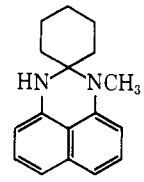


III

Despite the lack of general success with a number of ketones as noted above it was decided to treat some acyclic ketones with 1,8-diaminonaphthalene. This led to a series of compounds of the type III as indicated in Table IV. Unsubstituted ketones of four- to seven-membered rings together with a number of substituted cyclopentanones and cyclohexanones all gave the desired product. Use of cyclohexane-1,4-dione gave IV. If dried under mild conditions, IV contained 1.5 moles of solvent whether recrystallized from ethanol or from acetone. Drying either of these solvated materials under more vigorous conditions gave unsolvated IV.



IV



V

Methylation of III (*n* = 3) with methyl iodide and sodium hydride gave the N-methyl compound V. All attempts to dimethylate III (*n* = 3) or to carry out further methylation of V under a variety of conditions failed to give any N,N′-dimethyl compound. Reaction of compounds of the type III with hydrogen chloride gave monohydrochlorides and in a few cases compounds containing 1.5 moles of hydrogen chloride. In no case could a dihydrochloride be isolated. The results are shown in Table V.

The structure of the compounds of the type I can be based on analogy with the work of Sachs[4] and Vinot.[5] It is of particular importance to note that Vinot[5] converted I (R = H; R′ = *n*-Pr) to the corresponding perimidine by dehydrogenation with palladium on carbon and that we[3] have converted I (R = H; R′ = $C_6H_4N(CH_2CH_2Cl)_2$-*p*) to II by a similar method. Further all of our compounds reported in Tables II and IV as well as those reported earlier[3] contain a sharp aromatic band at 1575–1605 cm^{-1} (mainly between 1575 and 1595 cm^{-1}) (KBr disk) in the infrared. No other peak appears between 1570 and 1700 cm^{-1} except for a band at 1640 cm^{-1} in the one amide included in Table IV. This excludes the possibility that the compounds may have been formed by reaction at only one amino group to give Schiff bases containing a primary amine. If this latter type of compound had been formed, one would expect to find both C=N

(1) Part XIII: D. W. Alwani, A. C. Noble, and F. D. Popp, *J. Med. Chem.*, **9**, 421 (1966).

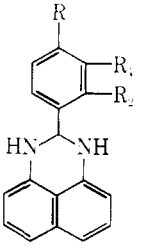
(2) Supported in part by research grants from the American Cancer Society (T-177 D) and from the National Cancer Institute, U. S. Public Health Service (CA 06606-03).

(3) F. D. Popp and A. Catala, *J. Heterocyclic Chem.*, **1**, 108 (1964).

(4) F. Sachs, *Ann.*, **365**, 135 (1908).

(5) N. Vinot, *Compt. Rend.*, **252**, 899 (1961).

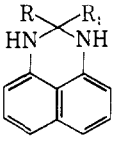
TABLE I
SCREENING DATA[a] ON COMPOUNDS REPORTED IN REF 3



R	R_1	R_2	T/C, % (dose, mg/kg) LE[b]	DA[c]	SI[d]	CA[e]	Other
$N(CH_2CH_2Cl)_2$	H	H	96 (400)	...	...	34 (250)	98 (200)[f]
F	H	H	94 (200)	...	...	112 (200)	90 (250)[g]
Cl	H	H	...	...	...	91 (200)	...
Cl	Cl	H	...	...	...	24 (250)	...
$N(CH_3)_2$	H	H	97 (200)	100 (100)	86 (200)	...	...
C_6H_5	H	H	...	...	...	55 (500)	...
Br	H	H	97 (200)	100 (100)	116 (200)	...	...
H	H	NO_2	90 (200)	94 (100)	75 (200)	...	...
CH_3O	H	H	88 (200)	100 (100)	74 (200)	...	...
OH	H	H	88 (200)	100 (100)	95 (200)	...	...
H	CH_3O	H	92 (200)	100 (100)	67 (200)	...	...
CH_3O	CH_3O	H	92 (200)	94 (100)	116 (200)	...	...
$-OCH_2O-$		H[h]	93 (400)	...	...	...	86 (500)[g] 80 (100)[i]

[a] Data are from the Cancer Chemotherapy National Service Center, Bethesda, Md. (CCNSC). T/C = (tumor/control; values are given as per cent. [b] L1210 lymphoid leukemia. [c] Dunning leukemia (ascites). [d] P1798 lymphosarcoma. [e] Adenocarcinoma 755. [f] Walker carcinoma 256. [g] Sarcoma 180. [h] Previously reported by N. Vinot.[5] [i] S91 Cloudman melanoma.

