Department of Chemistry, Clarkson College of Technology

Synthesis of Potential Antineoplastic Agents. XI. Some 2-Aryl-2,3-dihydro-1H-perimidines and a Perimidine Mustard (1,2)

Frank D. Popp and Adria Catala

French (3) recently reported some carcinostatic activity against adenocarcinoma 755 by certain 2-aryl-perimidines (I). With some activity present in this nucleus it was felt that it would be of interest to introduce the bis(2-chloroethyl)amine (nitrogen mustard group) group into this molecule in hopes of preparing a doubly active agent.

The initial attempts to prepare a perimidine mustard (I, R = $-N(CH_2CH_2Cl)_2$) were centered around the condensation of the substituted benzoyl chloride II (4) with 1,8-diaminonaphthalene. This method led to a near quantitative yield of a solid with the expected infrared spectrum. Purification of this crude product, however, proved extremely difficult and another route, based on the work of Vinot (5), was chosen. The substituted benzaldehyde III (6) was allowed to react with 1,8-diaminonaphthalene to give a quantitative yield of IV (R = $-N(CH_2CH_2Cl)_2$, R_1 = R_2 = H). Dehydrogenation of IV with palladium on carbon in hot xylene gave the desired compound I (R = $-N(CH_2CH_2Cl)_2$). The infrared spectrum was essentially identical with that of the material from the acid chloride reaction but the compound could be more easily purified. Despite repeated purification the compound gave low carbon analysis. This perimidine mustard was inactive against both the Dunning leukemia (7) and the adenocarcinoma 755 (8).

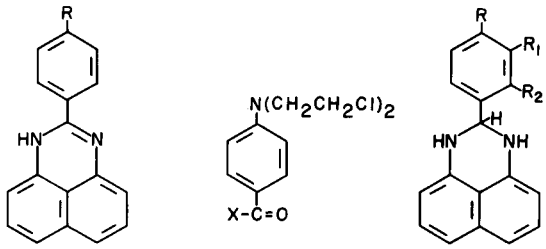
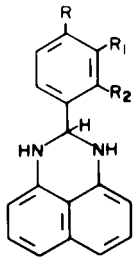


TABLE I

2-Aryl-2,3-dihydro-1H-perimidines



R	R_1	R_2	Yield, %	M.p.	Analysis (a) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$N(CH_2CH_2Cl)_2$	H	H	99	156-157	65.29	5.48	10.88	65.09	5.28	11.02
$N(CH_2CH_2Cl)_2$	H	CH_3	93	142-144	66.00	5.79	10.49	65.70	6.06	10.20
F	H	H	88	189-190	77.25	4.96	10.60	77.55	5.20	10.51
Cl	H	H	83	163-164	72.72	4.67	9.98	72.57	4.71	9.82
Cl	Cl	H	50	129-130 (b)	64.77	3.84	8.89	64.75	4.00	8.84
$N(CH_3)_2$	H	H	79	166-167	78.86	6.62	14.52	78.54	6.88	14.42
C_6H_5	H	H	90	184-185	85.68	5.63	8.69	85.56	5.72	8.55
Br	H	H	60	138-140	62.78	4.03	8.62	62.55	4.14	8.44
H	H	NO_2	94	191-192	70.09	4.50	14.42	70.13	4.21	14.48
H	H	H	54	128-129	82.89	5.73	11.38	82.84	5.77	11.24
CH_3O	H	H	94	151-152	78.24	5.84	10.14	77.90	5.96	10.30
OH	H	H	84	172-173	77.84	5.39	10.60	77.80	5.69	10.33
H	CH_3O	H	91	153-154	78.24	5.84	10.14	78.01	5.72	10.12
CH_3O	CH_3O	H	94	214-216	74.48	5.92	9.15	74.21	6.01	9.29

(a) Analysis by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England. (b) Recrystallized from aqueous-ethanol.

Compound IV (R = $-N(CH_2CH_2Cl)_2$, $R_1 = R_2 = H$) was completely inactive at doses of 500 mg./kg. against an established Dunning leukemia in rats (7) as was the related compound with R_2 as CH_3 and the compound from III and 1,2-diaminonaphthalene. In view of this lack of activity against a nitrogen mustard sensitive tumor it was surprising to find that IV (R = $-N(CH_2CH_2Cl)_2$, $R_1 = R_2 = H$) was active against the adenocarcinoma 755 (T/C = 34%) (8). In view of the activity against the adenocarcinoma 755 and the lack of activity against the Dunning leukemia a number of other compounds of the type IV were prepared for screening. These dihydroperimidines are included in Table I.

EXPERIMENTAL

Condensation of Aldehydes with 1,8-Diaminonaphthalene.

A mixture of 3.16 g. (0.02 mole) of 1,8-diaminonaphthalene and 0.02 mole of the benzaldehyde derivative in absolute ethanol was heated on a steam bath for 20 min., cooled, filtered, and recrystallized from 95% ethanol to give the compounds shown in Table I.

Condensation of Benzaldehyde Mustard with 1,2-Diaminonaphthalene.

In a similar manner equal molar amounts of 1,2-diaminonaphthalene and 4-[bis(2-chloroethyl)amino]benzaldehyde gave a 78% yield of material, m.p. 139-140°.

Anal. Calcd. for $C_{21}H_{21}N_3Cl_2$: C, 65.29; H, 5.48; N, 10.88; Cl, 18.36. Found: C, 64.88; H, 5.43; N, 10.80; Cl, 18.41.

2-(4-[Bis(2-chloroethyl)amino]phenyl)perimidine.

A mixture of 5 g. of 2-(4-[Bis(2-chloroethyl)amino]phenyl)-2,3-dihydro-1H-perimidine and 2 g. of 10% Pd/C in 50 ml. of xylene was refluxed for 40 min. and filtered hot. Upon cooling a solid was collected and recrystallized from 95% ethanol to give 1.93 g. (39%), m.p. 114-116°.

Anal. Calcd. for $C_{21}H_{19}N_3Cl_2$: C, 65.63; H, 4.98; N, 10.94; Cl, 18.46. Found: C, 64.60; H, 4.91; N, 11.01; Cl, 18.38.

REFERENCES

(1) Part X, F. D. Popp, *J. Med. Chem.*, 7, 210 (1964).

(2) This work was supported in part by research grants from the American Cancer Society (T 177C) and from the National Cancer Institute, U.S.P.H.S. (CA 06606-01).

(3) F. A. French, *Proc. Am. Assn. Cancer Res.*, 3, 319 (1962).

(4) R. C. Elderfield and T. K. Liao, *J. Org. Chem.*, 26, 4996 (1961).

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

(6) R. H. Wiley and G. Irick, *J. Org. Chem.*, 26, 593 (1961).

(7) Private communication from Dr. Leo Rane, University of Miami Medical School.

(8) Data supplied by the C.C.N.S.C.

Received November 12, 1963

Potsdam, New York