Hexahydropyrimidines. V.[1] A Study of 2-Substituted 1,3-Bis(α-cyanobenzyl)-hexahydropyrimidines and 2-Substituted 1,3-Bis(α-cyano-*p*-methoxybenzyl)-hexahydropyrimidines as Prospective Antitumor Agents[2]

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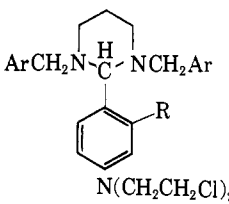
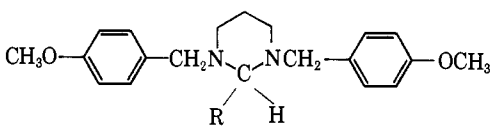
A series of 2-substituted 1,3-bis(α-cyano-*p*-methoxybenzyl)hexahydropyrimidines and 2-substituted 1,3-bis(α-cyanobenzyl)hexahydropyrimidines has been prepared and tested for antitumor activity. None of these compounds showed appreciable antineoplastic activity in tissue culture or animal studies.

In some rather recent publications it has been shown that 1,2,3-substituted hexahydropyrimidines of the general structure I and II possessed appreciable antitumor activity.[1,3] Furthermore, cyano derivatives



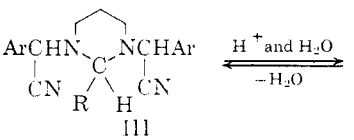
I, R = H, CH_3
Ar = aryl or substituted aryl



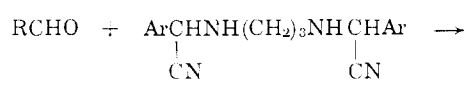
II, R = alkyl or substituted aryl

of both antimetabolites and alkylating agents have recently shown promise as anticancer agents in preliminary test studies. For example, 6-(cyanomethylthio)purine exhibits marked inhibition towards Adenocarcinoma 755[4] in mice, and 4-[N,N-bis(2-chloroethyl)-amino]benzylidenemalononitrile and related compounds are active against Dunning leukemia[5] in rats. In addition, a series of bicyclic nitriles and related compounds were recently prepared by the Diels–Alder reaction for evaluation as antitumor agents,[6] and they also showed activity. Since some of the aforementioned publications indicate that the cyano group may enhance the activity of some molecules, it was decided that compounds of type III would be of interest to prepare and examine for antitumor activity as a continuation of our previous work.

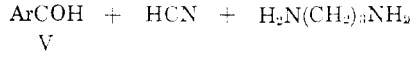
To date, it is not understood by what mechanism these compounds of type I and II act in the biological system. However, an attempt is being made to determine whether the molecule as a whole is the effective agent or whether it is one of the products which might be formed by acid or enzymatic hydrolysis. It has been suggested[1,3] that hexahydropyrimidines may be regarded as potential aldehydes, since, *in vitro*, they readily hydrolyze under mild acidic conditions to liberate the free aldehydes, which in themselves, may act as antitumor agents. A similar situation may exist with compounds of type III which upon hydrolysis may yield the free aldehyde in addition to a dicyano compound. The dicyano compound may possess activity or it may hydrolyze further to give hydrogen cyanide and the aldehyde V either of which may show antitumor activity at the tumor site.



III



IVa, Ar = C_6H_5
b, Ar = *p*-$C_6H_4OCH_3$



V

The hexahydropyrimidines summarized in Tables I and II were synthesized by condensing an equimolar proportion of the aldehydes and secondary 1,3-diaminopropane of general structure IV in refluxing absolute ethanol. The diamines employed in this project were prepared by treating the desired aldehyde with potassium cyanide and 1,3-diaminopropane dihydrochloride in a refluxing methanol–water mixture according to the procedure of Schlesinger.[7]

Biological Results.—The representative examples of the cyanohexahydropyrimidines described in this paper were screened under the direction of the Cancer Chemotherapy National Service Center for anticancer activity in mice in doses up to 200 mg./kg. and in cell culture tests. These compounds were toxic at the high dose levels. The tested compounds displayed no significant activity against Walker 256, Sarcoma 180, leukemia L1210, Dunning ascites leukemia, *in vivo* test systems. However, the first compound in Table I has given an ED_{50} value of less than 4 γ/ml. in a KB human epidermoid carcinoma.

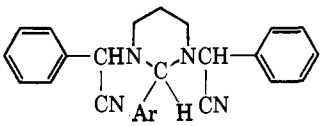
Experimental

All melting points are corrected unless otherwise stated. The microanalyses were performed by Midwest Microlaboratories,

(1) J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **7**, 115 (1964).
(2) This investigation was supported by a Public Health Service Research Grant No. CA-08888-01 from the National Cancer Institute.
(3) J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **6**, 682 (1963).
(4) T. P. Johnson, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, **80**, 6265 (1958); H. E. Skipper and J. A. Montgomery, *Cancer Res.*, **19**, 287 (1959); L. R. Duval, *Cancer Chemotherapy Rept.* **11**, 232 (1961).
(5) F. D. Popp, *J. Org. Chem.*, **25**, 646 (1960).
(6) P. Scheiner and W. R. Vaughan, *ibid.*, **26**, 1923 (1961).
(7) N. Schlesinger, *Ber.*, **58**, 1880 (1925).