TABLE II
2-SUBSTITUTED 2,3-DIHYDRO-1H-PERIMIDINES (I)



R	R_1	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
$3,4,5\text{-}(CH_3O)_3C_6H_2$	H	82	216–217	71.40	5.99	8.33	71.20	5.89	7.96
$3\text{-}BrC_6H_4$	H	99	165–166	62.78	4.02	8.61	62.44	4.25	8.72
1-Naphthyl	H	78	182–183	85.10	5.44	9.45	84.88	5.66	9.38
2-Furyl	H	99	96–97	76.25	5.11	11.85	76.34	5.09	11.86
2-Thienyl	H	84	126–127	71.39	4.79	11.10	71.24	4.78	11.00
3-Pyridyl	H	71	171–172	77.71	5.30	16.95	77.75	5.38	16.96
$CH_3CH_2CH_2$	H	65	77–79[a]						
$CH_3(CH_2)_4$	H	65	60–61[b]						
CH_3	CH_3	69	116–119[c]						

[a] Lit.[5] mp 79–80°. [b] Lit.[5] mp 57–58°. [c] Lit.[4] mp 117°.

stretching and NH deformation peaks in the region of the infrared in question.

The screening results for some of the compounds of the type III and V are included in Table III. Compound III (n = 3) is active against Sarcoma 180 and Lewis lung carcinoma while the related N-methyl compound V only shows appreciable activity against Sarcoma 180. The five-membered analog (III, n = 2) and its 2-carbethoxy derivative are active against tissue culture (KB) and Lewis lung carcinoma, respectively. It can be seen that although a few of the dihydroperimidines do possess antineoplastic activity this is not general and there appears to be no correlation of structure to activity in the cases of active compounds.

Experimental Section[6]

Condensation of Aldehydes and Ketones with 1,8-Diaminonaphthalene.—Mixtures of equimolar quantities of 1,8-diaminonaphthalene and the carbonyl compound in absolute ethanol (usually 50 ml/0.01 mole) were refluxed for 1–30 hr, cooled, filtered, and recrystallized from ethanol to give the compounds shown in Tables II and IV.

Hydrochloride Salts.—Hydrogen chloride was bubbled through an ether solution of the dihydroperimidines to give after recrystallization from ethanol the compounds listed in Table V.

Dispiro[perimidine-2(3H),1′-cyclohexane-4′,2″(3″H)-perimidine] (IV).—A mixture of 0.04 mole of 1,8-diaminonaphthalene and 0.02 mole of cyclohexane-1,4-dione in ethanol was refluxed for 2 hr. After cooling, the material was filtered to give a 93.5% yield, mp 327°. Recrystallization from ethanol produced no change in melting point.

Anal. Calcd for $C_{28}H_{24}N_4 \cdot 1.5C_2H_5OH$: C, 75.46; H, 7.21; N, 12.14; mol wt, 461.6. Found: C, 74.90; H, 7.32; N, 12.06; mol wt, 456.

Recrystallization from acetone also gave material of the same melting point.

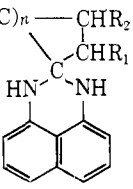
(6) Melting points were taken in capillaries and are corrected. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

TABLE III
SCREENING DATA[a] ON COMPOUNDS OF THE TYPES I, III, AND V

Type	Aldehyde or ketone used to prepare the dihydroperimidine	T/C, % (dose, mg/kg) LE[b]	SA[c]	LL[d]	Other[e]
I	3,4,5-Trimethoxybenzaldehyde	98 (400)	48 (500)	89 (200)	...
I	3-Bromobenzaldehyde	96 (400)	61 (500)	45 (400)	...
I	1-Naphthaldehyde	96 (400)	64 (500)	165 (400)	...
I	Thiophene-2-carboxaldehyde	105 (400)	83 (500)	130 (400)	...
I	Pyridine-3-carboxaldehyde	95 (200)	...	...	70 (200)[f] 87 (100)[g]
I	Butyraldehyde[h]	97 (400)	...	...	95 (400)[f] 95 (200)[g]
I	Heptaldehyde	93 (100)	...	...	72 (100)[f] 96 (50)[g]
I	Acetone	100 (25)	104 (50)	76 (50)	...
III	Cyclopentanone[i]	98 (100)	...	...	72 (100)[f] 103 (50)[g]
III	Ethyl 2-cyclopentanonecarboxylate[j]	...	106 (125)	50 (100)	91 (100)[k]
III	Cyclohexanone	104 (200)	33 (250)	53 (100)	...
III	Ethyl 2-cyclohexanonecarboxylate[l]	...	94 (500)	...	...
V	Cyclohexanone	101 (200)	40 (500)	80 (200)	...

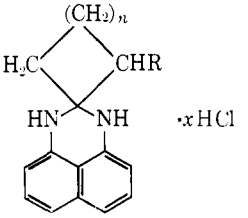
[a] See footnote *a*, Table I. L1210 lymphoid leukemia. [c] Sarcoma 180. [d] Lewis lung carcinoma. [e] See also footnotes *h*, *i*, *j*, and *l*. [f] P1798 lymphosarcoma. [g] Dunning leukemia. [h] KB cell culture, $ED_{50} = 3.0 \times 10^0$ μg/ml, slope − 0.96. [i] KB cell culture, $ED_{50} = 3.6 \times 10^0$ μg/ml, slope −0.45. [j] KB cell culture, $ED_{50} = 3.1 \times 10^1$ μg/ml, slope −0.87. [k] Walker carcinosarcoma 256 (im). [l] KB cell culture $ED_{50} = 3.4 \times 10^1$ μg/ml, slope −0.87.

TABLE IV
SPIROPERIMIDINES (III)



n	R_1	R_2	Yield, %	Mp, °C	Calcd, % C	H	N	Found, % C	H	N
1	H	H	50	109–110	79.96	6.71	13.32	79.81	6.73	13.41
2	H	H	77	87–88	80.32	7.19	12.49	80.37	7.08	12.55
2	$CO_2C_2H_5$	H	48	111–112	72.92	6.80	9.45	73.07	6.71	9.27
2	CONH-naphthyl-1	H	40	212	79.36	5.89	10.68	79.19	5.85	10.61
3	H	H	77	111–113	80.62	7.63	11.76	80.74	7.66	11.58
3	CH_3	H	68	106–107	80.91	7.99	11.10	80.82	7.87	11.09
3	H	CH_3	62	123–124	80.91	7.99	11.10	80.74	7.84	11.19
3	$CO_2C_2H_5$	H	52	138–139	73.52	7.15	9.03	73.25	7.28	8.92
4	H	H	52	67–68	80.91	7.99	11.10	80.61	7.93	11.26

TABLE V
HYDROCHLORIDE SALTS OF SPIROPERIMIDINES



n	R	*x*	Mp, °C	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
2	H	1	250	69.09	6.57	10.74		68.94	6.72	10.71	
2	$CO_2C_2H_5$	1	215	64.95	6.36	8.42	10.65	64.89	6.30	8.48	10.72
3	H	1	247	69.93	6.97	10.20	12.90	69.55	6.84	10.00	13.25
3	$CO_2C_2H_5$	1.5	181	62.50	6.94	7.68		62.34	6.71	8.01	
	V	1.5	175	66.50	7.06	9.13		66.29	7.32	9.24	

Anal. Calcd for $C_{26}H_{24}N_4 \cdot 1.5C_3H_6O$: C, 76.38; H, 6.93; N, 11.68. Found: C, 75.91; H, 7.04; N, 11.24.

Thorough drying of either of the above at elevated temperatures and reduced pressure again gave material of the same melting point.

Anal. Calcd for $C_{26}H_{24}N_4$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.56; H, 6.25; N, 14.19.

1-Methylspiro[cyclohexane-1,2′(3′H)-perimidine] (V).—A mixture of 0.02 mole of III (n = 3), 0.04 mole of methyl iodide, and 0.02 mole of sodium hydride in anhydrous benzene was refluxed for 24 hr. The solid obtained was recrystallized from ether–hexane to give a 68% yield of material, mp 101–102°.

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.87; H, 8.03; N, 11.05.