TABLE I

2-SUBSTITUTED 1,3-BIS(α-CYANOBENZYL)HEXAHYDROPYRIMIDINES

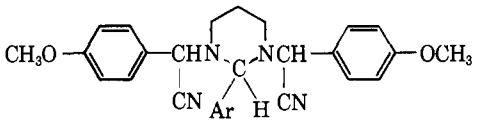


Ar	Yield, % (pure)	M.p., °C. (cor.)	Nitrogen, % Calcd.	Found
H[a]	51	135–136	17.70	17.65
Phenyl[b]	70	204–205	14.28	14.36
o-Methoxyphenyl[a]	60	230–231	13.26	13.15
o-Hydroxyphenyl[a]	51	189–190	13.71	13.51
p-Methoxyphenyl[c]	53	206–207	13.26	13.33
p-Dimethylaminophenyl[a]	58	218–219	16.08	16.15
2-Hydroxy-3-methoxyphenyl[d]	48	171–172.5	12.78	12.90
n-Hexyl[a]	47	106–107	13.98	13.85
4-[N,N-Bis(2-chloroethyl)amino]-2-methylphenyl[b]	42	189–190	12.81	12.81
			Cl, 12.97	Cl, 12.74
4-[N,N-Bis(2-chloroethyl)amino]phenyl[d]	49	196–197	13.14	13.09
			Cl, 13.31	Cl, 13.16

[a] Recrystallized from methanol. [b] Recrystallized from benzene–methanol. [c] Recrystallized from methanol–acetonitrile. [d] Recrystallized from ethanol–acetonitrile.

TABLE II

2-SUBSTITUTED 1,3-BIS(α-CYANO-*p*-METHOXYBENZYL)-HEXAHYDROPYRIMIDINES



Ar	Yield, % (pure)	M.p., °C. (cor.)	Nitrogen, % Calcd.	Found
n-Hexyl[a]	35	170–171.5	12.17	12.30
Phenyl[b]	83	158–159	12.38	12.31
o-Hydroxyphenyl[b]	40	175–176	11.95	11.80
o-Methoxyphenyl[c]	44	210–211	11.60	11.55
2-Hydroxy-3-methoxyphenyl[d]	55	164–165.5 dec.	11.23	11.20
p-Methoxyphenyl[a]	55	169–170	11.61	11.67

[a] Recrystallized from methanol. [b] Recrystallized from ethanol. [c] Recrystallized from methanol–acetonitrile. [d] Recrystallized from ethanol–acetonitrile.

Indianapolis, Ind. Aldehydes used were either reagent grade or purified by distillation or recrystallization from appropriate solvents.

N,N′-Bis(α-cyanobenzyl)-1,3-diaminopropane (IVa).—To a refluxing mixture of 13.03 g. (0.2 mole) of potassium cyanide and 14.69 g. (0.1 mole) of 1,3-diaminopropane dihydrochloride in 100 ml. of methanol–water (1:1) was slowly added (30 min.) 21.23 g. (0.2 mole) of benzaldehyde with stirring; a yellow oil separated from the solution. The mixture was refluxed for an additional 1 hr., cooled to room temperature, and diluted with 50 ml. of distilled water. As the mixture cooled, a white product separated which was filtered and washed successively with water then methanol (95%). Two crystallizations from ethanol afforded 21.2 g. (70%) of colorless plates, m.p. 99–100° (lit.[7] m.p. 97–98°). In several runs yields varied from 70–75%.

N,N′-Bis(α-cyano-*p*-methoxybenzyl)-1,3-diaminopropane (IVb).—This diamine was prepared similarly to IVa using 13.02 g. (0.2 mole) of potassium cyanide, 14.69 g. (0.1 mole) of 1,3-diaminopropane dihydrochloride, and 27.23 g. (0.2 mole) of anisaldehyde which yielded 30.0 g. (82%) of desired product, m.p. 92–94°. Recrystallization from methanol provided a colorless, crystalline analytical sample, m.p. 93–94°.

Anal. Calcd. for $C_{21}H_{24}N_4O_2$: N, 15.37. Found: N, 15.35.

2-Substituted 1,3-Bis(α-cyanobenzyl)hexahydropyrimidines (Table I).—A solution of 4.92 g. (0.02 mole) of 4-[N,N-bis(2-chloroethyl)amino]benzaldehyde in 30 ml. of absolute ethanol was added dropwise with stirring during 30 min. to a refluxing solution of 6.1 g. (0.02 mole) of diamine (IVa) in 30 ml. of absolute ethanol. After the addition had been completed, the resulting mixture was refluxed for 45 min., and excess ethanol was removed under reduced pressure. The residue was crystallized from a mixture of ethanol–acetonitrile (1:1) to yield 5.1 g. (49%) of a colorless crystalline product. Two recrystallizations from ethanol–acetonitrile provided an analytical sample, m.p. 196–197°.

Anal. Calcd. for $C_{30}H_{31}Cl_2N_5$: Cl, 13.31; N, 13.14. Found: Cl, 13.16; N, 13.09.

2-Substituted 1,3-Bis(α-cyano-*p*-methoxybenzyl)hexahydropyrimidines (Table II).—These compounds were prepared as above using aldehydes and N,N′-bis(α-cyano-*p*-methoxybenzyl)-1,3-diaminopropane.

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